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Published in:
PLoS Genetics

DOI:
[10.1371/journal.pgen.1003212](https://doi.org/10.1371/journal.pgen.1003212)

2013

[Link to publication](#)

Citation for published version (APA):

Couch, F. J., Wang, X., McGuffog, L., Lee, A., Olswold, C., Kuchenbaecker, K. B., Soucy, P., Fredericksen, Z., Barrowdale, D., Dennis, J., Gaudet, M. M., Dicks, E., Kosel, M., Healey, S., Sinilnikova, O. M., Lee, A., Bacot, F., Vincent, D., Hogervorst, F. B. L., ... Antoniou, A. C. (2013). Genome-Wide Association Study in BRCA1 Mutation Carriers Identifies Novel Loci Associated with Breast and Ovarian Cancer Risk. *PLoS Genetics*, 9(3), Article e1003212. <https://doi.org/10.1371/journal.pgen.1003212>

Total number of authors:
262

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Genome-Wide Association Study in *BRCA1* Mutation Carriers Identifies Novel Loci Associated with Breast and Ovarian Cancer Risk

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Abstract

BRCA1-associated breast and ovarian cancer risks can be modified by common genetic variants. To identify further cancer risk-modifying loci, we performed a multi-stage GWAS of 11,705 *BRCA1* carriers (of whom 5,920 were diagnosed with breast and 1,839 were diagnosed with ovarian cancer), with a further replication in an additional sample of 2,646 *BRCA1* carriers. We identified a novel breast cancer risk modifier locus at 1q32 for *BRCA1* carriers (rs2290854, $P = 2.7 \times 10^{-8}$, HR = 1.14, 95% CI: 1.09–1.20). In addition, we identified two novel ovarian cancer risk modifier loci: 17q21.31 (rs17631303, $P = 1.4 \times 10^{-8}$, HR = 1.27, 95% CI: 1.17–1.38) and 4q32.3 (rs4691139, $P = 3.4 \times 10^{-8}$, HR = 1.20, 95% CI: 1.17–1.38). The 4q32.3 locus was not associated with ovarian cancer risk in the general population or *BRCA2* carriers, suggesting a *BRCA1*-specific association. The 17q21.31 locus was also associated with ovarian cancer risk in 8,211 *BRCA2* carriers ($P = 2 \times 10^{-4}$). These loci may lead to an improved understanding of the etiology of breast and ovarian tumors in *BRCA1* carriers. Based on the joint distribution of the known *BRCA1* breast cancer risk-modifying loci, we estimated that the breast cancer lifetime risks for the 5% of *BRCA1* carriers at lowest risk are 28%–50% compared to 81%–100% for the 5% at highest risk. Similarly, based on the known ovarian cancer risk-modifying loci, the 5% of *BRCA1* carriers at lowest risk have an estimated lifetime risk of developing ovarian cancer of 28% or lower, whereas the 5% at highest risk will have a risk of 63% or higher. Such differences in risk may have important implications for risk prediction and clinical management for *BRCA1* carriers.

Citation: Couch FJ, Wang X, McGuffog L, Lee A, Olsword C, et al. (2013) Genome-Wide Association Study in *BRCA1* Mutation Carriers Identifies Novel Loci Associated with Breast and Ovarian Cancer Risk. *PLoS Genet* 9(3): e1003212. doi:10.1371/journal.pgen.1003212

Editor: Kent W. Hunter, National Cancer Institute, United States of America

Received: September 7, 2012; **Accepted:** November 14, 2012; **Published:** March 27, 2013

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Funding: The study was supported by NIH grant CA128978, an NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201), a U.S. Department of Defense Ovarian Cancer Idea award (W81XWH-10-1-0341), grants from the Breast Cancer Research Foundation and the Komen Foundation for the Cure; Cancer Research UK grants C12292/A11174 and C1287/A10118; the European Commission's Seventh Framework Programme grant agreement 223175 (HEALTH-F2-2009-223175). Breast Cancer Family Registry Studies (BCFR): supported by the National Cancer Institute, National Institutes of Health 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), Columbia University (U01 CA69398), Fox Chase Cancer Center (U01 CA69631), Huntsman Cancer Institute (U01 CA69446), and University of Melbourne (U01 CA69638). The Australian BCFR 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. Melissa C. Southey is a NHMRC Senior Research Fellow and a Victorian Breast Cancer Research Consortium Group Leader. Carriers at FCCC were also identified with support from National Institutes of Health grants P01 CA16094 and R01 CA22435. The New York BCFR was also supported by National Institutes of Health grants P30 CA13696 and P30 ES009089. The Utah BCFR was also supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH grant UL1 RR025764, and by Award Number P30 CA042014 from the National Cancer Institute. Baltic Familial Breast Ovarian Cancer Consortium (BFBOCC): BFBOCC is partly supported by Lithuania (BFBOCC-LT), Research Council of Lithuania grant LIG-19/2010, and Hereditary Cancer Association (Paveldimo vėžio asociacija). Latvia (BFBOCC-LV) is partly supported by LSC grant 10.0010.08 and in part by a grant from the ESF Nr.2009/0220/1DP/1.1.1.2.0/09/APIA/VIAA/016. *BRCA*-gene mutations and breast cancer in South African women (BMBSA): BMBSA was supported by grants from the Cancer Association of South Africa (CANSA) to Elizabeth J. van Rensburg. Beckman Research Institute of the City of Hope (BRICOH): Susan L. Neuhausen was partially supported by the Morris and Horowitz Families Endowed Professorship. BRICOH was supported by NIH R01CA74415 and NIH P30 CA033752. Copenhagen Breast Cancer Study (CBCS): The CBCS study was supported by the NEYE Foundation. Spanish National Cancer Centre (CNIO): This work was partially supported by Spanish Association against Cancer (AECC08), RTICC 06/0020/1060, FISPI08/1120, Mutua Madrileña Foundation (FMMA) and SAF2010-20493. City of Hope Cancer Center (COH): The City of Hope Clinical Cancer Genetics Community Research Network is supported by Award Number RC4A153828 (PI: Jeffrey N. Weitzel) from the National Cancer Institute and the Office of the Director, National Institutes of Health. CONSORZIO STUDI ITALIANI SUI TUMORI EREDITARI ALLA MAMMELLA (CONSIT TEAM): CONSIT TEAM was funded by grants from Fondazione Italiana per la Ricerca sul Cancro (Special Project "Hereditary tumors"), Italian Association for Cancer Research (AIRC, IG 8713), Italian Ministry of Health (Extraordinary National Cancer Program 2006, "Alleanza contro il Cancro" and "Progetto Tumori Femminili), Italian Ministry of Education, University and Research (Prin 2008) Centro di Ascolto Donne Operate al Seno (CAOS) association 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 '5×1000'). German Cancer Research Center (DKFZ): The DKFZ study was supported by the DKFZ. The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON): HEBON is supported by the Dutch Cancer Society grants NK11998-1854, NK12004-3088, NK12007-3756, the NWO grant 91109024, the Pink Ribbon grant 110005, and the BBMRI grant CP46/NWO. Epidemiological study of *BRCA1* & *BRCA2* mutation carriers (EMBRACE): EMBRACE is supported by Cancer Research UK Grants C1287/A10118 and C1287/A11990. D. Gareth Evans and Fiona Lalloo are supported by an 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. Rosalind A. Eeles and Elizabeth Bancroft are supported by Cancer Research UK Grant C5047/A8385. Fox Chase Cancer Center (FCCC): The authors acknowledge support from The University of Kansas Cancer Center and the Kansas Bioscience Authority Eminent Scholar Program. Andrew K. Godwin was funded by 5U01CA113916, R01CA140323, and by the Chancellors Distinguished Chair in Biomedical Sciences

Professorship. German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC): The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) is supported by the German Cancer Aid (grant no 109076, Rita K. Schmutzler) and by the Center for Molecular Medicine Cologne (CMMC). Genetic Modifiers of cancer risk in *BRCA1/2* mutation carriers (GEMO): The GEMO study was supported by the Ligue National Contre le Cancer; the Association "Le cancer du sein, parlons-en!" Award and the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program. Gynecologic Oncology Group (GOG): This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office and Tissue Bank (CA 27469), Statistical and Data Center (CA 37517), and GOG's Cancer Prevention and Control Committee (CA 101165). Drs. Mark H. Greene and Phuong L. Mai were supported by funding from the Intramural Research Program, NCI, NIH. Hospital Clinico San Carlos (HCSC): HCSC was supported by RETICC 06/0020/0021, FIS research grant 09/00859, Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, and the European Regional Development Fund (ERDF). Helsinki Breast Cancer Study (HEBCS): The HEBCS was financially supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (132473), the Finnish Cancer Society, the Nordic Cancer Union, and the Sigrid Juselius Foundation. Study of Genetic Mutations in Breast and Ovarian Cancer patients in Hong Kong and Asia (HRBCP): HRBCP is supported by The Hong Kong Hereditary Breast Cancer Family Registry and the Dr. Ellen Li Charitable Foundation, Hong Kong. Molecular Genetic Studies of Breast and Ovarian Cancer in Hungary (HUNBOCS): HUNBOCS was supported by Hungarian Research Grant KTIA-OTKA CK-80745 and the Norwegian EEA Financial Mechanism HU0115/NA/2008-3/OP-9. Institut Català d'Oncologia (ICO): The ICO study was supported by the Asociación Española Contra el Cáncer, Spanish Health Research Foundation, Ramón Areces Foundation, Carlos III Health Institute, Catalan Health Institute, and Autonomous Government of Catalonia and contract grant numbers: ISCIIIRETIC RD06/0020/1051, PI09/02483, PI10/01422, PI10/00748, 2009SGR290, and 2009SGR283. International Hereditary Cancer Centre (IHCC): Supported by the Polish Foundation of Science. Katarzyna Jaworska is a fellow of International PhD program, Postgraduate School of Molecular Medicine, Warsaw Medical University. Iceland Landspítali-University Hospital (ILUH): The ILUH group was supported by the Icelandic Association "Walking for Breast Cancer Research" and by the Landspítali University Hospital Research Fund. Interdisciplinary Health Research Internal Team BReast CAncer susceptibility (INHERIT): INHERIT work was supported by the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program, the Canadian Breast Cancer Research Alliance grant 019511 and the Ministry of Economic Development, Innovation and Export Trade grant PSR-SIIRI-701. Jacques Simard is Chairholder of the Canada Research Chair in Oncogenetics. Istituto Oncologico Veneto (IOVHBOCS): The IOVHBOCS study was supported by Ministero dell'Istruzione, dell'Università e della Ricerca and Ministero della Salute ("Progetto Tumori Femminili" and RFP5 2006-5-341353,ACC2/R6.9"). Kathleen Cuninghame Consortium for Research into Familial Breast Cancer (kConFab): kConFab is supported by grants from the National Breast Cancer Foundation and the National Health and Medical Research Council (NHMRC) and by the Queensland Cancer Fund; the Cancer Councils of New South Wales, Victoria, Tasmania, and South Australia; and the Cancer Foundation of Western Australia. Amanda B. Spurdle is an NHMRC Senior Research Fellow. The Clinical Follow Up Study was funded from 2001–2009 by NHMRC and currently by the National Breast Cancer Foundation and Cancer Australia #628333. Mayo Clinic (MAYO): MAYO is supported by NIH grant CA128978, an NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201), a U.S. Department of Defence Ovarian Cancer Idea award (W81XWH-10-1-0341) and grants from the Breast Cancer Research Foundation and the Komen Foundation for the Cure. McGill University (MCGILL): The McGill Study 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 (MSKCC): The MSKCC study was supported by Breast Cancer Research Foundation, Niehaus Clinical Cancer Genetics Initiative, Andrew Sabin Family Foundation, and Lymphoma Foundation. Modifier Study of Quantitative Effects on Disease (MODSQUAD): MODSQUAD was supported by the European Regional Development Fund and the State Budget of the Czech Republic (RECAMO, CZ.1.05/2.1.00/03.0101). Women's College Research Institute, Toronto (NAROD): NAROD was supported by NIH grant: 1R01 CA149429-01. National Cancer Institute (NCI): Drs. Mark H. Greene and Phuong L. Mai were supported by the Intramural Research Program of the US National Cancer Institute, NIH, and by support services contracts NO2-CP-11019-50 and NO2-CP-65504 with Westat, Rockville, MD. National Israeli Cancer Control Center (NICCC): NICCC is supported by Clalit Health Services in Israel. Some of its activities are supported by the Israel Cancer Association and the Breast Cancer Research Foundation (BCRF), NY. N. N. Petrov Institute of Oncology (NNPIO): The NNPIO study has been supported by the Russian Foundation for Basic Research (grants 11-04-00227, 12-04-00928, and 12-04-01490), the Federal Agency for Science and Innovations, Russia (contract 02.740.11.0780), and through a Royal Society International Joint grant (JP090615). The Ohio State University Comprehensive Cancer Center (OSU-CCG): OSUCCG is supported by the Ohio State University Comprehensive Cancer Center. South East Asian Breast Cancer Association Study (SEABASS): SEABASS is supported by the Ministry of Science, Technology and Innovation, Ministry of Higher Education (UM.C/HIR/MOHE/06) and Cancer Research Initiatives Foundation. Sheba Medical Centre (SMC): The SMC study was partially funded through a grant by the Israel Cancer Association and the funding for the Israeli Inherited Breast Cancer Consortium. Swedish Breast Cancer Study (SWE-BRCA): SWE-BRCA collaborators are supported by the Swedish Cancer Society. The University of Chicago Center for Clinical Cancer Genetics and Global Health (UCHICAGO): UCHICAGO is supported by grants from the US National Cancer Institute (NIH/NCI) 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 California Los Angeles (UCLA): The UCLA study was supported by the Jonsson Comprehensive Cancer Center Foundation and the Breast Cancer Research Foundation. University of California San Francisco (UCSF): The UCSF study was supported by the UCSF Cancer Risk Program and the Helen Diller Family Comprehensive Cancer Center. United Kingdom Familial Ovarian Cancer Registries (UKFOCR): UKFOCR was supported by a project grant from CRUK to Paul Pharoah. University of Pennsylvania (UPENN): The UPENN study was supported by the National Institutes of Health (NIH) (R01-CA102776 and R01-CA083855), Breast Cancer Research Foundation, Rooney Family Foundation, Susan G. Komen Foundation for the Cure, and the Macdonald Family Foundation. Victorian Familial Cancer Trials Group (VFCTG): The VFCTG study was supported by the Victorian Cancer Agency, Cancer Australia, and National Breast Cancer Foundation. Women's Cancer Research Initiative (WCRI): The WCRI at the Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, is funded by the American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Breast and ovarian cancer risk estimates for *BRCA1* mutation carriers vary by the degree of family history of the disease, suggesting that other genetic factors modify cancer risks for this population [1–4]. Studies by the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) have shown that a subset of common alleles influencing breast and ovarian cancer risk in the general population are also associated with cancer risk in *BRCA1* mutation carriers [5–11]. In particular, the breast cancer associations were limited to loci associated with estrogen receptor (ER)-negative breast cancer in the general population (6q25.1, 12p11 and *TOX3*) [8–11].

To systematically search for loci associated with breast or ovarian cancer risk for *BRCA1* carriers we previously conducted a

two-stage genome-wide association study (GWAS) [12]. The initial stage involved analysis of 555,616 SNPs in 2383 *BRCA1* mutation carriers (1,193 unaffected and 1,190 affected). After replication testing of 89 SNPs showing the strongest association, with 5,986 *BRCA1* mutation carriers, a locus on 19p13 was shown to be associated with breast cancer risk for *BRCA1* mutation carriers. The same locus was also associated with the risk of estrogen-receptor (ER) negative and triple negative (ER, Progesterone and HER2 negative) breast cancer in the general population [12,13].

The Collaborative Oncological Gene-environment Study (COGS) consortium recently developed a 211,155 SNP custom genotyping array (iCOGS) in order to provide cost-effective genotyping of common and rare genetic variants to identify novel loci that explain the residual genetic variance of breast, ovarian

Author Summary

BRCA1 mutation carriers have increased and variable risks of breast and ovarian cancer. To identify modifiers of breast and ovarian cancer risk in this population, a multi-stage GWAS of 14,351 *BRCA1* mutation carriers was performed. Loci 1q32 and *TCF7L2* at 10q25.3 were associated with breast cancer risk, and two loci at 4q32.2 and 17q21.31 were associated with ovarian cancer risk. The 4q32.3 ovarian cancer locus was not associated with ovarian cancer risk in the general population or in *BRCA2* carriers and is the first indication of a *BRCA1*-specific risk locus for either breast or ovarian cancer. Furthermore, modeling the influence of these modifiers on cumulative risk of breast and ovarian cancer in *BRCA1* mutation carriers for the first time showed that a wide range of individual absolute risks of each cancer can be estimated. These differences suggest that genetic risk modifiers may be incorporated into the clinical management of *BRCA1* mutation carriers.

and prostate cancers and fine-map known susceptibility loci. A total of 32,557 SNPs on the iCOGS array were selected on the basis of the *BRCA1* GWAS for the purpose of identifying breast and ovarian cancer risk modifiers for *BRCA1* mutation carriers. Genotype data from the iCOGS array were obtained for 11,705 samples from *BRCA1* carriers and the 17 most promising SNPs were then genotyped in an additional 2,646 *BRCA1* carriers. In this manuscript we report on the novel risk modifier loci identified by this multi-stage GWAS. No study has previously shown how the absolute risks of breast and ovarian cancer for *BRCA1* mutation carriers vary by the combined effects of risk modifying loci. Here we use the results from this study, in combination with previously identified modifiers, to obtain absolute risks of developing breast and ovarian cancer for *BRCA1* mutation carriers based on the joint distribution of all known genetic risk modifiers.

Materials and Methods

Ethics statement

All carriers participated in clinical or research studies at the host institutions, approved by local ethics committees.

Study subjects

BRCA1 mutation carriers were recruited by 45 study centers in 25 countries through CIMBA. The majority were recruited through cancer genetics clinics, and enrolled into national or regional studies. The remainder were identified by population-based sampling or community recruitment. Eligibility for CIMBA association studies was restricted to female carriers of pathogenic *BRCA1* mutations age 18 years or older at recruitment. Information collected included year of birth, mutation description, self-reported ethnic ancestry, age at last follow-up, ages at breast or ovarian cancer diagnoses, and age at bilateral prophylactic mastectomy and oophorectomy. Information on tumour characteristics, including ER-status of the breast cancers, was also collected. Related individuals were identified through a unique family identifier. Women were included in the analysis if they carried mutations that were pathogenic according to generally recognized criteria.

GWAS stage 1 samples. A total of 2,727 *BRCA1* mutation carriers were genotyped on the Illumina Infinium 610K array (Figure 1). Of these 1,426 diagnosed with a first breast cancer under age 40 were considered “affected” in the breast cancer

association analysis and 683 diagnosed with an ovarian cancer at any time were considered as “affected” in the ovarian cancer analysis. “Unaffected” in both analyses were over age 35 (Table S1) [12].

Replication study samples. All eligible *BRCA1* carriers from CIMBA with sufficient DNA were genotyped, including those used in Stage 1. In total, 13,310 samples from 45 centers in 25 countries were genotyped using the iCOGS array (Table S2). Among the 13,310 samples, those that were genotyped in the GWAS stage 1 SNP selection stage are referred to as “stage 1” samples, and the remainder are “stage 2” samples. An additional 2,646 *BRCA1* samples “stage 3” were genotyped on an iPLEX Mass Array of 17 SNPs from 12 loci selected after an interim analysis of iCOGS array data and were available for analysis after quality control (QC) (Figure 1). Carriers of pathogenic mutations in *BRCA2* were drawn from a parallel GWAS of genetic modifiers for *BRCA2* mutation carriers. *BRCA2* mutation carriers were recruited from CIMBA through 47 studies which were largely the same as the studies that contributed to the *BRCA1* GWAS with similar eligibility criteria. Samples from *BRCA2* mutation carriers were also genotyped using the iCOGS array. Details of this experiment are described elsewhere [14]. A total of 8,211 samples were available for analysis after QC.

iCOGS SNP array

The iCOGS array was designed in a collaboration among the Breast Cancer Association Consortium (BCAC), Ovarian Cancer Association Consortium (OCAC), the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) and CIMBA. The general aims for designing the iCOGS array were to replicate findings from GWAS for identifying variants associated with breast, ovarian or prostate cancer (including subtypes and SNPs potentially associated with disease outcome), to facilitate fine-mapping of regions of interest, and to genotype “candidate” SNPs of interest within the consortia, including rarer variants. Each consortium was given a share of the array: nominally 25% of the SNPs each for BCAC, PRACTICAL and OCAC; 17.5% for CIMBA; and 7.5% for SNPs of common interest between the consortia. The final design comprised 220,123 SNPs, of which 211,155 were successfully manufactured. A total of 32,557 SNPs on the iCOGS array were selected based on 8 separate analyses of stage 1 of the CIMBA *BRCA1* GWAS that included 2,727 *BRCA1* mutation carriers [12]. After imputation for all SNPs in HapMap Phase II (CEU) a total of 2,568,349 (imputation $r^2 > 0.30$) were available for analysis. Markers were evaluated for associations with: (1) breast cancer; (2) ovarian cancer; (3) breast cancer restricted to Class 1 mutations (loss-of-function mutations expected to result in a reduced transcript or protein level due to nonsense-mediated RNA decay); (4) breast cancer restricted to Class 2 mutations (mutations likely to generate stable proteins with potential residual or dominant negative function); (5) breast cancer by tumor ER-status; (6) breast cancer restricted to *BRCA1* 185delAG mutation carriers; (7) breast cancer restricted to *BRCA1* 5382insC mutation carriers; and (8) breast cancer by contrasting the genotype distributions in *BRCA1* mutation carriers, against the distribution in population-based controls. Analyses (1) and (2) were based on both imputed and observed genotypes, whereas the rest were based on only the observed genotypes. SNPs were ranked according to the 1 d.f. score-test for trend P-value (described below) and selected for inclusion based on nominal proportions of 61.5%, 20%, 2.5%, 2.5%, 2.5%, 0.5%, 0.5% and 10.0% for analyses (1) to (8). SNP duplications were not allowed and SNPs with a pairwise $r^2 \geq 0.90$ with a higher-ranking SNP were only allowed (up to a maximum

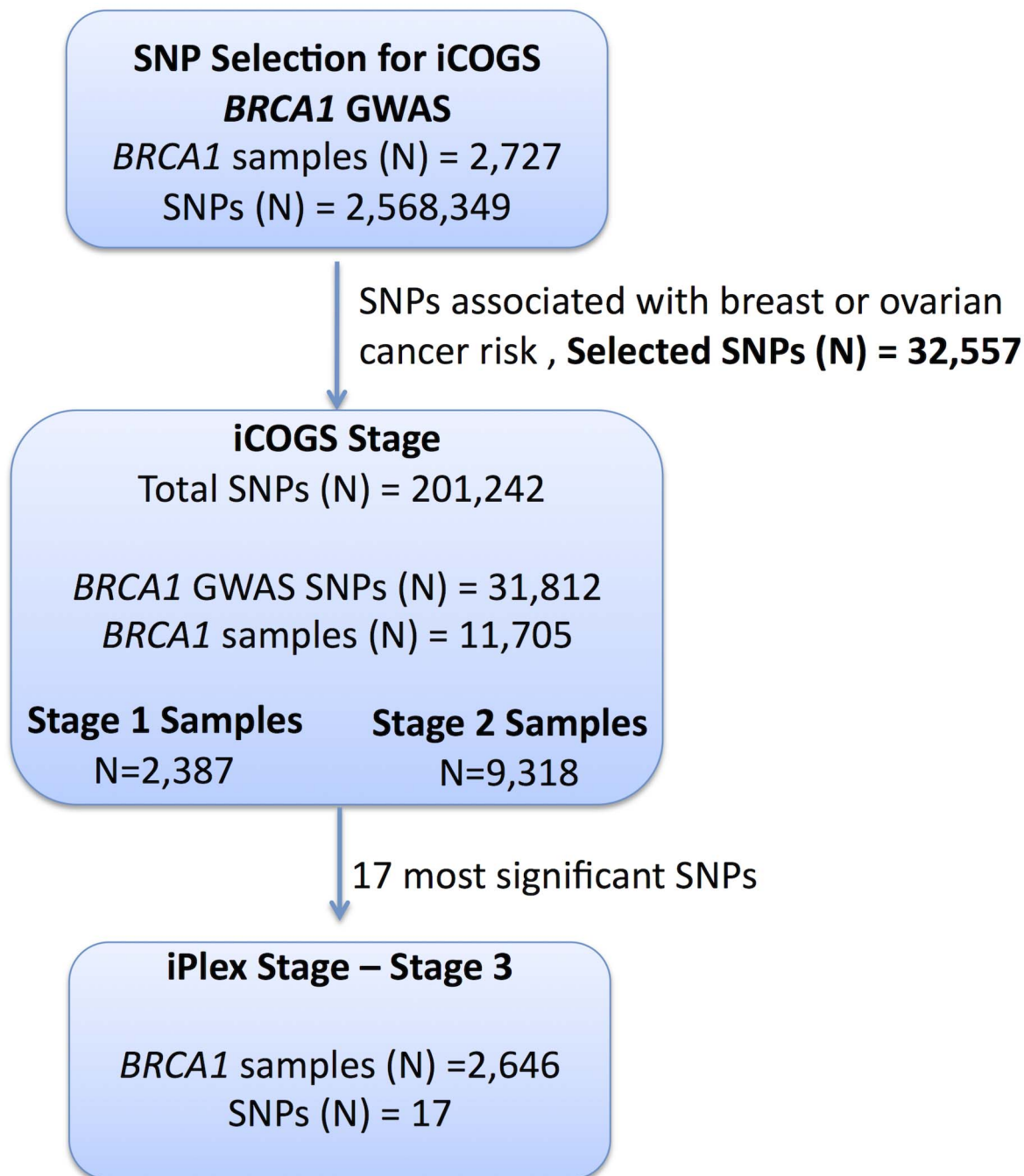


Figure 1. Study design for selection of the SNPs and genotyping of *BRCA1* samples. GWAS data from 2,727 *BRCA1* mutation carriers were analysed for associations with breast and ovarian cancer risk and 32,557 SNPs were selected for inclusion on the iCOGS array. A total of 11,705 *BRCA1* samples (after quality control (QC) checks) were genotyped on the 31,812 *BRCA1*-GWAS SNPs from the iCOGS array that passed QC. Of these samples, 2,387 had been genotyped at the SNP selection stage and are referred to as “stage 1” samples, whereas 9,318 samples were unique to the iCOGS study (“Stage 2” samples). Next, 17 SNPs that exhibited the most significant associations with breast and ovarian cancer were selected for genotyping in a third stage involving an additional 2,646 *BRCA1* samples (after QC).
doi:10.1371/journal.pgen.1003212.g001

of 2) if the P-value for association was $<10^{-4}$ for analyses (1) and (2) and $<10^{-5}$ for other analyses. SNPs with poor Illumina design scores were replaced by the SNP with the highest r^2 (among SNPs with $r^2 > 0.80$ based on HapMap data) that had a good quality design score. The analysis of associations with breast and ovarian cancer risks presented here included all 32,557 SNPs on iCOGS that were selected on the basis of the *BRCA1* GWAS.

Genotyping and quality control

iCOGS genotyping. Genotyping was performed at Mayo Clinic. Genotypes for samples genotyped on the iCOGS array were called using Illumina’s GenCall algorithm (Text S1). A total of 13,510 samples were genotyped for 211,155 SNPs. The sample and SNP QC process is summarised in Table S3. Of the 13,510 samples, 578 did not fulfil eligibility criteria based on phenotypic

data and were excluded. A step-wise QC process was applied to the remaining samples and SNPs. Samples were excluded due to inferred gender errors, low call rates (<95%), low or high heterozygosity and sample duplications (cryptic and intended). Of the 211,155 markers genotyped, 9,913 were excluded due to Y-chromosome origin, low call rates (<95%), monomorphic SNPs, or SNPs with Hardy-Weinberg equilibrium (HWE) $P < 10^{-7}$ under a country-stratified test statistic [15] (Table S3). SNPs that gave discordant genotypes among known sample duplicates were also excluded. Multi-dimensional scaling was used to exclude individuals of non-European ancestry. We selected 37,149 weakly correlated autosomal SNPs (pair-wise $r^2 < 0.10$) to compute the genomic kinship between all pairs of *BRCA1* carriers, along with 197 HapMap samples (CHB, JPT, YRI and CEU). These were converted to distances and subjected to multidimensional scaling (Figure S1). Using the first two components, we calculated the proportion of European ancestry for each individual [12] and excluded samples with >22% non-European ancestry (Figure S1). A total of 11,705 samples and 201,242 SNPs were available for analysis, including 31,812 SNPs selected by the *BRCA1* GWAS. The genotyping cluster plots for all SNPs that demonstrated genome-wide significance level of association or are presented below, were checked manually for quality (Figure S2).

iPLEX analysis. The most significant SNPs from 4 loci associated with ovarian cancer and 8 loci associated with breast cancer were selected (17 SNPs in total) for stage 3 genotyping. Genotyping using the iPLEX Mass Array platform was performed at Mayo Clinic. CIMBA QC procedures were applied. Samples that failed for $\geq 20\%$ of the SNPs were excluded from the analysis. No SNPs failed HWE ($P < 0.01$). The concordance among duplicates was $\geq 98\%$. Mutation carriers of self-reported non-European ancestry were excluded. A total of 2,646 *BRCA1* samples were eligible for analysis after QC.

Statistical methods

The main analyses were focused on the evaluation of associations between each genotype and breast cancer or ovarian cancer risk separately. Analyses were carried out within a survival analysis framework. In the breast cancer analysis, the phenotype of each individual was defined by age at breast cancer diagnosis or age at last follow-up. Individuals were followed until the age of the first breast cancer diagnosis, ovarian cancer diagnosis, or bilateral prophylactic mastectomy, whichever occurred first; or last observation age. Mutation carriers censored at ovarian cancer diagnosis were considered unaffected. For the ovarian cancer analysis, the primary endpoint was the age at ovarian cancer diagnosis. Mutation carriers were followed until the age of ovarian cancer diagnosis, or risk-reducing salpingo-oophorectomy (RRSO) or age at last observation. In order to maximize the number of ovarian cancer cases, breast cancer was not considered as a censoring event in this analysis, and mutation carriers who developed ovarian cancer after a breast cancer diagnosis were considered as affected in the ovarian cancer analysis.

Association analysis. The majority of mutation carriers were sampled through families seen in genetic clinics. The first tested individual in a family is usually someone diagnosed with cancer at a relatively young age. Such study designs tend to lead to an over-sampling of affected individuals, and standard analytical methods like Cox regression may lead to biased estimates of the risk ratios [16,17]. To adjust for this potential bias the data were analyzed within a survival analysis framework, by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes. A detailed description of the retrospective likelihood approach has been published [17,18]. The associations

between genotype and breast cancer risk at both stages were assessed using the 1 d.f. score test statistic based on this retrospective likelihood [17,18]. To allow for the non-independence among related individuals, we accounted for the correlation between the genotypes by estimating the kinship coefficient for each pair of individuals using the available genomic data [16,19,20] and by robust variance estimation based on reported family membership [21]. We chose to present P-values based on the kinship adjusted score test as it utilises the degree of relationship between individuals. A genome-wide level of significance of 5×10^{-8} was used [22]. These analyses were performed in R using the GenABEL [23] libraries and custom-written functions in FORTRAN and Python.

To estimate the magnitude of the associations (HRs), the effect of each SNP was modeled either as a per-allele HR (multiplicative model) or as genotype-specific HRs, and were estimated on the log-scale by maximizing the retrospective likelihood. The retrospective likelihood was fitted using the pedigree-analysis software MENDEL [17,24]. As sample sizes varied substantially between contributing centers heterogeneity was examined at the country level. All analyses were stratified by country of residence and used calendar-year and cohort-specific breast cancer incidence rates for *BRCA1* [25]. Countries with small number of mutation carriers were combined with neighbouring countries to ensure sufficiently large numbers within each stratum (Table S2). USA and Canada were further stratified by reported Ashkenazi Jewish (AJ) ancestry due to large numbers of AJ carriers. In stage 3 analysis involving several countries with small numbers of mutation carriers, we assumed only 3 large strata (Europe, Australia, USA/Canada). The combined iCOGS stage and stage 3 analysis was also stratified by stage of the experiment. The analysis of associations by breast cancer ER-status was carried out by an extension of the retrospective likelihood approach to model the simultaneous effect of each SNP on more than one tumor subtype [26] (Text S1).

Competing risk analysis. The associations with breast and ovarian cancer risk simultaneously were assessed within a competing risk analysis framework [17] by estimating HRs simultaneously for breast and ovarian cancer risk. This analysis provides unbiased estimates of association with both diseases and more powerful tests of association in cases where an association exists between a variant and at least one of the diseases [17]. Each individual was assumed to be at risk of developing either breast or ovarian cancer, and the probabilities of developing each disease were assumed to be independent conditional on the underlying genotype. A different censoring process was used, whereby individuals were followed up to the age of the first breast or ovarian cancer diagnosis and were considered to have developed the corresponding disease. No follow-up was considered after the first cancer diagnosis. Individuals censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of RRSO were assumed to be unaffected for the corresponding disease. The remaining individuals were censored at the last observation age and were assumed to be unaffected for both diseases.

Imputation. For the SNP selection process, the MACH software was used to impute non-genotyped SNPs based on the phased haplotypes from HapMap Phase II (CEU, release 22). The IMPUTE2 software [27] was used to impute non-genotyped SNPs for samples genotyped on the iCOGS array (stage 1 and 2 only), based on the 1,000 Genomes haplotypes (January 2012 version). Associations between each marker and cancer risk were assessed using a similar score test to that used for the observed SNPs, but based on the posterior genotype probabilities at each imputed marker for each individual. In all analyses, we considered only SNPs with imputation information/accuracy $r^2 > 0.30$.

Absolute breast and ovarian cancer risks by combined SNP profile. We estimated the absolute risk of developing breast and ovarian cancer based on the joint distribution of all SNPs that were significantly associated with risk for *BRCA1* mutation carriers based on methods previously applied to *BRCA2* carriers [28]. We assumed that the average, age-specific breast and ovarian cancer incidences for *BRCA1* mutation carriers, over all modifying loci, agreed with published penetrance estimates for *BRCA1* [25]. The model assumed independence among the modifying loci and we used only the SNP with the strongest evidence of association from each region. We used only loci identified through the *BRCA1* GWAS that exhibited associations at a genome-wide significance level, and loci that were identified through population-based GWAS of breast or ovarian cancer risk, but were also associated with those risks for *BRCA1* mutation carriers. For each SNP, we used the per-allele HR and minor allele frequencies estimated from the present study. Genotype frequencies were obtained under the assumption of HWE.

Results

Samples from 11,705 *BRCA1* carriers from 45 centers in 25 countries yielded high-quality data for 201,242 SNPs on the iCOGS array. The array included 31,812 *BRCA1* GWAS SNPs, which were analyzed here for their associations with breast and ovarian cancer risk for *BRCA1* mutation carriers (Table S2). Of the 11,705 *BRCA1* mutation carriers, 2,387 samples had also been genotyped for stage 1 of the GWAS and 9,318 were unique to the stage 2 iCOGS study.

Breast cancer associations

When restricting analysis to stage 2 samples (4,681 unaffected, 4,637 affected), there was little evidence of inflation in the association test-statistic ($\lambda = 1.038$; Figure S3). Combined analysis of stage 1 and 2 samples (5,784 unaffected, 5,920 affected) revealed 66 SNPs in 28 regions with $P < 10^{-4}$ (Figure S4). These included variants from three loci (19p13, 6q25.1, 12p11) previously associated with breast cancer risk for *BRCA1* mutation carriers (Table 1). Further evaluation of 18 loci associated with breast cancer susceptibility in the general population found that only the *TOX3*, *LSP1*, 2q35 and *RAD51L1* loci were significantly associated with breast cancer for *BRCA1* carriers (Table 1, Table S4).

After excluding SNPs from the known loci, there were 39 SNPs in 25 regions with $P = 1.2 \times 10^{-6}$ – 1.0×10^{-4} . Twelve of these SNPs were genotyped by iPLEX in an additional 2,646 *BRCA1* carriers (1,252 unaffected, 1,394 affected, “stage 3” samples, Table S5). There was additional evidence of association with breast cancer risk for four SNPs at two loci ($P < 0.01$, Table 2). When all stages were combined, SNPs rs2290854 and rs6682208 ($r^2 = 0.84$) at 1q32, near *MDM4*, had combined *P*-values of association with breast cancer risk of 1.4×10^{-7} and 4×10^{-7} , respectively. SNPs rs11196174 and rs11196175 ($r^2 = 0.96$) at 10q25.3 (in *TCF7L2*) had combined *P*-values of 7.5×10^{-7} and 1.2×10^{-6} . Analysis within a competing risks framework, where associations with breast and ovarian cancer risks are evaluated simultaneously [17], revealed stronger associations with breast cancer risk for all 4 SNPs, but no associations with ovarian cancer (Table 3). In particular, we observed a genome-wide significant association between the minor allele of rs2290854 from 1q32 and breast cancer risk (per-allele HR: 1.14; 95%CI: 1.09–1.20; $p = 2.7 \times 10^{-8}$). Country-specific HR estimates for all SNPs are shown in Figure S5. Analyses stratified by *BRCA1* mutation class revealed no significant evidence of a difference in the associations of any of the SNPs by the predicted functional consequences of *BRCA1* mutations (Table S6). SNPs in the *MDM4* and *TCF7L2* loci were

associated with breast cancer risk for both class1 and class2 mutation carriers.

Both the 1q32 and 10q25.3 loci were primarily associated with ER-negative breast cancer for *BRCA1* (rs2290854: ER-negative HR = 1.16, 95%CI: 1.10–1.22, $P = 1.2 \times 10^{-7}$; rs11196174: HR = 1.14, 95%CI: 1.07–1.20, $P = 9.6 \times 10^{-6}$), although the differences between the ER-negative and ER-positive HRs were not significant (Table S7). Given that ER-negative breast cancers in *BRCA1* and *BRCA2* mutation carriers are phenotypically similar [29], we also evaluated associations between these SNPs and ER-negative breast cancer in 8,211 *BRCA2* mutation carriers. While the 10q25.3 SNPs were not associated with overall or ER-negative breast cancer risk for *BRCA2* carriers, the 1q32 SNPs were associated with ER-negative (rs2290854 HR = 1.16, 95%CI: 1.01–1.34, $P = 0.033$; rs6682208 HR = 1.19, 95%CI: 1.04–1.35, $P = 0.016$), but not ER-positive breast cancer (rs2290854 *P*-diff = 0.006; rs6682208 *P*-diff = 0.001). Combining the *BRCA1* and *BRCA2* samples provided strong evidence of association with ER-negative breast cancer (rs2290854: $P = 1.25 \times 10^{-8}$; rs6682208: $P = 2.5 \times 10^{-7}$).

The iCOGS array included additional SNPs from the 1q32 region that were not chosen based on the *BRCA1* GWAS. Of these non-*BRCA1* GWAS SNPs, only SNP rs4951407 was more significantly associated with risk than the *BRCA1*-GWAS selected SNPs ($P = 3.3 \times 10^{-6}$, HR = 1.12, 95%CI: 1.07–1.18, using stage 1 and stage 2 samples). The evidence of association with breast cancer risk was again stronger under the competing risks analysis (HR = 1.14, 95%CI: 1.08–1.20, $P = 6.1 \times 10^{-7}$). Backward multiple regression analysis, considering only the genotyped SNPs ($P < 0.01$), revealed that the most parsimonious model included only rs4951407. SNPs from the 1000 Genomes Project, were imputed for the stage 1 and stage 2 samples (Figure S6). Only imputed SNP rs12404974, located between *PIK3C2B* and *MDM4* ($r^2 = 0.77$ with rs4951407), was more significantly associated with breast cancer ($P = 2.7 \times 10^{-6}$) than any of the genotyped SNPs. None of the genotyped or imputed SNPs from 10q25.3 provided *P*-values smaller than those for rs11196174 and rs11196175 (Figure S7).

Ovarian cancer associations

Analyses of associations with ovarian cancer risk using the stage 2 samples (8,054 unaffected, 1,264 affected) revealed no evidence of inflation in the association test-statistic ($\lambda = 1.039$, Figure S3). In the combined analysis of stage 1 and 2 samples (9866 unaffected, 1839 affected), 62 SNPs in 17 regions were associated with ovarian cancer risk for *BRCA1* carriers at $P < 10^{-4}$ (Figure S3). These included SNPs in the 9p22 and 3q25 loci previously associated with ovarian cancer risk in both the general population and *BRCA1* carriers [6,7] (Table 1). Associations ($P < 0.01$) with ovarian cancer risk were also observed for SNPs in three other known ovarian cancer susceptibility loci (8q24, 17q21, 19p13), but not 2q31 (Table 1). For all loci except 9p22, SNPs were identified that displayed smaller *P*-values of association than previously published results [5–7].

After excluding SNPs from known ovarian cancer susceptibility regions, there were 48 SNPs in 15 regions with $P = 5 \times 10^{-7}$ to 10^{-4} . Five SNPs from four of these loci were genotyped in the stage 3 samples (2,204 unaffected, 442 with ovarian cancer). Three SNPs showed additional evidence of association with ovarian cancer risk ($P < 0.02$, Table 2; Table S5). In the combined stage 1–3 analyses, SNPs rs17631303 and rs183211 ($r^2 = 0.68$) on chromosome 17q21.31 had *P*-values for association of 1×10^{-8} and 3×10^{-8} respectively, and rs4691139 at 4q32.3 had a *P*-value of 3.4×10^{-8} (Table 2).

The minor alleles of rs17631303 (HR = 1.27, 95%CI: 1.17–1.38) and rs183211 (HR = 1.25, 95%CI: 1.16–1.35) at 17q21.31 were associated with increased ovarian cancer risk (Table 2). Analysis of

Table 1. Associations with breast or ovarian cancer risk for loci previously reported to be associated with cancer risk for BRCA1 mutation carriers.

Strongest association in current set of 31,812 BRCA1 GWAS SNPs										Association for published SNP in set of all iCOGS SNPs			
Locus	Previously published association in BRCA1					Strongest association in current set of 31,812 BRCA1 GWAS SNPs					Association for published SNP in set of all iCOGS SNPs		
	SNP	all1/all2 (freq)	HR (95%CI)	P	SNP	all1/all2 (freq)	r ²	HR (95%CI)	P	Best tag SNP (r ²)	all1/all2 (freq)	HR (95%CI)	P
<i>Loci previously associated with breast cancer risk for BRCA1 carriers</i>													
19p13	rs8170	G/A (0.17)	1.26 (1.17–1.35)	2.3 × 10 ⁻⁹	rs8100241	G/A (0.52)	0.31	0.84 (0.80–0.88)	4.3 × 10 ⁻¹³	rs8170 (1.0)	G/A (0.17)	1.22 (1.14–1.29)	4.8 × 10 ⁻¹⁰
6q25.1	rs2046210	C/T (0.35)	1.17 (1.11–1.23)	4.5 × 10 ⁻⁹	rs3734805	A/C (0.08)	0.25	1.28 (1.18–1.39)	5 × 10 ⁻⁹	rs2046210* (1.0)	G/A (0.35)	1.15 (1.10–1.21)	2.8 × 10 ⁻⁸
12p11	rs10771399	A/G (0.11)	0.87 (0.81–0.94)	3.2 × 10 ⁻⁴	rs7957915	A/G (0.14)	0.85	0.85 (0.79–0.91)	8.1 × 10 ⁻⁶	rs10771399*	A/G (0.11)	0.85 (0.79–0.92)	2.7 × 10 ⁻⁵
TOX3	rs3803662	C/T (0.29)	1.09 (1.03–1.16)	0.0049	rs4784220	A/G (0.38)	0.52	1.08 (1.03–1.13)	0.0021	rs3803662*	G/A (0.29)	1.05 (1.00–1.11)	0.075
2q35	rs13387042 ^a	G/A (0.52)	1.02 (0.96–1.07)	0.57	rs13389571	A/G (0.05)	0.02	0.86 (0.77–0.96)	0.011	rs13387042*	A/G (0.48)	1.01 (0.96–1.06)	0.74
<i>Known ovarian cancer susceptibility loci</i>													
9p22	rs3814113	T/C (0.34)	0.78 (0.72–0.85)	4.8 × 10 ⁻⁹	rs3814113	A/G (0.34)	1.00	0.77 (0.71–0.83)	5.9 × 10 ⁻¹¹	rs3814113 (1.0)	A/G (0.34)	0.77 (0.71–0.83)	5.9 × 10 ⁻¹¹
2q31	rs2072590	T/C (0.31)	1.06 (0.98–1.14)	0.16	rs1026032	A/G (0.26)	0.75	1.08 (0.99–1.17)	0.064	rs2072590* (1.0)	C/A (0.32)	1.05 (0.97–1.14)	0.20
8q24	rs10088218	G/A (0.13)	0.89 (0.81–0.99)	0.029	rs9918771	A/C (0.17)	0.31	0.86 (0.78–0.95)	0.0021	rs10088218 (1.0)	G/A (0.13)	0.86 (0.78–0.96)	0.0096
3q25	rs2665390	T/C (0.075)	1.25 (1.10–1.42)	2.7 × 10 ⁻³	rs7651446	C/A (0.043)	0.71	1.46 (1.25–1.71)	6.6 × 10 ⁻⁶	rs344008 (1.0)	G/A (0.075)	1.21 (1.07–1.38)	3.8 × 10 ⁻³
17q21	rs9303542	T/C (0.26)	1.08 (1.00–1.17)	0.06	rs11651753	G/A (0.43)	0.36	1.14 (1.06–1.23)	4.6 × 10 ⁻⁴	rs9303542* (1.0)	A/G (0.26)	1.12 (1.04–1.22)	8.0 × 10 ⁻³
19p13 ^b	rs67397200	C/G (0.28)	1.16 (1.05–1.29)	3.8 × 10 ⁻⁴	c19_pos17158477	G/C (0.038)	0.01	0.64 (0.49–0.83)	7.0 × 10 ⁻⁴	rs67397200 (c19_pos17262404)	G/C (0.28)	1.12 (1.01–1.23)	0.027

Freq = frequency of allele 2 in unaffected BRCA1 carriers.
 HR = Per allele Hazard Ratio associated with allele 2, under a single disease risk model, unless specified.
 r² = correlation between the SNP in the present study and the published SNP.
 *SNP not in BRCA1 GWAS SNP allocation on iCOGS chip.
^a: rs13387042 was previously found to be associated only under the 2-df model.
^b: analysis under a competing risks model.
 doi:10.1371/journal.pgen.1003212.t001

Table 2. Associations with breast and ovarian cancer risk for SNPs found to be associated with risk at all 3 stages of the experiment.

SNP, Chr, Position, Allele1/ Allele2	Stage	Number		Allele 2 Frequency		HR* (95% CI)			P-trend
		Unaffected	Affected	Unaffected	Affected	Per Allele	Heterozygote	Homozygote	
Breast Cancer									
rs2290854, 1q32, 202782648, G/A	Stage 1	1104	1283	0.30	0.34	1.19 (1.08–1.30)	1.28 (1.12–1.47)	1.31 (1.06–1.61)	4.2 × 10 ⁻⁴
	Stage 2	4681	4637	0.31	0.33	1.09 (1.03–1.16)	1.10 (1.02–1.19)	1.18 (1.03–1.35)	0.003
	Stages1+2	5785	5920	0.31	0.33	1.12 (1.06–1.17)	1.15 (1.07–1.23)	1.21 (1.08–1.36)	1.7 × 10 ⁻⁵
	Stage 3	1252	1393	0.30	0.33	1.19 (1.07–1.32)	1.24 (1.07–1.43)	1.36 (1.06–1.74)	0.0013
	Combined	7037	7313	0.31	0.33	1.13 (1.08–1.18)	1.16 (1.09–1.24)	1.24 (1.11–1.37)	1.4 × 10 ⁻⁷
rs6682208, 1q32, 202832806, G/A	Stage 1	1104	1283	0.32	0.35	1.14 (1.04–1.25)	1.24 (1.09–1.42)	1.20 (0.98–1.47)	0.0070
	Stage 2	4681	4637	0.32	0.34	1.10 (1.04–1.17)	1.09 (1.01–1.19)	1.21 (1.06–1.38)	0.0014
	Stages1+2	5785	5920	0.32	0.34	1.11 (1.05–1.17)	1.13 (1.05–1.21)	1.21 (1.08–1.35)	5.4 × 10 ⁻⁵
	Stage 3	1250	1394	0.30	0.34	1.19 (1.07–1.32)	1.31 (1.14–1.51)	1.28 (1.01–1.63)	8.6 × 10 ⁻⁴
	Combined	7035	7314	0.32	0.34	1.12 (1.07–1.17)	1.16 (1.09–1.23)	1.22 (1.11–1.35)	4.3 × 10 ⁻⁷
rs11196174, 10q25.3, 114724086, A/G	Stage 1	1103	1282	0.27	0.32	1.15 (1.05–1.27)	1.17 (1.03–1.34)	1.31 (1.05–1.63)	0.0038
	Stage 2	4681	4636	0.29	0.31	1.10 (1.04–1.17)	1.13 (1.04–1.23)	1.17 (1.01–1.35)	0.0017
	Stages1+2	5784	5918	0.28	0.31	1.12 (1.06–1.18)	1.14 (1.06–1.23)	1.21 (1.07–1.37)	3.1 × 10 ⁻⁵
	Stage 3	1251	1393	0.28	0.31	1.16 (1.05–1.29)	1.08 (0.93–1.25)	1.46 (1.15–1.85)	0.0057
	Combined	7035	7311	0.28	0.31	1.13 (1.07–1.18)	1.13 (1.06–1.21)	1.26 (1.13–1.40)	7.5 × 10 ⁻⁷
rs11196175, 10q25.3, 114726604, A/G	Stage 1	1101	1280	0.27	0.31	1.15 (1.05–1.27)	1.18 (1.03–1.35)	1.29 (1.03–1.62)	0.0043
	Stage 2	4674	4627	0.28	0.30	1.10 (1.03–1.17)	1.13 (1.04–1.22)	1.17 (1.01–1.35)	0.0020
	Stages1+2	5775	5907	0.28	0.30	1.12 (1.06–1.18)	1.14 (1.06–1.22)	1.21 (1.07–1.37)	3.9 × 10 ⁻⁵
	Stage 3	1251	1394	0.27	0.31	1.16 (1.04–1.29)	1.06 (0.91–1.22)	1.48 (1.17–1.87)	0.0075
	Combined	7026	7301	0.28	0.31	1.12 (1.07–1.18)	1.12 (1.05–1.20)	1.26 (1.13–1.41)	1.2 × 10 ⁻⁶
Ovarian Cancer									
rs17631303, 17q21, 40872185, A/G	Stage 1	1797	574	0.19	0.25	1.46 (1.22–1.74)	1.36 (1.01–1.68)	2.46 (1.53–3.96)	1.3 × 10 ⁻⁵
	Stage 2	7996	1257	0.19	0.21	1.20 (1.07–1.35)	1.10 (0.96–1.26)	1.83 (1.34–2.48)	1.5 × 10 ⁻³
	Stages1+2	9793	1831	0.19	0.22	1.27 (1.16–1.40)	1.15 (1.03–1.29)	2.03 (1.16–2.61)	3.0 × 10 ⁻⁷
	Stage 3	2204	442	0.17	0.21	1.27 (1.07–1.51)	1.24 (0.99–1.56)	1.67 (1.07–2.62)	0.014
	Combined	11997	2273	0.19	0.22	1.27 (1.17–1.38)	1.17 (1.06–1.29)	1.95 (1.57–2.42)	1.4 × 10 ⁻⁸
rs183211, 17q21, 42143493, G/A	Stage 1	1812	575	0.22	0.28	1.45 (1.23–1.71)	1.37 (1.11–1.69)	2.29 (1.53–3.41)	2.5 × 10 ⁻⁵
	Stage 2	8054	1264	0.23	0.25	1.20 (1.07–1.33)	1.13 (0.99–1.28)	1.62 (1.22–2.14)	1.1 × 10 ⁻³
	Stages1+2	9866	1839	0.23	0.26	1.25 (1.15–1.37)	1.16 (1.04–1.29)	1.83 (1.46–2.28)	5.7 × 10 ⁻⁷
	Stage 3	2204	442	0.22	0.26	1.25 (1.06–1.48)	1.15 (0.92–1.44)	1.79 (1.21–2.67)	0.018
	Combined	12070	2281	0.23	0.26	1.25 (1.16–1.35)	1.16 (1.05–1.27)	1.82 (1.5–2.21)	3.1 × 10 ⁻⁸
rs4691139, 4q32.3, 166128171, A/G	Stage 1	1812	575	0.47	0.53	1.24 (1.08–1.42)	1.46 (1.13–1.88)	1.55 (1.16–2.05)	3.6 × 10 ⁻³
	Stage 2	8054	1264	0.48	0.52	1.18 (1.08–1.29)	1.29 (1.10–1.50)	1.40 (1.17–1.67)	1.3 × 10 ⁻⁴
	Stages1+2	9866	1839	0.48	0.52	1.20 (1.11–1.29)	1.33 (1.17–1.52)	1.44 (1.24–1.67)	1.1 × 10 ⁻⁶
	Stage 3	2204	441	0.47	0.52	1.20 (1.04–1.39)	1.19 (0.91–1.54)	1.44 (1.08–1.94)	9 × 10 ⁻³
	Combined	12070	2280	0.48	0.52	1.20 (1.17–1.38)	1.30 (1.16–1.46)	1.44 (1.26–1.65)	3.4 × 10 ⁻⁸

*HRs estimated under the single disease risk models.
doi:10.1371/journal.pgen.1003212.t002

the associations within a competing risks framework, revealed no association with breast cancer risk (Table 3). The ovarian cancer effect size was maintained in the competing risk analysis but the significance of the association was slightly weaker ($P = 2 \times 10^{-6}$ –

1×10^{-5}). This is expected because 663 ovarian cancer cases occurring after a primary breast cancer diagnosis were excluded for this analysis. The evidence of association was somewhat stronger under the genotype-specific model (2-df $P = 1.6 \times 10^{-9}$

Table 3. Analysis of associations with breast and ovarian cancer risk simultaneously (competing risks analysis) for SNPs found to be associated with breast or ovarian cancer.

SNP, Chr, Position, Allele1/Allele2	Unaffected (Allele2 Freq)	Ovarian Cancer (Allele2 Freq)	Breast Cancer (Allele2 Freq)	Ovarian Cancer		Breast Cancer	
				HR (95% CI)	P	HR (95% CI)	P
<i>SNPs found to be associated with breast cancer risk.</i>							
rs2290854, 1q32, 202782648, G/A	5473 (0.31)	1618 (0.31)	7259 (0.33)	1.08 (0.99–1.18)	0.08	1.14 (1.09–1.20)	2.7×10^{-8}
rs6682208, 1q32, 202832806, G/A	5471 (0.32)	1618 (0.33)	7260 (0.34)	1.08 (1.00–1.18)	0.06	1.13 (1.08–1.19)	1.2×10^{-7}
rs11196174, 10q25.3, 114724086, A/G	5471 (0.28)	1618 (0.29)	7257 (0.31)	1.07 (0.98–1.16)	0.16	1.14 (1.08–1.19)	3.2×10^{-7}
rs11196175, 10q25.3, 114726604, A/G	5465 (0.28)	1615 (0.29)	7247 (0.31)	1.07 (0.97–1.16)	0.16	1.14 (1.08–1.19)	3.9×10^{-7}
<i>SNPs found to be associated with ovarian cancer risk.</i>							
rs17631303, 17q21, 40872185, A/G	5445 (0.19)	1610 (0.22)	7215 (0.19)	1.26 (1.14–1.39)	1.0×10^{-5}	1.02 (0.96–1.08)	0.52
rs183211, 17q21, 42143493, G/A	5473 (0.23)	1618 (0.26)	7260 (0.23)	1.25 (1.14–1.38)	3.5×10^{-6}	1.02 (0.97–1.08)	0.42
rs4691139, 4q32.3, 166128171, A/G	5473 (0.48)	1617 (0.53)	7269 (0.48)	1.21 (1.12–1.31)	2.8×10^{-6}	0.98 (0.93–1.02)	0.28

doi:10.1371/journal.pgen.1003212.t003

and $P = 2.6 \times 10^{-9}$ for rs17631303 and rs183211 respectively in all samples combined) with larger HR estimates for the rare homozygote genotypes than those expected under a multiplicative model (Table 2).

Previous studies of the known common ovarian cancer susceptibility alleles found significant associations with ovarian cancer for both *BRCA1* and *BRCA2* carriers [6,7]. Thus, we evaluated the associations between the 17q21.31 SNPs and ovarian cancer risk for *BRCA2* carriers using iCOGS genotype data (7580 unaffected and 631 affected). Both rs17631303 and rs183211 were associated with ovarian cancer risk for *BRCA2* carriers ($P = 1.98 \times 10^{-4}$ and 9.26×10^{-4}), with similar magnitude and direction of association as for *BRCA1* carriers. Combined analysis of *BRCA1* and *BRCA2* mutation carriers provided strong evidence of association ($P = 2.80 \times 10^{-10}$ and 2.01×10^{-9} , Table 4).

The combined analysis of stage 1 and 2 samples, and *BRCA2* carriers, identified seven SNPs on the iCOGS array (pairwise r^2 range: 0.68–1.00) from a 1.3 Mb (40.8–42.1 Mb, build 36.3) region of 17q21.31 that were strongly associated ($P < 1.27 \times 10^{-9}$) with ovarian cancer risk (Table 4, Figure 2). Stepwise-regression analysis based on observed genotype data retained only one of the seven SNPs in the model, but it was not possible to distinguish between the SNPs. Imputation through the 1000 Genomes Project, revealed several SNPs in 17q21.31 with stronger associations (Figure 2, Table S8) than the most significant genotyped SNP in the combined *BRCA1/2* analysis (rs169201, $P = 6.24 \times 10^{-11}$). The most significant SNP (rs140338099 (17-44034340), $P = 3 \times 10^{-12}$), located in *MAPT*, was highly correlated ($r^2 = 0.78$) with rs169201 in *NSF* (Figure 2). This locus appears to be distinct from a previously identified ovarian cancer susceptibility locus located >1 Mb distal on 17q21 (spanning 43.3–44.3 Mb, build 36.3) [30]. None of the SNPs in the novel region were strongly correlated with any of the SNPs in the 43.3–44.3 Mb region (maximum $r^2 = 0.07$, Figure S8). The most significantly associated SNP from the *BRCA1* GWAS from the 43.3–44.3 Mb locus was rs11651753 ($p = 4.6 \times 10^{-4}$) (Table 1) ($r^2 < 0.023$ with the seven most significant SNPs in the novel 17q21.31 region). An analysis of the joint associations of rs11651753 and rs17631303 from the two 17q21 loci with ovarian cancer risk for *BRCA1* carriers (Stage 1 and 2 samples) revealed that both SNPs remained significant in the model (P -for inclusion = 0.001 for rs11651753, 1.2×10^{-6} for rs17631303), further suggesting that the two regions are independently associated with ovarian cancer for *BRCA1* carriers.

The minor allele of rs4691139 at the novel 4q32.3 region was also associated with an increased ovarian cancer risk for *BRCA1* carriers (per-allele HR = 1.20, 95%CI:1.17–1.38, Table 2), but was not associated with breast cancer risk (Table 3). No other SNPs from the 4q32.3 region on the iCOGS array were more significantly associated with ovarian cancer for *BRCA1* carriers. Analysis of associations with variants identified through 1000 Genomes Project-based imputation of the Stage 1 and 2 samples, revealed 19 SNPs with stronger evidence of association ($P = 5.4 \times 10^{-7}$ to 1.1×10^{-6}) than rs4691139 (Figure S9). All were highly correlated (pairwise $r^2 > 0.89$) and the most significant (rs4588418) had $r^2 = 0.97$ with rs4691139. There was no evidence for association between rs4691139 and ovarian cancer risk for *BRCA2* carriers (HR = 1.08, 95%CI: 0.96–1.21, $P = 0.22$).

Absolute risks of developing breast and ovarian cancer

The current analyses suggest that 10 loci are now known to be associated with breast cancer risk for *BRCA1* mutation carriers: 1q32, 10q25.3, 19p13, 6q25.1, 12p11, *TOX3*, 2q35, *LSP1* and *RAD51L1* all reported here and *TERT* [31]. Similarly, seven loci are associated with ovarian cancer risk for *BRCA1* mutation

Table 4. Associations with SNPs at the novel 17q21 region with ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers.

SNP, Allele1/Allele2	<i>BRCA1</i> (Stage 1 & 2 samples)				<i>BRCA2</i>				<i>BRCA1</i> & <i>BRCA2</i> samples combined	
	Unaffected (All2 freq)	Ovarian Cancer (All2 freq)	HR* (95%CI)	P-trend	Unaffected (All2 freq)	Ovarian Cancer (All2 freq)	HR* (95%CI)	P-trend	HR* (95%CI)	P-trend
	rs17631303, A/G	9793 (0.19)	1831 (0.22)	1.27 (1.16–1.40)	3.04 × 10 ⁻⁷	7481 (0.19)	626 (0.24)	1.32 (1.15–1.52)	1.98 × 10 ⁻⁴	1.32 (1.15–1.52)
rs2077606, G/A	9736 (0.19)	1810 (0.22)	1.27 (1.15–1.40)	5.51 × 10 ⁻⁷	7421 (0.19)	613 (0.23)	1.31 (1.13–1.50)	5.60 × 10 ⁻⁴	1.31 (1.13–1.50)	1.27 × 10 ⁻⁹
rs2532348, A/G	9511 (0.21)	1789 (0.24)	1.25 (1.14–1.37)	8.71 × 10 ⁻⁷	7407 (0.23)	615 (0.28)	1.33 (1.17–1.51)	4.62 × 10 ⁻⁵	1.33 (1.17–1.51)	2.49 × 10 ⁻¹⁰
rs183211, G/A	9866 (0.23)	1839 (0.26)	1.25 (1.15–1.37)	5.67 × 10 ⁻⁷	7580 (0.25)	631 (0.30)	1.26 (1.11–1.43)	9.26 × 10 ⁻⁴	1.26 (1.11–1.43)	2.01 × 10 ⁻⁹
rs169201, A/G	9865 (0.20)	1839 (0.23)	1.27 (1.15–1.37)	5.04 × 10 ⁻⁷	7578 (0.21)	631 (0.26)	1.36 (1.19–1.55)	1.72 × 10 ⁻⁵	1.36 (1.19–1.55)	6.24 × 10 ⁻¹¹
rs199443, G/A	9849 (0.20)	1835 (0.23)	1.26 (1.15–1.39)	5.15 × 10 ⁻⁷	7580 (0.21)	631 (0.26)	1.35 (1.18–1.54)	2.57 × 10 ⁻⁵	1.35 (1.18–1.54)	8.87 × 10 ⁻¹¹
rs199534, A/C	9865 (0.20)	1839 (0.23)	1.26 (1.15–1.39)	6.26 × 10 ⁻⁷	7575 (0.21)	630 (0.26)	1.35 (1.18–1.55)	1.90 × 10 ⁻⁵	1.35 (1.18–1.55)	8.57 × 10 ⁻¹¹

*HRs estimated under the single disease risk model. doi:10.1371/journal.pgen.1003212.t004

carriers: 9p22, 8q24, 3q25, 17q21, 19p13, 17q21.31 and 4q32.3. Figure S10 shows the range of combined HRs at different percentiles of the combined genotype distribution, based on the single SNP HR and minor allele estimates from Table 1, Table 2, and Table S4 and for TERT from Bojesen et al [31] and assuming that all SNPs interact multiplicatively. Relative to *BRCA1* mutation carriers at lowest risk, the median, 5th and 95th percentile breast cancer HRs were 3.40, 2.27, and 5.35 respectively. These translate to absolute risks of developing breast cancer by age 80 of 65%, 51% and 81% for those at median, 5th and 95th percentiles of the combined genotype distribution (Figure 3, Figure S10). Similarly, the median, 5th and 95th percentile combined HRs for ovarian cancer were 6.53, 3.75 and 11.12 respectively, relative to those at lowest ovarian cancer risk (Figure S10). These HRs translate to absolute risks of developing ovarian cancer of 44%, 28% and 63% by age 80 for the median, 5th and 95th percentile of the combined genotype distribution (Figure 3).

Discussion

In this study we analyzed data from 11,705 *BRCA1* mutation carriers from CIMBA who were genotyped using the iCOGS high-density custom array, which included 31,812 SNPs selected on the basis of a *BRCA1* GWAS. This study forms the large-scale replication stage of the first GWAS of breast and ovarian cancer risk modifiers for *BRCA1* mutation carriers. We have identified a novel locus at 1q32, containing the *MDM4* oncogene, that is associated with breast cancer risk for *BRCA1* mutation carriers ($P < 5 \times 10^{-8}$). A separate locus at 10q23.5, containing the *TCF7L2* gene, provided strong evidence of association with breast cancer risk for *BRCA1* carriers but did not reach a GWAS level of significance. We have also identified two novel loci associated with ovarian cancer for *BRCA1* mutation carriers at 17q21.31 and 4q32.2 ($P < 5 \times 10^{-8}$). We further confirmed associations with loci previously shown to be associated with breast or ovarian cancer risk for *BRCA1* mutation carriers. In most cases stronger associations were detected with either the same SNP reported previously (due to increased sample size) or other SNPs in the regions. Future fine mapping studies of these loci will aim to identify potentially causal variants for the observed associations.

Although the 10q25.3 locus did not reach the strict GWAS level of significance for association with breast cancer risk, the association was observed at all three independent stages of the experiment. Additional evidence for the involvement of this locus in breast cancer susceptibility comes from parallel studies of the Breast Cancer Association Consortium (BCAC). SNPs at 10q25.3 had also been independently selected for inclusion on the iCOGS array through population based GWAS of breast cancer. Analyses of those SNPs in BCAC iCOGS studies also found that SNPs at 10q25.3 were associated with breast cancer risk in the general population [32]. Thus, 10q25.3 is likely a breast cancer risk-modifying locus for *BRCA1* mutation carriers. The most significant SNPs at 10q25.3 were located in *TCF7L2*, a transcription factor that plays a key role in the Wnt signaling pathway and in glucose homeostasis, and is expressed in normal and malignant breast tissue (The Cancer Genome Atlas (TCGA)). Variation in the *TCF7L2* locus has previously been associated with Type 2 diabetes in a number of GWAS. The most significantly associated SNPs with Type 2 diabetes (rs7903146 and rs4506565) [22,33] were also associated with breast cancer risk for *BRCA1* mutation carriers in stage 1 and 2 analyses ($p = 3.7 \times 10^{-4}$ and $p = 2.5 \times 10^{-4}$ respectively); these SNPs were correlated with the most significant hit (rs11196174) for *BRCA1* breast cancer ($r^2 = 0.40$ and 0.37 based

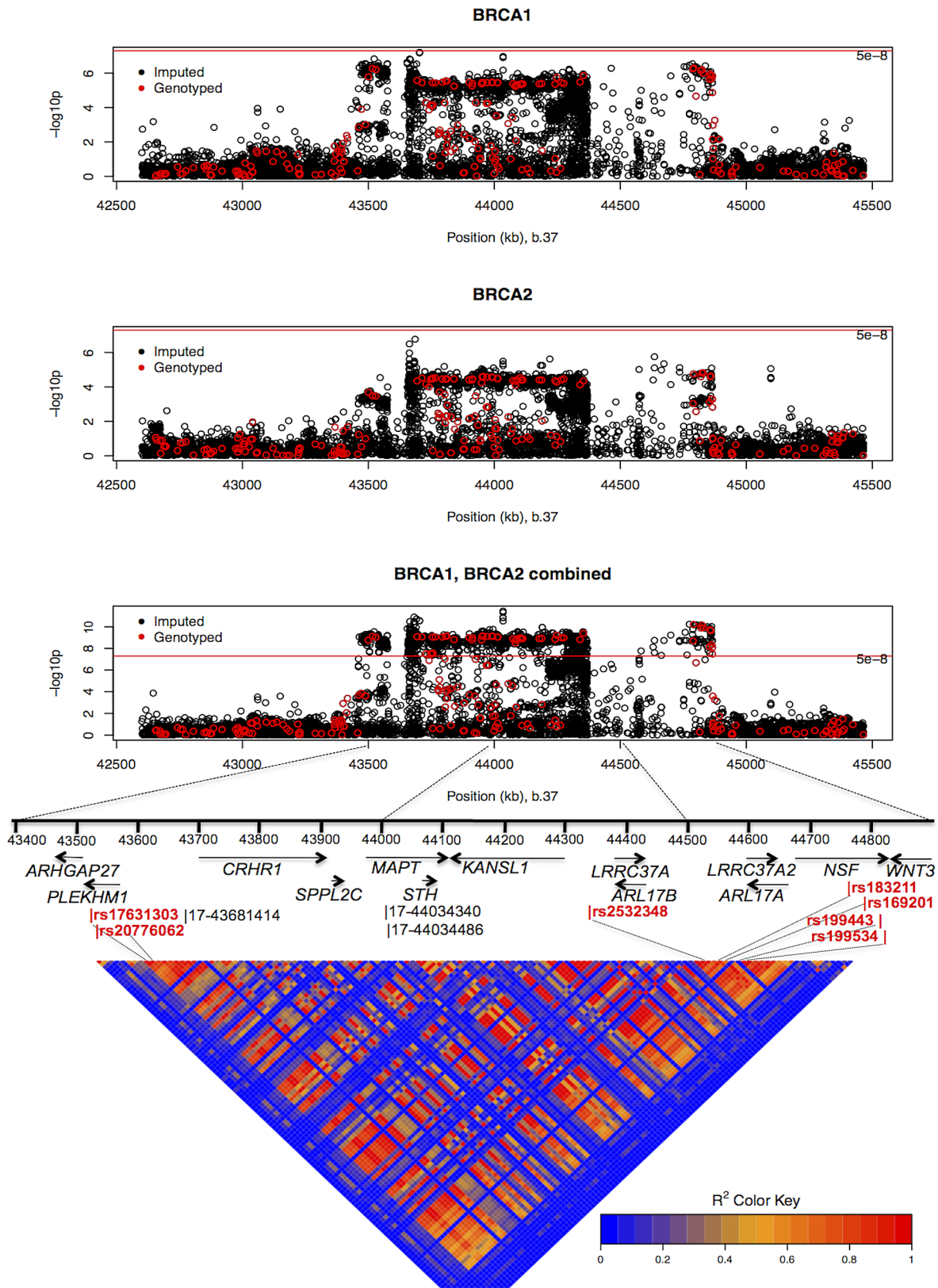


Figure 2. Mapping of the 17q21 locus. *Top 3 panels:* P-values of association ($-\log_{10}$ scale) with ovarian cancer risk for genotyped and imputed SNPs (1000 Genomes Project CEU), by chromosome position (b.37) at the 17q21 region, for *BRCA1*, *BRCA2* mutation carriers and combined. Results based on the kinship-adjusted score test statistic (1 d.f.). *Fourth panel:* Genes in the region spanning (43.4–44.9 Mb, b.37) and the location of the most significant genotyped SNPs (in red font) and imputed SNPs (in black font). *Bottom panel:* Pairwise r^2 values for genotyped SNPs on iCOG array in the 17q21 region covering positions (43.4–44.9 Mb, b.37). doi:10.1371/journal.pgen.1003212.g002

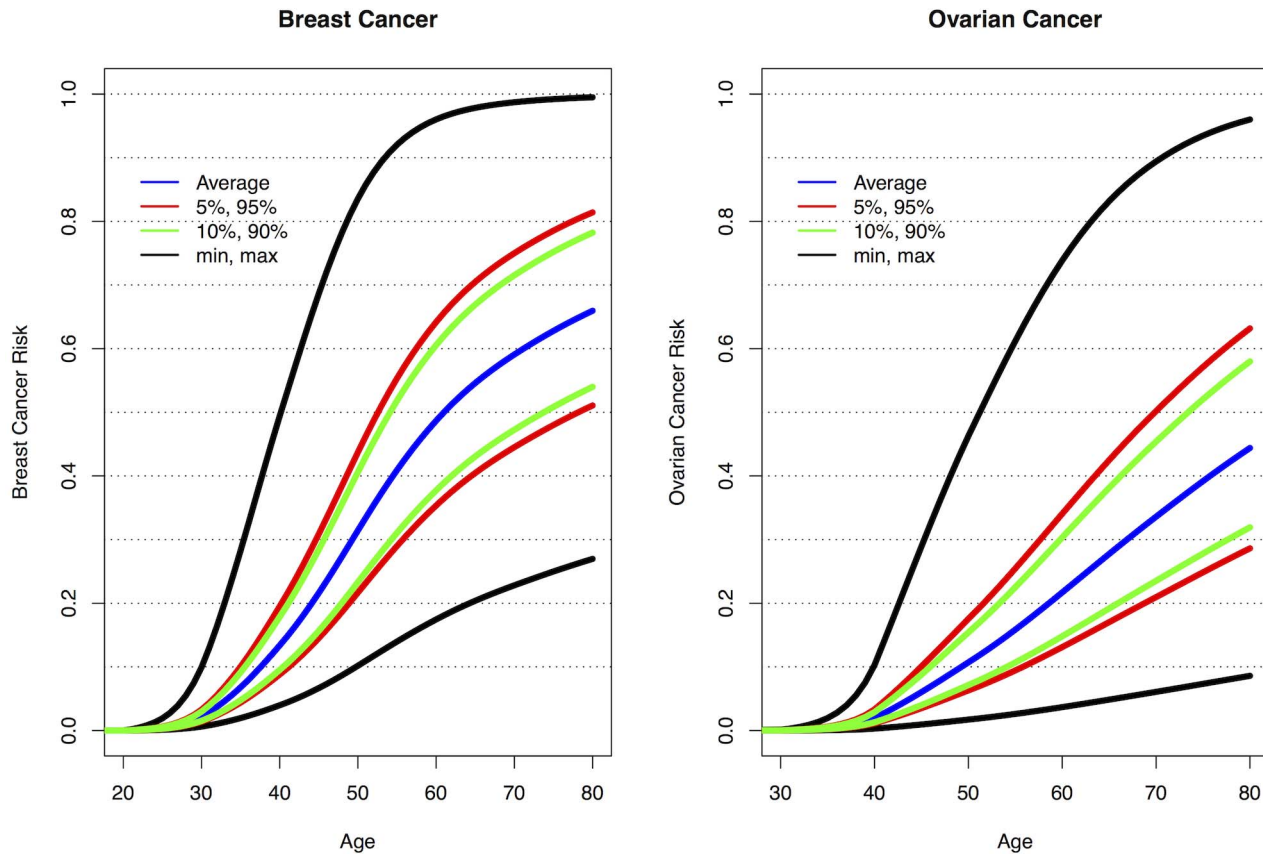


Figure 3. Predicted breast and ovarian cancer absolute risks for *BRCA1* mutation carriers at the 5th, 10th, 90th, and 95th percentiles of the combined SNP profile distributions. The minimum, maximum and average risks are also shown. Predicted cancer risks are based on the associations of known breast or ovarian cancer susceptibility loci (identified through GWAS) with cancer risk for *BRCA1* mutation carriers and loci identified through the present study. Breast cancer risks based on the associations with: 1q32, 10q25.3, 19p13, 6q25.1, 12p11, *TOX3*, 2q35, *LSP1*, *RAD51L1* (based on HR and minor allele frequency estimates from Table 1, Table 2, and Table S4) and *TERT* [31]. Ovarian cancer risks based on the associations with: 9p22, 8q24, 3q25, 17q21, 19p13 (Table 1) and 17q21.31, 4q32.3 (Table 2). Only the top SNP from each region was chosen. Average breast and ovarian cancer risks were obtained from published data [25]. The methods for calculating the predicted risks have been described previously [28].

doi:10.1371/journal.pgen.1003212.g003

on stage 1 and 2 samples). This raises the possibility that variants in this locus influence breast cancer indirectly through effects on cellular metabolism.

We found that SNPs at 1q32 were primarily associated with ER-negative breast cancer risk for *BRCA1* mutation carriers. There was also evidence of association with ER-negative breast cancer for *BRCA2* mutation carriers. SNPs at the 1q32 region were independently selected for inclusion on iCOGS through GWAS of breast cancer in the general population by BCAC. In parallel analyses of iCOGS data by BCAC, 1q32 was found to be associated with ER-negative breast cancer [34] but not overall breast cancer risk [32]. Taken together, these results are in agreement with our findings and in line with the observation that the majority of *BRCA1* breast cancers are ER-negative. However, they are not in agreement with a previous smaller candidate-gene study that found an association between a correlated SNP in *MDM4* ($r^2 > 0.85$) and overall breast cancer risk [35]. The 1q32 locus includes the *MDM4* oncogene which plays a role in regulation of p53 and MDM2 and the apoptotic response to cell stress. *MDM4* is expressed in breast tissue and is amplified and overexpressed along with *LRRN2* and *PIK3C2B* in breast and other tumor types (TCGA) [36–38]. Although fine mapping will be

necessary to identify the functionally relevant SNPs in this locus, we found evidence of cis-regulatory variation impacting *MDM4* expression [39–41] (Text S1, Table S9, Figure S11), suggesting that common variation in the 1q32 locus may influence the risk of breast cancer through direct effects on *MDM4* expression.

Several correlated SNPs at 17q21.31 from the iCOGS array provided strong evidence of association with ovarian cancer risk in both *BRCA1* and *BRCA2* mutation carriers. A subsequent analysis of these SNPs, which were selected through the *BRCA1* GWAS, in case-control samples from the Ovarian Cancer Association Consortium (OCAC), revealed that the 17q21.31 locus is associated with ovarian cancer risk in the general population [Wey et al, personal communication]. Thus, 17q21.31 is likely a novel susceptibility locus for ovarian cancer in *BRCA1* mutation carriers. The most significant associations at 17q21.31 were clustered in a large region of strong linkage disequilibrium which has previously been identified as a “17q21.31 inversion” (~900 kb long) consisting of two haplotypes (termed H1 and H2) [42]. The minor allele of rs2532348 (MAF = 0.21), which tags H2, was associated with increased ovarian cancer risk for *BRCA1* mutation carriers (Table 4). The 1.3 Mb 17q21.31 locus contains 13 genes and several predicted pseudogenes (Figure 2), several of which are

expressed in normal ovarian surface epithelium and ovarian adenocarcinoma [43]. Variation in this region has been associated with Parkinson's disease (*MAPT*, *PLEKHMI*, *NSF*, *c17orf69*) progressive supranuclear palsy (*MAPT*), celiac disease (*WNT3*), bone mineral density (*CRHR1*) (NHGRI GWAS catalog) and intracranial volume [44]. Of the top hits for these phenotypes, SNP rs199533 in *NSF*, previously associated with Parkinson's disease [45] and rs9915547 associated with intracranial volume [44] were strongly associated with ovarian cancer ($P < 10^{-9}$ in *BRCA1/2* combined). Whether these phenotypes have shared causal variants in this locus remains to be elucidated. Further exploration of the functional relevance of the strongest hits in the 17q21.31 locus ($P < 10^{-8}$ in *BRCA1/2* combined) provided evidence that cis-regulatory variation alters expression of several genes at 17q21, including *PLEKHMI*, *c17orf69*, *ARHGAP27*, *MAPT*, *KANSL1* and *WNT3* [39,41] (Table S9, Figure S12), suggesting that ovarian cancer risk may be associated with altered expression of one or more genes in this region.

Our analyses revealed that a second novel locus at 4q32.3 was also associated with ovarian cancer risk for *BRCA1* mutation carriers ($P < 5 \times 10^{-8}$). However, we found no evidence of association for these SNPs with ovarian cancer risk for *BRCA2* mutation carriers using 8,211 CIMBA samples genotyped using the iCOGS array. Likewise, no evidence of association was found between rs4691139 at 4q32.3 and ovarian cancer risk in the general population based on data by OCAC data derived from 18,174 cases and 26,134 controls (odds ratio = 1.00, 95%CI:0.97–1.04, $P = 0.76$) [46]. The confidence intervals rule out a comparable effect to that found in *BRCA1* carriers. Therefore, our findings may represent a *BRCA1*-specific association with ovarian cancer risk, the first of its kind. The 4q32.2 region contains several members of the *TRIM* (Tripartite motif containing) gene family, *c4orf39* and *TMEM192*. *TRIM60*, *c4orf39* and *TMEM192* are expressed in normal ovarian epithelium and/or ovarian tumors (TCGA).

In summary, we have identified a novel locus at 1q32 associated with breast cancer risk for *BRCA1* mutation carriers, which was also associated with ER-negative breast cancer for *BRCA2* carriers and in the general population. A separate locus at 10q23.5 provided strong evidence of association with breast cancer risk for *BRCA1* carriers. We have also identified 2 novel loci associated with ovarian cancer for *BRCA1* mutation carriers. Of these, the 4q32.2 locus was associated with ovarian cancer risk for *BRCA1* carriers but not for *BRCA2* carriers or in the general population. Additional functional characterisation of the loci will further improve our understanding of the biology of breast and ovarian cancer development in *BRCA1* carriers. Taken together with other identified genetic modifiers, 10 loci are now known to be associated with breast cancer risk for *BRCA1* mutation carriers (1q32, 10q25.3, 19p13, 6q25.1, 12p11, *TOX3*, 2q35, *LSP1*, *RAD51L1* and *TERT*) and seven loci are known to be associated with ovarian cancer risk for *BRCA1* mutation carriers (9p22, 8q24, 3q25, 17q21, 19p13 and 17q21.31, 4q32.3).

As *BRCA1* mutations confer high breast and ovarian cancer risks, the results from the present study, taken together with other identified genetic modifiers, demonstrate for the first time that they can result in large differences in the absolute risk of developing breast or ovarian cancer for *BRCA1* between genotypes. For example, the breast cancer lifetime risks for the 5% of *BRCA1* carriers at lowest risk are predicted to be 28–50% compared to 81–100% for the 5% at highest risk (Figure 3). Based on the distribution of ovarian cancer risk modifiers, the 5% of *BRCA1* mutation carriers at lowest risk will have a lifetime risk of developing ovarian cancer of 28% or lower whereas the 5% at

highest risk will have a lifetime risk of 63% or higher. Similarly, the breast cancer risk by age 40 is predicted to be 4–9% for the 5% of *BRCA1* carriers at lowest risk compared to 20–49% for the 5% at highest risk, whereas the ovarian cancer risk at age 50 ranges from 3–7% for the 5% at lowest risk and from 18–47% for the 5% at highest risk. The risks at all ages for the 10% at highest or lowest risk of breast and ovarian cancer are predicted to be similar to those for the highest and lowest 5%. Thus, at least 20% of *BRCA1* mutation carriers are predicted to have absolute risks of disease that are different from the average *BRCA1* carriers. These large differences in cancer risks may have practical implications for the clinical management of *BRCA1* mutation carriers, for example in deciding the timing of interventions. Such risks, in combination with other lifestyle and hormonal risk factors could be incorporated into cancer risk prediction algorithms for use by clinical genetics centers. These algorithms could then be used to inform the development of effective and consistent clinical recommendations for the clinical management of *BRCA1* mutation carriers.

Supporting Information

Figure S1 Multidimensional scaling of stage 1 and stage 2 (genotyped on iCOGS) samples. Panel A: Graphical representation of the first two components, for the *BRCA1* carriers, for subgroups defined by the common 185delAG (c.68_69delAG) *BRCA1* Jewish founder mutation, the 5382insC (c.5266dupC) Eastern European founder mutation and Hapap individuals (CEU: European; ASI: Includes CHB and JPT populations; YRI: African). Panel B: Red dots represent the samples with >22% non-European ancestry, excluded from the analysis. (PDF)

Figure S2 Genotyping cluster plots in the *BRCA1* samples for the key associated SNPs. (PDF)

Figure S3 Quantile-quantile plot for the kinship adjusted score test statistic for stage 2 samples (1 degree of freedom χ^2 trend test) for the associations with breast cancer (panel A) and ovarian cancer (panel B) risk for *BRCA1* mutation carriers. The $y = x$ line corresponds to the expected distribution, under the hypothesis of no inflation. Inflation was estimated using the values of the lowest 90% test statistics. (PDF)

Figure S4 P-values (on $-\log_{10}$ scale) by chromosomal position, for the associations of 31,812 *BRCA1* GWAS SNPs with breast (panel A) and ovarian (panel B) cancer risk for *BRCA1* mutation carriers in the combined stage 1 and stage 2 samples. Blue lines correspond to a P-value of 10^{-5} ; red lines correspond to P-value 5×10^{-8} . (PDF)

Figure S5 Forest plots of the associations by country of residence of *BRCA1* mutation carriers in the combined stage 1, stage 2 and stage 3 samples for SNPs found to be associated with breast and ovarian cancer risk for *BRCA1* mutation carriers. Squares indicate the country specific, per-allele HR estimates for the SNPs. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% confidence intervals. There was some evidence of heterogeneity in country-specific HR estimates for the rs2290854 and rs6682208 SNP ($P = 0.04$ and 0.02 respectively, Figure S3), but after accounting for opposite effects of these SNPs in Finland/Denmark, there was no evidence of heterogeneity. There was some evidence of heterogeneity in the country-specific HRs for rs17631303 ($P_{\text{het}} = 0.004$, $df = 19$) but this was no longer present after excluding one country (Poland, P-

het = 0.12, df = 18), or when restricting analyses to Stage 1 and 2 samples only (P-het = 0.09, df = 19). There was no evidence of heterogeneity for correlated SNP rs183211 (P-het = 0.10). There was no evidence of heterogeneity in the country-specific HRs for any of the other SNPs (P > 0.68).

(PDF)

Figure S6 *MDM4* regional association plot using *BRCA1* stage 1 and stage 2 samples. P-values for association ($-\log_{10}$ scale) with breast cancer risk for *BRCA1* mutation carriers for genotyped SNPs (diamond symbols \diamond) and SNPs imputed from the 1000 genomes project data (square symbols \square), by position (hg18) on chromosome 1. Red gradient represents r^2 value with the most significant genotyped SNP rs4951407. The blue peaks represent recombination rate in the region.

(PDF)

Figure S7 *TCF7L2* regional association plot using *BRCA1* stage 1 and stage 2 samples. P-values for association ($-\log_{10}$ scale) with breast cancer risk for *BRCA1* mutation carriers for genotyped SNPs (diamond symbols \diamond) and SNPs imputed from the 1000 genomes project data (square symbols \square), by position (hg18) on chromosome 1. Missing genotypes were replaced by imputed results. Red gradient represents r^2 value with the most significant genotyped SNP rs1196174. The blue peaks represent recombination rate in the region.

(PDF)

Figure S8 Linkage disequilibrium patterns between the SNPs in the novel (17q21.31) and previously identified regions on 17q21. SNPs in the novel region are uncorrelated with SNPs in the 43.3–44.3 Mb region (positions according to hg build 36.3).

(PDF)

Figure S9 4q32.3 regional association plot using *BRCA1* stage 1 and stage 2 samples. P-values for association ($-\log_{10}$ scale) with ovarian cancer risk for *BRCA1* mutation carriers for genotyped SNPs (diamond symbols \diamond) and imputed SNPs from the 1000 genomes project data (square symbols \square), by position (hg18) on chromosome 1. Red gradient represents r^2 value with the most significant genotyped SNP rs4691139. Blue peaks represent recombination rate in the region.

(PDF)

Figure S10 Combined Hazard Ratios (HR) for breast and ovarian cancer for *BRCA1* mutation carriers. (A) HR for Breast Cancer based on 10 loci associated with breast cancer risk for *BRCA1* mutation carriers. (B) Ovarian Cancer based on 7 loci associated with ovarian cancer risk for *BRCA1* mutation carriers. All HRs computed relative to the lowest risk category. The Y-axes translate the combined HRs into absolute risks of developing breast or ovarian cancer by age 80. The absolute risks and HRs at different percentiles of the combined genotype distribution are also marked. The combined HRs were obtained under the assumption that the loci interact multiplicatively.

(PDF)

Figure S11 Cis-eQTL and allelic expression (AE) analyses at *MDM4* locus. A) Cis-eQTLs for SNPs at *MDM4* locus using expression data from primary human osteoblasts (HOb). B) AE mapping for cis-regulatory variation in *MDM4* locus using primary skin fibroblasts. Coordinates (hg18) for locus shown on top; blue tracks indicate the $-\log_{10}$ (P value) of the association across all SNPs tested. The location of transcripts in this region is shown below.

(PDF)

Figure S12 Cis-eQTL and allelic expression (AE) analyses at chr17q21.31 locus. (Upper panel) Cis-eQTLs for SNPs at c17orf69 locus using expression data from primary human osteoblasts. Allelic expression mapping for cis-regulatory variation in *KANSL1* (middle panel) and *WNT3* loci (lower panel) using a CEU population panel of lymphoblastoid cells. Coordinates (hg18) for loci are shown on top; blue tracks indicate the $-\log_{10}$ (P value) of the association across all SNPs tested. The location of transcripts in these regions are shown.

(PDF)

Table S1 Affected and unaffected *BRCA1* mutation carriers by study country in the breast and ovarian cancer analysis used in SNP selection for the iCOGS array.

(DOCX)

Table S2 Origin of *BRCA1* samples by Country and Stage used in the current analysis.

(DOCX)

Table S3 Sample and SNP quality control summary.

(DOCX)

Table S4 Associations with breast cancer risk for *BRCA1* mutation carriers, for known breast cancer susceptibility variants.

(DOCX)

Table S5 Associations with *BRCA1* breast or ovarian cancer risk for SNPs genotyped at stages 1, 2, and 3.

(DOCX)

Table S6 Analysis of breast cancer associations by *BRCA1* mutation class.

(DOCX)

Table S7 Associations with Breast Cancer ER status in *BRCA1* carriers for SNPs genotyped in stages 1–3.

(DOCX)

Table S8 Imputed SNPs at the novel 17q21 region with P-values less than the most significant genotyped SNP (rs169201).

(DOCX)

Table S9 SNPs associated ($P < 1 \times 10^{-5}$) with local expression and Allelic Imbalance.

(DOCX)

Text S1 Supplementary Methods.

(DOCX)

Acknowledgments

Antonis C. Antoniou is a Cancer Research–UK Senior Cancer Research Fellow. Douglas F. Easton is a Cancer Research UK Principal Research Fellow. Georgia Chenevix-Trench is an NHMRC Senior Principal Research Fellow.

iCOGS: CIMBA acknowledges the contributions of Kyriaki Michailidou, Jonathan Tyrer, and Ali Amin Al Olama to the iCOGS statistical analyses; Shahana Ahmed, Melanie J. Maranian, and Catherine S. Healey for their contributions to the iCOGS genotyping quality control process; and the staff of the genotyping unit in the Medical Genomics Facility at the Mayo Clinic under the supervision of Dr. Julie Cunningham.

Breast Cancer Family Registry (BCFR) Studies: Samples from the NC-BCFR were processed and distributed by the Coriell Institute for Medical Research. We wish to thank members and participants in the Breast Cancer Family Registry for their contributions to the study. The ABCFS would like to also thank Maggie Angelakos, Judi Maskiell, and Gillian Dite. 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.

Baltic Familial Breast Ovarian Cancer Consortium (BFBOCC): BFBOCC acknowledges Vilius Rudaitis and Laimonas Griškevičius. BFBOCC-LV acknowledges oncologists Janis Eglitis, Anna Krilova and Aivars Stengrevics.

BRCA-gene mutations and breast cancer in South African women (BMBSA): BMBSA thanks the families who contributed to the BMBSA study.

Beckman Research Institute of the City of Hope (BRICOH): BRICOH thanks Greg Wilhoite and Marie Pinto for their work in participant enrollment and biospecimen and data management.

Copenhagen Breast Cancer Study (CBCS): CBCS thanks the Danish Breast Cancer Cooperative Group (DBCG) for clinical data.

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

CONsorzio Studi ITaliani sui Tumori Ereditari Alla Mam-mella (CONsIT TEAM): CONsIT TEAM acknowledges Daniela Zaffaroni of the Fondazione IRCCS Istituto Nazionale Tumori (INT), Milan, Monica Barile of Istituto Europeo di Oncologia (IEO), Milan, Riccardo Dolcetti of the Centro di Riferimento Oncologico (CRO) IRCCS, Aviano (PN), Maurizio Genuardi of University of Florence, Florence, Giuseppe Giannini of “La Sapienza” University, Rome, Adele Patrini of the Ospedale di Circolo-Università dell’Insubria, Varese, Antonella Savarese and Aline Martayain of the Istituto Nazionale Tumori Regina Elena (IRE), Rome and Stefania Tommasi of the Istituto Nazionale Tumori “Giovanni Paolo II”, Bari and the personnel of the CGT-lab at IFOM-IEO Campus, Milan, Italy.

Dana-Farber Cancer Institute (DFCI): DFCI thanks the study staff and participants.

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON): HEBON recognizes Netherlands Cancer Institute, Amsterdam, NL: M.A. Rookus, F.B.L. Hogervorst, S. Verhoef, F.E. van Leeuwen, M.K. Schmidt, J. de Lange; Erasmus Medical Center, Rotterdam, NL: J.M. Collée, A.M.W. van den Ouweland, M.J. Hoening, C. Seynaeve; Leiden University Medical Center, NL: C.J. van Asperen, J.T. Wijnen, R.A. Tollenaar, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, NL: C.M. Kets, A.R. Mensenkamp; University Medical Center Utrecht, NL: M.G.E.M. Ausems, R.B. van der Luijt; Amsterdam Medical Center, NL: C.M. Aalfs, T.A.M. van Os; VU University Medical Center, Amsterdam, NL: J.J.P. Gille, Q. Waisfisz, H.E.J. Meijers-Heijboer; University Hospital Maastricht, NL: E.B. Gómez-García, M.J. Blok; University Medical Center Groningen, NL: J.C. Oosterwijk, H. van der Hout, M.J. Mourits, G.H. de Bock.

Epidemiological study of BRCA1 & BRCA2 mutation carriers (EMBRACE): Douglas F. Easton is the PI of the study. EMBRACE acknowledges the Coordinating Centre, Cambridge: Susan Peock, Debra Frost, Steve Ellis, Elena Fineberg, Radka Platte. North of Scotland Regional Genetics Service, Aberdeen: Zosia Miedzybrodzka, Helen Gregory. Northern Ireland Regional Genetics Service, Belfast: Patrick Morrison, Lisa Jeffers. West Midlands Regional Clinical Genetics Service, Birmingham: Trevor Cole, Kai-ren Ong, Jonathan Hoffman. South West Regional Genetics Service, Bristol: Alan Donaldson, Margaret James. East Anglian Regional Genetics Service, Cambridge: Marc Tischkowitz, Joan Paterson, Amy Taylor. Medical Genetics Services for Wales, Cardiff: Alexandra Murray, Mark T. Rogers, Emma McCann. St James’s Hospital, Dublin & National Centre for Medical Genetics, Dublin: M. John Kennedy, David Barton. South East of Scotland Regional Genetics Service, Edinburgh: Mary Porteous, Sarah Drummond. Peninsula Clinical Genetics Service, Exeter: Carole Brewer, Emma Kivuva, Anne Searle, Selina Goodman, Kathryn Hill. West of Scotland Regional Genetics Service, Glasgow: Rosemarie Davidson, Victoria Murday, Nicola Bradshaw, Lesley Snadden, Mark Longmuir, Catherine Watt, Sarah Gibson, Eshika Haque, Ed Tobias, Alexis Duncan. South East Thames Regional Genetics Service, Guy’s Hospital London: Louise Izatt, Chris Jacobs, Caroline Langman. North West Thames Regional Genetics Service, Harrow: Huw Dorkins, Angela Brady, Athalie Melville, Kashmir Randhawa. Leicestershire Clinical Genetics Service, Leicester: Julian Barwell. Yorkshire Regional Genetics Service, Leeds: Julian Adlard, Gemma Serra-Feliu. Cheshire & Merseyside Clinical Genetics Service, Liverpool: Ian Ellis, Catherine Houghton. Manchester Regional Genetics Service, Manchester: D Gareth Evans, Fiona Laloo, Jane Taylor. North East Thames Regional Genetics Service, NE Thames, London: Lucy Side, Alison Male, Cheryl Berlin. Nottingham Centre for Medical Genetics,

Nottingham: Jacqueline Eason, Rebecca Collier. Northern Clinical Genetics Service, Newcastle: Fiona Douglas, Oonagh Claber, Irene Jobson. Oxford Regional Genetics Service, Oxford: Lisa Walker, Diane McLeod, Dorothy Halliday, Sarah Durell, Barbara Stayner. The Institute of Cancer Research and Royal Marsden NHS Foundation Trust: Rosalind A. Eeles, Susan Shanley, Nazneen Rahman, Richard Houlston, Astrid Stormorken, Elizabeth Bancroft, Elizabeth Page, Audrey Ardern-Jones, Kelly Kohut, Jennifer Wiggins, Elena Castro, Emma Killeck, Sue Martin, Gillian Rea, Anjana Kulkarni. North Trent Clinical Genetics Service, Sheffield: Jackie Cook, Oliver Quarrell, Cathryn Bardsley. South West Thames Regional Genetics Service, London: Shirley Hodgson, Sheila Goff, Glen Brice, Lizzie Winchester, Charlotte Eddy, Vishakha Tripathi, Virginia Attard, Anna Lehmann. Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton: Diana Eccles, Anneke Lucassen, Gillian Crawford, Donna McBride, Sarah Smalley.

Fox Chase Cancer Center (FCCC): FCCC thanks Dr. Betsy Bove for her technical support.

German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC): GC-HBOC thanks all family members who participated in this study, Wolfram Heinritz, Center Leipzig, and Dieter Schäfer, Center Frankfurt, for providing DNA samples and Juliane Köhler for excellent technical assistance.

Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers (GEMO): GEMO thanks 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, Sylvie Mazoyer, Francesca Damiola, Laure Barjhoux, Carole Vernet-Pierre, Sophie Giraud, Mélanie Léone; and Service de Génétique Oncologique, Institut Curie, Paris: Dominique Stoppa-Lyonnet, Marion Gauthier-Villars, Bruno Buecher, Claude Houdayer, Virginie Moncoutier, Muriel Belotti, Carole Tirapo, Antoine de Pauw. Institut Gustave Roussy, Villejuif: Brigitte Bressac-de-Paillerets, Olivier Caron. 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. 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, Claude Adenis. Hôpital René Huguenin/Institut Curie, St Cloud: Etienne Rouleau, Rosette Lidereau, Liliane Demange, Catherine Nogues. Centre Paul Strauss, Strasbourg: Danièle Muller, Jean-Pierre Fricker. Institut Bergonié, Bordeaux: Emmanuelle Barou-Simonet, Françoise Bonnet, Virginie Bubiën, Nicolas Sevenet, Michel Longy. Institut Claudius Regaud, Toulouse: Christine Toulas, Rosine Guimbaud, Laurence Gladieff, Viviane Feillel. CHU Grenoble: Dominique Leroux, Hélène Dreyfus, Christine Rebischung, Magalie Peysselon. CHU Dijon: Fanny Coron, Laurence Faivre. CHU St-Etienne: Fabienne Prieur, Marine Lebrun, Caroline Kientz. Hôtel Dieu Centre Hospitalier, Chambéry: Sandra 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. CHU Vandoeuvre-les-Nancy : Johanna Sokolowska, Myriam Bronner. Creighton University, Omaha, USA: Henry T. Lynch, Carrie L. Snyder.

GFAST: G-FAST acknowledges the contribution of Bruce Poppe and Anne De Paepe and the technical support of Ilse Coene en Brecht Crombez.

Hospital Clinico San Carlos (HCSC): HCSC acknowledges Alicia Tosar for her technical assistance

Helsinki Breast Cancer Study (HEBCS): HEBCS thanks Carl Blomqvist, Kirsimari Aaltonen and RN Irja Erkkilä for their help with the HEBCS data and samples.

Study of Genetic Mutations in Breast and Ovarian Cancer patients in Hong Kong and Asia (HRBCP): HRBCP thanks Hong Kong Sanatorium and Hospital for their continual support.

Molecular Genetic Studies of Breast and Ovarian Cancer in Hungary (HUNBOCS): HUNBOCS thanks Hungarian Breast and Ovarian Cancer Study Group members (Janos Papp, Aniko Bozsik, Kristof

Arvai, Judit Franko, Maria Balogh, Gabriella Varga, Judit Ferenczi, Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary) and the clinicians and patients for their contributions to this study.

Interdisciplinary HEalth Research Internal Team BREast CAncer susceptibility (INHERIT): INHERIT thanks Dr Martine Dumont, Martine Tranchant for sample management and skillful technical assistance. J.S. is Chairholder of the Canada Research Chair in Oncogenetics.

Kathleen Cuninghams Consortium for Research into Familial Breast Cancer (kConFab): kConFab thanks 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.

Modifier Study of Quantitative Effects on Disease (MOD-SQUAD): MODSQUAD acknowledges ModSQuAD members Csilla Szabo and Zohra Ali-Kahn Catts (University of Delaware, Newark, USA); Lenka Foretova and Eva Machackova (Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic); and Michal Zikan, Petr Pohlreich and Zdenek Kleibl (Oncogynecologic Center and Department of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University, Prague, Czech Republic).

National Israeli Cancer Control Center (NICCC): NICCC thanks the NICCC National Familial Cancer Consultation Service team led by Sara Dishon, the laboratory team led by Dr. Flavio Lejbkowitz, and the research field operations team led by Dr. Mila Pinchev.

Ontario Cancer Genetics Network (OCGN): OCGN thanks the study staff and participants.

The Ohio State University Comprehensive Cancer Center (OSUCCG): OSU CCG acknowledges Kevin Sweet, Caroline Craven and Michelle O'Connor who were instrumental in accrual of study participants, ascertainment of medical records and database management. Samples were processed by the OSU Human Genetics Sample Bank.

South East Asian Breast Cancer Association Study (SEABASS): SEABASS thanks 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.

Sheba Medical Centre (SMC): SMC acknowledges the assistance of the Meirav Comprehensive breast cancer center team at the Sheba Medical Center for assistance in this study.

Swedish Breast Cancer Study (SWE-BRCA): SWE-BRCA Acknowledges SWE-BRCA collaborators from Lund University and University Hospital: Åke Borg, Håkan Olsson, Helena Jernström, Karin Henriksson, Katja Harbst, Maria Soller, Niklas Loman, Ulf Kristofferson; Gothenburg Sahlgrenska University Hospital: Anna Öfverholm, Margareta Nordling, Per Karlsson, Zakaria Einbeigi; Stockholm and Karolinska University Hospital: Anna von Wachenfeldt, Annelie Liljegren, Annika Lindblom, Brita Arver, Gisela Barbany Bustinza, Johanna Rantala; Umeå University Hospital: Beatrice Melin, Christina Edwindsdotter Ardnor, Monica Emanuelsson; Uppsala University: Hans Ehrencrona, Maritta Hellström Pigg, Richard Rosenquist; Linköping University Hospital: Marie Stenmark-Askmal, Sigrun Liedgren.

The University of Chicago Center for Clinical Cancer Genetics and Global Health (UCHICAGO): UCHICAGO thanks Cecilia Zvocec, Qun Niu, physicians, genetic counselors, research nurses and staff of the Cancer Risk Clinic for their contributions to this resource, and the many families who contribute to our program. OIO is an ACS Clinical Research Professor.

University of California Los Angeles (UCLA): UCLA thanks Joyce Seldon MSGC and Lorna Kwan, MPH for assembling the data for this study.

University of California San Francisco (UCSF): UCSF thanks Ms. Salina Chan for her data management and the following genetic counselors for participant recruitment: Beth Crawford, Nicola Stewart, Julie Mak, and Kate Lamvik.

United Kingdom Familial Ovarian Cancer Registries (UK-FOCR): UKFOCR thanks Paul Pharoah, Simon Gayther, Carole Pye,

Patricia Harrington and Eva Wozniak for their contributions towards the UKFOCR.

Victorian Familial Cancer Trials Group (VFCTG): VFCTG thanks Sarah Sawyer and Rebecca Driessen for assembling this data and Ella Thompson for performing all DNA amplification.

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Conceived and designed the experiments: Fergus J Couch, Douglas F Easton, Georgia Chenevix-Trench, Kenneth Offit, Antonis C Antoniou. Performed the experiments: Fergus J Couch, Julie Cunningham, Xianshu Wang, Curtis Olsword, Matthew Kosel, Adam Lee, Mia M Gaudet, Kenneth Offit, François Bacot, Daniel Vincent, Daniel Tessier. Analyzed the data: Antonis C Antoniou, Karoline B Kuchenbaecker, Lesley McGuffog, Daniel Barrowdale, Andrew Lee, Joe Dennis, Ed Dicks, Vernon S Pankratz, Zachary Fredericksen, Curtis Olsword, Matthew Kosel. Contributed reagents/materials/analysis tools: Penny Soucy, Kristen Stevens, Jacques Simard, Tomi Pastinen, Sue Healey, Olga M Sinilnikova, Andrew Lee. Wrote the manuscript: Fergus J Couch, Douglas F Easton, Antonis C Antoniou. Collected data and samples and provided critical review of the manuscript: Fergus J Couch, Xianshu Wang, Lesley McGuffog, Curtis Olsword, Karoline B Kuchenbaecker, Penny Soucy, Zachary Fredericksen, Daniel Barrowdale, Joe Dennis, Mia M Gaudet, Ed Dicks, Matthew Kosel, Olga M Sinilnikova, François Bacot, Daniel Vincent, Frans BL Hogervorst, Susan Peock, Dominique Stoppa-Lyonnet, Anna Jakubowska, Paolo Radice, Rita Katharina Schmutzler, Susan M Domchek, Marion Piedmonte, Christian F Singer, Thomas v O Hansen, Susan L Neuhausen, Csilla I Szabo, Ignacio Blanco, Mark H Greene, Beth Y Karlan, Catherine M Phelan, Jeffrey N Weitzel, Marco Montagna, Edith Olah, Irene L Andrulis, Andrew K Godwin, Drakoulis Yamnouchakos, David E Goldgar, Trinidad Caldes, Heli Nevanlinna, Ana Osorio, Mary Beth Terry, Mary B Daly, Elizabeth J van Rensburg, Ute Hamann, Susan J Ramus, Amanda Ewart Toland, Maria A Caligo, Olufunmilayo I Olopade, Nadine Tung, Kathleen Claes, Mary S Beattie, Melissa C Southey, Evgeny N Imyanitov, Ramunas Janavicius, Esther M John, Ava Kwong, Orland Diez, Rosa B Barkardottir, Banu K Arun, Gad Rennert, Soo-Hwang Teo, Patricia A Ganz, Annemarie H van der Hout, Carolien HM van Deurzen, Encarna B Gómez Garcia, Flora E van Leeuwen, Hanne EJ Meijers-Heijboer, Johannes JP Gille, Margreet GEM Ausems, Marinus J Blok, Marjolijn JL Ligtenberg, Matti A Rookus, Peter Devilee, Theo AM van Os, Juul T Wijnen, Debra Frost, Radka Platte, D Gareth Evans, Louise Izatt, Rosalind A Eeles, Julian Adlar, Diana M Eccles, Carole Brewer, Patrick J Morrison, Lucy E Side, Alan Donaldson, Mark T Rogers, Jacqueline Eason, Helen Gregory, Emma McCann, Alain Calender, Agnès Hardouin, Pascaline Berthet, Capucine Delnatte, Catherine Nogues, Dominique Leroux, Etienne Rouleau, Fabienne Prieur, Hagay Sobol, Laurence Venat-Bouvet, Laurent Castera, Marion Gauthier-Villars, Mélanie Léoné, Yves-Jean Bignon, Elżbieta Złowocka-Perłowska, Katarzyna Durda, Katarzyna Jaworska, Tomasz Huzarski, Alessandra Viel, Bernard Peissel, Bernardo Bonanni, Giulia Melloni, Laura Ottini, Laura Papi, Liliana Varesco, Maria Grazia Tibiletti, Valeria Pensotti, Norbert Arnold, Christoph Engel, Dorothea Gadzicki, Andrea Gehrig, Karin Kast, Kerstin Rhiem, Dieter Niederacher, Nina Ditsch, Hansjoerg Plendl, Sabine Preisler-Adams, Raymonda Varon-Mateeva, Barbara Wappenschmidt, Bernhard H F Weber, Brita Arver, Marie Stenmark-Askmal, Richard Rosenquist, Zakaria Einbeigi, Katherine L Nathanson, Timothy R Rebbeck, Stephanie V Blank, David E Cohn, Gustavo C Rodriguez, Michael Friedlander, Victoria L Bae-Jump, Anneliese Fink-Retter, Christine Rappaport, Daphne Gschwander Kaulich, Georg Pfeiler, Muy-Kheng Tea, Bella Kaufman, Shani Shimon Paluch, Yael Laitman, Anne-Marie Gerdes, Inge Sokilde Pedersen, Sanne Traasdahl Moeller, Torben A Kruse, Uffe Birk Jensen, Joseph Vijai, Mark Robson, Noah Kauff, Anna Marie Mulligan, Gord Glendon, Hilmi Ozcelik, Bent Ejlersen, Finn C Nielsen, Lars Jonson, Mette K Andersen, Yuan Chun Ding, Lenka Foretova, Alex Teulé, Miquel Angel Pujana, Phuong L Mai, Jennifer T Loud, Sandra Orsulic, Steven A Narod, Josef Herzog, Sharon R Sand, Silvia Tognazzo, Simona Agata, Tibor Vaszko, Joellen Weaver, Alexandra V Stavropoulou, Saundra S Buys, Atocha Romero, Miguel de la Hoya, Kristiina Aittomäki, Taru A Muranen, Mercedes Duran, Wendy K Chung, Cecilia M Dorfling, Dezheng Huo, Salina B Chan, Anna P Sokolenko, Laima Tihomirova, Tara M Friebe, Bjarni A Agnarsson, Karen H Lu, Flavio Lejbkowitz, Paul A James, Per Hall, Alison M Dunning, Daniel Tessier, Susan L Slager, Jacques Simard, Tomi Pastinen,

Vernon S Pankratz, Kenneth Offit, Douglas F Easton, Georgia Chenevix-Trench, Antonis C Antoniou, Andrew Lee, Adam Lee, Adriana Lasz, Alexander Miron, Caroline Seynaeve, Christian Sutter, Eitan Friedman, Elena Fineberg, Christine Lasset, Amanda B Spurdle, Anne-Bine Skytte, Alfons Meindl, Claude Houdayer, Fiona Douglas Francesca Damiola, Catherine Houghton, Alex Murray, Jan Lubinski, Conxi Lazaro, Christine Walsh, Chen Wang, Jenny Lester, Huw Dorkins, Helmut Deissler, Ian

Campbell, Isabelle Coupier, Judith Balmaña, Joan Brunet, Javier Benitez, Jackie Cook, Jocelyne Chiquette, Judy Garber, Jacek Gronwald, Kara Sarrel, Kristen Stevens, Laurie Small, Leigha Senter, Linda Steele, Mads Thomassen, Marc Tischkowitz, Niklas Loman, Noralane M Lindor, Pascal Pujol, Paolo Peterlongo, Steve Ellis, Stefanie Engert, Sue Healey, Shirley Hodgson, Steven Hart, Sylvie Mazoyer, Siranoush, Manoukian, Senno Verhoef, Sara Volorio.

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