Am J Hum Genet. 2020 Sep 28;S0002-9297(20)30321-9.
doi: 10.1016/j.ajhg.2020.09.001. Online ahead of print.

Breast cancer polygenic risk score and contralateral breast cancer risk

Iris Kramer[1], Maartje J. Hooning[2], Nasim Mavaddat[3], Michael Hauptmann[4, 5], Renske Keeman[1], Ewout W Steyerberg[6, 7], Daniele Giardiello[1, 6], Antonis C. Antoniou[3], Paul D.P. Pharoah[3, 8], Sander Canisius[1, 9], Zumuruda Abu-Ful [10], Irene L. Andrulis[11, 12], Hoda Anton-Culver[13], Kristan J. Aronson[14], Annelie Augustinsson[15], Heiko Becher[16, 17], Matthias W. Beckmann[18], Sabine Behrens[19], Javier Benitez[20, 21], Marina Bermisheva[22], Natalia V. Bogdanova[23-25], Stig E. Bojesen[26-28], Manjeet K. Bolla[3], Bernardo Bonanni[29], Hiltrud Brauch[30-32], Michael Bremer[23], Sara Y. Brucker[33], Barbara Burwinkel[34, 35], Jose E. Castelao[36], Tsun L. Chan[37, 38], Jenny Chang-Claude[19, 39], Stephen J. Chanock[40], Georgia Chenevix-Trench[41], Ji-Yeob Choi[42, 43], Christine L. Clarke[44], NBCS Collaborators[45-56], J. Margriet Collée[57], Fergus J. Couch[58], Angela Cox[59], Simon S. Cross[60], Kamila Czene[61], Mary B. Daly[62], Peter Devilee[63, 64], Thilo Dörk[24], Isabel dos-Santos-Silva[65], Alison M. Dunning[8], Miriam Dwek[66], Diana M. Eccles[67], D. Gareth Evans[68, 69], Peter A. Fasching[18, 70], Henrik Flyger[71], Manuela Gago-Dominguez[72, 73], Montserrat García-Closas[40], José A. García-Sáenz[74], Graham G. Giles[75-77], David E. Goldgar[78], Anna González-Neira[21], Christopher A. Haiman[79], Niclas Håkansson[80], Ute Hamann[81], Mikael Hartman[82, 83], Bernadette A.M. Heemskerk-Gerritsen[2], Antoinette Hollestelle[2], John L. Hopper[76], Ming-Feng Hou[84], Anthony Howell[85], ABCTB Investigators[86], kConFab Investigators[87, 88], Hidemi Ito[89, 90], Milena Jakimovska[91], Anna Jakubowska[92, 93], Wolfgang Janni[94], Esther M. John[95], Audrey Jung[19], Daehee Kang[42, 43, 96], C. Marleen Kets[97], Elza Khusnutdinova[22, 98], Yon-Dschun Ko[99], Vessela N. Kristensen[45, 56], Allison W. Kurian[95, 100], Ava Kwong[37, 101, 102], Diether Lambrechts[103, 104], Loic Le Marchand[105], Jingmei Li[106], Annika Lindblom[107, 108], Jan Lubiński[92], Arto Mannermaa[109-111], Mehdi

Manoochehri[81], Sara Margolin[112, 113], Keitaro Matsuo[89, 90], Dimitrios Mavroudis[114], Alfons Meindl[115], Roger L. Milne[75-77], Anna Marie Mulligan[116, 117], Taru A. Muranen[118], Susan L. Neuhausen[119], Heli Nevanlinna[118], William G. Newman[68, 69], Andrew F. Olshan[120], Janet E. Olson[121], Håkan Olsson[15], Tjoung-Won Park-Simon[24], Julian Peto[65], Christos Petridis[122], Dijana Plaseska-Karanfilska[91], Nadege Presneau[66], Katri Pylkäs[123, 124], Paolo Radice[125], Gad Rennert[10], Atocha Romero[126], Rebecca Roylance[127], Emmanouil Saloustros[128], Elinor J. Sawyer[129], Rita K. Schmutzler[130-132], Lukas Schwentner[94], Christopher Scott[121], Mee-Hoong See[133], Mitul Shah[8], Chen-Yang Shen[134, 135], Xiao-Ou Shu[136], Sabine Siesling[137, 138], Susan Slager[121], Christof Sohn[139], Melissa C. Southey[75, 77, 140], John J. Spinelli[141, 142], Jennifer Stone[76, 143], William J. Tapper[67], Maria Tengström[109, 144, 145], Soo Hwang Teo[146, 147], Mary Beth Terry[148], Rob A.E.M. Tollenaar[149], Ian Tomlinson[150, 151], Melissa A. Troester[120], Celine M. Vachon[152], Chantal van Ongeval[153], Elke M. van Veen[68, 69], Robert Winqvist[123, 124], Alicja Wolk[80, 154], Wei Zheng[136], Argyrios Ziogas[13], Douglas F. Easton[3, 8], Per Hall[61, 112], Marjanka K. Schmidt[1, 155]

[1] The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Division of Molecular Pathology, Amsterdam, 1066 CX, The Netherlands.

[2] Erasmus MC Cancer Institute, Department of Medical Oncology, Rotterdam, 3015 CN, The Netherlands.

[3] University of Cambridge, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Cambridge, CB1 8RN, UK.

[4] The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Department of Epidemiology and Biostatistics, Amsterdam, 1066 CX, The Netherlands.

[5] Brandenburg Medical School Theodor Fontane, Institute of Biostatistics and Registry Research, Neuruppin, 16816, Germany.

[6] Leiden University Medical Center, Department of Biomedical Data Sciences, Leiden, 2333 ZA, The Netherlands.

[7] Erasmus MC Cancer Institute, Department of Public Health, Rotterdam, 3015 GD, The Netherlands.

[8] University of Cambridge, Centre for Cancer Genetic Epidemiology, Department of Oncology, Cambridge, CB1 8RN, UK.

[9] The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Division of Molecular Carcinogenesis, Amsterdam, 1066 CX, The Netherlands.

[10] Carmel Medical Center and Technion Faculty of Medicine, Clalit National Cancer Control Center, Haifa, 35254, Israel.

[11] Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Fred A. Litwin Center for Cancer Genetics, Toronto, ON, M5G 1X5, Canada.

[12] University of Toronto, Department of Molecular Genetics, Toronto, ON, M5S 1A8, Canada.

[13] University of California Irvine, Department of Epidemiology, Genetic Epidemiology Research Institute, Irvine, CA, 92617, USA.

[14] Queen's University, Department of Public Health Sciences, and Cancer Research Institute, Kingston, ON, K7L 3N6, Canada.

[15] Lund University, Department of Cancer Epidemiology, Clinical Sciences, Lund, 222 42, Sweden.

[16] University Medical Center Hamburg-Eppendorf, Institute of Medical Biometry and Epidemiology, Hamburg, 20246, Germany.

[17] Charité –Universitätsmedizin Berlin, Institute of Biometry and Clinical Epidemiology, Berlin, 10117, Germany.

[18] University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Department of Gynecology and Obstetrics, Comprehensive Cancer Center ER-EMN, Erlangen, 91054, Germany.

[19] German Cancer Research Center (DKFZ), Division of Cancer Epidemiology, Heidelberg, 69120, Germany.

[20] Centro de Investigación en Red de Enfermedades Raras (CIBERER), Madrid, 28029, Spain.

[21] Spanish National Cancer Research Centre (CNIO), Human Cancer Genetics Programme, Madrid, 28029, Spain.

[22] Ufa Federal Research Centre of the Russian Academy of Sciences, Institute of Biochemistry and Genetics, Ufa, 450054, Russia.

[23] Hannover Medical School, Department of Radiation Oncology, Hannover, 30625, Germany.

[24] Hannover Medical School, Gynaecology Research Unit, Hannover, 30625, Germany.

[25] N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, 223040, Belarus.

[26] Copenhagen University Hospital, Copenhagen General Population Study, Herlev and Gentofte Hospital, Herlev, 2730, Denmark.

[27] Copenhagen University Hospital, Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Herlev, 2730, Denmark.

[28] University of Copenhagen, Faculty of Health and Medical Sciences, Copenhagen, 2200, Denmark.

[29] IEO, European Institute of Oncology IRCCS, Division of Cancer Prevention and Genetics, Milan, 20141, Italy.

[30] Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, 70376, Germany.

[31] University of Tübingen, iFIT-Cluster of Excellence, Tübingen, 72074, Germany.

[32] German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, 69120, Germany.

[33] University of Tübingen, Department of Gynecology and Obstetrics, Tübingen, 72076, Germany.

[34] German Cancer Research Center (DKFZ), Molecular Epidemiology Group, C080, Heidelberg, 69120, Germany.

[35] University of Heidelberg, Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg, Heidelberg, 69120, Germany.

[36] Instituto de Investigacion Sanitaria Galicia Sur (IISGS), Xerencia de Xestion Integrada de Vigo-SERGAS, Oncology and Genetics Unit, Vigo, 36312, Spain.

[37] Cancer Genetics Centre, Hong Kong Hereditary Breast Cancer Family Registry, Happy Valley, Hong Kong.

[38] Hong Kong Sanatorium and Hospital, Department of Pathology, Happy Valley, Hong Kong.

[39] University Medical Center Hamburg-Eppendorf, Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), Hamburg, 20246, Germany.

[40] National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Division of Cancer Epidemiology and Genetics, Bethesda, MD, 20850, USA.

[41] QIMR Berghofer Medical Research Institute, Department of Genetics and Computational Biology, Brisbane, Queensland, 4006, Australia.

[42] Seoul National University Graduate School, Department of Biomedical Sciences, Seoul, 03080, Korea.

[43] Seoul National University, Cancer Research Institute, Seoul, 03080, Korea.

[44] University of Sydney, Westmead Institute for Medical Research, Sydney, New South Wales, 2145, Australia.

[45] Oslo University Hospital-Radiumhospitalet, Department of Cancer Genetics, Institute for Cancer Research, Oslo, 0379, Norway.

[46] University of Oslo, Institute of Clinical Medicine, Faculty of Medicine, Oslo, 0450, Norway.

[47] Vestre Viken Hospital, Department of Research, Drammen, 3019, Norway.

[48] Oslo University Hospital-Ullevål, Section for Breast- and Endocrine Surgery, Department of Cancer, Division of Surgery, Cancer and Transplantation Medicine, Oslo, 0450, Norway.

[49] Oslo University Hospital, Department of Radiology and Nuclear Medicine, Oslo, 0379, Norway.

[50] Akershus University Hospital, Department of Pathology, Lørenskog, 1478, Norway.

[51] Oslo University Hospital, Department of Tumor Biology, Institute for Cancer Research, Oslo, 0379, Norway.

[52] Oslo University Hospital-Radiumhospitalet, Department of Oncology, Division of Surgery, Cancer and Transplantation Medicine, Oslo, 0379, Norway.

[53] Oslo University Hospital-Radiumhospitalet, National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Oslo, 0379, Norway.

[54] Akershus University Hospital, Department of Oncology, Lørenskog, 1478, Norway.

[55] Oslo University Hospital, Oslo Breast Cancer Research Consortium, Oslo, 0379, Norway.

[56] Oslo University Hospital and University of Olso, Department of Medical Genetics, Oslo, 0379, Norway.

[57] Erasmus University Medical Center, Department of Clinical Genetics, Rotterdam, 3015 CN, The Netherlands.

[58] Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, MN, 55905, USA.

[59] University of Sheffield, Sheffield Institute for Nucleic Acids (SInFoNiA), Department of Oncology and Metabolism, Sheffield, S10 2TN, UK.

[60] University of Sheffield, Academic Unit of Pathology, Department of Neuroscience, Sheffield, S10 2TN, UK.

[61] Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, 171 65, Sweden.

[62] Fox Chase Cancer Center, Department of Clinical Genetics, Philadelphia, PA, 19111, USA.

[63] Leiden University Medical Center, Department of Pathology, Leiden, 2333 ZA, The Netherlands.

[64] Leiden University Medical Center, Department of Human Genetics, Leiden, 2333 ZA, The Netherlands.

[65] London School of Hygiene and Tropical Medicine, Department of Non-Communicable Disease Epidemiology, London, WC1E 7HT, UK.

[66] University of Westminster, School of Life Sciences, London, W1B 2HW, UK.

[67] University of Southampton, Faculty of Medicine, Southampton, SO17 1BJ, UK.

[68] University of Manchester, Manchester Academic Health Science Centre, Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester, M13 9WL, UK.

[69] St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, North West Genomics Laboratory Hub, Manchester Centre for Genomic Medicine, Manchester, M13 9WL, UK.

[70] University of California at Los Angeles, David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, Los Angeles, CA, 90095, USA.

[71] Copenhagen University Hospital, Department of Breast Surgery, Herlev and Gentofte Hospital, Herlev, 2730, Denmark.

[72] Grupo de Medicina Xenómica, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, 15706, Spain.

[73] University of California San Diego, Moores Cancer Center, La Jolla, CA, 92037, USA.

[74] Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Medical Oncology Department, Hospital Clínico San Carlos, Madrid, 28040, Spain.

[75] Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Victoria, 3004, Australia.

[76] The University of Melbourne, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Melbourne, Victoria, 3010, Australia.

[77] Monash University, Precision Medicine, School of Clinical Sciences at Monash Health, Clayton, Victoria, 3168, Australia.

[78] Huntsman Cancer Institute, University of Utah School of Medicine, Department of Dermatology, Salt Lake City, UT, 84112, USA.

[79] University of Southern California, Department of Preventive Medicine, Keck School of Medicine, Los Angeles, CA, 90033, USA.

[80] Karolinska Institutet, Institute of Environmental Medicine, Stockholm, 171 77, Sweden.

[81] German Cancer Research Center (DKFZ), Molecular Genetics of Breast Cancer, Heidelberg, 69120, Germany.

[82] National University of Singapore and National University Health System, Saw Swee Hock School of Public Health, Singapore, 119077, Singapore.

[83] National University Health System, Department of Surgery, Singapore, 119228, Singapore.

[84] Kaohsiung Medical University, Chung-Ho Memorial Hospital, Kaohsiung, 807, Taiwan.

[85] University of Manchester, Division of Cancer Sciences, Manchester, M13 9PL, UK.

[86] University of Sydney, Australian Breast Cancer Tissue Bank, Westmead Institute for Medical Research, Sydney, New South Wales, 2145, Australia.

[87] Peter MacCallum Cancer Center, Melbourne, Victoria, 3000, Australia.

[88] The University of Melbourne, Sir Peter MacCallum Department of Oncology, Melbourne, Victoria, 3000, Australia.

[89] Aichi Cancer Center Research Institute, Division of Cancer Epidemiology and Prevention, Nagoya, 464-8681, Japan.

[90] Nagoya University Graduate School of Medicine, Division of Cancer Epidemiology, Nagoya, 466-8550, Japan.

[91] MASA, Research Centre for Genetic Engineering and Biotechnology 'Georgi D. Efremov', Skopje, 1000, Republic of North Macedonia.

[92] Pomeranian Medical University, Department of Genetics and Pathology, Szczecin, 71-252, Poland.

[93] Pomeranian Medical University, Independent Laboratory of Molecular Biology and Genetic Diagnostics, Szczecin, 71-252, Poland.

[94] University Hospital Ulm, Department of Gynaecology and Obstetrics, Ulm, 89075, Germany.

[95] Stanford Cancer Institute, Stanford University School of Medicine, Department of Epidemiology & Population Health, Stanford, CA, 94304, USA.

[96] Seoul National University College of Medicine, Department of Preventive Medicine, Seoul, 03080, Korea.

[97] The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Department of Clinical Genetics, Amsterdam, 1066 CX, The Netherlands.

[98] Bashkir State University, Department of Genetics and Fundamental Medicine, Ufa, 450000, Russia.

[99] Johanniter Krankenhaus, Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Bonn, 53177, Germany.

[100] Stanford University School of Medicine, Department of Health Research and Policy, Stanford, CA, 94305, USA.

[101] The University of Hong Kong, Department of Surgery, Pok Fu Lam, Hong Kong.

[102] Hong Kong Sanatorium and Hospital, Cancer Genetics Center and Department of Surgery, Happy Valley, Hong Kong.

[103] VIB Center for Cancer Biology, Leuven, 3001, Belgium.

[104] University of Leuven, Laboratory for Translational Genetics, Department of Human Genetics, Leuven, 3000, Belgium.

[105] University of Hawaii Cancer Center, Epidemiology Program, Honolulu, HI, 96813, USA.

[106] Genome Institute of Singapore, Human Genetics Division, Singapore, 138672, Singapore.

[107] Karolinska Institutet, Department of Molecular Medicine and Surgery, Stockholm, 171 76, Sweden.

[108] Karolinska University Hospital, Department of Clinical Genetics, Stockholm, 171 76, Sweden.

[109] University of Eastern Finland, Translational Cancer Research Area, Kuopio, 70210, Finland.

[110] University of Eastern Finland, Institute of Clinical Medicine, Pathology and Forensic Medicine, Kuopio, 70210, Finland.

[111] Kuopio University Hospital, Biobank of Eastern Finland, Kuopio, Finland.

[112] Södersjukhuset, Department of Oncology, Stockholm, 118 83, Sweden.

[113] Karolinska Institutet, Department of Clinical Science and Education, Södersjukhuset, Stockholm, 118 83, Sweden.

[114] University Hospital of Heraklion, Department of Medical Oncology, Heraklion, 711 10, Greece.

[115] University of Munich, Campus Großhadern, Department of Gynecology and Obstetrics, Munich, 81377, Germany.

[116] University of Toronto, Department of Laboratory Medicine and Pathobiology, Toronto, ON, M5S 1A8, Canada.

[117] University Health Network, Laboratory Medicine Program, Toronto, ON, M5G 2C4, Canada.

[118] Helsinki University Hospital, Department of Obstetrics and Gynecology, University of Helsinki, Helsinki, 00290, Finland.

[119] Beckman Research Institute of City of Hope, Department of Population Sciences, Duarte, CA, 91010, USA.

[120] University of North Carolina at Chapel Hill, Department of Epidemiology, Gillings School of Global Public Health and UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA.

[121] Mayo Clinic, Department of Health Sciences Research, Rochester, MN, 55905, USA.

[122] King's College London, Research Oncology, Guy’s Hospital, London, SE1 9RT, UK.

[123] University of Oulu, Laboratory of Cancer Genetics and Tumor Biology, Cancer and Translational Medicine Research Unit, Biocenter Oulu, Oulu, 90220, Finland.

[124] Northern Finland Laboratory Centre Oulu, Laboratory of Cancer Genetics and Tumor Biology, Oulu, 90220, Finland.

[125] Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Milan, 20133, Italy.

[126] Hospital Universitario Puerta de Hierro, Medical Oncology Department, Madrid, 28222, Spain.

[127] UCLH Foundation Trust, Department of Oncology, London, NW1 2PG, UK.

[128] University Hospital of Larissa, Department of Oncology, Larissa, 411 10, Greece.

[129] King's College London, School of Cancer & Pharmaceutical Sciences, Comprehensive Cancer Centre, Guy's Campus, London, UK.

[130] Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Familial Breast and Ovarian Cancer, Cologne, 50937, Germany.

[131] Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Integrated Oncology (CIO), Cologne, 50937, Germany.

[132] Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, 50931, Germany.

[133] University of Malaya, Breast Cancer Research Unit, University Malaya Cancer Research Institute, Faculty of Medicine, Kuala Lumpur, 50603, Malaysia.

[134] Academia Sinica, Institute of Biomedical Sciences, Taipei, 115, Taiwan.

[135] China Medical University, School of Public Health, Taichung, Taiwan.

[136] Vanderbilt University School of Medicine, Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Nashville, TN, 37232, USA.

[137] Netherlands Comprehensive Cancer Organisation (IKNL), Department of Research, Utrecht, 3511 DT, The Netherlands.

[138] University of Twente, Department of Health Technology and Service Research, Technical Medical Center, Enschede, 7522 NB, The Netherlands.

[139] University Hospital and German Cancer Research Center, National Center for Tumor Diseases, Heidelberg, 69120, Germany.

[140] The University of Melbourne, Department of Clinical Pathology, Melbourne, Victoria, 3010, Australia.

[141] BC Cancer, Population Oncology, Vancouver, BC, V5Z 1G1, Canada.

[142] University of British Columbia, School of Population and Public Health, Vancouver, BC, V6T 1Z4, Canada.

[143] Curtin University and University of Western Australia, The Curtin UWA Centre for Genetic Origins of Health and Disease, Perth, Western Australia, 6000, Australia.

[144] Kuopio University Hospital, Department of Oncology, Cancer Center, Kuopio, 70210, Finland.

[145] University of Eastern Finland, Institute of Clinical Medicine, Oncology, Kuopio, 70210, Finland.

[146] Cancer Research Malaysia, Breast Cancer Research Programme, Subang Jaya, Selangor, 47500, Malaysia.

[147] University of Malaya, Department of Surgery, Faculty of Medicine, Kuala Lumpur, 50603, Malaysia.

[148] Columbia University, Department of Epidemiology, Mailman School of Public Health, New York, NY, 10032, USA.

[149] Leiden University Medical Center, Department of Surgery, Leiden, 2333 ZA, The Netherlands.

[150] University of Birmingham, Institute of Cancer and Genomic Sciences, Birmingham, B15 2TT, UK.

[151] University of Oxford, Wellcome Trust Centre for Human Genetics and Oxford NIHR Biomedical Research Centre, Oxford, OX3 7BN, UK.

[152] Mayo Clinic, Department of Health Science Research, Division of Epidemiology, Rochester, MN, 55905, USA.

[153] Leuven Cancer Institute, University Hospitals Leuven, Leuven Multidisciplinary Breast Center, Department of Oncology, Leuven, 3000, Belgium.

[154] Uppsala University, Department of Surgical Sciences, Uppsala, 751 05, Sweden.

[155] The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Division of Psychosocial Research and Epidemiology, Amsterdam, 1066 CX, The Netherlands.

***Correspondence:** Marjanka K Schmidt, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands; +31205122767; mk.schmidt@nki.nl

Abstract

Previous research has shown that polygenic risk scores (PRS) can be used to stratify women according to their risk of developing primary invasive breast cancer. This study aimed to evaluate the association between a recently validated PRS of 313 germline variants (PRS_{313}) and contralateral breast cancer (CBC) risk. We included 56,068 women of European ancestry diagnosed with first invasive breast cancer from 1990 onwards with follow-up from the Breast Cancer Association Consortium. Metachronous CBC risk (N=1,027) according to the distribution of the PRS_{313} was quantified using Cox regression analyses. We assessed PRS_{313} interaction with age at first diagnosis, family history, morphology, ER-, PR-, and HER2-status, and (neo)adjuvant therapy. In Asian studies, with limited follow-up, CBC risk associated with PRS_{313} was assessed using logistic regression for 340 women with CBC compared with 12,133 women with unilateral breast cancer. Higher PRS_{313} was associated with increased CBC risk: hazard ratio per standard deviation (SD)=1.25 (95%CI=1.18-1.33) for Europeans, and an OR per SD=1.15 (95%CI=1.02-1.29) for Asians. The absolute lifetime risks of CBC, accounting for death as competing risk, were 12.4% for European women at the 10^{th} percentile and 20.5% at the 90^{th} percentile of the PRS_{313}. We found no evidence of confounding by, or interaction with patient characteristics, characteristics of the primary tumor, or treatment. The C-index for the PRS_{313} alone was 0.563 (95%CI=0.547-0.586). In conclusion, the PRS_{313} is an independent factor associated with CBC risk, and may be incorporated in CBC risk prediction models to help improve stratification of patients and optimize surveillance and treatment strategies.

Introduction

Due to the high incidence of breast cancer and improving survival, an increasing number of breast cancer survivors are at risk of developing contralateral breast cancer (CBC). The 10-year cumulative incidence of CBC is ~4%[1; 2], however estimates vary widely depending on factors such as germline genetics, family history, and (neo)adjuvant systemic therapy for the first breast cancer[3]. The risk of developing CBC is particularly high in women carrying rare mutations in certain genes including *BRCA1, BRCA2,* and *CHEK2*, with approximately two- to fourfold higher risks reported compared with non-carriers[3].

Recently, genome-wide association studies (GWAS) have identified multiple common germline variants that are associated with first primary breast cancer risk[4; 5]. These are associated with small differences in risk individually, but their combined effects can be summarized in a polygenic risk score (PRS), which has been shown to stratify women according to their risk of developing breast cancer[6-9]. Using a large GWAS dataset from the Breast Cancer Association Consortium (BCAC), we previously developed and validated a 313-variant PRS (PRS_{313}) among women of European descent. In independent prospective studies, this PRS_{313} predicted the risk of primary invasive breast cancer with an odds ratio (OR) per standard deviation (SD) of 1.61 (95% confidence interval (95%CI)=1.57-1.65)[7]. The PRS_{313} has also been externally validated using the UK Biobank cohort.

The aim of the current study was to evaluate the association between PRS_{313} and CBC risk, using data from BCAC. Other studies have shown associations between risk of CBC and both a 67-variant PRS[10] and individual variants[11], but not yet with PRS_{313}, the most extensively validated PRS. Further, the data-set currently evaluated is larger than those previously tested. We carried out two types of analyses. We conducted a cohort study among studies of European ancestry women with follow-up data available, and performed Cox regression analyses to

estimate hazard ratios (HRs) for CBC. Potential confounding and interaction with patient characteristics, characteristics of the primary tumor, or treatment were tested. In addition, to directly compare the OR reported for PRS_{313} and first breast cancer, we selected case-case series and performed logistic regression analyses comparing the PRS_{313} distribution in women with CBC versus those with unilateral breast cancer. These analyses were conducted separately in European and Asian women (follow-up was too limited to perform a cohort study for the Asian population).

Material and Methods

Study subjects

Case-case series

We selected women who were diagnosed with breast cancer and women without any diagnosis of breast cancer from the BCAC including all women of European ancestry, based on genotyping data, selecting only those studies which reported on CBC (62 studies) (Figure S1A, Table S1-S2). BCAC database version freeze 12 was used. All women diagnosed with invasive breast cancer as a first cancer were included in the analysis; the small number of tumors with unknown invasiveness were considered invasive (Table S2). In the case-case series, a CBC was defined as a breast cancer (in situ or invasive) in the contralateral breast irrespective of the time since the first breast cancer. The case-case series comprised 81,000 women with unilateral breast cancer, 3,607 women with CBC, and 62,830 women without any diagnosis of breast cancer (Figure S1A). We also compared unilateral breast cancers to women without any diagnosis of breast cancer to reproduce earlier published estimates[7] in our set of studies with information available on CBC.

We selected for a separate analysis women of Asian ancestry of the BCAC data comprising 12,133 women with unilateral breast cancer, 340 women with CBC, and 13,398 women without any diagnosis of breast cancer from eight studies (Figure S1B, Table S2).

Cohort

In the cohort we used metachronous CBC as the outcome, defined as a breast cancer in the contralateral breast (in situ or invasive) diagnosed at least three months after the first breast cancer. We used a cut-off of three months to increase the likelihood that these CBCs represent true second primary tumors rather than metastases or synchronous bilateral tumors. We selected all women diagnosed with breast cancer from the European case-case series and

excluded four studies that did not provide follow-up information on vital status (Figure S1A). We did not include Asian women since follow-up was too limited in these studies. We additionally excluded 6,207 women with no follow-up and 2,208 women who developed synchronous CBC, distant metastasis, or who died or last known to be alive within three months after the first breast cancer diagnosis. Since BCAC also included prevalent cases, we excluded 3,796 women who developed CBC or were censored before study entry. The case-case series included women diagnosed between 1947 and 2018. In the cohort, we excluded 2,235 women who were diagnosed with their first breast cancer before 1990 or who had missing year of first diagnosis. We restricted to women diagnosed from 1990 onwards so that diagnostic procedures and treatment would be more representative of current practice. Moreover, clinico-pathological, treatment and follow-up data were more complete after 1990. In addition, we excluded 16 studies (9,783women) without information about metachronous CBC events (Figure S1A). After these exclusions, the cohort for this analysis comprised data from 42 studies, including 56,068 women with invasive breast cancer among whom 1,027 metachronous CBC occurred (Table S2).

All individuals provided written informed consent, and all studies were approved by the relevant institutional review boards. BCAC data were centrally harmonized and cleaned in communication with the study data managers and principal investigators. Data collection for individual studies is described in Table S1.

UK biobank cohort

We performed a secondary analysis of the association between the overall breast cancer PRS_{313} and risk of second breast cancer among 10,567 women in the UK biobank cohort. For details see Supplement UK biobank.

Genotyping and PRS

DNA samples from participants were genotyped using the iCOGS array[12; 13] or the OncoArray[4; 14], with genotypes for variants not on the arrays estimated by imputation[4; 13]. The PRS_{313} was calculated as a weighted sum of the minor allele dosages; the variant selection and weights are as given by Mavaddat et al.[7]. We also calculated estimates for a previously published PRS_{77}[6], and estrogen receptor (ER)-specific PRSs (ER-positive PRS_{313} and ER-negative PRS_{313})[7]. The ER-specific PRSs were constructed by defining subtype-specific weights for the 313 variants using a hybrid approach[7]. Variants and corresponding coefficients used to construct the PRS are shown in Table S3. We standardized the PRS in our analyses by dividing it by the SD of the PRS of the controls (PRS_{77} SD=0.45; PRS_{313} SD=0.61; ER-positive PRS_{313} SD=0.65; ER-negative PRS_{313} SD=0.59) exactly as was done in the analyses of the PRS and first breast cancer risk[6; 7]. This allows a direct comparison of the magnitude of the CBC relative risk estimation to that of the first breast cancer.

For samples genotyped with both OncoArray and iCOGS array (9,071 samples), OncoArray data were used in preference as the imputation quality was generally higher. The intraclass correlation coefficient (ICC) between the PRS derived from the two platforms was 0.99 (95%CI=0.99-0.99) for the PRS_{77}, and 0.96 (95%CI=0.95-0.96) for PRS_{313} (Figure S2). Given the high correlation between the two platforms, PRS measures from both platforms were used in the analyses without adjustment.

Statistical analysis

Cohort

The primary outcome in the cohort was the development of metachronous CBC. Cox proportional hazards models were used to estimate HRs for metachronous CBC risk by PRS, stratified by country. Since previous studies have shown that age at first breast cancer

diagnosis is an important predictor of CBC[3], the analyses were performed with attained age as the time scale. Time at risk started three months after the first breast cancer diagnosis and ended at the age of CBC diagnosis, distant metastasis (where available), death, or end of follow-up, whichever came first. For patients that had a study entry more than three months after first breast cancer diagnosis, follow-up started at the age of study entry. We also performed a fixed-effect meta-analysis of country-specific effects using the STATA command *metan*. We performed a fixed-effect meta-analysis over a random-effect meta-analysis since there was no evidence for heterogeneity in effect sizes between countries (I-squared=0%, Figure S3). For some analyses, only invasive CBC was used as the outcome; in these analyses we censored on in situ CBC. Separate analyses were conducted for ER-positive CBC (censored on ER-negative- and ER-unknown CBC) and ER-negative CBC (censored on ER-positive- and ER-unknown CBC).

We evaluated the linearity of the association between PRS_{313} per unit SD and CBC risk using restricted cubic splines with three knots. There was no evidence for violation of the linearity assumption. Therefore, in the main analysis, the PRS_{313} was treated as a continuous covariate, and estimated the HR per unit SD of the $PRS_{313.}$ Violation of the proportional hazard assumption was assessed by inspection of the Schoenfeld residuals[15]. As a second analysis, we used the per SD log HR of the PRS_{313} to calculate the predicted HR at different percentiles of the PRS_{313}, compared to the 50^{th} percentile. Third, the PRS_{313} was categorized into percentile groups (0^{th} to 10^{th}, 10^{th} to 20^{th}, 20^{th} to 40^{th}, 40^{th} to 60^{th}, 60^{th} to 80^{th}, 80^{th} to 90^{th}, 90^{th} to 100^{th}) to illustrate the differences between PRS_{313} subgroups, with the middle quintile (40^{th} to 60^{th}) as the reference.

We also performed multivariable Cox regression analyses to determine whether the log HR of CBC risk by PRS changed when adjusting for year of first breast cancer diagnosis, family history of breast cancer in a first degree relative, and several clinical characteristics of the first

158 breast cancer such as nodal status, tumor size, morphology, ER-, progesterone receptor (PR)-
159 and human epidermal growth factor receptor 2 (HER2)-status, (neo)adjuvant chemotherapy,
160 adjuvant endocrine therapy, and radiotherapy. These analyses were performed in all patients, a
161 complete case set (excluding patients with unknown values for the covariates), and in a set
162 excluding studies oversampling cases with family history. Potential effect modification of the
163 PRS_{313} effect by the same variables was evaluated by fitting interaction terms in different
164 models using complete case sets, including the standardized PRS_{313}, modifier, and interaction.
165
166 The discriminative ability of different models; ([model 1] PRS_{313} alone, [model 2] other risk
167 factors (the adjustment variables from the multivariable Cox regression analyses), [model 3]
168 PRS_{313} + other risk factors) was calculated using Harrell's C-index[16]. Since no standard
169 performance measures are currently available to account for left-truncated follow-up time (*i.e.*,
170 to start analyses at age at study entry), we used time since first breast cancer as the time scale
171 to calculate the C-index.
172
173 *Absolute risks*
174 We followed the procedure as previously described[17]. Absolute risks of developing CBC at
175 PRS_{313} percentiles were calculated using the estimated log HRs per SD from the breast cancer
176 cohort (BCAC) under the log-linear model, assuming the PRS is normally distributed. The
177 PRS_{313}- and age-specific incidences were constrained to the age-specific CBC incidences from
178 women diagnosed with a first invasive breast cancer in the period 2003-2010 from the
179 Netherlands Cancer Registry (NCR)[1]. The age-specific CBC incidences were calculated overall
180 and for age-specific groups, censoring on death and distant metastasis. We used data from the
181 NCR since this registry has complete coverage of all newly diagnosed cancers in the
182 Netherlands. The NCR cohort included all females aged ≥18 years and follow-up for second
183 cancers was complete until February 1, 2016[1]. We then applied the competing risk of dying on

the absolute CBC risks. The absolute CBC risk (AR_g) by age *t* in PRS_{313} category *g*, taking into account the competing risk of dying was calculated by:

$$AR_g(t) = \sum_{u=0}^{t-1} \mu_g(u) S_g(u) S_m(u)$$

Where $\mu_g\ (t)$ is the CBC incidence associated with PRS_{313} category *g*, $S_g\ (t)$ the probability of being free of CBC to age *t,* and $S_m\ (t)$ the probability of surviving to age *t*.

Case-case series

For the case-case series (European and Asian), logistic regression models were used to estimate the ORs for CBC risk (comparing with unilateral breast cancer) and for unilateral breast cancer risk (comparing with women without any diagnosis of breast cancer) associated with PRS_{313}. All analyses were adjusted for age and country (Table S1). For all unilateral- and contralateral breast cancer patients we used age at first breast cancer diagnosis, and for women without any diagnosis of breast cancer we used age at baseline questionnaire.

For direct comparison with the estimate reported for PRS_{313} and first breast cancer, we also performed logistic regression analyses in the same BCAC study participants included in the validation of the association between PRS_{313} and first breast cancer risk[7]. This validation set comprised a subsample from 24 studies and included 3,781 women with unilateral breast cancer, 94 women with CBC, and 3,753 women without any diagnosis of breast cancer (Table S2). For this analysis, we adjusted for 10 principal components, in line with Mavaddat et al.[7].

For European women who had follow-up time available more than three months after the first breast cancer diagnosis, a sensitivity analysis was performed for metachronous CBC (1,702 CBCs). We also did a separate analysis for invasive CBC (N=3,246), by excluding CBC in situ.

All P-values are two sided; tests with P<.05 are referred to as statistically significant. Analyses were performed using STATA, version 13.1 (StataCorp) and R version 3.3.2.

Results

European (cohort) Cox regression analyses

The cohort included 56,068 women diagnosed with first invasive breast cancer with 1,027 metachronous CBC events. Median follow-up was 8.4 years. Patient, tumor, and treatment characteristics are summarized in Table S4.

The associations between the different PRSs and CBC risk are shown in Table 1. The HR for CBC per SD of PRS_{313} was 1.25 (95%CI=1.18-1.33). For comparison, the HR per SD for PRS_{77} was 1.21 (95%CI=1.14-1.29). Women within the 0^{th} to 10^{th} and the 90^{th} to 100^{th} percentile of the PRS_{313} had 0.59-fold (95%CI=0.45-0.78) and 1.38-fold (95%CI=1.13-1.69) risks of CBC, respectively, compared with women within the 40^{th} to 60^{th} percentile (Figure 1, Table S5). The predicted HRs of CBC for women at the 10^{th} and 90^{th} percentile of the PRS_{313} were 0.75 and 1.33, respectively, compared to the 50^{th} percentile (Figure 1). Since we observed evidence of departure from the proportional hazards assumption (P=0.02)[15], we also calculated HRs stratified for follow-up duration (<five and ≥five years). The HR by SD of the PRS_{313} was 1.21 (95%CI=1.10-1.32) for CBC diagnosed ≤five years after first breast cancer diagnosis (CBC N=428), and 1.28 (95%CI=1.18-1.38) for CBC diagnosed >five years after first diagnosis (CBC N=599).

The HR per SD of PRS_{313} for ER-positive invasive CBC was 1.38 (95%CI=1.23-1.55), compared to a HR per SD of the ER-positive PRS_{313} of 1.37 (95%CI=1.22-1.54) (Table 1). For ER-negative invasive CBC, the HR per SD was 0.92 (95%CI=0.75-1.12) for PRS_{313} and 1.06 (95%CI=0.86-1.30) for the ER-negative PRS_{313}.

Sensitivity analysis using the overall PRS_{313} showed a HR per SD of 1.24 (95%CI=1.16-1.32) for invasive CBC risk. When we used time since first breast cancer as the time scale, we found

similar results (HR per SD=1.25, 95%CI=1.18-1.33). Meta-analysis of country-specific effects showed a HR per SD of 1.25 (95%CI=1.18-1.33) for CBC risk by PRS_{313} (Figure S3).

The association between the PRS_{313} and CBC risk did not change when adjusting for patient, tumor, and treatment characteristics, nor when excluding studies oversampling cases with a family history (Table S6). When considering potential modifiers of the effect of the PRS_{313} on CBC risk (Table 2), we found that the HR was the lowest in women aged <40 years at first breast cancer diagnosis (HR per SD=1.13; 95%CI=0.98-1.31), and tended to increase with age, although these effects were not statistically significant ($P_{heterogeneity}$=.26; P_{trend}=.05). We found no indication for effect modification by family history ($P_{heterogeneity}$=.63), morphology ($P_{heterogeneity}$=.14), ER-status ($P_{heterogeneity}$=.13), PR-status (P=.26), HER2-status ($P_{heterogeneity}$=.42), chemotherapy ($P_{heterogeneity}$=.60), endocrine therapy ($P_{heterogeneity}$=.79), or radiotherapy ($P_{heterogeneity}$ =.40) (Table 2).

The C-index was 0.563 (95%CI=0.547-0.586) for the model only including PRS_{313}, 0.605 (95%CI=0.591-0.629) for the model only including other risk factors, and 0.623 (95%CI=0.608-0.645) for the complete model (Table 3).

Absolute risks

Based on the HR estimates for PRS_{313}, the predicted CBC risk by age 80 years was 12.4% at the 10^{th} percentile of the PRS_{313}, compared with 20.5% at the 90^{th} percentile of the PRS_{313} (Figure 2), accounting for death as competing risk. When death was not taken into account as competing risk, the corresponding predicted risks by age 80 were 17.0% at the 10% percentile and 27.9% at the 90^{th} percentile of the PRS_{313} (Figure S4). Table 4 shows the five- and 10-year cumulative CBC risks by PRS_{313} for different age groups, accounting for death as competing risk (Table S7 shows results without competing risks).

European and Asian (case-case series) logistic regression analyses

Figure 3 shows the distribution of the PRS_{313} per SD in the European case-case series. Median PRS_{313} was -0.4 (interquartile range [IQR]=1.35) for control women without any diagnosis of breast cancer (N=81,000), 0.2 (IQR=1.36) for women with unilateral breast cancer (N=62,830), and 0.5 (IQR=1.40) for women with CBC (N=3,607). The OR for unilateral breast cancer per SD of the PRS_{313} was 1.82 (95%CI=1.80-1.84) compared to control women (Table S8). The OR for CBC per SD of PRS_{313} was 1.30 (95%CI=1.26-1.35) compared to unilateral breast cancer.

In sensitivity analyses, the OR per SD of PRS_{313} was 1.27 (95%CI=1.21-1.33) for metachronous CBC and the OR per SD was 1.29 (95%CI=1.24-1.33) for invasive CBC, compared to unilateral breast cancer. When analyses were restricted to the validation set of Mavaddat et al[7], the OR for unilateral breast cancer per SD of the PRS_{313} was 1.67 (95%CI=1.59-1.76) compared to control women, and the OR for CBC per SD of PRS_{313} was 1.39 (95%CI=1.13-1.70) compared to unilateral breast cancer (Table S8).

For women of Asian descent, the OR for unilateral breast cancer per SD of the PRS_{313} was 1.56 (95%CI=1.52-1.60) compared to control women, and the OR for CBC per SD of PRS_{313} was 1.15 (95%CI=1.02-1.29) compared to women with unilateral breast cancer (Table S8).

Discussion

Previous studies have shown that a PRS, summarizing the effects of common germline variants, can be used to stratify women with respect to their risk to develop a primary breast cancer[6-9]. In this study, we observed a clear association between the PRS_{313} and CBC risk in women of both European and Asian ancestry. The association was observed in both the case-case series and the cohort. The HRs per SD of CBC for women at the 10th and 90th percentile of the continuous predicted PRS_{313} were 0.75 and 1.33, respectively, compared to the 50th percentile. This translates to absolute risks at the 10th and the 90th percentile of the PRS_{313} of 12.4% and 20.5%, respectively, by age 80 years. We estimated a C-index for the PRS_{313}, summarizing its discriminatory ability, of 0.563 in the European cohort.

One previous study has investigated the effect of a PRS, including 67 variants, and CBC risk[10]. This study found a risk ratio of 1.75 (95%CI=1.41-2.18) for women in the upper quartile of the PRS compared with women in the lowest quartile. To facilitate comparison, we performed a similar analysis in our case-case series, showing an OR of 1.98 (95%CI=1.79-2.18), adjusted for country and age at first diagnosis, for women in the upper quartile of the PRS_{313}. This indicates the PRS_{313} improves stratification relative to PRSs including fewer variants. Moreover, in our cohort, the C-index for the PRS alone improved from 0.547 (95%CI=0.536-0.575) for the previously reported PRS_{77}[6] to 0.563 (95%CI=0.547-0.586) for the PRS_{313}.

We found no evidence that the association between the PRS_{313} and CBC risk was confounded by family history, adjuvant therapy, morphology, age, or tumor receptor status of the first breast cancer, nor that there was effect modification by those factors. The absence of notable effect modification is in line with the abovementioned study of a 67-variant PRS and CBC risk; no heterogeneity in association was found by age, family history, morphology, ER-status, and adjuvant treatment[10].

We considered the UK biobank cohort the most logical choice, given the large number of women diagnosed with breast cancer with information available on the PRS_{313}, for an external validation of our findings. However, it became apparent that the UK biobank cohort had no information available on the laterality of the tumor. Therefore, it was not possible to distinguish between contralateral and ipsilateral breast cancers and we performed analyses using any second breast cancer as the endpoint. This secondary analysis did confirm the association between the PRS_{313} and second breast cancer risk (HR per SD=1.13, 95%CI=1.01-1.27), but with a lower estimate than in our cohort. The lower estimate may be explained by the inclusion of the ipsilateral breast cancers, which may be more likely to be recurrences than new primary breast cancers compared to CBCs. Indeed, when we used ipsilateral breast cancer as the outcome in our BCAC cohort, we found no association with the PRS_{313} (HR=1.02, 95%CI=0.90-1.15).

The association between the PRS_{313} and CBC risk (OR per SD=1.30; 95%CI=1.26-1.35) in the BCAC database was weaker (expressed in terms of an OR) than was found for first breast cancer among independent prospective studies (OR per SD=1.61; 95%CI=1.57-1.65). Under a simple polygenic model, the relative risk would be expected to be similar for the second breast cancer. The attenuated estimate for CBC might however be explained by several factors. Some attenuation of the estimate might have been due to dilution in the end-point definition, *i.e.*, if some of the CBCs were metastases. Previous studies investigating the clonal relatedness of first breast cancers and CBCs using tumor sequencing have shown that 6-12% of CBCs represent metastases[18; 19]. This hypothesis would be consistent with our finding of a slightly stronger association between the PRS_{313} and late CBCs, diagnosed >five years after the first breast cancer, than for early CBCs, diagnosed ≤five years after the first cancer, since the latter are more likely to be metastases. In addition, 3-5% of the breast cancer patients will be *BRCA1*

or BRCA2 mutation carriers[20; 21], who have high CBC risks. It has been shown that the relative risk associated with PRS is lower (for the first breast cancer) for *BRCA1* and *BRCA2* mutation carriers than in the general population[22], diluting the overall relative risk for CBC. More generally, it is possible that the CBC association may be attenuated due to the effect of other, unmeasured, genetic or other risk factors. If the risks are high, cases with higher PRS_{313} will have, on average, lower values of other risk factors, due to elimination of the highest risk individuals, again attenuating the CBC association. Finally, given the limited information on family history in our dataset, the estimate could have been biased due to a family history effect not detected in our data.

There was some suggestion that the relative risk associated with PRS_{313} decreased with younger age, (P_{trend}=.05), and, specifically, was lower for women aged <40 years (HR per SD=1.13; 95%CI=0.98-1.31). Interestingly, Mavaddat et al[7] also found a lower relative risk below age 40 for first breast cancer. This effect may reflect the different characteristics of breast cancers at young ages, both in terms of germline susceptibility and pathology[23; 24]. For example, the proportion of ER-negative breast cancers is higher at young ages, and the PRS is less predictive for ER-negative disease[6; 7; 24].

In the logistic regression analyses in Asian women, the association between the PRS_{313} and CBC risk was slightly weaker than in European women. This finding is consistent with a study investigating the association between a 287-variant PRS and first breast cancer risk in the Asian population[25], which showed an attenuated OR in Asian women (OR=1.52, 95%CI=1.49-1.56) compared to European women (OR=1.61, 95%CI=1.57-1.66). The lower estimate for Asian women might reflect the fact the PRS_{313} was developed in European populations, and the different LD structure in Asians may attenuate the association since the variants in the PRS are likely to be surrogates for the causal variants. Other explanations for the attenuated estimate

may be the slightly younger age at first breast cancer diagnosis and the higher proportion ER-negative CBCs in Asian women compared to European women in our study. Finally, the imputation quality for variants was somewhat lower, on average, for the Asian than for the European dataset, with three variants on OncoArray and four variants on ICOGs with an imputation quality score<0.3 (Table S3). Nevertheless, we included those variants in the PRS for both European and Asian women, to keep the PRS comparable between ethnicities and studies. Future studies including larger numbers of Asian women, and women of other ethnicities, are needed to generate population-specific PRSs and to validate our findings in these groups.

A major strength of this study is the very large sample size in the BCAC dataset, including genotype information for ~150,000 women and a large number of CBC events. A limitation of this study is missing data on the patient, tumor, and treatment characteristics, which reduces the power of the multivariable Cox regression analyses and interaction analyses. In addition, registration of CBC was not complete; the 10-year cumulative CBC incidence was 2.2% in the BCAC dataset, compared to 3.8% using complete data from the Netherlands Cancer Registry[1]. For this reason, we estimated relative risk estimates using the BCAC data and applied these to external registry data to obtain absolute risk estimates. The underreporting of CBC should not bias our HR estimates, given that the event rate is low and reporting of CBC is unlikely to be related to the PRS_{313}. Moreover, we reran the cohort analysis in the subset of countries with a 10-year cumulative CBC incidence ≥3.0% in the BCAC dataset, and the estimates were very similar to the main analyses (HR per SD=1.23, 95%CI=1.14-1.33) (Figure S3).

In conclusion, the PRS_{313} is predictive for the development of CBC. We found no evidence for confounding or effect modification by other previously established CBC risk factors. The PRS_{313} is therefore likely to be an independent risk factor for CBC. Since the predictive ability of the

PRS on its own is modest, it should be combined with other breast cancer risk factors to provide more useful CBC risk prediction models. More accurate risk prediction will help identify women at high CBC risk who will benefit from additional surveillance and/or risk reducing mastectomy, and equally important, to identify those women at low risk in order to avoid unnecessary surgeries.

Supplemental Data

Supplemental data include four figures, eight tables, supplement UK biobank and acknowledgements.

Data and Code Availability

Data used in this manuscript may be requested through the original providers. Data of the Breast Cancer Association Consortium may be requested for non-profit research through an application procedure with the Breast Cancer Association Consortium; more information: http://bcac.ccge.medschl.cam.ac.uk/bcacdata/. Data of the UK biobank needs to be requested through UK biobank; more information: https://www.ukbiobank.ac.uk/researchers/

Acknowledgements

Acknowledgements are included in the Supplement.

Funding

This work was supported by the Alpe d'HuZes/Dutch Cancer Society (KWF Kankerbestrijding) (grant number A6C/6253).

BCAC is funded by Cancer Research UK [C1287/A16563, C1287/A10118], the European Union's Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), and by the European Community´s Seventh Framework Programme under grant agreement number 223175 (grant number HEALTH-F2-2009-223175) (COGS). The EU Horizon 2020 Research and Innovation Programme funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Genotyping of the OncoArray was funded by the NIH Grant U19 CA148065, and Cancer UK Grant C1287/A16563 and the PERSPECTIVE project supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research (grant GPH-129344) and, the Ministère de l'Économie, Science et Innovation du Québec through Genome Québec and the PSRSIIRI-701 grant, and the Quebec Breast Cancer Foundation. Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, and Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund.

The Australian Breast Cancer Family Study (ABCFS) was supported by grant UM1 CA164920 from the National Cancer Institute (USA). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. J.L.H. is a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellow. M.C.S. is a NHMRC Senior Research Fellow. The ABCS study was supported by the Dutch Cancer Society [grants NKI 2007-3839; 2009 4363]. The Australian Breast Cancer Tissue Bank (ABCTB) was supported by

the National Health and Medical Research Council of Australia, The Cancer Institute NSW and the National Breast Cancer Foundation. The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erlangen. The BBCS is funded by Cancer Research UK and Breast Cancer Now and acknowledges NHS funding to the NIHR Biomedical Research Centre, and the National Cancer Research Network (NCRN). The BCEES was funded by the National Health and Medical Research Council, Australia and the Cancer Council Western Australia and acknowledges funding from the National Breast Cancer Foundation (JS). For the BCFR-NY, BCFR-PA, BCFR-UT this work was supported by grant UM1 CA164920 from the National Cancer Institute. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR. The BCINIS study was supported in part by the BCRF (Breast Cancer Research Foundation, NY, USA). For BIGGS, ES is supported by NIHR Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London, United Kingdom. IT is supported by the Oxford Biomedical Research Centre. The BREast Oncology GAlician Network (BREOGAN) is funded by Acción Estratégica de Salud del Instituto de Salud Carlos III FIS PI12/02125/Cofinanciado FEDER, FIS PI17/00918/Cofinanciado FEDER; Acción Estratégica de Salud del Instituto de Salud Carlos III FIS Intrasalud (PI13/01136); Programa Grupos Emergentes, Cancer Genetics Unit, Instituto de Investigacion Biomedica Galicia Sur. Xerencia de Xestion Integrada de Vigo-SERGAS, Instituto de Salud Carlos III, Spain; Grant 10CSA012E, Consellería de Industria Programa Sectorial de Investigación Aplicada, PEME I + D e I + D Suma del Plan Gallego de Investigación, Desarrollo e Innovación Tecnológica de la Consellería de Industria de la Xunta de Galicia, Spain; Grant EC11-192. Fomento de la Investigación Clínica Independiente, Ministerio de Sanidad, Servicios Sociales e Igualdad, Spain; and Grant FEDER-Innterconecta. Ministerio de Economia y Competitividad, Xunta de Galicia, Spain. The

BSUCH study was supported by the Dietmar-Hopp Foundation, the Helmholtz Society and the German Cancer Research Center (DKFZ). CBCS is funded by the Canadian Cancer Society (grant # 313404) and the Canadian Institutes of Health Research. CCGP is supported by funding from the University of Crete. The CGPS was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council, and Herlev and Gentofte Hospital. The CNIO-BCS was supported by the Instituto de Salud Carlos III, the Fondo de Investigación Sanitario (PI16/00440 with FEDER funds), and CIBERER (Spanish Network on Rare diseases). The CTS was initially supported by the California Breast Cancer Act of 1993 and the California Breast Cancer Research Fund (contract 97-10500) and is currently funded through the National Institutes of Health (R01 CA77398, UM1 CA164917, and U01 CA199277). Collection of cancer incidence data was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885. HAC receives support from the Lon V Smith Foundation (LVS39420). The University of Westminster curates the DietCompLyf database funded by Against Breast Cancer Registered Charity No. 1121258 and the NCRN. FHRISK is funded from NIHR grant PGfAR 0707-10031. The GC-HBOC (German Consortium of Hereditary Breast and Ovarian Cancer) is supported by the German Cancer Aid (grant no 110837, coordinator: Rita K. Schmutzler, Cologne). This work was also funded by the European Regional Development Fund and Free State of Saxony, Germany (LIFE - Leipzig Research Centre for Civilization Diseases, project numbers 713-241202, 713-241202, 14505/2470, 14575/2470). The GENICA was funded by the Federal Ministry of Education and Research (BMBF) Germany grants 01KW9975/5, 01KW9976/8, 01KW9977/0 and 01KW0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany. The GESBC was supported by the

Deutsche Krebshilfe e. V. [70492] and the German Cancer Research Center (DKFZ). GLACIER was supported by Breast Cancer Now, CRUK and Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. The HABCS study was supported by the Claudia von Schilling Foundation for Breast Cancer Research, by the Lower Saxonian Cancer Society, and by the Rudolf Bartling Foundation. The HEBCS was financially supported by the Helsinki University Hospital Research Fund, the Finnish Cancer Society, and the Sigrid Juselius Foundation. The HERPACC was supported by MEXT Kakenhi (No. 170150181 and 26253041) from the Ministry of Education, Science, Sports, Culture and Technology of Japan, by a Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from Ministry Health, Labour and Welfare of Japan, by Health and Labour Sciences Research Grants for Research on Applying Health Technology from Ministry Health, Labour and Welfare of Japan, by National Cancer Center Research and Development Fund, and "Practical Research for Innovative Cancer Control (15ck0106177h0001)" from Japan Agency for Medical Research and development, AMED, and Cancer Bio Bank Aichi. The HMBCS was supported by a grant from the Friends of Hannover Medical School and by the Rudolf Bartling Foundation. The HUBCS was supported by a grant from the German Federal Ministry of Research and Education (RUS08/017), and by the Russian Foundation for Basic Research and the Federal Agency for Scientific Organizations for support the Bioresource collections and RFBR grants 14-04-97088, 17-29-06014 and 17-44-020498. ICICLE was supported by Breast Cancer Now, CRUK and Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. Financial support for KARBAC was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Cancer Society, The Gustav V Jubilee foundation and Bert von Kantzows foundation. The KARMA study was supported by Märit and Hans Rausings Initiative Against Breast Cancer. The KBCP was financially supported by the special Government Funding (EVO) of Kuopio University Hospital grants, Cancer Fund of North Savo,

the Finnish Cancer Organizations, and by the strategic funding of the University of Eastern Finland. kConFab is supported by a grant from the National Breast Cancer Foundation, and previously by the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. Financial support for the AOCS was provided by the United States Army Medical Research and Materiel Command [DAMD17-01-1-0729], Cancer Council Victoria, Queensland Cancer Fund, Cancer Council New South Wales, Cancer Council South Australia, The Cancer Foundation of Western Australia, Cancer Council Tasmania and the National Health and Medical Research Council of Australia (NHMRC; 400413, 400281, 199600). G.C.T. and P.W. are supported by the NHMRC. RB was a Cancer Institute NSW Clinical Research Fellow. LMBC is supported by the 'Stichting tegen Kanker'. DL is supported by the FWO. The MABCS study is funded by the Research Centre for Genetic Engineering and Biotechnology "Georgi D. Efremov", MASA. The MARIE study was supported by the Deutsche Krebshilfe e.V. [70-2892-BR I, 106332, 108253, 108419, 110826, 110828], the Hamburg Cancer Society, the German Cancer Research Center (DKFZ) and the Federal Ministry of Education and Research (BMBF) Germany [01KH0402]. MBCSG is supported by grants from the Italian Association for Cancer Research (AIRC) and by funds from the 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 “5x1000”). The MCBCS was supported by the NIH grants CA192393, CA116167, CA176785 an NIH Specialized Program of Research Excellence (SPORE) in Breast Cancer [CA116201], and the Breast Cancer Research Foundation and a generous gift from the David F. and Margaret T. Grohne Family Foundation. The Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and 1074383 and by infrastructure provided by Cancer Council Victoria. Cases and

their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database. The Multiethnic Cohort Study (MEC) was funded by NIH grant U01 CA164973. The MEC was support by NIH grants CA63464, CA54281, CA098758, CA132839 and CA164973. The MISS study is supported by funding from ERC-2011-294576 Advanced grant, Swedish Cancer Society, Swedish Research Council, Local hospital funds, Berta Kamprad Foundation, Gunnar Nilsson. The MMHS study was supported by NIH grants CA97396, CA128931, CA116201, CA140286 and CA177150. MYBRCA is funded by research grants from the Malaysian Ministry of Higher Education (UM.C/HlR/MOHE/06) and Cancer Research Malaysia. MYMAMMO is supported by research grants from Yayasan Sime Darby LPGA Tournament and Malaysian Ministry of Higher Education (RP046B-15HTM). The NBCS has received funding from the K.G. Jebsen Centre for Breast Cancer Research; the Research Council of Norway grant 193387/V50 (to A-L Børresen-Dale and V.N. Kristensen) and grant 193387/H10 (to A-L Børresen-Dale and V.N. Kristensen), South Eastern Norway Health Authority (grant 39346 to A-L Børresen-Dale) and the Norwegian Cancer Society (to A-L Børresen-Dale and V.N. Kristensen). The NBHS was supported by NIH grant R01CA100374. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. The Northern California Breast Cancer Family Registry (NC-BCFR) and Ontario Familial Breast Cancer Registry (OFBCR) were supported by grant UM1 CA164920 from the National Cancer Institute (USA). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR. The Carolina Breast Cancer Study was funded by Komen Foundation, the National Cancer Institute (P50 CA058223, U54 CA156733, U01 CA179715), and the North Carolina University Cancer Research Fund. The OBCS was supported by research grants from the Finnish Cancer

Foundation, the Academy of Finland (grant number 250083, 122715 and Center of Excellence grant number 251314), the Finnish Cancer Foundation, the Sigrid Juselius Foundation, the University of Oulu, the University of Oulu Support Foundation and the special Governmental EVO funds for Oulu University Hospital-based research activities. The ORIGO study was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16). The PBCS was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. The POSH study is funded by Cancer Research UK (grants C1275/A11699, C1275/C22524, C1275/A19187, C1275/A15956 and Breast Cancer Campaign 2010PR62, 2013PR044. PROCAS is funded from NIHR grant PGfAR 0707-10031. DGE, AH and WN are supported by the all Manchester NIHR Biomedical Research Centre (IS-BRC-1215-20007). The RBCS was funded by the Dutch Cancer Society (DDHK 2004-3124, DDHK 2009-4318). The SASBAC study was supported by funding from the Agency for Science, Technology and Research of Singapore (A*STAR), the US National Institute of Health (NIH) and the Susan G. Komen Breast Cancer Foundation. The SBCS was supported by Sheffield Experimental Cancer Medicine Centre and Breast Cancer Now Tissue Bank. SEARCH is funded by Cancer Research UK [C490/A10124, C490/A16561] and supported by the UK National Institute for Health Research Biomedical Research Centre at the University of Cambridge. The University of Cambridge has received salary support for PDPP from the NHS in the East of England through the Clinical Academic Reserve. SEBCS was supported by the BRL (Basic Research Laboratory) program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (2012-0000347). SGBCC is supported by the National Research Foundation Singapore (NRF-NRFF2017-02), NUS start-up Grant, National University Cancer Institute Singapore (NCIS) Centre Grant [NMRC/CG/NCIS/2010, NMRC/CG/012/2013, CGAug16M005], Saw Swee Hock School of Public Health Research Programme of Research Seed Funding (Breast Cancer Prevention Program), Asian Breast Cancer Research Fund, and

the NMRC Clinician Scientist Award (SI Category) [NMRC/CSA-SI/0015/2017]. Controls from Singapore were recruited by the Singapore Consortium of Cohort Studies-Multi-ethnic cohort (SCCS-MEC), which was funded by the Biomedical Research Council, grant number: 05/1/21/19/425. SKKDKFZS is supported by the DKFZ. The SMC is funded by the Swedish Cancer Foundation and the Swedish Research Council (VR 2017-00644) grant for the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER). The SZBCS was supported by Grant PBZ_KBN_122/P05/2004 and the program of the Minister of Science and Higher Education under the name "Regional Initiative of Excellence" in 2019-2022 project number 002 / RID / 2018/19, amount of financing 12 000 000 PLN. The TWBCS is supported by the Taiwan Biobank project of the Institute of Biomedical Sciences, Academia Sinica, Taiwan. The UCIBCS component of this research was supported by the NIH [CA58860, CA92044] and the Lon V Smith Foundation [LVS39420].

Declaration of Interests

Dr. Beckmann conducts research funded by Amgen, Novartis and Pfizer, outside the submitted work. Dr. Fasching conducts research funded by Amgen, Novartis and Pfizer, outside the submitted work. He received honoraria from Roche, Novartis and Pfizer. Dr. Nevanlinna received honorarium from Astra Zeneca outside the submitted work.

References

1. Kramer, I., Schaapveld, M., Oldenburg, H.S.A., Sonke, G.S., McCool, D., van Leeuwen, F.E., Van de Vijver, K.K., Russell, N.S., Linn, S.C., Siesling, S., et al. (2019). The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype. J Natl Cancer Inst.

2. Xiong, Z., Yang, L., Deng, G., Huang, X., Li, X., Xie, X., Wang, J., Shuang, Z., and Wang, X. (2018). Patterns of Occurrence and Outcomes of Contralateral Breast Cancer: Analysis of SEER Data. Journal of clinical medicine 7.

3. Akdeniz, D., Schmidt, M.K., Seynaeve, C.M., McCool, D., Giardiello, D., van den Broek, A.J., Hauptmann, M., Steyerberg, E.W., and Hooning, M.J. (2019). Risk factors for metachronous contralateral breast cancer: A systematic review and meta-analysis. Breast (Edinburgh, Scotland) 44, 1-14.

4. Michailidou, K., Lindström, S., Dennis, J., Beesley, J., Hui, S., Kar, S., Lemaçon, A., Soucy, P., Glubb, D., Rostamianfar, A., et al. (2017). Association analysis identifies 65 new breast cancer risk loci. Nature 551, 92.

5. Milne, R.L., Kuchenbaecker, K.B., Michailidou, K., Beesley, J., Kar, S., Lindstrom, S., Hui, S., Lemacon, A., Soucy, P., Dennis, J., et al. (2017). Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. Nature genetics 49, 1767-1778.

6. Mavaddat, N., Pharoah, P.D., Michailidou, K., Tyrer, J., Brook, M.N., Bolla, M.K., Wang, Q., Dennis, J., Dunning, A.M., Shah, M., et al. (2015). Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 107.

7. Mavaddat, N., Michailidou, K., Dennis, J., Lush, M., Fachal, L., Lee, A., Tyrer, J.P., Chen, T.H., Wang, Q., Bolla, M.K., et al. (2019). Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. American journal of human genetics 104, 21-34.

8. Brentnall, A.R., van Veen, E.M., Harkness, E.F., Rafiq, S., Byers, H., Astley, S.M., Sampson, S., Howell, A., Newman, W.G., Cuzick, J., et al. (2019). A case-control evaluation of 143 single

nucleotide polymorphisms for breast cancer risk stratification with classical factors and mammographic density. International journal of cancer.

9. Shieh, Y., Hu, D., Ma, L., Huntsman, S., Gard, C.C., Leung, J.W., Tice, J.A., Vachon, C.M., Cummings, S.R., Kerlikowske, K., et al. (2016). Breast cancer risk prediction using a clinical risk model and polygenic risk score. Breast cancer research and treatment 159, 513-525.

10. Robson, M.E., Reiner, A.S., Brooks, J.D., Concannon, P.J., John, E.M., Mellemkjaer, L., Bernstein, L., Malone, K.E., Knight, J.A., Lynch, C.F., et al. (2017). Association of Common Genetic Variants With Contralateral Breast Cancer Risk in the WECARE Study. JNCI: Journal of the National Cancer Institute 109, djx051-djx051.

11. Teraoka, S.N., Bernstein, J.L., Reiner, A.S., Haile, R.W., Bernstein, L., Lynch, C.F., Malone, K.E., Stovall, M., Capanu, M., Liang, X., et al. (2011). Single nucleotide polymorphisms associated with risk for contralateral breast cancer in the Women's Environment, Cancer, and Radiation Epidemiology (WECARE) Study. Breast cancer research : BCR 13, R114.

12. Michailidou, K., Beesley, J., Lindstrom, S., Canisius, S., Dennis, J., Lush, M.J., Maranian, M.J., Bolla, M.K., Wang, Q., Shah, M., et al. (2015). Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nature genetics 47, 373-380.

13. Michailidou, K., Hall, P., Gonzalez-Neira, A., Ghoussaini, M., Dennis, J., Milne, R.L., Schmidt, M.K., Chang-Claude, J., Bojesen, S.E., Bolla, M.K., et al. (2013). Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nature genetics 45, 353-361, 361e351-352.

14. Amos, C.I., Dennis, J., Wang, Z., Byun, J., Schumacher, F.R., Gayther, S.A., Casey, G., Hunter, D.J., Sellers, T.A., Gruber, S.B., et al. (2017). The OncoArray Consortium: A Network for Understanding the Genetic Architecture of Common Cancers. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 26, 126-135.

15. Schoenfeld, D.A. (1983). Sample-size formula for the proportional-hazards regression model. Biometrics 39, 499-503.

16. Harrell, F.E., Jr., Califf, R.M., Pryor, D.B., Lee, K.L., and Rosati, R.A. (1982). Evaluating the yield of medical tests. Jama 247, 2543-2546.

17. Antoniou, A.C., Beesley, J., McGuffog, L., Sinilnikova, O.M., Healey, S., Neuhausen, S.L., Ding, Y.C., Rebbeck, T.R., Weitzel, J.N., Lynch, H.T., et al. (2010). Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction. Cancer research 70, 9742-9754.

18. Klevebring, D., Lindberg, J., Rockberg, J., Hilliges, C., Hall, P., Sandberg, M., and Czene, K. (2015). Exome sequencing of contralateral breast cancer identifies metastatic disease. Breast cancer research and treatment 151, 319-324.

19. Begg, C.B., Ostrovnaya, I., Geyer, F.C., Papanastasiou, A.D., Ng, C.K.Y., Sakr, R.A., Bernstein, J.L., Burke, K.A., King, T.A., Piscuoglio, S., et al. (2018). Contralateral breast cancers: Independent cancers or metastases? International journal of cancer 142, 347-356.

20. Thompson, D., and Easton, D. (2004). The genetic epidemiology of breast cancer genes. Journal of mammary gland biology and neoplasia 9, 221-236.

21. van den Broek, A.J., van 't Veer, L.J., Hooning, M.J., Cornelissen, S., Broeks, A., Rutgers, E.J., Smit, V.T., Cornelisse, C.J., van Beek, M., Janssen-Heijnen, M.L., et al. (2016). Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34, 409-418.

22. Kuchenbaecker, K.B., McGuffog, L., Barrowdale, D., Lee, A., Soucy, P., Dennis, J., Domchek, S.M., Robson, M., Spurdle, A.B., Ramus, S.J., et al. (2017). Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. J Natl Cancer Inst 109.

23. Azim, H.A., Jr., Michiels, S., Bedard, P.L., Singhal, S.K., Criscitiello, C., Ignatiadis, M., Haibe-Kains, B., Piccart, M.J., Sotiriou, C., and Loi, S. (2012). Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clinical cancer research : an official journal of the American Association for Cancer Research 18, 1341-1351.
24. Anders, C.K., Hsu, D.S., Broadwater, G., Acharya, C.R., Foekens, J.A., Zhang, Y., Wang, Y., Marcom, P.K., Marks, J.R., Febbo, P.G., et al. (2008). Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26, 3324-3330.
25. Ho, W.K., Tan, M.M., Mavaddat, N., Tai, M.C., Mariapun, S., Li, J., Ho, P.J., Dennis, J., Tyrer, J.P., Bolla, M.K., et al. (in press) European polygenic risk score for prediction of breast cancer shows similar performance in Asian women. *Nat Commun*.

Figure 1. Estimates for contralateral breast cancer risk by percentile categories of the 313-variant PRS (PRS_{313})

The figure shows the hazard ratios per SD and 95% confidence intervals for percentiles of the PRS_{313} relative to the middle quintile (underlying table can be found in Table S5). The solid line denotes the estimates for contralateral breast cancer risk with the PRS_{313} fitted as a continuous covariate. Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[7]. The analyses were performed with attained age as time scale. PRS = polygenic risk score, SD = standard deviation

Figure 2. Predicted contralateral breast cancer risk by percentile of the 313-variant PRS (PRS_{313}) with death as competing risk

Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[7] The CBC incidences were calculated based on incidence data from the Netherlands Cancer Registry[1] and relative risks estimated as described in the Material and Methods. PRS = polygenic risk score, CBC = contralateral breast cancer

Figure 3. Distribution of the 313-variant PRS (PRS_{313}) in 62,830 control women without any diagnosis of breast cancer, 81,000 women with unilateral breast cancer, and 3,607 women with contralateral breast cancer

Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[7]. PRS = polygenic risk score, BC = breast cancer, CBC = contralateral breast cancer, SD = standard deviation

Table 1. Association between PRSs and contralateral breast cancer risk in the cohort (N=56,068)

Polygenic risk score (PRS)	No. of CBC	HR per unit SD[a]	95%CI	P-value
PRS_{77} [b]				
All CBC	1,027	1.21	1.14-1.29	<.001
Invasive CBC	923	1.21	1.13-1.29	<.001
PRS_{313} [b]				
All CBC	1,027	1.25	1.18-1.33	<.001
Invasive CBC	923	1.24	1.16-1.32	<.001
ER-positive invasive CBC[d]	275	1.38	1.23-1.55	<.001
ER-negative invasive CBC[d]	97	0.92	0.75-1.12	.39
ER-positive PRS_{313} [b,c]				
All CBC	1,027	1.23	1.16-1.31	<.001
Invasive CBC	923	1.22	1.15-1.30	<.001
ER-positive invasive CBC[d]	275	1.37	1.22-1.54	<.001
ER-negative PRS_{313} [b,c]				
All CBC	1,027	1.25	1.17-1.33	<.001
Invasive CBC	923	1.24	1.16-1.33	<.001
ER-negative invasive CBC[d]	97	1.06	0.86-1.30	.58

Abbreviations: PRS = polygenic risk score, No. = number, CBC = contralateral breast cancer, HR = hazard ratio, CI = confidence interval, ER = estrogen receptor, SD = standard deviation

[a] All analyses were performed with attained age as time scale

[b] Coefficients to construct the PRSs are shown in Table S3. All PRSs were standardized by the same SD as was used by Mavaddat et al.[7]. The SD was 0.45 for overall breast cancer PRS_{77}, 0.61 for overall breast cancer PRS_{313}, 0.65 for ER-positive PRS_{313}, and 0.59 for ER-negative PRS_{313}

[c] ER-specific PRSs were constructed using a hybrid method, as described by Mavaddat et al.[7]

[d] Patients with ER-unknown CBC (N=551) were censored in these analyses

Table 2. Association between the 313-variant PRS (PRS_{313}) and contralateral breast cancer risk for subgroups

Subgroups	No. of patients	No. of CBC	HR per unit SD[a,b]	95%CI	P-value	$P_{hetero-geneity}$[c,d]	P_{trend}[c,e]
All patients	56,068	1,027	1.25	1.18-1.33	<.001	-	-
Age at first breast cancer diagnosis (years)						.26	.05
<40	5,877	171	1.13	0.98-1.31	.09		
40-49	11,928	265	1.25	1.11-1.41	<.001		
50-59	16,882	320	1.22	1.09-1.36	<.001		
60+	21,381	271	1.36	1.21-1.52	<.001		
Family history (first degree relative)						.63	-
no	33,623	618	1.26	1.16-1.36	<.001		
yes	10,369	302	1.22	1.09-1.36	<.001		
Morphology						.14	-
ductal	37,324	621	1.21	1.12-1.31	<.001		
lobular	5,878	118	1.32	1.10-1.59	.002		
mixed (ductal and lobular)	2,174	46	1.52	1.15-2.02	.004		
other	3,344	70	1.20	0.96-1.50	.11		
ER-status						.13	-
negative	9,527	194	1.13	0.98-1.30	.08		
positive	38,090	670	1.28	1.19-1.38	<.001		
PR-status						.26	-
negative	13,098	244	1.16	1.03-1.32	.02		
positive	27,044	554	1.27	1.17-1.38	<.001		
HER2-status						.42	-
negative	23,787	352	1.29	1.17-1.44	<.001		
positive	4,969	60	1.45	1.13-1.85	.004		
(Neo)adjuvant chemotherapy						.60	-
no	18,110	361	1.28	1.16-1.42	<.001		
yes	18,559	363	1.24	1.12-1.37	<.001		
(Neo)adjuvant endocrine therapy						.79	-
no	10,781	242	1.28	1.13-1.44	<.001		
yes	27,322	460	1.30	1.19-1.43	<.001		
Radiotherapy						.40	-
no	11,023	188	1.33	1.15-1.53	<.001		
yes	29,142	617	1.24	1.15-1.34	<.001		

Abbreviations: PRS = polygenic risk score, No. = number, CBC = contralateral breast cancer, HR = hazard ratio, CI = confidence interval, ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2

[a] HR for CBC risk by unit SD of PRS_{313}. All analyses were performed with attained age as time scale

[b] Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by standard deviation=0.61, in line with Mavaddat et al.[7]

[c] The interaction between the PRS_{313} and each subgroup was tested in different models including the standardized PRS_{313}, modifier, and interaction. Patients with unknown values were excluded from these analyses. Since attained age was used as time scale in all models, the model with age at first breast cancer only included the PRS_{313} and interaction

[d] P for interaction based on test for heterogeneity across categories

[e] P for interaction based on a trend test with age as continuous variable

Table 3. Discriminatory ability (C-index) of the 313-variant PRS (PRS_{313}) and other risk factors for contralateral breast cancer risk in the cohort

	C-index (95%CI)[a,b]
Model 1 PRS_{313}[c] alone	0.563 (0.547-0.586)
Model 2 Other risk factors[d]	0.605 (0.591-0.629)
Model 3 PRS_{313}[c] + other risk factors[d]	0.623 (0.608-0.645)

Abbreviations: PRS = polygenic risk score, CI = confidence interval

[a] The Harrell's C-index was obtained by the STATA stcox postestimation command 'estat concordance', using time since first breast cancer on the time scale without taking delayed entry (prevalent cases) into account. We did not consider delayed-entry since no standard performance measures are currently available in the statistical literature to account for left-truncated follow-up time. The median of delayed entry was 0.4 years (standard deviation=2.7) in our study

[b] The 95% CIs were obtained by use of the 'somersd' package in STATA

[c] Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[7]

[d] Including age at first diagnosis, year of first diagnosis, family history for breast cancer in a first degree relative, and clinical characteristics of the first breast cancer (nodal status, tumor size, differentiation grade, morphology, estrogen receptor status, human epidermal growth factor receptor 2 status, chemotherapy, endocrine therapy, radiotherapy)

Table 4. Five- and ten-year cumulative risks of contralateral breast cancer by the 313-variant PRS (PRS_{313}) for different age groups with death as competing risk

	5-year cumulative CBC risks (%) range by age					10-year cumulative CBC risks (%) range by age				
Age at first breast cancer diagnosis (years)	**5^{th} percentile PRS_{313}**	**10^{th} percentile PRS_{313}**	**50^{th} percentile PRS_{313}**	**90^{th} percentile PRS_{313}**	**95^{th} percentile PRS_{313}**	**5^{th} percentile PRS_{313}**	**10^{th} percentile PRS_{313}**	**50^{th} percentile PRS_{313}**	**90^{th} percentile PRS_{313}**	**95^{th} percentile PRS_{313}**
30-34	1.9-3.1	2.1-3.4	2.7-4.5	3.6-5.9	4.0-6.5	3.1-4.1	3.4-4.5	4.5-5.9	5.9-7.7	6.5-8.5
35-39	0.8-2.1	0.9-2.3	1.2-3.0	1.5-3.9	1.7-4.3	2.1-3.5	2.3-3.8	3.0-5.0	3.9-6.6	4.3-7.2
40-44	1.5-2.8	1.7-3.1	2.2-4.1	2.9-5.3	3.2-5.9	2.8-4.6	3.1-5.0	4.1-6.6	5.3-8.6	5.9-9.4
45-49	1.4-2.5	1.5-2.7	2.0-3.6	2.6-4.7	2.9-5.2	2.5-3.9	2.7-4.3	3.6-5.6	4.7-7.4	5.2-8.1
50-54	1.4-2.8	1.5-3.0	1.9-4.0	2.6-5.2	2.8-5.8	2.8-4.5	3.0-4.9	4.0-6.4	5.2-8.4	5.8-9.3
55-59	1.6-3.1	1.8-3.4	2.3-4.5	3.1-5.9	3.4-6.5	3.1-4.8	3.4-5.2	4.5-6.9	5.9-9.0	6.5-9.9
60-64	1.7-3.3	1.9-3.6	2.5-4.7	3.3-6.2	3.6-6.8	3.3-5.0	3.6-5.4	4.7-7.1	6.2-9.3	6.8-10.2
65-70	1.5-3.2	1.6-3.5	2.1-4.6	2.8-6.1	3.1-6.7	3.2-4.1	3.5-4.5	4.6-5.9	6.1-7.7	6.7-8.5

Abbreviations: PRS = polygenic risk score, CBC = contralateral breast cancer
Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al[7]. The CBC incidences for each age group were calculated based on incidence data from the Netherlands Cancer Registry[1] and relative risks estimated as described in the Material and Methods. Death was taken into account as competing risk.