Ovarian cancer susceptibility alleles and risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers

S. J. Ramus, A. C. Antoniou, Nina Ditsch

Angaben zur Veröffentlichung / Publication details:

Ramus, S. J., A. C. Antoniou, and Nina Ditsch. 2012. "Ovarian cancer susceptibility alleles and risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers." *Human Mutation* 33 (4): 690–702. https://doi.org/10.1002/humu.22025.

Ovarian Cancer Susceptibility Alleles and Risk of Ovarian Cancer in *BRCA1* and *BRCA2* Mutation Carriers

Susan J. Ramus,[1†] Antonis C Antoniou,[2†*] Karoline B. Kuchenbaecker,[2] Penny Soucy,[3] Jonathan Beesley,[4] Xiaoqing Chen,[4] Lesley McGuffog,[2] Olga M. Sinilnikova,[5,6] Sue Healey,[4] Daniel Barrowdale,[2] Andrew Lee,[2] Mads Thomassen,[7] Anne-Marie Gerdes,[8] Torben A. Kruse,[7] Uffe Birk Jensen,[9] Anne-Bine Skytte,[10] Maria A. Caligo,[11] Annelie Liljegren,[12] Annika Lindblom,[13] Håkan Olsson,[14] Ulf Kristoffersson,[15] Marie Stenmark-Askmalm,[16] Beatrice Melin,[17] SWE-BRCA,[18] Susan M. Domchek,[19] Katherine L. Nathanson,[19] Timothy R. Rebbeck,[19] Anna Jakubowska,[20] Jan Lubinski,[20] Katarzyna Jaworska,[20,21] Katarzyna Durda,[20] Elżbieta Złowocka,[20] Jacek Gronwald,[20] Tomasz Huzarski,[20] Tomasz Byrski,[20] Cezary Cybulski,[20] Aleksandra Toloczko-Grabarek,[20] Ana Osorio,[22] Javier Benitez,[22] Mercedes Duran,[23] Maria-Isabel Tejada,[24] Ute Hamann,[25] Matti Rookus,[26] Flora E. van Leeuwen,[27] Cora M. Aalfs,[28] Hanne E.J. Meijers-Heijboer,[29] Christi J. van Asperen,[30] K.E.P. van Roozendaal,[31] Nicoline Hoogerbrugge,[32] J. Margriet Collée,[33] Mieke Kriege,[33] Rob B. van der Luijt,[34] HEBON,[35] EMBRACE,[36] Susan Peock,[36] Debra Frost,[36] Steve D. Ellis,[36] Radka Platte,[36] Elena Fineberg,[36] D. Gareth Evans,[37] Fiona Lalloo,[37] Chris Jacobs,[38] Ros Eeles,[39] Julian Adlard,[40] Rosemarie Davidson,[41] Diana Eccles,[42] Trevor Cole,[43] Jackie Cook,[44] Joan Paterson,[45] Fiona Douglas,[46] Carole Brewer,[47] Shirley Hodgson,[48] Patrick J. Morrison,[49] Lisa Walker,[50] Mary E. Porteous,[51] M. John Kennedy,[52] Harsh Pathak,[53] Andrew K. Godwin,[53] Dominique Stoppa-Lyonnet,[54–56] Virginie Caux-Moncoutier,[54] Antoine de Pauw,[54] Marion Gauthier-Villars,[54] Sylvie Mazoyer,[6] Mélanie Léoné,[5] Alain Calender,[5] Christine Lasset,[57,58] Valérie Bonadona,[57,58] Agnès Hardouin,[59] Pascaline Berthet,[59] Yves-Jean Bignon,[60] Nancy Uhrhammer,[60] Laurence Faivre,[61,62] Catherine Loustalot,[62] GEMO,[63] Saundra Buys,[64] Mary Daly,[65] Alex Miron,[66] Mary Beth Terry,[67] Wendy K. Chung,[67] Esther M John,[68] Melissa Southey,[69] David Goldgar,[70] Christian F Singer,[71] Muy-Kheng Tea,[71] Georg Pfeiler,[71] Anneliese Fink-Retter,[71] Thomas v. O. Hansen,[72] Bent Ejlertsen,[73] Oskar Th. Johannsson,[74] Kenneth Offit,[75] Tomas Kirchhoff,[76] Mia M. Gaudet,[77] Joseph Vijai,[78] Mark Robson,[79] Marion Piedmonte,[80] Kelly-Anne Phillips,[81] Linda Van Le,[82] James S Hoffman,[83] Amanda Ewart Toland,[84] Marco Montagna,[85] Silvia Tognazzo,[85] Evgeny Imyanitov,[86] Claudine Isaacs,[87] Ramunas Janavicius,[88] Conxi Lazaro,[89] Ignacio Blanco,[90] Eva Tornero,[89] Matilde Navarro,[90] Kirsten B. Moysich,[91] Beth Y. Karlan,[92] Jenny Gross,[92] Edith Olah,[93] Tibor Vaszko,[93] Soo-Hwang Teo,[94] Patricia A. Ganz,[95] Mary S. Beattie,[96] Cecelia M Dorfling,[97] Elizabeth J van Rensburg,[97] Orland Diez,[98] Ava Kwong,[99] Rita K. Schmutzler,[100] Barbara Wappenschmidt,[100] Christoph Engel,[101] Alfons Meindl,[102] Nina Ditsch,[103] Norbert Arnold,[104] Simone Heidemann,[105] Dieter Niederacher,[106] Sabine Preisler-Adams,[107] Dorotehea Gadzicki,[108] Raymonda Varon-Mateeva,[109] Helmut Deissler,[110] Andrea Gehrig,[111] Christian Sutter,[112] Karin Kast,[113] Britta Fiebig,[114] Dieter Schäfer,[115] Trinidad Caldes,[116] Miguel de la Hoya,[116] Heli Nevanlinna,[117] Kristiina Aittomäki,[118] Marie Plante,[119] Amanda B. Spurdle,[4] kConFab,[120] Susan L. Neuhausen,[121] Yuan Chun Ding,[121] Xianshu Wang,[122] Noralane Lindor,[123] Zachary Fredericksen,[124] V. Shane Pankratz,[124] Paolo Peterlongo,[125,126] Siranoush Manoukian,[127] Bernard Peissel,[127] Daniela Zaffaroni,[127] Bernardo Bonanni,[128] Loris Bernard,[129,130] Riccardo Dolcetti,[131] Laura Papi,[132] Laura Ottini,[133] Paolo Radice,[125,126] Mark H. Greene,[134] Phuong L. Mai,[134] Irene L. Andrulis,[135] Gord Glendon,[136] Hilmi Ozcelik,[135] OCGN,[136] Paul D.P. Pharoah,[137] Simon A. Gayther,[1] Jacques Simard,[3] Douglas F. Easton,[2] Fergus J. Couch,[122] and Georgia Chenevix-Trench,[4] on behalf of the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)

[1]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, California; [2]Center for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; [3]Cancer Genomics Laboratory, Centre Hospitalier Universitaire de Québec and Laval University, Quebec City, Canada; [4]Genetics and Population Health Division, Queensland Institute of Medical Research, Herston, Australia; [5]Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Centre Hospitalier Universitaire de Lyon / Centre Léon Bérard, Lyon, France; [6]INSERM U1052, CNRS UMR5286, Université Lyon 1, Centre de Recherche en Cancérologie de Lyon, Lyon, France; [7]Department of Clinical Genetics, Odense University Hospital, Odense, Denmark; [8]Department of Clincial Genetics, Rigshospital and Copenhagen University, Copenhagen, Denmark; [9]Department of Clinical Genetics, Skejby Hospital, Aarhus, Denmark; [10]Department of Clinical Genetics, Vejle Hospital, Vejle, Denmark; [11]Section of Genetic Oncology, Department of Laboratory Medicine, University and University Hospital of Pisa, Pisa, Italy; [12]Department of Oncology, Karolinska University Hospital, Stockholm, Sweden; [13]Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden; [14]Department of Oncology, Lund University Hospital, Lund, Sweden; [15]Department of Clinical Genetics, Lund University Hospital, Lund, Sweden; [16]Division of Clinical Genetics, Department of Clinical and Experimental Medicine,

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

†Contributed equally to the study.

*Correspondence to: Antonis C Antoniou, Cancer Research UK Senior Cancer Research Fellow, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, CB1 8RN, United Kingdom. E-mail: a.antoniou@srl.cam.ac.uk

Linköping University, Linkoping, Sweden; [17] Department of Radiation Sciences, Oncology, Umeå University, Umea, Sweden; [18] Swedish Breast Cancer Study, Stockholm, Sweden; [19] Abramson Cancer Center, and Perelman School of Medicine, Philadelphia, University of Pennsylvania; [20] Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland; [21] Postgraduate School of Molecular Medicine, Warsaw Medical University, Warsaw, Poland; [22] Human Genetics Group, Spanish National Cancer Centre (CNIO), Madrid, Spain, and Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain; [23] Institute of Biology and Molecular Genetics, University of Valladolid, Valladolid, Spain; [24] Molecular Genetics Laboratory, Cruces Hospital Barakaldo, Bizkaia, Spain; [25] Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany; [26] Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands; [27] Department of Epidemiology, Division of Psychosocial Research & Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands; [28] Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands; [29] Department of Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands; [30] Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; [31] Department of Clinical Genomics, MUMC, Maastricht, The Netherlands; [32] Hereditary Cancer Clinic, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; [33] Department of Medical Oncology, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands; [34] Department of Medical Genetics, University Medical Center Utrecht, The Netherlands; [35] Hereditary Breast Ovarian Cancer Group, Amsterdam, The Netherlands; [36] Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; [37] Genetic Medicine, Manchester Academic Health Sciences Centre, Central Manchester University Hospitals NHS Foundation, Manchester, United Kingdom; [38] Clinical Genetics, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom; [39] Oncogenetics Team, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, United Kingdom; [40] Yorkshire Regional Genetics Service, Leeds, United Kingdom; [41] Ferguson-Smith Centre for Clinical Genetics, Yorkhill Hospitals, Glasgow, United Kingdom; [42] University of Southampton Faculty of Medicine, Southampton University Hospitals NHS Trust, Southampton, United Kingdom; [43] West Midlands Regional Genetics Service, Birmingham Women's Hospital Healthcare NHS Trust, Edgbaston, Birmingham, United Kingdom; [44] Sheffield Clinical Genetics Service, Sheffield Children's Hospital, Sheffield, United Kingdom; [45] Department of Clinical Genetics, East Anglian Regional Genetics Service, Addenbrookes Hospital, Cambridge, United Kingdom; [46] Institute of Genetic Medicine, Centre for Life, Newcastle Upon Tyne Hospitals NHS Trust, Newcastle Upon Tyne, United Kingdom; [47] Department of Clinical Genetics, Royal Devon and Exeter Hospital, Exeter, United Kingdom; [48] Medical Genetics Unit, St George's, University of London, London, United Kingdom; [49] Northern Ireland Regional Genetics Centre, Belfast Health and Social Care Trust, and Department of Medical Genetics, Queens University Belfast, Belfast, United Kingdom; [50] Oxford Regional Genetics Service, Churchill Hospital, Oxford, United Kingdom; [51] South East of Scotland Regional Genetics Service, Western General Hospital, Edinburgh, United Kingdom; [52] Academic Unit of Clinical and Molecular Oncology, Trinity College Dublin and St James's Hospital, Dublin, Ireland; [53] Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, Kansas; [54] Service de Génétique Oncologique, Institut Curie, Paris, France; [55] Unité INSERM U830, Institut Curie, Paris, France; [56] Université Paris Descartes, Faculté de Médecine, Paris, France; [57] Université Lyon 1, CNRS UMR5558, Lyon, France; [58] Unité de Prévention et d'Epidémiologie Génétique, Centre Léon Bérard, Lyon, France; [59] Centre François Baclesse, Caen, France; [60] Département d'Oncogénétique, Centre Jean Perrin, Université d'Auvergne, Auvergne, France; [61] Centre de Génétique, CHU Dijon, Université de Bourgogne, Dijon, France; [62] Centre Georges François Leclerc, Dijon, France; [63] GEMO study: Cancer Genetics Network "Groupe Génétique et Cancer", Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France; [64] Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City; [65] Fox Chase Cancer Center, Philadelphia, Pennsylvania; [66] Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts; [67] Department of Epidemiology, Columbia University, New York, NY; [68] Department of Epidemiology, Cancer Prevention Institute of California, Fremont, California; [69] Genetic Epidemiology Laboratory, Department of Pathology, University of Melbourne, Melbourne, Australia; [70] Department of Dermatology, University of Utah School of Medicine, Salt Lake City, Utah; [71] Department of OB/GYN and Comprehensive Cancer Center, Medical University of Austria, Vienna, Austria; [72] Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [73] Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [74] Department of Oncology, Landspitali University Hospital, Reykjavik, Iceland, Faculty of Medicine, University of Iceland, Reykjavik, Iceland; [75] Clinical Cancer Genetics Laboratory, Memorial Sloane Kettering Cancer Center, New York, NY; [76] Department of Environmental Medicine, NYU Cancer Institute, New York University School of Medicine, New York, NY; [77] Epidemiology Research Program, American Cancer Society, Atlanta, Georgia; [78] Clinical Cancer Genetics Laboratory, Memorial Sloane Kettering Cancer Center, New York, NY; [79] Memorial Sloan-Kettering Cancer Center, New York, NY; [80] Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; [81] Division of Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne, Australia; [82] Gynecologic Oncology Group, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [83] The Hospital of Central Conneticut, New Britian, Conneticut; [84] Divison of Human Cancer Genetics, Departments of Internal Medicine and Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio; [85] Immunology and Molecular Oncology Unit, Istituto Oncologico Veneto IOV - IRCCS, Padua, Italy; [86] Laboratory of Molecular Oncology, N.N. Petrov Institute of Oncology, St.-Petersburg, Russia; [87] Lombardi Comprehensive Cancer Center, Georgetown University, Washington DC; [88] Vilnius University Hospital Santariskiu Clinics, Hematology, Oncology and Transfusion Medicine Center, Department of Molecular and Regenerative Medicine; State Research Institute Inovative Medicine Center, Vilnius, Lithuania; [89] Molecular Diagnostic Unit, Hereditari Cancer Program, IDIBELL-Catalan Institute of Oncology, Catalanes, Spain; [90] Genetic Counseling Unit, Hereditari Cancer Program, IDIBELL-Catalan Institute of Oncology, Catalanes, Spain; [91] Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York; [92] Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California; [93] Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary; [94] Cancer Research Initiatives Foundation, Sime Darby Medical Centre, Malaysia and University Malaya Cancer Research Institute, University Malaya, Kuala Lumpur, Malaysia; [95] UCLA Schools of Medicine and Public Health, Division of Cancer Prevention & Control Research, Jonsson Comprehensive Cancer Center, Los Angeles, California; [96] University of California, San Francisco, Departments of Medicine, Epidemiology, and Biostatistics, San Francisco, California;

[97] Cancer Genetics Laboratory, Department of Genetics, University of Pretoria, Pretoria, South Africa; [98] Oncogenetics Laboratory. Vall d'Hebron Institute of Oncology (VHIO); University Hospital Vall d'Hebron, Barcelona, Spain; [99] The Hong Kong Hereditary Breast Cancer Family Registry; Cancer Genetics Center, Hong Kong Sanatorium and Hospital, Hong Kong; Department of Surgery, The University of Hong Kong, Hong Kong, Hong Kong; [100] Centre of Familial Breast and Ovarian Cancer, Department of Gynaecology and Obstetrics and Centre for Integrated Oncology (CIO), University Hospital of Cologne, Cologne, Germany; [101] Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; [102] Department of Gynaecology and Obstetrics, Division of Tumor Genetics, Klinikum rechts der Isar, Technical University Munich, Munich, Germany; [103] Department of Gynaecology and Obstetrics, Ludwig-Maximilian University Munich, Munich, Germany; [104] Department of Gynaecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Kiel, Germany; [105] Institute of Human Genetics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Kiel, Germany; [106] Department of Gynaecology and Obstetrics, University Hospital Düsseldorf, Heinrich-Heine University Düsseldorf, Dusseldorf, Germany; [107] Institute of Human Genetics, University of Münster, Münster, Germany; [108] Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany; [109] Institute of Human Genetics, Campus Virchov Klinikum, Charite Berlin, Germany; [110] Department of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany; [111] Centre of Familial Breast and Ovarian Cancer, Department of Medical Genetics, Institute of Human Genetics, University Würzburg, Wuzburg, Germany; [112] Institute of Human Genetics, Department of Human Genetics, University Hospital Heidelberg, Heidelberg, Germany; [113] Department of Gynaecology and Obstetrics, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany; [114] Institute of Human Genetics, University Regensburg, Regensburg, Germany; [115] Institute of Human Genetics, University Hospital Frankfurt a.M., Frankfurt, Germany; [116] Molecular Oncology Laboratory, Hospital Clinico San Carlos, Madrid, Spain; [117] Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; [118] Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland; [119] Gynaecologic Oncology Service, Centre Hospitalier Universitaire de Québec (CHUQ), Côte du Palais, Québec, Canada; [120] Kathleen Cuningham Consortium for Research into Familial Breast Cancer–Peter MacCallum Cancer Center, Melbourne, Australia; [121] Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, California; [122] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota; [123] Department of Medical Genetics, Mayo Clinic, Rochester, Minnesota; [124] Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota; [125] Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Preventive and Predicted Medicine, Fondazione IRCCS Istituto Nazionale Tumori (INT), Milan, Italy; [126] IFOM, Fondazione Istituto FIRC di Oncologia Molecolare, Milan, Italy; [127] Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale Tumori (INT), Milan, Italy; [128] Division of Cancer Prevention and Genetics, Istituto Europeo di Oncologia (IEO), Milan, Italy; [129] Department of Experimental Oncology, Istituto Europeo di Oncologia, Milan, Italy; [130] Consortium for Genomics Technology (Cogentech), Milan, Italy; [131] Cancer Bioimmunotherapy Unit, Centro di Riferimento Oncologico, IRCCS, Aviano (PN), Italy; [132] Medical Genetics Unit, Department of Clinical Physiopathology, University of Florence, Firenze, Italy; [133] Department of Molecular Medicine, "Sapienza" University of Rome, Rome, Italy; [134] Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland; [135] Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario M5G 1×5, Cancer Care Ontario, Departments of Molecular Genetics and Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada; [136] Ontario Cancer Genetics Network: Cancer Care Ontario, Ontario, Canada; [137] Department of Oncology, University of Cambridge, Cambridge, United Kingdom

ABSTRACT: Germline mutations in *BRCA1* and *BRCA2* are associated with increased risks of breast and ovarian cancer. A genome-wide association study (GWAS) identified six alleles associated with risk of ovarian cancer for women in the general population. We evaluated four of these loci as potential modifiers of ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. Four single-nucleotide polymorphisms (SNPs), rs10088218 (at 8q24), rs2665390 (at 3q25), rs717852 (at 2q31), and rs9303542 (at 17q21), were genotyped in 12,599 *BRCA1* and 7,132 *BRCA2* carriers, including 2,678 ovarian cancer cases. Associations were evaluated within a retrospective cohort approach. All four loci were associated with ovarian cancer risk in *BRCA2* carriers; rs10088218 per-allele hazard ratio (HR) = 0.81 (95% CI: 0.67–0.98) P-trend = 0.033, rs2665390 HR = 1.48 (95% CI: 1.21–1.83) P-trend = 1.8×10^{-4}, rs717852 HR = 1.25 (95% CI: 1.10–1.42) P-trend = 6.6×10^{-4}, rs9303542 HR = 1.16 (95% CI: 1.02–1.33) P-trend = 0.026. Two loci were associated with ovarian cancer risk in *BRCA1* carriers; rs10088218 per-allele HR = 0.89 (95% CI: 0.81–0.99) P-trend = 0.029, rs2665390 HR = 1.25 (95% CI: 1.10–1.42) P-trend = 6.1×10^{-4}. The HR estimates for the remaining loci were consistent with odds ratio estimates for the general population. The identification of multiple loci modifying ovarian cancer risk may be useful for counseling women with *BRCA1* and *BRCA2* mutations regarding their risk of ovarian cancer.

Hum Mutat 33:690–702, 2012.

KEY WORDS: ovarian cancer; BRCA1; BRCA2; association; SNP

Introduction

Pathogenic mutations in the *BRCA1* (MIM# 113705) and *BRCA2* (MIM# 600185) genes confer high risks of ovarian and breast cancer [Miki et al., 1994; Wooster et al., 1995]. Breast cancer risks by age 70 have been estimated to range between 40% and 87% for *BRCA1* and 40–84% for *BRCA2* mutation carriers, whereas

ovarian cancer risk estimates range between 16–68% and 11–27% for *BRCA1* and *BRCA2* mutation carriers, respectively [Antoniou et al., 2003; Antoniou et al., 2008; Begg et al., 2008; Chen et al., 2006; Ford et al., 1998; Hopper et al., 1999; Milne et al., 2008; Simchoni et al., 2006; Struewing et al., 1997; Thompson et al., 2001; Thompson et al., 2002]. Recent genome-wide association studies (GWAS) have identified common alleles associated with risk of breast, ovarian, and other cancers [reviewed Easton and Eeles, 2008; McCarthy and Hirschhorn, 2008; Song et al., 2009]. These common variants are plausible candidates for modifiers of disease risk for mutation carriers. The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) has provided convincing evidence that variants identified through GWAS of breast cancer are also associated with the risk of developing breast cancer for *BRCA1* and/or *BRCA2* mutation carriers [Antoniou et al., 2008a; Antoniou et al., 2009; Antoniou et al., 2010b; Antoniou et al., 2011].

Similarly, CIMBA has investigated the influence of ovarian cancer GWAS variants on ovarian cancer risk in *BRCA1* and *BRCA2* carriers. The first ovarian cancer susceptibility locus identified by a GWAS was rs3814113 at 9p22.2. The minor C allele was associated with a decreased risk of ovarian cancer (odds ratio (OR) = 0.82, 95% confidence interval (CI): 0.79–0.86, $P = 5.1 \times 10^{-19}$) [Song et al., 2009]. A previous CIMBA study showed that the minor allele of rs3814113 was also associated with a reduced risk of ovarian cancer for both *BRCA1* and *BRCA2* carriers (HR = 0.78 for both *BRCA1* and *BRCA2* mutation carriers) [Ramus et al., 2011].

A breast cancer GWAS in *BRCA1* mutation carriers found that locus 19p13 is associated with breast cancer risk for *BRCA1* mutation carriers. Two alleles on 19p13, rs8170C>T and rs2363956G>T, showed independent associations with breast cancer risk [Antoniou et al., 2010a]. Analysis of the associations of these SNPs with ovarian cancer risk in 843 ovarian cancer cases showed no evidence that this locus modifies ovarian cancer risk for *BRCA1* mutation carriers. However, the same two alleles were identified at the same time as ovarian cancer susceptibility alleles in a population-based ovarian cancer GWAS - rs8170 (OR = 1.12, 95% CI: 1.07–1.17, P-trend = 3.6×10^{-6}, serous OR = 1.18, 95% CI: 1.12–1.25, P-trend = 2.7×10^{-9}) and rs2363956 (OR = 1.1, 95% CI: 1.06–1.15, P-trend = 1.2×10^{-7}, serous OR = 1.16, 95% CI: 1.11–1.21, P-trend = 3.8×10^{-11}) [Bolton et al., 2010]. Subsequent genotyping of SNPs rs8170 and rs67397200 (an SNP correlated with both rs8170 and rs2363956 and identified via imputation), in a larger series of *BRCA1* and *BRCA2* mutation carriers from CIMBA, confirmed that both SNPs are associated with breast cancer risk. This analysis, which included 1,399 *BRCA1* ovarian cancer cases and 428 *BRCA2* ovarian cancer cases, also found that the 19p13 SNPs were associated with ovarian cancer risk in both *BRCA1* and *BRCA2* carriers in an analysis of the simultaneous breast and ovarian cancer associations in *BRCA1* carriers [Couch et al., in press].

Four additional ovarian cancer susceptibility loci were identified in a GWAS of more than 10,000 cases and 17,000 controls: rs2072590G>T (2q31) OR = 1.16 (95% CI: 1.12–1.21) P-trend = 4.5×10^{-14}, rs2665390T>C (3q25) OR = 1.19 (95% CI: 1.11–1.27) P-trend = 3.2×10^{-7}, rs10088218G>A (8q24) OR = 0.84 (95% CI: 0.80–0.89) P-trend = 3.2×10^{-9}, and rs9303542A>G (17q21) OR = 1.11 (95% CI: 1.06–1.16) P-trend = 1.4×10^{-6} [Goode et al., 2010]. All these associations were stronger for serous ovarian cancer, the most common histology observed in BRCA-related ovarian cancer, than for all histologies. To investigate whether these SNPs are associated with risk of ovarian and breast cancer for mutation carriers, we genotyped these SNPs (or, in the case of rs2072590, a surrogate SNP, rs717852A>G, $r^2 = 0.96$) for 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers from 40 studies that were part of CIMBA.

Materials and Methods

Subjects

All subjects were female carriers of pathogenic mutations in *BRCA1* or *BRCA2* from 40 studies from Europe, North America, South Africa, and Australia (Supp. Table S1). Pathogenic mutations were defined as protein-truncating mutations or mutations listed on the Breast Cancer Information Core (BIC) http://research.nhgri.nih.gov/bic/ as described previously [Antoniou et al., 2007]. All subjects were 18 years or older at recruitment. The majority of carriers (>97%) were recruited through cancer genetics clinics offering genetic testing, and enrolled into national or regional studies. Some carriers were identified by population-based sampling of cases, and some by community recruitment. Only women of self-reported white, European ancestry were included in the analysis. Subjects were excluded if they were from a country other than the country in which the study is conducted, or if they carried mutations in both genes. If a woman was enrolled in two different studies, only one of the samples was included in the analysis. These duplicate samples were identified by dates of birth and diagnosis and from available genotyping data. Subject information included year of birth; age at last follow-up; ages at breast and/or ovarian cancer diagnosis; and age at bilateral prophylactic mastectomy or oophorectomy. Related subjects were identified through a unique family identifier. *BRCA1* mutations were classified based on their predicted functional consequence. Class 1 was comprised of loss of function mutations subject to nonsense-mediated decay whereas class 2 mutations were those expected to generate a stable protein (details described previously [Antoniou et al., 2008a]). Subjects participated in clinical or research studies at the host institutions under ethically-approved protocols. Further details about CIMBA are described elsewhere [Chenevix-Trench et al., 2007].

Genotyping

The DNA samples from 12,599 *BRCA1* and 7,132 *BRCA2* carriers from 40 studies were genotyped for SNPs rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) using the iPLEX (Sequenom, San Diego, CA) Mass Array platform (Supp. Table S1) at four genotyping centers. We used a correlated SNP ($r^2 = 0.96$), rs717852, to replace a failed assay for rs2072590. All genotyping data were subjected to a standard set of quality control criteria. Samples from affected and unaffected subjects were randomly arrayed within plates. No template controls were included on every 384-well plate and at least 2% of the samples were tested in duplicate. Samples were excluded if they consistently failed genotyping, defined as a pass rate of < 80% for all SNPs in this genotyping round. For a study to be included in the analysis, the genotype data were required to attain or exceed a call-rate threshold of 95% and a concordance between duplicates of 98%. We also evaluated the deviation from Hardy-Weinberg equilibrium (HWE) for unrelated subjects. For none of these studies was HWE rejected at a predefined threshold of $P = 0.001$. An additional quality control criterion was consistent results for 95 DNA samples from a standard test plate (Coriell Institute, Camden, NJ) genotyped at all centers. If the genotyping was inconsistent for more than one sample in the test plate, the study was excluded. A total of 19,731 carriers with genotype data were eligible for inclusion in the analysis (12,599 *BRCA1* and 7,132 *BRCA2* carriers) (Supp. Table S1). Three studies failed quality control for rs717852 and one for rs2665390.

Table 1. Summary Characteristics for the 19,731 Eligible *BRCA1* and *BRCA2* Carriers[a] Used in the Analysis

	BRCA1		*BRCA2*	
Characteristic	Unaffected	Ovarian cancer	Unaffected	Ovarian cancer
Number	10,535	2,064	6,518	614
Person-years follow-up	459,178	104,942	304,789	34,605
Median age at censure (IQR)	42 (35–50)	50 (45–56)	45 (38–55)	56 (49–63)
Age at censure, N (%)				
< 30	1,536 (14.6)	93 (4.5)	796 (12.2)	24 (3.9)
30–39	2,945 (28.0)	171 (8.3)	1,402 (21.5)	15 (2.4)
40–49	3,375 (32.0)	760 (36.8)	2,017 (31.0)	129 (21.0)
50–59	1,721 (16.3)	707 (34.8)	1,297 (19.9)	217 (35.3)
60–69	656 (6.2)	269 (13.0)	667 (10.2)	175 (28.5)
70+	302 (2.9)	64 (3.1)	339 (5.2)	54 (8.8)
Year of birth, N (%)				
<1920	50 (0.5)	8 (0.4)	56 (0.9)	11 (1.8)
1920–1929	204 (1.9)	123 (6.0)	199 (3.1)	67 (10.9)
1930–1939	548 (5.2)	337 (16.3)	499 (7.7)	163 (26.6)
1940–1949	1,495 (14.2)	678 (32.9)	1,122 (17.2)	323 (37.8)
1950–1959	2,757 (26.2)	641 (31.1)	1,736 (26.6)	115 (18.7)
1960–1969	3,113 (29.6)	256 (12.4)	1,747 (26.8)	23 (3.8)
1970+	2,368 (22.5)	21 (1.0)	1,159 (17.8)	3 (0.5)
Mutation class, N (%)				
Class 1[b]	6,460 (61.3)	1,481 (71.8)	6,058 (92.9)	576 (93.8)
Class 2[b]	3,294 (31.3)	459 (22.2)	163 (2.5)	9 (1.5)
Other	781 (7.4)	124 (6.0)	297 (4.6)	29 (4.7)

[a] Carriers of self-reported white European ancestry only.
[b] See methods for definitions.
IQR, interquartile range.

Statistical Analysis

The primary aim of this study was to evaluate the association between each genotype and ovarian cancer risk. The primary endpoint was therefore the age at diagnosis of ovarian cancer. For this purpose, individuals were censored at the age of the ovarian cancer diagnosis, or risk-reducing salpingo-oophorectomy (RRSO) or the age at last observation. 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. To address the fact that mutation carriers were not sampled at random with respect to their disease phenotype, analysis was conducted by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes as previously described [Antoniou et al., 2007; Barnes et al., In Press]. This method has been shown to provide unbiased estimates of the risk ratios within the present sampling frame [Barnes et al., In Press]. The effect of each SNP was modeled either as a per-allele hazard ratio (HR) (multiplicative model) or as separate HRs for heterozygotes and homozygotes, and these were estimated on the logarithmic scale. The HRs were assumed to be independent of age (i.e., we used a Cox proportional-hazards model). The assumption of proportional hazards was tested by adding a "genotype x age" interaction term to the model in order to fit models in which the HR changed with age. Analyses were carried out with the pedigree-analysis software MENDEL [Lange et al., 1988] and details of this approach have been described previously [Antoniou et al., 2007; Barnes et al., In Press]. We examined between study/country heterogeneity by comparing the models that allowed for study-specific log HRs against models in which the same log HR was assumed to apply to all studies.

To investigate whether our results were influenced by any of our assumptions, we performed additional sensitivity analyses. If any of the SNPs were associated with disease survival, the inclusion of prevalent cases may influence the HR estimates. We therefore repeated our analysis by excluding mutation carriers diagnosed more than 5 years prior to the age at recruitment into the study. We also examined whether SNP associations differed by type of *BRCA1* mutations as described above.

The associations of these SNPs with breast cancer risk were assessed within a competing risk analysis framework [Barnes et al., In Press; Ramus et al., 2011] by estimating HRs simultaneously for breast and ovarian cancers. In this model, each individual was 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 in this case, 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 were censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of bilateral oophorectomy and in such circumstances were assumed to be unaffected for the corresponding disease. The remaining individuals were censored at the age at last observation and were assumed to be unaffected for both diseases.

To ensure a sufficiently large number of mutation carriers within each stratum, we grouped studies from the same country. All analyses were stratified and used calendar year and cohort-specific cancer incidences for *BRCA1* and *BRCA2* [Antoniou et al., 2008b]. For sensitivity analyses, strata with small numbers of mutation carriers were grouped. We used a robust variance-estimation approach to allow for the nonindependence among related carriers [Boos, 1992].

Results

In total, 12,599 *BRCA1* and 7,132 *BRCA2* carriers were eligible for analysis of associations between ovarian cancer risk and rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21). The primary analysis included 2,678 mutation carriers who were followed up to the age at diagnosis of invasive ovarian cancer (cases) and 17,053 carriers who were censored as unaffected (Table 1).

Table 2. SNP Genotype Distributions and Associations with Ovarian Cancer Risk

Mutation	Genotype	Unaffected N (%)	Affected[a] N (%)	HR	95% CI	*P*-value
8q24–rs10088218						
BRCA1	GG	7,978 (76.1)	1,574 (76.3)	1		
	AG	2,325 (22.2)	461 (22.4)	0.93	0.83–1.05	
	AA	176 (1.7)	27 (1.3)	0.61	0.41–0.91	
	2-df test					0.032
	per allele			0.89	0.81–0.99	0.029
BRCA2	GG	4,865 (74.7)	485 (79.0)	1		
	AG	1,537 (23.6)	116 (18.9)	0.73	0.59–0.91	
	AA	113 (1.7)	13 (2.1)	1.12	0.61–2.04	
	2-df test					0.014
	per allele			0.81	0.67–0.98	0.033
3q25–rs2665390						
BRCA1	TT	8,242 (85.6)	1,623 (83.1)	1		
	TC	1,330 (13.8)	314 (16.1)	1.25	1.08–1.44	
	CC	58 (0.6)	17 (0.9)	1.57	0.91–2.69	
	2-df test					2.7×10^{-3}
	per allele			1.25	1.10–1.42	6.1×10^{-4}
BRCA2	TT	5,226 (85.3)	449 (78.6)	1		
	TC	862 (14.1)	118 (20.7)	1.58	1.26–1.98	
	CC	38 (0.6)	4 (0.7)	1.20	0.34–4.19	
	2-df test					3.2×10^{-4}
	per allele			1.48	1.21–1.83	1.8×10^{-4}
2q31–rs717852						
BRCA1	TT	4,134 (47.0)	863 (45.3)	1		
	CT	3,807 (43.2)	862 (45.3)	1.11	0.99–1.23	
	CC	864 (9.8)	179 (9.4)	1.06	0.88–1.27	
	2-df test					0.18
	per allele			1.06	0.98–1.14	0.16
BRCA2	TT	3,029 (48.6)	245 (42.0)	1		
	CT	2,645 (42.4)	272 (46.6)	1.30	1.08–1.56	
	CC	558 (9.0)	67 (11.5)	1.51	1.13–2.01	
	2-df test					3.2×10^{-3}
	per allele			1.25	1.10–1.42	6.6×10^{-4}
17q21–rs9303542						
BRCA1	TT	5,695 (54.2)	1,076 (52.3)	1		
	TC	4,085 (38.9)	826 (40.1)	1.08	0.98–1.20	
	CC	729 (6.9)	157 (7.6)	1.15	0.95–1.40	
	2-df test					0.17
	per allele			1.08	1.00–1.17	0.06
BRCA2	TT	3,445 (53.0)	296 (48.3)	1		
	TC	2,593 (39.9)	264 (43.1)	1.19	1.00–1.42	
	CC	462 (7.1)	53 (8.7)	1.31	0.95–1.81	
	2-df test					0.082
	per allele			1.16	1.02–1.33	0.026

[a]Ovarian cancer.
Analysis restricted to mutation carriers of white European ancestry.

The minor allele of rs2665390 (3q25) was associated with a significantly increased risk of ovarian cancer for both *BRCA1* carriers (per-allele HR = 1.25, 95% CI: 1.10–1.42, P-trend = 6.1×10^{-4}) and *BRCA2* carriers (per allele HR = 1.48, 95% CI: 1.21–1.83, P-trend = 1.8×10^{-4}) (Table 2). The minor allele of rs10088218 (8q24) was associated with a significantly decreased risk of ovarian cancer for both *BRCA1* carriers (per-allele HR = 0.89, 95% CI: 0.81–0.99, P-trend = 0.029), and *BRCA2* carriers (per allele HR = 0.81, 95% CI: 0.67–0.98, P-trend = 0.033). The two remaining SNPs, rs717852 (2q31) and rs9303542 (17q21), were associated with ovarian cancer risk for *BRCA2* carriers (rs717852-per allele HR = 1.25, 95% CI: 1.10–1.42, P-trend = 6.6×10^{-4}; rs9303542-per allele HR = 1.16, 95% CI: 1.02–1.33, P-trend = 0.026). The estimated HRs in *BRCA1* carriers for these two SNPs were also >1 but not significantly different from 1, nor did they differ significantly from the HRs in *BRCA2* carriers. There was no evidence that the HRs varied by age for either *BRCA1* or *BRCA2* mutation carriers (*BRCA1*-rs10088218 $P = 0.34$, rs2665390 $P = 0.24$, rs717852 $P = 0.09$, rs9303542 $P = 0.58$; *BRCA2*-rs10088218 $P = 0.66$, rs2665390 $P = 0.95$, rs717852 $P = 0.88$, rs9303542 $P = 0.67$). The country-specific HRs are shown in Figure 1. There was no evidence of heterogeneity in HRs across the studies/countries (*BRCA1*-rs10088218 $P = 0.27$, rs2665390 $P = 0.59$, rs717852 $P = 0.60$, rs9303542 $P = 0.10$; *BRCA2* -rs10088218 $P = 0.16$, rs2665390 $P = 0.32$, rs717852 $P = 0.75$, rs9303542 $P = 0.49$).

To determine if any survival bias was introduced by including long-term survivors, we excluded all ovarian cancer cases recruited 5 or more years after diagnosis (Supp. Table S2). All HR estimates were similar to those from the primary analysis although only three were significant in the reduced sample set.

We examined the associations between the SNPs and ovarian cancer risk by the *BRCA1* mutation-type based on the predicted functional consequence (Supp. Table S2). We found no evidence of a difference in the per-allele HR by *BRCA1* mutation type for rs10088218 (8q24) (P for difference in HR = 0.99). For rs2665390 (3q25) the estimated HR for class 1 mutations was somewhat higher (per-allele HR = 1.34 [95% CI: 1.15-1.56] P-trend = 2.2×10^{-4})

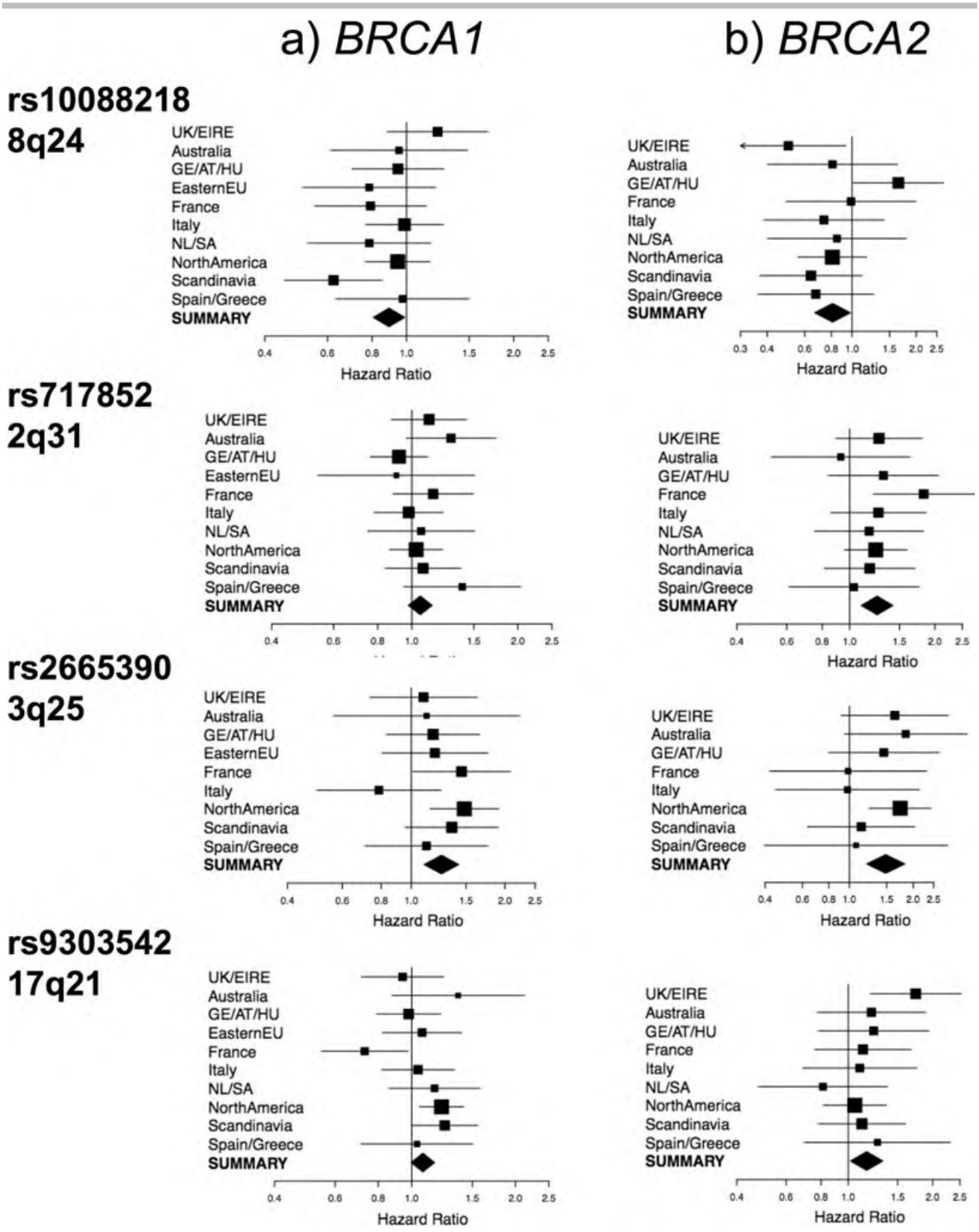

Figure 1. Forest plots of study-specific HRs for ovarian cancer risk in (a) *BRCA1* mutation carriers, (b) *BRCA2* mutation carriers. Country-specific per-allele HR estimates for the SNPs rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) in *BRCA1* and *BRCA2* mutation carriers. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% confidence intervals. Diamonds indicate the summary HR estimates for all of the CIMBA. For *BRCA2,* some of the smaller studies have been combined with others from the same country. GE/AT/HU denotes the stratum for Germany, Austria, and Hungary. NL/SA denotes the stratum for the Netherlands and South Africa.

Table 3. Competing Risk Analysis

					Breast cancer			Ovarian cancer		
		Unaffected N (%)	Breast cancer N (%)	Ovarian cancer N (%)	HR	95% C.I.	*P*-value	HR	95% C.I.	*P*-value
8q24—rs10088218										
BRCA1	GG	3,661 (77.0)	4,772 (75.5)	1,119 (76.4)	1			1		
	AG	1,025 (21.5)	1,431 (22.6)	330 (22.5)	1.03	0.94–1.11		0.96	0.83–1.11	
	AA	70 (1.5)	117 (1.9)	16 (1.1)	1.08	0.84–1.38		0.55	0.32–0.94	
	2-df test						0.72			0.083
	per allele				1.03	0.96–1.10	0.44	0.91	0.80–1.03	0.13
BRCA2	GG	2,123 (73.9)	2,861 (75.3)	366 (80.6)	1			1		
	AG	699 (24.3)	877 (23.1)	77 (17.0)	0.91	0.82–1.02		0.60	0.46–0.78	
	AA	53 (1.8)	62 (1.6)	11 (2.4)	0.85	0.61–1.18		1.17	0.60–2.27	
	2-df test						0.17			7.7×10^{-4}
	per allele				0.92	0.84–1.00	0.061	0.72	0.57–0.91	5.7×10^{-3}
3q25–rs2665390										
BRCA1	TT	3,716 (85.2)	4,995 (85.7)	1,151 (82.8)	1			1		
	TC	614 (14.1)	801 (13.7)	229 (16.4)	1.00	0.90–1.11		1.27	1.06–1.51	
	CC	31 (0.7)	33 (0.6)	11 (0.8)	0.80	0.53–1.19		1.22	0.62–2.41	
	2-df test						0.54			0.028
	per allele				0.98	0.89–1.08	0.70	1.23	1.06–1.44	8.5×10^{-3}
BRCA2	TT	2,282 (85.5)	3,067 (85.1)	326 (76.8)	1			1		
	TC	368 (13.8)	517 (14.4)	95 (22.5)	1.02	0.89–1.16		1.75	1.34–2.27	
	CC	19 (0.7)	20 (0.6)	3 (0.7)	0.72	0.39–1.35		1.02	0.21–5.10	
	2-df test						0.57			1.6×10^{-4}
	per allele				0.99	0.87–1.12	0.82	1.59	1.25–2.02	1.9×10^{-4}
2q31–rs717852										
BRCA1	TT	1,817 (47.3)	2,576 (46.5)	606 (45.5)	1			1		
	CT	1,667 (43.5)	2,400 (43.3)	602 (45.1)	1.01	0.94–1.09		1.10	0.96–1.25	
	CC	356 (9.3)	562 (10.2)	125 (9.4)	1.13	0.99–1.29		1.10	0.87–1.40	
	2-df test						0.18			0.32
	per allele				1.04	0.99–1.10	0.14	1.08	0.98–1.19	0.15
BRCA2	TT	1,345 (49.8)	1,752 (47.5)	177 (41.4)	1			1		
	CT	1,112 (41.2)	1,603 (43.5)	202 (47.2)	1.08	0.98–1.19		1.39	1.11–1.74	
	CC	244 (9.0)	331 (9.0)	50 (11.5)	1.03	0.87–1.21		1.60	1.13–2.26	
	2-df test						0.30			3.8×10^{-3}
	per allele				1.04	0.97–1.12	0.30	1.31	1.12–1.53	8.5×10^{-4}
17q21–rs9303542										
BRCA1	TT	2,537 (53.1)	3,470 (54.8)	764 (52.3)	1			1		
	TC	1,891 (39.6)	2,434 (38.5)	586 (40.1)	0.98	0.91–1.05		1.08	0.95–1.23	
	CC	349 (7.3)	426 (6.7)	111 (7.6)	0.95	0.82–1.09		1.10	0.87–1.40	
	2-df test						0.70			0.44
	per allele				0.98	0.92–1.03	0.41	1.06	0.97–1.17	0.22
BRCA2	TT	1,517 (52.8)	2,012 (53.1)	212 (46.7)	1			1		
	TC	1,136 (39.6)	1,520 (40.1)	203 (44.9)	0.98	0.89–1.08		1.26	1.02–1.55	
	CC	218 (7.6)	259 (6.8)	38 (8.4)	0.87	0.73–1.05		1.17	0.79–1.74	
	2-df test						0.35			0.099
	per allele				0.96	0.89–1.03	0.22	1.16	0.99–1.35	0.075

Associations with breast and ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. Analysis restricted to mutation carriers of European ancestry.

compared to class 2 mutations (HR = 1.08 (95% CI: 0.78–1.36), P-trend = 0.85), but the difference in HRs was not significant (P = 0.06). Similar patterns in the HRs between class 1 and class 2 mutations were seen for rs9303542 (17q21) and rs717852 (2q31), but none of the differences were significant (P = 0.20 and P = 0.36, respectively).

To determine whether these four SNPs were also associated with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers, we performed an analysis in which we estimated HRs for breast and ovarian cancer simultaneously within a bivariate outcome model (Table 3). There was no evidence of association between these SNPs and breast cancer risk for mutation carriers. The estimated HRs for ovarian cancer risk under this analysis were similar to those estimated in the main analysis. However, some of the results were no longer significant due to the fact that mutation carriers diagnosed with ovarian cancer after a breast cancer diagnosis are censored at breast cancer, which results in a reduced number of ovarian cancer cases. The 3q25 SNP, rs2665390, was significantly associated with ovarian cancer risk for both *BRCA1* and BRCA2 carriers (per-allele HR = 1.23, 95% CI: 1.06-1.44, P-trend = 8.5×10^{-3} and per-allele HR = 1.59, 95% CI: 1.25–2.02, P-trend = 1.9×10^{-4}, respectively). As in the primary analysis, rs717852 (2q31) was only associated with an increased ovarian cancer risk in *BRCA2* carriers (HR = 1.31, 95% CI: 1.12–1.53, P-trend = 8.5×10^{-4}). The magnitude of the association between SNP rs10088218 (8q24) and ovarian cancer risk in *BRCA2* carriers was somewhat larger than in the primary analysis (HR = 0.72, 95% CI: 0.57–0.91, P-trend = 5.7×10^{-3}).

Discussion

Recent studies have shown that common genetic variants identified from ovarian cancer GWAS are associated with susceptibility to ovarian cancer for *BRCA1* and/or *BRCA2* mutation carriers [Couch et al., in press; Ramus et al., 2011]. In the present study, we genotyped four SNPs, rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) that were found to be associated with ovarian cancer in women from the general population. We found

that all SNPs were associated with ovarian cancer risk for *BRCA2* mutation carriers. There was significant evidence that two of the SNPs (rs10088218 at 8q24 and rs2665390 at 3q25) were also associated with ovarian cancer risk for *BRCA1* mutation carriers. For the remaining two SNPs at 2q31 and 17q21, the associations with ovarian cancer risk in *BRCA1* mutations did not reach statistical significance. However, the estimated HRs were still consistent with both the estimated HRs in *BRCA2* carriers, and the estimated ORs in the general population. Thus these data, combined with those for the previously detected ovarian cancer risk SNPs at 9p22.2 [Ramus et al., 2011] and 19p13 [Couch et al, in press], indicate that all six known common susceptibility loci for ovarian cancer, are also associated with the ovarian cancer risk in *BRCA1* and *BRCA2* carriers, and moreover that the relative risk of ovarian cancer is generally similar to that in the general population.

In the general population, the magnitude of the associations with ovarian cancer risk were stronger for cases with the serous histological subtype for rs2072590 (2q31) $P_{heterogeneity} = 2.9 \times 10^{-4}$, rs10088218 (8q24) $P_{heterogeneity} = 1.1 \times 10^{-7}$, and rs2665390 (3q25) $P_{heterogeneity} = 0.02$ [Goode et al., 2010]. However, we were not able to assess this interaction in the *BRCA1* and *BRCA2* carriers, due to small numbers and incomplete pathology data for histological subtype.

When the data were analyzed within a competing risks framework, we observed no evidence that these SNPs were associated with breast cancer risk for *BRCA1* or *BRCA2* mutation carriers. None of the published breast cancer GWAS using women from the general population [Ahmed et al., 2009; Easton et al., 2007; Gold et al., 2008; Hunter et al., 2007; Thomas et al., 2009] have reported associations for these SNPs at the strict genome-wide levels of significance. These results indicate that, for both groups of mutation carriers and for the general population, the predominant association is with ovarian cancer risk and that the association with breast cancer risk, if any, is very weak.

The fine-mapping and functional follow-up of the risk alleles from the ovarian cancer GWAS are currently being performed. Therefore, the gene most likely to be driving the ovarian cancer risk in each region has not yet been identified but the closest genes to each SNP and the genes in the linkage disequilibrium block provide some insight to the potential candidates. The rs2665390 SNP is located at 3q25, and is intronic to the *TIPARP* gene, a member of the poly (ADP-ribose) polymerase (PARP) superfamily. *BRCA1-BRCA2*–deficient cells can use the *PARP1* alternative DNA repair mechanism to survive, and synthetic inhibition of *PARP1* has been developed as a new therapy for breast and ovarian cancer patients with mutations in these genes [Fong et al., 2009]. There are no other candidate genes within 200 kb of this SNP and the five other genes within the linkage disequilibrium block (*LEKR1, LOC730091, PA2G4P4, SSR3,* and *KCNAB1*) are not known to have functions that suggest a role in cancer [www.genecards.org; Safran et al., 2010].

The rs717852 SNP is located at 2q31 in a region containing a family of homeobox (*HOX*) genes; *HOXD10, HOXD11, HOXD12, HOXD13, HOXD3, HOXD4, HOXD8, HOXD9,* and *HOXD1. HOX* genes are involved in regulating embryogenesis and organogenesis and altered expression of *HOX* genes has been reported in many cancers [Buzzai and Licht, 2008; Shiraishi et al., 2002.]. The other genes in this region, *KIAA1715, EVX2,* and *MTX2,* do not have a reported role in cancer [www.genecards.org; Safran et al., 2010]. The ovarian cancer risk-associated SNP rs2072590 is downstream of *HOXD3* and upstream of *HOXD1*, and it tags SNPs in the *HOXD3* 3′ untranslated region. The genotyped SNP rs717852 is intronic of *HOXD3.*

Common variants that confer susceptibility to multiple cancer phenotypes, including prostate, colorectal, breast, and bladder cancers have been identified in a 500-kb region of a gene desert at 8q24, approximately 200 kb 5′ of *MYC* [Jia et al., 2009]. Functional studies have suggested that transcriptional regulation of *MYC* may explain these associations [Jia et al., 2009; Pomerantz et al., 2009]. In contrast, rs10088218 is >700 kb 3′ of *MYC.* Variants in this region may also be capable of distant regulation of *MYC.* However, *PVT1,* a noncoding RNA which is an MYC protein target, is another plausible candidate in this region. *PVT1* is amplified in breast and ovarian tumors, and is overexpressed in transformed cells [Guan et al., 2007]. A prostate cancer risk variant at the 8q24 locus, located 0.5 Mb upstream of the *PVT1* gene has recently been shown to be associated with increased expression of the *PVT1* gene rather than affecting MYC expression [Meyer et al., 2011].

The final SNP, rs9303542 at 17q21, is intronic to *SKAP1*, a src kinase-associated phosphoprotein, which regulates mitotic progression [Fang et al., 2009]. SKAP1 has been shown to suppress activation of *RAS* and *RAF1* genes that may have a role in the early-stage development of ovarian cancer [Kosco et al., 2008]. The region also contains 10 *HOXB* genes and, as described earlier, altered expression of *HOX* genes has been reported in many cancers. Of the other 12 genes in this region, the only ones with a suggested role in cancer are, *PRAC,* encoding a small nuclear protein which is a prostate cancer susceptibility candidate, *CBX1,* which may play an important role in the epigenetic control of chromatin structure and gene expression, and *CDK5RAP3* that may be involved in cell proliferation [www.genecards.org; Safran et al., 2010].

We have previously demonstrated that common risk alleles for breast cancer increase the risk of breast cancer to a similar relative extent in *BRCA1* and *BRCA2* carriers (once estrogen receptor status is taken into account). These results demonstrate that the same holds true for ovarian cancer loci identified through GWAS, and provides a general model in which common susceptibility loci and *BRCA1* and *BRCA2* mutations interact multiplicatively on the risk of developing ovarian cancer [Wacholder et al., 2011]. Although the HR conferred by each locus is modest, the HRs are much larger in combination. These translate to small differences in absolute risk between different genotypes for the vast majority of women at low risk of this disease, but the absolute risk differences for mutation carriers will be much greater. As more genetic modifiers of ovarian cancer risk are identified, in the future, such information combined with other risk factors such as parity and oral contraceptive use could be incorporated into risk prediction algorithms such as BOADICEA [Antoniou et al., 2008b]. This could enable the stratification of mutation carriers into different ovarian cancer risk categories and could potentially be used for guiding the clinical management of mutation carriers with respect to screening or prophylactic surgery.

Acknowledgments

This work was supported by Cancer Research UK grants C12292/A11174 and C1287/A10118, NHMRC grants to GCT, and grants from the NIH (CA128978), and the U.S. Department of Defense Ovarian Cancer Idea award (W81XWH-10-1-0341) to FJC. The research leading to these results has received funding from the European Community's Seventh Framework Programme No. 223175 (HEALTH-F2-2009-223175); European Community's Seventh Framework Programme under grant agreement No. 223175 (HEALTH-F2-2009-223175). ACA is a CR-UK Senior Cancer Research Fellow, DFE is CR-UK Principal Research Fellow, GCT is a NHMRC Senior Principal Research Fellow and JS is Chairholder of the Canada Research Chair in Oncogenetics. This work was supported by the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program (grant number CRN_87521); and the Canadian Breast Cancer Research Alliance (grant number 019511)

Breast Cancer Family Registry (BCFR): was 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 and Principal Investigators, including Cancer Care Ontario (U01 CA69467), Columbia University (U01 CA69398), Fox Chase Cancer Center (U01 CA69631), Huntsman Cancer Institute (U01 CA69446), Northern California Cancer Center (U01 CA69417), University of Melbourne (U01 CA69638), and Research Triangle Institute Informatics Support Center (RFP No. N02PC45022-46). 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.

BRCA-gene mutations and breast cancer in South African women (BMBSA): was supported by grants from the Cancer Association of South Africa (CANSA) to Elizabeth J. van Rensburg.

Copenhagen Breast Cancer Study (CBCS): was supported by the Neye Foundation.

Spanish National Cancer Center (CNIO). This study was partially supported by Fundación Mutua Madrileña, Asociación Española Contra el Cáncer, the Spanish Minestry of Science and Innovation FIS PI08/1120 and Cancer Network RD06/0020/1060. Funded in part by the Basque Foundation for Health Innovation and Research (BIOEF: BIO07/CA/006).

CONsorzio Studi Italiani Tumori Ereditari Alla Mammella (CONSIT TEAM) was supported by grants from Associazione Italiana per la Ricerca sul Cancro (4017) and by funds from Italian citizens who allocated the 5 × 1,000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects "5 × 1,000") to PP. Supported by grants from Ministero della Salute ("Progetto Tevere"—Linea 1 RC D/08/02B—"Progetto Tumori Femminili"—F/08/0PZ—Linea1 RC CORR/08) to SM. Supported by grants from Associazione Italiana per la Ricerca sul Cancro (8713) to LO. Supported by grants from Fondazione Italiana per la Ricerca sul Cancro (Special Project "Hereditary tumors"), Ministero della Salute (RFPS-2006-3-340203, Extraordinary National Cancer Program 2006 "Alleanza contro il Cancro", and "Progetto Tumori Femminili") and Ministero dell'Universita' e Ricerca (RBLAO3-BETH) to PR.

Deutsches Krebsforschungszentrum (DKFZ) study: was supported by the DKFZ.

Epidemiological study of BRCA1 & BRCA2 mutation carriers (EMBRACE) was 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. Ros Eeles, Elizabeth Bancroft, and Lucia D'Mello were also supported by Cancer Research UK Grant (C5047/A8385).

Fox Chase Cancer Center (FCCC): was supported by the National Institutes of Health (U01 CA69631, 5U01 CA113916, R01 CA140323 to A.K.G.); the Ovarian Cancer Research Fund, and the Eileen Stein Jacoby Fund. The author acknowledges support from The University of Kansas Cancer Center and the Kansas Bioscience Authority Eminent Scholar Program. A.K.G. is the Chancellors Distinguished Chair in Biomedical Sciences endowed Professor.

The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC): was supported by a grant of the German Cancer Aid (grant 109076) and by the Centre of Molecular Medicine Cologne (CMMC).

Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers (GEMO) study (Cancer Genetics Network "Groupe Génétique et Cancer", Fédération Nationale des Centres de Lutte Contre le Cancer, France) was supported by the Ligue National Contre le Cancer; Association for International Cancer Research Grant (AICR-07-0454); and the Association "Le cancer du sein, parlons-en!" Award.

Georgetown. CI received support from the Familial Cancer Registry at Georgetown University (NIH/NCI grant P30-CA051008), the Cancer Genetics Network (HHSN261200744000C), and Swing For the Cure.

Gynecologic Oncology Group (GOG): KAP is the Cancer Council Victoria, Colebatch Clinical Research Fellow.

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON). The HEBON study is supported by the Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, NKI2007-3756 and the ZonMW grant 91109024.

Hospital Clinico San Carlos (HCSC): was supported by The National Institute of Health Carlos III (RTICC 06/0020/0021).

Helsinki Breast Cancer Study (HEBCS): was supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (132473), the Finnish Cancer Society, and the Sigrid Juselius Foundation.

The Hong Kong Hereditary Breast Cancer Family Registry (HRBCP): thanks the Dr. Ellen Li Charitable Foundation and Kuok Foundation for grant support.

Hungarian Breast and Ovarian Cancer Study (HUNBOCS) was supported by Hungarian Research Grant KTIA-OTKA CK-80745 to Edith Olah.

International Hereditary Cancer Center (IHCC): was supported by the State Committee for Scientific Research (PBZ_KBN_122/P05/2004). Katarzyna Jaworska is a fellow of International PhD program, Postgraduate School of Molecular Medicine, Warsaw Medical University, supported by the Polish Foundation of Science.

Iceland Landspitali-University Hospital (ILUH): The ILUH group was supported by a grant from the Icelandic Association "Walking for Breast Cancer Research" and by the Landspitali University Hospital Research Fund.

Istituto Oncologico Veneto Hereditary Breast and Ovarian Cancer Study (IOVHBOCS) was supported by Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR), and "Ministero della Salute" ("Progetto Tumori Femminili and grant numbersRFPS 2006-5-341353, ACC2/R6.9").

Kathleen Cuningham Consortium for Research into Familial Breast Cancer (KCONFAB) was supported by grants from the National Breast Cancer Foundation, 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. ABS is a Senior Research Fellow of the NHMRC.

The research of the MAGIC consortium at the University of Pennsylvania was funded by RO1-CA083855 and RO1-CA102776 to TRR.

Mayo Clinic Study (MAYO) was supported by the National Institutes of Health (R01 CA128978 and P50 CA116201); the Komen race for the cure (KG081527); the Breast Cancer Research Foundation and the U.S. Department of Defense Ovarian Cancer Idea award (W81XWH-10-1-0341).

Memorial Sloane Kettering Cancer Center (MSKCC) was supported by the Breast Cancer Research Foundation and the Lomangino Family Research Fund.

National Cancer Institute (NCI): was supported by the Intramural Research Program of the US National Cancer Institute at the National Institutes of Health, and by support services contracts NO2-CP-11019-50 and N02-CP-65504 with Westat, Inc, Rockville, MD to PLM and MHG.

N.N. Petrov Institute of Oncology (NNPIO): was supported by the Russian Foundation for Basic Research (grant numbers 10-04-92601, 10-04-92110, 11-04-00227), the Federal Agency for Science and Innovations (contract 16.512.11.2237), the Commission of the European Communities (grant number PITN-GA-2009-238132), and through a Royal Society International Joint grant (JP090615).

Ontario Cancer Genetics Network (OCGN): was supported by Cancer Care Ontario, Canada (ILA); and 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 and PIs. 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 CFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the CFR.

The Ohio State University Clinical Cancer Genetics (OSUCCG): was supported by the Ohio State University Comprehensive Cancer Center.

Pisa Breast Cancer Study (PBCS): was supported by Fondazione Cassa di Risparmio di Pisa Grant n.122/07 and grant 2010 from ITT (Istituto Toscano Tumori).

Swedish Breast Cancer Study (SWE-BRCA): was supported by the Swedish Cancer Society.

Beckman Research Institute City of Hope (BRICOH) was supported by the National Institutes of Health (R01 CA74415 to SLN and YCD) University of

California, Los Angeles (UCLA) was supported by funding from the Jonsson Comprehensive Cancer Center Foundation.
University of California San Francisco (UCSF): was supported by the Clinical and Translational Science Institute at the University of California, San Francisco (to MSB).
UK and Gilda Radner Familial Ovarian Cancer Registries (UKGRFOCR): UKFOCR was supported by a project grant from CRUK to PP. We would like to acknowledge the Roswell Park Alliance Foundation for their continued support of the Gilda Radner Ovarian Family Cancer Registry.
University of Pennsylvania (UPENN) was supported by Breast Cancer Research Foundation (BRCF) to KLN and Komen Foundation for the Cure to SMD.
Women's Cancer Program (WCP): was supported in part by the American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN).
Breast Cancer Family Registry (BCFR): Samples from the FCCC, HCI, and NCCC were processed and distributed by the Coriell Institute for Medical Research.
Baltic Familial Breast Ovarian Cancer Consortium (BFBOCC): A special acknowledgement for Laima Tihomirova (Latvian Biomedical Research and Study Center, Riga, Latvia) for providing samples and data for joint Lithuanian-Latvian BFBOCC study.
Spanish National Cancer Center (CNIO) and the Spanish Consortium: thanks R.M. Alonso, G. Pita, and R.M. Milne for their assistance. We also thank IBGM-CSIC, Universidad de Valladolid, and Junta de Castilla y León.
CONsorzio Studi Italiani Tumori Ereditari Alla Mammella (CONSIT TEAM): thanks Gaia Roversi, Elisa Cattaneo, and Marco A. Pierotti of the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Monica Barile of the Istituto Europeo di Oncologia, Milan, Italy and the personnel of the Cancer Genetic Testing laboratory at the IFOM-IEO Campus, Milan, Italy.
Epidemiological study of BRCA1 & BRCA2 mutation carriers (EMBRACE): Douglas F. Easton is the PI of the study. EMBRACE Collaborating Centers are: Coordinating Centre, Cambridge: Susan Peock, Debra Frost, Steve D. 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: Joan Paterson, Sarah Downing, 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, Anna Whaite. North West Thames Regional Genetics Service, Harrow: Huw Dorkins. 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 Lalloo, 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: Ros Eeles, Susan Shanley, Nazneen Rahman, Richard Houlston, Elizabeth Bancroft, Lucia D'Mello, Elizabeth Page, Audrey Ardern-Jones, Kelly Kohut, Jennifer Wiggins, Elena Castro, Anita Mitra, Lisa Robertson. 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. Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton: Diana Eccles, Anneke Lucassen, Gillian Crawford, Donna McBride, Sarah Smalley.
Fox Chase Cancer Center (FCCC): thanks Ms. JoEllen Weaver and Dr. Betsy Bove for their technical support.
The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC): thanks all the families for providing samples for this study and the German Cancer Aid for establishing the GC-HBOC and their longstanding patronage.
Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers (GEMO): thanks all the GEMO collaborating groups for their contribution to this study. GEMO Collaborating Centers are: Coordinating Centers, Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Centre Hospitalier Universitaire de Lyon / Centre Léon Bérard, & Equipe ≪ Génétique du cancer du sein≫, Centre de Recherche en Cancérologie de Lyon: Olga Sinilnikova, Sylvie Mazoyer, Laure Barjhoux, Carole Verny-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, Audrey Remenieras, Véronique Byrde, Olivier Caron, Gilbert Lenoir. Centre Jean Perrin, Clermont–Ferrand: Yves-Jean Bignon, Nancy Uhrhammer. Centre Léon Bérard, Lyon: Christine Lasset, Valérie Bonadona. Centre François Baclesse, Caen: Agnès Hardouin, Pascaline Berthet. Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, François Eisinger. Groupe Hospitalier Pitié-Salpétrière, Paris: Florence Coulet, Chrystelle Colas, Florent Soubrier. CHU de 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 Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy. Institut Claudius Regaud, toulouse: Christine Toulas, Rosine Guimbaud, Laurence Gladieff, Viviane Feillel. CHU de Grenoble: Dominique Leroux, Hélène Dreyfus, Christine Rebischung, Magalie Peysselon. CHU de Dijon: Fanny Coron, Laurence Faivre. CHU de St-Etienne: Fabienne Prieur, Marine Lebrun, Caroline Kientz. Hôtel Dieu Centre Hospitalier, Chambéry: Sandra Fert Ferrer. Centre Antoine Lacassagne, Nice: Marc Frénay. CHU de Limoges: Laurence Vénat-Bouvet. CHU de Nantes: Capucine Delnatte. CHU Bretonneau, Tours: Isabelle Mortemousque. Creighton University, Omaha, USA: Henry T.Lynch, Carrie L.Snyder.
Gynecologic Oncology Group (GOG): We thank the investigators of the Australia New Zealand Gynaecological Oncology Group (ANZGOG).
Helsinki Breast Cancer Study (HEBCS): thanks Dr. Carl Blomqvist, Tuomas Heikkinen, and Taru Muranen for their help with the patient data and samples.
The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON): HEBON Collaborating Centers: Coordinating center: Netherlands Cancer Institute, Amsterdam, NL: F.B.L. Hogervorst, S. Verhoef, M. Verheus, L.J. van 't Veer, F.E. van Leeuwen, M.A. Rookus; Erasmus Medical Center, Rotterdam, NL: M. Collée, A.M.W. van den Ouweland, A. Jager, M.J. Hooning, M.M.A. Tilanus-Linthorst, C. Seynaeve; Leiden University Medical Center, NL, Leiden: C.J. van Asperen, J.T. Wijnen, M.P. Vreeswijk, R.A. Tollenaar, P. Devilee; Radboud University Nijmegen Medical Center, Nijmegen, NL: M.J. Ligtenberg, N. Hoogerbrugge; University Medical Center Utrecht, Utrecht, NL: M.G. Ausems, R.B. van der Luijt; Amsterdam Medical Center, NL: C.M. Aalfs, T.A. van Os; VU University Medical Center, Amsterdam, NL: J.J.P. Gille, Q. Waisfisz, H.E.J. Meijers-Heijboer; University Hospital Maastricht, Maastricht, NL: E.B. Gomez-Garcia, C.E. van Roozendaal, Marinus J. Blok, B. Caanen; University Medical Center Groningen University, NL: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits; The Netherlands Foundation for the detection of hereditary tumours, Leiden, NL: H.F. Vasen.
The Hong Kong Hereditary Breast Cancer Family Registry (HRBCP) wish to thank the Hong Kong Sanatorium and Hospital Molecular Pathology Laboratory staff for their technical support and the nurses, research assistants, doctors, and genetic counselors who have assisted in patient recruitment.

Interdisciplinary Health Research International Team Breast Cancer Susceptibility (INHERIT BRCAs): We would like to thank Stéphane Dubois, Dr Martine Dumont, Martine Tranchant (Cancer Genomics Laboratory, CRCHUQ) for sample management and skillful technical assistance, Sylvie Desjardins and Marc-André Rodrigue (Plateforme de séquençage et de génotypage des génome du CRCHUL/CHUQ) for iPLEX genotyping and Pascal Belleau for data quality control analyses.
Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (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 (funded 2001–2009 by NHMRC and currently by the National Breast Cancer Foundation and Cancer Australia #628333) for their contributions to this resource, and the many families who contribute to kConFab.
Memorial Sloan-Kettering Cancer Center (MSKCC): On behalf of the MSKCC study, we acknowledge the Starr Cancer Consortium, the Breast Cancer Research Foundation, the Norman and Carol Stone Cancer Research Initiative, the Kate and Robert Niehaus Clinical Cancer Research Initiative, the Lymphoma Foundation, and the Sabin Family Research Initiative.
Ontario Cancer Genetics Network (OCGN): thanks Mona Gill, Lucine Collins, Nalan Gokgoz, Teresa Selander, Nayana Weerasooriya, and members of the Ontario Cancer Genetics Network for their contributions to the study.
The Ohio State University Clinical Cancer Genetics (OSUCCG): thanks the Human Cancer Genetics Sample bank for sample preparation and Leigha Senter and Kevin Sweet for ascertainment of study participants and collection of phenotype data.
Swedish Breast Cancer Study (SWE-BRCA): SWE-BRCA collaborators: Per Karlsson, Margareta Nordling, Annika Bergman, and Zakaria Einbeigi, Gothenburg, Sahlgrenska University Hospital; Marie Stenmark-Askmalm and Sigrun Liedgren, Linköping University Hospital; Åke Borg, Niklas Loman, Håkan Olsson, Maria Soller, Helena Jernström, Katja Harbst and Karin Henriksson, Lund University Hospital; Annika Lindblom, Brita Arver, Anna von Wachenfeldt, Annelie Liljegren, Gisela Barbany-Bustinza and Johanna Rantala, Stockholm, Karolinska University Hospital; Beatrice Melin, Henrik Grönberg, Eva-Lena Stattin and Monica Emanuelsson, Umeå University Hospital; Hans Ehrencrona, Richard Rosenquist, and Niklas Dahl, Uppsala University Hospital.
Beckman Research Institute of City of Hope was supported by the National Institutes of Health (R01 CA74415 to SLN)) and the Morris and Horowitz Families Endowment.
University of California, Los Angeles (UCLA): thanks Ms. Joyce Seldon for her genetic counselling services, and Ms. Lorna Kwan for database management.
University of California San Francisco (UCSF): thanks Ms. Salina Chan for her database support and management and to Ms. Beth Crawford for her genetic counseling services.
UK and Gilda Radner Familial Ovarian Cancer Registries (UKGRFOCR): UKFOCR thanks Carole Pye, Patricia Harrington and Eva Wozniak for family recruitment and technical support. GRFOCR would like to acknowledge Lara Sucheston (Department of Cancer Prevention and Control) and Kunle Odunsi (Departments Gynecologic Oncology and Immunology).
ACA is a CR-UK Senior Cancer Research Fellow, DFE is CR-UK Principal Research Fellow, GCT is a NHMRC Senior Principal Research Fellow and. JS is Chairholder of the Canada Research Chair in Oncogenetics.

References

Ahmed S, Thomas G, Ghoussaini M, Healey CS, Humphreys MK, Platte R, Morrison J, Maranian M, Pooley KA, Luben R, Eccles D, Evans DG, and many others. 2009. Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nat Genet 41:585–590.

Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, and many others. 2003. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72:1117–1130.

Antoniou AC, Beesley J, McGuffog L, Sinilnikova OM, Healey S, Neuhausen SL, Ding YC, Rebbeck TR, Weitzel JN, Lynch HT, Isaacs C, Ganz PA, and many others. 2010b. Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction. Cancer Res 70:9742–9754.

Antoniou AC, Cunningham AP, Peto J, Evans DG, Lalloo F, Narod SA, Risch HA, Eyfjord JE, Hopper JL, Southey MC, Olsson H, Johannsson O, and many others. 2008b. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Brit J Cancer 98:1457–1466.

Antoniou AC, Kartsonaki C, Sinilnikova OM, Soucy P, McGuffog L, Healey S, Lee A, Peterlongo P, Manoukian S, Peissel B, Zaffaroni D, Cattaneo E, and many others. 2011. Common alleles at 6q25.1 and 1p11.2 are associated with breast cancer risk for BRCA1 and BRCA2 mutation carriers. Hum Mol Genet 20:3304–3321. Advanced access published on 18 May 2011.

Antoniou AC, Sinilnikova OM, McGuffog L, Healey S, Nevanlinna H, Heikkinen T, Simard J, Spurdle AB, Beesley J, Chen X; Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer, Neuhausen SL, Ding YC, and many others. 2009. Common variants in LSP1, 2q35 and 8q24 and breast cancer risk for BRCA1 and BRCA2 mutation carriers. Hum Mol Genet 18:4442–4456.

Antoniou AC, Sinilnikova OM, Simard J, Léoné M, Dumont M, Neuhausen SL, Struewing JP, Stoppa-Lyonnet D, Barjhoux L, Hughes DJ, Coupier I, Belotti M, and many others. 2007. RAD51 135G–>C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. Am J Hum Genet 81:1186–1200.

Antoniou AC, Spurdle AB, Sinilnikova OM, Healey S, Pooley KA, Schmutzler RK, Versmold B, Engel C, Meindl A, Arnold N, Hofmann W, Sutter C, and many others. 2008a. Common breast cancer-predisposition alleles are associated with breast cancer risk in BRCA1 and BRCA2 mutation carriers. Am J Hum Genet 82:937–948.

Antoniou AC, Wang X, Fredericksen ZS, McGuffog L, Tarrell R, Sinilnikova OM, Healey S, Morrison J, Kartsonaki C, Lesnick T, Ghoussaini M, Barrowdale D; EMBRACE, and many others. 2010a. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. Nat Genet 42:885–892.

Barnes DR, Lee A, EMBRACE Investigators, kConFab Investigators, Easton DF, Antoniou AC. Evaluation of association methods for analysing modifiers of disease risk in carriers of high-risk mutations. Genet Epidemiol In press.

Begg CB, Haile RW, Borg A, Malone KE, Concannon P, Thomas DC, Langholz B, Bernstein L, Olsen JH, Lynch CF, Anton-Culver H, Capanu M, Liang X, Hummer AJ, Sima C, Bernstein JL. 2008. Variation of breast cancer risk among BRCA1/2 carriers. JAMA 299:194–201.

Bolton KL, Tyrer J, Song H, Ramus SJ, Notaridou M, Jones C, Sher T, Gentry-Maharaj A, Wozniak E, Tsai YY, Weidhaas J, Paik D, and many others. 2010. Common variants at 19p13 are associated with susceptibility to ovarian cancer. Nat Genet 42:880–884.

Boos D.D. 1992. On generalised score tests. Am Stat 46:327–333.

Buzzai M, Licht JD. 2008. New molecular concepts and targets in acute myeloid leukemia. Curr Opin Hematol 15:82–87.

Chen S, Iversen ES, Friebel T, Finkelstein D, Weber BL, Eisen A, Peterson LE, Schildkraut JM, Isaacs C, Peshkin BN, Corio C, Leondaridis L, Tomlinson G, Dutson D, Kerber R, Amos CI, Strong LC, Berry DA, Euhus DM, Parmigiani G. 2006. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. J Clin Oncol 24:863-871.

Chenevix-Trench G, Milne RL, Antoniou AC, Couch FJ, Easton DF, Goldgar DE; CIMBA. 2007. An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA). Breast Cancer Res 9:104 (doi:10.1186/bcr1670).

Couch FJ, Gaudet MM, Antoniou AA, Ramus SJ, Kuchenbaecker KB, Soucy P, Beesley J, Chen X, Wang X, Kirchhoff T, McGuffog L, Barrowdale D, and many others. Common variants at the 19p13.1 and *ZNF365* loci are associated with ER subtypes of breast cancer and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers Cancer Epi Bio Prevent (In Press).

Easton DF, Eeles RA. 2008. Genome-wide association studies in cancer. Hum Mol Genet 17:R109–R115.

Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, and many others. 2007. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 447:1087–1093.

Fang L, Seki A, Fang G. 2009. SKAP associates with kinetochores and promotes the metaphase-to-anaphase transition. Cell Cycle 8:2819–2827.

Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, Ashworth A, Carmichael J, Kaye SB, Schellens JH, de Bono JS. 2009. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361:123-134.

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M, and the Breast Cancer Linkage Consortium. 1998. Genetic heterogeneity and penetrance analysis of the BRCA1 and

BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 62:676–689.

Gold B, Kirchhoff T, Stefanov S, Lautenberger J, Viale A, Garber J, Friedman E, Narod S, Olshen AB, Gregersen P, Kosarin K, Olsh A, Bergeron J, Ellis NA, Klein RJ, Clark AG, Norton L, Dean M, Boyd J, Offit K. 2008. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. Proc Natl Acad Sci USA 105:4340–4345.

Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, Widschwendter M, Vierkant RA, Larson MC, Kjaer SK, Birrer MJ, Berchuck A, and many others. 2010. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet 42:874–879.

Guan Y, Kuo WL, Stilwell JL, Takano H, Lapuk AV, Fridlyand J, Mao JH, Yu M, Miller MA, Santos JL, Kalloger SE, Carlson JW, Ginzinger DG, Celniker SE, Mills GB, Huntsman DG, Gray JW. 2007. Amplification of PVT1 contributes to the pathophysiology of ovarian and breast cancer. Clin Cancer Res 13:5745–5755.

Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, Easton DF, Venter DJ. 1999. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidem Biomar Prev 8:741–747.

Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, Wacholder S, Wang Z, Welch R, Hutchinson A, Wang J, Yu K, and many others. 2007. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 39:870–874.

Jia L, Landan G, Pomerantz M, Jaschek R, Herman P, Reich D, Yan C, Khalid O, Kantoff P, Oh W, Manak JR, Berman BP, Henderson BE, Frenkel B, Haiman CA, Freedman M, Tanay A, Coetzee GA. 2009. Functional enhancers at the gene-poor 8q24 cancer-linked locus. PLoS Genet 5:e1000597. Epub 2009 Aug 14.

Kosco KA, Cerignoli F, Williams S, Abraham RT, Mustelin T. 2008. SKAP55 modulates T cell antigen receptor-induced activation of the Ras-Erk-AP1 pathway by binding RasGRP1. Mol Immunol 45:510–522.

Lange K, Weeks D, Boehnke M. 1988. Programs for Pedigree Analysis: MENDEL, FISHER, and dGENE. Genet Epidemiol 5:471–472.

McCarthy MI, Hirschhorn JN. 2008. Genome-wide association studies: past, present and future. Hum Mol Genet 17:R100–R101.

Meyer KB, Maia AT, O'Reilly M, Ghoussaini M, Prathalingam R, Porter-Gill P, Ambs S, Prokunina-Olsson L, Carroll J, Ponder BA. A Functional Variant at a Prostate Cancer Predisposition Locus at 8q24 Is Associated with PVT1 Expression. PLoS Genet 2011 7:e1002165. doi: 10.1371/journal.pgen.1002165. Epub 2011 Jul 21.

Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, and many others. 1994. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71.

Milne RL, Osorio A, Cajal TR, Vega A, Llort G, de la Hoya M, Díez O, Alonso MC, Lazaro C, Blanco I, Sánchez-de-Abajo A, Caldés T, and many others. 2008. The average cumulative risks of breast and ovarian cancer for carriers of mutations in BRCA1 and BRCA2 attending genetic counseling units in Spain. Clin Cancer Res 14:2861–2869.

Pomerantz MM, Ahmadiyeh N, Jia L, Herman P, Verzi MP, Doddapaneni H, Beckwith CA, Chan JA, Hills A, Davis M, Yao K, Kehoe SM, Lenz HJ, Haiman CA, Yan C, Henderson BE, Frenkel B, Barretina J, Bass A, Tabernero J, Baselga J, Regan MM, Manak JR, Shivdasani R, Coetzee GA, Freedman ML. 2009. The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. Nat Genet 41:882–884.

Ramus SJ, Kartsonaki C, Gayther SA, Pharoah PD, Sinilnikova OM, Beesley J, Chen X, McGuffog L, Healey S, Couch FJ, Wang X, Fredericksen Z, and many others. 2011. Genetic variation at 9p22.2 and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 103:105–116.

Safran M, Dalah I, Alexander J, Rosen N, Iny Stein T, Shmoish M, Nativ N, Bahir I, Doniger T, Krug H, Sirota-Madi A, Olender T, Golan Y, Stelzer G, Harel A, Lancet D. 2010. GeneCards Version 3: the human gene integrator database 2010; doi: 10.1093/database/baq020 Database (Oxford). 2010 Aug 5;2010:baq020. Print 2010.

Shiraishi M, Sekiguchi A, Oates AJ, Terry MJ, Miyamoto Y. 2002. HOX gene clusters are hotspots of de novo methylation in CpG islands of human lung adenocarcinomas. Oncogene 21:3659–3662.

Simchoni S, Friedman E, Kaufman B, Gershoni-Baruch R, Orr-Urtreger A, Kedar-Barnes I, Shiri-Sverdlov R, Dagan E, Tsabari S, Shohat M, Catane R, King MC, Lahad A, Levy-Lahad E. 2006. Familial clustering of site-specific cancer risks associated with BRCA1 and BRCA2 mutations in the Ashkenazi Jewish population. Proc Natl Acad Sci USA 103:3770–3774.

Song H, Ramus SJ, Tyrer J, Bolton KL, Gentry-Maharaj A, Wozniak E, Anton-Culver H, Chang-Claude J, Cramer DW, DiCioccio R, Dörk T, Goode EL, and many others. 2009. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. Nat Genet 41:996–1000.

Struewing JP, Hartge P, Wacholder S. 1997. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336:1401–1408.

Thomas G, Jacobs KB, Kraft P, Yeager M, Wacholder S, Cox DG, Hankinson SE, Hutchinson A, Wang Z, Yu K, Chatterjee N, Garcia-Closas M, and many others. 2009. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 41:579–584.

Thompson D, Easton D, Breast Cancer Linkage Consortium. 2002. Variation in BRCA1 cancer risks by mutation position. Cancer Epidem Biomark Prev 11:329–336.

Thompson D, Easton D, the BCLC. 2001. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 68:410–419.

Wacholder S, Han SS, Weinberg CR. 2011. Inference from a multiplicative model of joint genetic effects or ovarian cancer risk. J Natl Cancer Inst 103:82–83.

Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G. 1995. Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789–792.