Association of Genetic Susceptibility Variants for Type 2 Diabetes with Breast Cancer Risk in Women of European Ancestry

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Acknowledgements

We thank all the individuals who took part in these studies and all the researchers, study staff, clinicians and other healthcare providers, technicians and administrative staff who have enabled this work to be carried out. In particular, we thank: Andrew Berchuck (OCAC); Rosalind A. Eeles, Ali Amin Al Olama, Zsofia Kote-Jarai, Sara Benlloch (PRACTICAL); Antonis Antoniou, Lesley McGuffog, Ken Offit (CIMBA); Joe Dennis, Andrew Lee, Ed Dicks, Craig Luccarini and the staff of the Centre for Genetic Epidemiology Laboratory; Javier Benitez, Anna Gonzalez-Neira and the staff of the CNIO genotyping unit; Jacques Simard, Daniel C. Tessier, Francois Bacot, Daniel Vincent, Sylvie LaBoissière, Frederic Robidoux and the staff of the McGill University and Génome Québec Innovation Centre; Sune F. Nielsen, Borge G. Nordestgaard, and the staff of the Copenhagen DNA laboratory; and Julie M. Cunningham, Sharon A. Windebank, Christopher A. Hilker, Jeffrey Meyer and the staff of Mayo Clinic Genotyping Core Facility; Maggie Angelakos, Judi Maskiell, Gillian Dite (ABCFS), Ellen van der Schoot, Femake Atsma (Sanquin Bloodbank); Emiel Rutgers, Senno Verhoef, Frans Hogervorst, the Thai

Ministry of Public Health (MOPH); Dr Prat Boonyawongviroj (former Permanent Secretary of MOPH); Dr Pornthep Siriwanarungsan (Department Director-General of Disease Control); Michael Schrauder, Matthias Rübner, Sonja Oeser, Silke Landrith, Eileen Williams, Elaine Ryder-Mills, Kara Sargus, Niall McInerney, Gabrielle Colleran, Andrew Rowan, Angela Jones, Christof Sohn, Andeas Schneeweiß, Peter Bugert (the Danish Breast Cancer Group); Núria Álvarez; the CTS Steering Committee (including Leslie Bernstein, James Lacey, Sophia Wang, Huiyan Ma, Yani Lu and Jessica Clague DeHart at the Beckman Research Institute of the City of Hope; Dennis Deapen, Rich Pinder, Eunjung Lee and Fred Schumacher at the University of Southern California; Pam Horn-Ross, Peggy Reynolds and David Nelson at the Cancer Prevention Institute of California; and Hannah Park at the University of California Irvine); Hartwig Ziegler; Sonja Wolf; Volker Hermann; The GENICA network [Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany; (HB, Wing-Yee Lo, Christina Justenhoven), Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany (Yon-Dschun Ko, Christian Baisch), Institute of Pathology, University of Bonn, Germany (Hans-Peter Fischer), Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ) Heidelberg, Germany (UH), Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Germany (Thomas Brüning, Beate Pesch, Sylvia Rabstein, Anne Lotz), Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany (Volker Harth)]; Tuomas Heikkinen; Irja Erkkilä; Kirsimari Aaltonen; Karl von Smitten; Natalia Antonenkova; Peter Hillemanns; Hans Christiansen; Eija Myöhänen; Helena Kemiläinen; Heather Thorne; Eveline Niedermayr; the AOCS Management Group (D Bowtell, G Chenevix-Trench, A deFazio, D Gertig, A Green, P Webb); the ACS Management Group (A Green, P Parsons, N Hayward, P Webb, D Whiteman); the LAABC data collection team, especially Annie Fung and June Yashiki; Gilian Peuteman; Dominiek Smeets; Thomas Van Brussel; Kathleen Corthouts; Nadia Obi; Judith Heinz; Sabine Behrens; Ursula Eilber; Muhabbet Celik; Til Olchers; The Mayo Clinic Breast Cancer Patient Registry;

Martine Tranchant; Marie-France Valois; Annie Turgeon; Lea Heguy; Phuah Sze Yee; Peter Kang; Kang In Nee; Shivaani Mariapun; Yoon Sook-Yee; Daphne Lee; Teh Yew Ching; Nur Aishah Mohd Taib; Meeri Otsukka; Kari Mononen; Teresa Selander; Nayana Weerasooriya; OFBCR staff: E Krol-Warmerdam, J Molenaar, J Blom; Louise Brinton; Neonila Szeszenia-Dabrowska; Beata Peplonska; Witold Zatonski; Pei Chao; Michael Stagner; Petra Bos; Jannet Blom; Ellen Crepin; Anja Nieuwlaat; Annette Heemskerk; the Erasmus MC Family Cancer Clinic; Sue Higham; Simon Cross; Helen Cramp; Dan Connley; Sabapathy Balasubramanian; Ian Brock; The Eastern Cancer Registration and Information Centre; the SEARCH and EPIC teams; Michael Kerin, Nicola Miller, Niall McInerney, Gabrielle Colleran (BIGGS), Pierre Kerbrat; Patrick Arveux; Romuald Le Scodan; Yves Raoul; Pierre Laurent-Puig; Claire Mulot (CECILE), Hartwig Ziegler, Sonja Wolf, Volker Hermann, Christa Stegmaier and Katja Butterbach (ESTHER), Taru A. Muranen (HEBCS), Natalia Antonenkova, Peter Hillemanns, Hans Christiansen and Johann H. Karstens (HMBCS), Gilian Peuteman, Dominiek Smeets, Thomas Van Brussel and Kathleen Corthouts (LMBC), Petra Seibold, Judith Heinz, Nadia Obi, Alina Vrieling, Sabine Behrens, Ursula Eilber, Muhabbet Celik, Til Olchers and Stefan Nickels (MARIE). MBCSG wish to thank Paolo Radice, Bernard Peissel and Daniela Zaffaroni of the Fondazione IRCCS Istituto Nazionale dei Tumori (INT); Bernardo Bonanni, Monica Barile and Irene Feroce of the Istituto Europeo di Oncologia (IEO) and Loris Bernard and the personnel of the Cogentech Cancer Genetic Test Laboratory. Cancer Council Victoria acknowledges the Traditional Owners of the land and waters throughout Victoria and pays respect to them, their culture and their Elders past, present and future. We would like to thank Martine Tranchant (Cancer Genomics Laboratory, CHU de Québec Research Center), Marie-France Valois, Annie Turgeon and Lea Heguy (McGill University Health Center, Royal Victoria Hospital; McGill University) for DNA extraction, sample management and skillful technical assistance. J.S. is Chairholder of the Canada Research Chair in Oncogenetics. OBCS thanks Arja Jukkola-Vuorinen, Mervi Grip, Saila Kauppila, Kari Mononen and Meeri Otsukka for data collection and sample preparation. Craig Luccarini; Don Conroy; Caroline Baynes; Kimberley Chua; the Ohio State University Human

Genetics Sample Bank; and Robert Pilarski. Data on SCCS cancer cases used in this publication were provided by the: Alabama Statewide Cancer Registry; Kentucky Cancer Registry, Lexington, KY; Tennessee Department of Health, Office of Cancer Surveillance; Florida Cancer Data System; North Carolina Central Cancer Registry, North Carolina Division of Public Health; Georgia Comprehensive Cancer Registry; Louisiana Tumor Registry; Mississippi Cancer Registry; South Carolina Central Cancer Registry; Virginia Department of Health, Virginia Cancer Registry; Arkansas Department of Health, Cancer Registry. DFBBCS thank Muriel Adank for selecting the samples and Margreet Ausems, Christi van Asperen, Senno Verhoef, and Rogier van Oldenburg for providing samples from their Clinical Genetic centers. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters for their help in creating the GWAS database, and Karol Estrada and Maksim V. Struchalin for their support in creation and analysis of imputed data. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

Financial Support:

The work conducted for this project at the Vanderbilt Epidemiology Center is supported in part by NIH grant R37CA070867 and endowment funds for the Ingram Professorship and Anne Potter Wilson Chair in Medicine. BCAC is funded by Cancer Research UK (C1287/A10118, C1287/A12014) and by the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2–2009-223175) (COGS). Meetings of the BCAC have been funded by the European Union COST programme (BM0606). Genotyping of the iCOGS array was funded by the European Union (HEALTH-F2-2009-223175), Cancer Research UK (C8197/A16565 and C1287/A10710), the Canadian Institutes of Health Research for the 'CIHR Team in Familial Risks of Breast Cancer' program and the Ministry of Economic Development, Innovation and Export Trade of Quebec (PSR-SIIRI-701). Additional support for the iCOGS infrastructure was provided by 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 Defense (W81XWH-10-1-0341), Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The Australia, California, and Ontario sites of the Breast Cancer Family Registry 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 ABCFS (Australia site of the BCFR) was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. John L. Hopper is a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellow and

M.C.S. is a NHMRC Senior Research Fellow. Work at the OFBCR (Ontario site of the BCFR) was also supported by the Canadian Institutes of Health Research 'CIHR Team in Familial Risks of Breast Cancer' program. The ABCS study was supported by the Dutch Cancer Society [grants NKI 2007-3839; 2009 4363] and BBMRI-NL, which is a Research Infrastructure financed by the Dutch government (NWO 184.021.007). The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erlangen. The BBCS is funded by Cancer Research UK and Breakthrough Breast Cancer and acknowledges NHS funding to the NIHR Biomedical Research Centre, and the National Cancer Research Network (NCRN). Elinor J. Sawyer is supported by NIHR Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London, UK. Core funding to the Wellcome Trust Centre for Human Genetics was provided by the Wellcome Trust (090532/Z/09/Z). Ian Tomlinson is supported by the Oxford Biomedical Research Centre. The BSUCH study was supported by the Dietmar-Hopp Foundation, the Helmholtz Society and the German Cancer Research Center (DKFZ). The CECILE study was funded by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Agence Nationale de Sécurité Sanitaire (ANSES), Agence Nationale de la Recherche (ANR). The CGPS was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council and Herlev Hospital. The CNIO-BCS was supported by the Genome Spain Foundation, the Red Temática de Investigación Cooperativa en Cáncer and grants from the Asociación Española Contra el Cáncer and the Fondo de Investigación Sanitario (PI11/00923 and PI081120). The Human Genotyping-CEGEN Unit, CNIO is supported by the Instituto de Salud Carlos III. 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). 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 ESTHER study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe). The GENICA 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, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus Bonn, Germany. The HEBCS was supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (266528), the Finnish Cancer Society, The Nordic Cancer Union and the Sigrid Juselius Foundation. The HMBCS was supported by the Rudolf Bartling Foundation. Financial support for KARBAC was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institute, the Stockholm Cancer Foundation and the Swedish Cancer Society. 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, the Academy of Finland and by the strategic funding of the University of Eastern Finland. kConFab is supported by grants from the National Breast Cancer Foundation, the NHMRC, the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia and the Cancer Foundation of Western Australia. The kConFab Clinical Follow Up Study was funded by the NHMRC (145684, 288704, 454508). Kelly-Anne Phillips is a National Breast Cancer Foundation Fellow (Australia). Financial support for the AOCS was provided by the United States Army Medical Research and Materiel Command (DAMD17-01-1-0729), the Cancer Council of Tasmania and Cancer Foundation of Western Australia and the NHMRC (199600). Georgia Chenevix-Trench and P.W. are supported by the NHMRC. LMBC is supported by the 'Stichting tegen Kanker' (232-2008 and 196-2010). Diether Lambrechts is supported by the FWO and the KULPFV/10/016-SymBioSysII and by a ERC consolidator grant. The MARIE study was

supported by the Deutsche Krebshilfe e.V. [70-2892-BR I, 106332, 108253, 108419], the Hamburg Cancer Society, the German Cancer Research Center 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 a 5/1000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects '5 × 1000'). The MCBCS was supported by the NIH grants (CA122340, CA128978) and a Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201), the Breast Cancer Research Foundation and a generous gift from the David F. and Margaret T. Grohne Family Foundation and the Ting Tsung and Wei Fong Chao Foundation. MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 209057, 251553 and 504711 and by infrastructure provided by Cancer Council Victoria. The MEC was supported by NIH grants CA63464, CA54281, CA098758 and CA132839. The work of MTLGEBCS was supported by the Quebec Breast Cancer Foundation, the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program – grant # CRN-87521 and the Ministry of Economic Development, Innovation and Export Trade – grant # PSR-SIIRI-701. The NBCS was supported by grants from the Norwegian Research council (155218/V40, 175240/S10 to A.L.B.D., FUGE-NFR 181600/V11 to V.N.K. and a Swizz Bridge Award to A.L.B.D.). 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. OBCS was supported by 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. This OFBCR 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 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 pKARMA study was supported by Märit and Hans Rausings Initiative Against Breast Cancer. The RBCS was funded by the Dutch Cancer Society (DDHK 2004-3124, DDHK 2009-4318). The SASBAC 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. KC was financed by the Swedish Cancer Society (5128-B07-01PAF). The SBCS was supported by Yorkshire Cancer Research S305PA, S299 and S295. SEARCH is funded by a programme grant from Cancer Research UK (C490/A10124) and supported by the UK National Institute for Health Research Biomedical Research Centre at the University of Cambridge. SKKDKFZS is supported by the DKFZ. The SZBCS was supported by Grant PBZ_KBN_122/P05/2004. The TNBCC was supported by: a Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201), a grant from the Breast Cancer Research Foundation, a generous gift from the David F. and Margaret T. Grohne Family Foundation and the Ting Tsung and Wei Fong Chao Foundation, the Stefanie Spielman Breast Cancer fund and the OSU Comprehensive Cancer Center, DBBR (a CCSG Share Resource by National Institutes of Health Grant P30 CA016056), the Hellenic Cooperative Oncology Group research grant (HR R_BG/04) and the Greek General Secretary for Research and Technology (GSRT) Program, Research Excellence II, the European Union (European Social Fund – ESF), and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - ARISTEIA. The UKBGS is funded by Breakthrough Breast Cancer and the Institute of Cancer Research (ICR). ICR acknowledges NHS funding to the NIHR Biomedical Research Centre. The DFBBCS GWAS was funded by The Netherlands Organisation for Scientific Research

(NWO) as part of a ZonMw/VIDI grant number 91756341. The generation and management of GWAS genotype data for the Rotterdam Study (control samples) is supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract

Purpose Type 2 diabetes (T2D) has been reported to be associated with an elevated risk of breast cancer. It is unclear, however, whether this association is due to shared genetic factors.

Methods We constructed a genetic risk score (GRS) using risk variants from 33 known independent T2D susceptibility loci and evaluated its relation to breast cancer risk using the data from two consortia, including 62,328 breast cancer patients and 83,817 controls of European ancestry. Unconditional logistic regression models were used to derive adjusted odds ratios (OR) and 95% confidence intervals (CI) to measure the association of breast cancer risk with T2D GRS or T2D-associated genetic risk variants. Meta-analyses were conducted to obtain summary ORs across all studies.

Results The T2D GRS was not found to be associated with breast cancer risk, overall, by menopausal status, or for estrogen receptor positive or negative breast cancer. Three T2D associated risk variants were individually associated with breast cancer risk after adjustment for multiple comparisons using the Bonferroni method (at $P < 0.001$), rs9939609 (*FTO*) (OR = 0.94, 95% CI = 0.92 – 0.95, $P = 4.13E-13$), rs7903146 (*TCF7L2*) (OR = 1.04, 95% CI = 1.02 – 1.06, $P = 1.26E-05$), and rs8042680 (*PRC1*) (OR = 0.97, 95% CI = 0.95 – 0.99, $P = 8.05E-04$).

Conclusions We have shown that several genetic risk variants were associated with the risk of both T2D and breast cancer. However, overall genetic susceptibility to T2D may not be related to breast cancer risk.

Key words: type 2 diabetes, genetic susceptibility, GWAS, breast cancer, epidemiology

Introduction

Globally, approximately 382 million people currently live with diabetes, and this number may rise to 592 million by 2035 [1]. Type 2 diabetes (T2D), accounts for over 90% of all diabetes cases [2]. Breast cancer is the most common cancer among women in many countries, including the United States [3]. Many epidemiological studies have linked T2D to increased breast cancer risk [4-8]. Recent meta-analyses have shown a more than 20% increase in risk of breast cancer among women with T2D compared to women without the disease [9-12]. T2D and breast cancer share some risk factors, including obesity in postmenopausal women and physical inactivity [13]. Elevated levels of circulating C-peptide and insulin-like growth factor-1, biomarkers related to insulin resistance, have also been associated with increased breast cancer risk [14,15]. It remains unclear, however, if the link between these two diseases is due to shared lifestyle risk factors or intrinsic etiology such as genetic susceptibility. Understanding how genetic variants related to T2D risk influence breast cancer risk may provide insights into the nature of the T2D-breast cancer relationship.

Recent genome-wide association studies (GWAS) have identified approximately 50 genetic variants associated with T2D risk. Some of these reported T2D-related genetic variants have been studied in relation to the risk of several cancers, including cancers of the pancreas [16], colon/rectum [17,18] and prostate [19]. The influence of these variants on breast cancer risk, however, has not been adequately studied. To date, only two studies have evaluated the association of a subset of these T2D-related genetic variants with breast cancer risk [20,21]. Both studies reported a null association, which may be due to small study size and low study power.

In this analysis, using data from two consortia including 62,328 breast cancer cases and 83,817 controls of women of European ancestry, we evaluated T2D-related genetic variants reported to date in relation to breast cancer risk. By constructing a T2D-related genetic risk score (T2D GRS) and evaluating its association

with breast cancer risk, we tested the hypothesis that, overall, the alleles that increase T2D risk may also increase breast cancer risk. We also tested the hypothesis that certain T2D-related genetic variants may be associated with breast cancer risk.

Methods

Study population

Included in this analysis were 62,328 breast cancer cases and 83,817 controls of women of European ancestry recruited either in the 39 studies (*Online Resource Table 1*) that participated in the Breast Cancer Association Consortium (BCAC), a part of the Collaborative Oncological Gene-Environment Study (COGS), or in the eleven studies (*Online Resource Table 2*) that are included in the Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE) project of Genetic Associations and Mechanism in Oncology (GAME-ON). From the BCAC, we included individual-level data for 46,325 breast cancer cases and 42,482 controls. The DRIVE project included 16,003 breast cases and 41,335 controls; however, only summary statistics for the association between T2D-related risk variants and breast cancer risk were available, and thus these summary statistics were used in our study. The study samples and participant data, including demographics and the traditional risk factors for breast cancer, were collected in each contributing study.

Single nucleotide polymorphism (SNP) selection

We searched for all reported genetic risk variants associated with T2D in European ancestry populations at a genome-wide significance level ($P < 5 \times 10^{-8}$, trait "Type 2 diabetes" or "Type 2 diabetes and other traits") using the US National Human Genome Resource Institute (NHGRI) Catalog of Published Genome-Wide Association Studies (GWAS Catalog, accessed November 19, 2012, at http://www.genome.gov/gwastudies). Fifty SNPs representing 33 independent loci (linkage disequilibrium (LD) $R^2 < 0.1$) were identified (*Fig. 1*).

Genetic risk score construction

The genetic risk scores were calculated in 46,325 cases and 42,482 controls included in the BCAC. At each of the 33 independent loci, we selected the SNP with the lowest *P*-value for association with T2D reported in GWASs to represent the locus in constructing the T2D GRS. Using these 33 SNPs, a weighted T2D GRS was constructed as a measure of the overall association of genetic risk variants with T2D. In the BCAC, eleven SNPs were directly genotyped and 22 were imputed with imputation quality threshold of $R^2 > 0.5$. The T2D GRS was created as $\sum_i^{33} w_i SNP_i$, where w_i is the logarithm of the odds ratio (OR) of the i^{th} SNP with T2D reported from previous GWAS, and SNP_i is the number of risk alleles carried by a given subject on the i^{th} SNP. We hypothesized that the risk allele for T2D would be associated with increased risk of breast cancer. The 33 individual T2D risk variants identified from the NHGRI GWAS catalog are presented in *Online Resource Table 3*.

Genotyping

In the BCAC, genotype data were obtained either from direct genotyping with a custom Illumina iSelect genotyping array (iCOGS) that contains 211,155 SNPs [22] or from imputation with the 1000 Genomes Project Phase I integrated variant set (version 3, March 2012 release) as the reference [23], using the program IMPUTE2 [24]. Details of the studies that participated in the BCAC, and the methodology used by the BCAC and iCOGS have been published elsewhere [22] and can also be found on the iCOGS website (http://ccge.medschl.cam.ac.uk/research/consortia/icogs/).

In the DRIVE project, genotype data were obtained either from direct genotyping using Illumina or Affymetrix arrays (*Online Resource Table 2*) or from imputation with the HapMap version 2 CEU panel (Utah residents of Northern and Western European ancestry) as a reference, using the program MACH v1.0 or IMPUTE [24]. Details of the studies that participated in DRIVE were described in previously published papers [22,25-28] or on the GAME-ON website (http://gameon.dfci.harvard.edu).

Statistical analysis

We evaluated the association between the T2D GRS and breast cancer risk using individual-level data from 46,325 breast cancer cases and 42,482 controls of European ancestry who participated in BCAC studies. Demographic characteristics and known breast cancer risk factors were summarized by case-control status using mean and standard deviation (SD) for continuous variables or frequency with percentage for categorical variables. Differences between cases and controls were compared using the Wilcoxon rank sum test (continuous variables) or the χ^2 test (categorical variables). To assess the association between the T2D GRS and breast cancer risk factors, we used control data and calculated the mean and SD of the T2D GRS by comparison groups for each categorical variable; the difference was tested by the Wilcoxon rank sum test. For continuous variables, the Pearson's correlations were measured. To account for potential population stratification within our study population, genetic ancestry was estimated by principal component (PC) analysis using EIGENSTRAT software [29] on 37,000 uncorrelated SNPs (including those selected as ancestry informative markers) on the chip. The mean value of the genomic inflation factor (λ) was 1.01 for the participating studies when PCs were included in the regression models, indicating little evidence of population stratification [22]. For all analyses, the top eight PCs were included in all regression models. For the LMBC study, the study-specific principal component was further adjusted. To assess the association between the T2D GRS and breast cancer risk, we first fitted unconditional logistic regression models adjusting for age and PCs within each of the 39 contributing studies individually and recorded the β coefficients with standard errors for T2D GRS quintiles (relative to the first quintile). We then conducted a meta-analysis on the results from these 39 studies using both fixed effect and mixed effect models. The odds ratios (ORs) with 95% confidence intervals (CI) from the fixed effects model are reported in *Table 1*, as are further analyses by estrogen receptor (ER) status, menopausal status, age group (<50 vs. ≥50 years), and body mass index (BMI, <25 vs. ≥25 kg/m^2).

We also used the SNP-set Kernel Association Test (SKAT) to evaluate whether any SNP in the T2D-associated SNP set may be related to breast cancer risk without making the assumption that the alleles that increase T2D risk may also increase breast cancer risk [30]. To evaluate the association of each individual SNP (per copy of risk allele) with breast cancer risk, we used individual-level data from the BCAC (46,325 cases and 42,482 controls) and summary results data from DRIVE (16,003 cases and 41,335 controls). We first estimated allelic OR for each SNP for each BCAC study with adjustment similar to that in the analyses for the association of T2D GRS with breast cancer risk described above and then combined the results across all BCAC studies with results from DRIVE using the inverse-variance meta-analysis with a fixed-effect model. Both consortium-specific results and combined results are reported in *Table 2*. For individual SNP analyses, statistical significance was considered after adjusting for multiple comparisons using the Bonferroni method (0.05/33). For all other analyses, statistical significance was considered at a two-sided 5% level unless stated otherwise. All analyses were conducted using R version 3.0.3 [31].

Results

Among the 88,807 BCAC participants studied, on average, cases were slightly older than controls (57.8 vs. 54.9 years, $P < 0.001$) and entered menopause at a younger age (48.5 vs. 48.7 years, $P < 0.01$)**,** as shown in *Online Resource Table 4*. More cases than controls were postmenopausal (69.3% vs. 68.1%, $P < 0.01$) or had a first-degree family history of breast cancer (27.7% vs. 11.2%, $P < 0.01$). Among postmenopausal women, cases and controls had comparable BMI ($P = 0.62$). Among controls, the T2D GRS was positively correlated with BMI (postmenopausal women, Pearson r = 0.018, $P = 0.03$), and inversely correlated with age at menarche (Pearson r = -0.021, $P < 0.01$). For other categorical variables examined, the mean T2D GRS values were virtually identical across different statuses *(Online Resource Table 4, right columns*).

Overall, the T2D GRS was not found to be associated with breast cancer risk (*P* for trend = 0.69, *Table 1*). No significant results were observed in analyses stratified by ER status (*P* for trend = 0.74 and 0.47 for ER+ and ER- breast cancer, respectively), menopausal status (*P* for trend = 0.74 and 0.93 for premenopausal and postmenopausal women, respectively), age group (*P* for trend = 0.74 and 0.62 for age<50 and age≥50 years, respectively), or BMI group (*P* for trend = 0.64 and 0.64 for BMI<25 and BMI≥25, respectively). Meta-analysis using mixed effect models gave similar results (data not shown). In a sensitivity analysis, which included only the eleven directly genotyped SNPs and 14 imputed SNPs with imputation $R^2 > 0.9$, similar results were observed (*Online Resource Table 5*).

Using SKAT tests and without making the assumption that the alleles that increase T2D risk also increase breast cancer risk, we found evidence for potential association for some of the T2D-related SNPs with breast cancer risk (*P* = 3.95E-10). Of the 33 independent SNPs investigated, seven were nominally associated with breast cancer risk using BCAC data alone (*Table 2*). Of these, the risk allele for T2D in four SNPs was associated with a reduced risk of breast cancer. After adjusting for multiple comparisons, the association for two SNPs, rs7903146 (*TCF7L2*, OR = 1.04, 95% CI = 1.02 – 1.07, *P* = 1.20E-04) and rs9939609 (*FTO*, OR = 0.93, 95% CI = 0.91 – 0.95, *P* = 3.63E-12), remained statistically significant, and both associations were replicated in DRIVE. SNP rs8042680 (*PRC1*) was related to breast cancer risk in the BCAC at *P* = 0.02 and in DRIVE at *P* = 6.18E-3; meta-analyses of these data yielded a significant association after adjusting for multiple comparisons (OR = 0.97, 95% CI = 0.99 – 0.99, *P* = 8.05E-4).

Discussion

In this large study, we investigated the association of 33 independent T2D related genetic variants with breast cancer risk individually and in combination (through the use of our GRS). Generally, we found no association between T2D GRS and risk of breast cancer overall or by ER status. Of the 33 T2D-associated SNPs

investigated in this study, three showed a significant association with breast cancer risk after adjusting for multiple comparisons: rs9939609 (*FTO*), rs7903146 (*TCF7L2*), and rs8042680 (*PRC1*). Although this study does not provide any evidence for an overall association of T2D susceptibility and breast cancer risk, it does show that some T2D-associated SNPs may be related to breast cancer risk.

It has been hypothesized that the association between T2D and breast cancer may be mediated through insulin resistance and hyperinsulinaemia [32]. T2D and breast cancer share some lifestyle risk factors, including obesity in postmenopausal women and physical inactivity. Indeed, it has been shown previously that the observed association between these two diseases may be, in part, due to residual confounding by BMI [33]. With a very large sample size, our study suggests that overall genetic susceptibility to T2D was not related to breast cancer risk, indicating that the previously observed association between T2D and breast cancer risk may be largely due to shared lifestyle risk factors. Our finding for a null association between T2D GRS and breast cancer risk is supported by two previous studies that investigated this association. In one of these studies, Chen et al. investigated 18 T2D-related SNPs among 503 European ancestry cases and 633 controls from the multiethnic cohort and PAGE studies [20]. In the other study, Hou et al. pooled data for 25 genotyped and 15 imputed T2D-related SNPs from seven studies and investigated this association among 1,142 European ancestry cases and 1,137 European ancestry controls [21]. Neither study reported a significant association between T2D GRS and overall breast cancer risk. However, these two studies had evaluated a smaller set of T2D risk variants than the current study and the sample size in both studies was substantially smaller than the current study, and thus the statistical power in these two previous studies was low. For example, for a given SNP with a minor allele frequency of 0.3, the current study had 99.6% power to detect an OR of 1.05 at a type I error rate of 0.05, while, the previous studies had <15% power to detect an OR of 1.05.

We identified three T2D risk variants that were associated with breast cancer risk. SNPs in strong correlation with each of these three variants have recently been identified in GWAS to be associated with

breast cancer risk. SNP rs9939609 (*FTO*) located in region 16q12.2, and rs7903146 (*TCF7L2*) located in region 10q25.2 are in perfect LD (R^2 = 1) with rs17817449 and rs7904519, respectively, which were identified in relation to breast cancer risk in a GWAS conducted using BCAC data [22]. SNP rs8042680 (*PRC1*) is in strong LD with rs2290203 (R^2 = 0.59, 9,270bp apart) that was recently identified as a risk variant for breast cancer in a GWAS conducted in East Asian women [34]. Interestingly, the T2D-risk allele of rs9939609 and rs8042680 are associated with a decreased risk of breast cancer. Though studies have suggested that TCF7L2 may associate with breast cancer through the wnt/β-catenin pathway [35,36], the exact mechanisms underlying these associations are unclear. Further studying these genes may uncover additional insights into the biology and genetics that link the risk of breast cancer and T2D.

The sample size for our study was very large. When comparing subjects in T2D GRS Q_5 to those in Q_1, our study had 80% power to detect an OR for breast cancer risk as low as 1.06 (or 0.94) at 5% type I error rate. Our study showed that the association between T2D GRS and breast cancer risk should be very small, if it exists. The GRS used in our study was constructed using SNPs with established association with T2D, as demonstrated convincingly in previous GWAS, and thus this GRS should have a clear association with T2D. Indeed, using the resources from the Nashville Breast Health Study [37], we showed that this GRS was related to T2D in a dose-response manner (*P* for trend < 0.01, *Online Resource Table 6*). However, there are some potential limitations of our study. The T2D treatment information was not available for the study, preventing us from conducting an in-depth evaluation of the potential influence of T2D treatment on the association of T2D risk variants with breast cancer risk. To reduce potential influence of T2D treatment, we conducted an analysis among younger patients (< 50 years old) who are less likely to have T2D diagnosis than the older age group. This analysis showed similar results in younger and older groups (*Table 2*), indicating that the influence of T2D treatment on the association of T2D risk variants with breast cancer risk should be small. Approximately two-thirds of the SNPs used to construct the T2D GRS were not directly genotyped. We

imputed these SNPs using 1000 Genomes Project data as the reference. The imputation quality was high. In a sensitivity analysis, we constructed an alternate T2D GRS using only the 11 directly genotyped SNPs and the 14 imputed SNPs which had almost perfect quality ($R^2 > 0.9$). This T2D GRS is highly correlated with the T2D GRS used in our primary analysis (Pearson's $r = 0.93$) and using the alternate T2D GRS did not change the results appreciably. Since we started this project, 14 new genetic loci for T2D have been identified. Unfortunately, we don't have any data for these 14 new loci for our study. However, the strength of the association of T2D risk is much weaker for these newly identified variants than the 33 variants identified previously and included in our study. Therefore, we believe that including these variants would not change the conclusion of this study. Finally, all participants in this study are of European ancestry, possibility affecting the generalizability of our study findings to other populations.

In conclusion, our study found no apparent association between a polygenetic score constructed using the known T2D risk variants identified to date in GWAS and breast cancer risk among women of European ancestry. It is possible that the previously reported association between these two diseases could be due to shared lifestyle risk factors for T2D and breast cancer, providing support for lifestyle modification as an effective prevention strategy to reduce the risk of both T2D and breast cancer. Our finding of significant associations of three T2D risk variants with breast cancer suggests a potential link of certain shared genetic and biological pathways for these common diseases.

References

1. Federation. ID (2013) IDF Diabetes Atlas. 6th edn., Brussels, Belgium: International Diabetes Federation
2. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic medicine : a journal of the British Diabetic Association 15 (7):539-553. doi:10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S
3. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics, 2014. CA: a cancer journal for clinicians 64 (1):9-29. doi:10.3322/caac.21208
4. Talamini R, Franceschi S, Favero A, Negri E, Parazzini F, La Vecchia C (1997) Selected medical conditions and risk of breast cancer. British journal of cancer 75 (11):1699-1703
5. Weiderpass E, Gridley G, Persson I, Nyren O, Ekbom A, Adami HO (1997) Risk of endometrial and breast cancer in patients with diabetes mellitus. International journal of cancer Journal international du cancer 71 (3):360-363
6. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, Borch-Johnsen K, Olsen JH (1997) Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. Journal of the National Cancer Institute 89 (18):1360-1365
7. Michels KB, Solomon CG, Hu FB, Rosner BA, Hankinson SE, Colditz GA, Manson JE, Nurses' Health S (2003) Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. Diabetes care 26 (6):1752-1758
8. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE (2006) Diabetes mellitus and breast cancer: a retrospective population-based cohort study. Breast cancer research and treatment 98 (3):349-356. doi:10.1007/s10549-006-9172-5
9. Xue F, Michels KB (2007) Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. The American journal of clinical nutrition 86 (3):s823-835
10. Larsson SC, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of breast cancer: a meta-analysis. International journal of cancer Journal international du cancer 121 (4):856-862. doi:10.1002/ijc.22717
11. Hardefeldt PJ, Edirimanne S, Eslick GD (2012) Diabetes increases the risk of breast cancer: a meta-analysis. Endocrine-related cancer 19 (6):793-803. doi:10.1530/ERC-12-0242
12. Boyle P, Boniol M, Koechlin A, Robertson C, Valentini F, Coppens K, Fairley LL, Boniol M, Zheng T, Zhang Y, Pasterk M, Smans M, Curado MP, Mullie P, Gandini S, Bota M, Bolli GB, Rosenstock J, Autier P (2012) Diabetes and breast cancer risk: a meta-analysis. British journal of cancer 107 (9):1608-1617. doi:10.1038/bjc.2012.414
13. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D (2010) Diabetes and cancer: a consensus report. CA: a cancer journal for clinicians 60 (4):207-221. doi:10.3322/caac.20078
14. Yang G, Lu G, Jin F, Dai Q, Best R, Shu XO, Chen JR, Pan XY, Shrubsole M, Zheng W (2001) Population-based, case-control study of blood C-peptide level and breast cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 10 (11):1207-1211
15. Endogenous H, Breast Cancer Collaborative G, Key TJ, Appleby PN, Reeves GK, Roddam AW (2010) Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. The Lancet Oncology 11 (6):530-542. doi:10.1016/S1470-2045(10)70095-4
16. Pierce BL, Austin MA, Ahsan H (2011) Association study of type 2 diabetes genetic susceptibility variants and risk of pancreatic cancer: an analysis of PanScan-I data. Cancer causes & control : CCC 22 (6):877-883. doi:10.1007/s10552-011-9760-5
17. Cheng I, Caberto CP, Lum-Jones A, Seifried A, Wilkens LR, Schumacher FR, Monroe KR, Lim U, Tiirikainen M, Kolonel LN, Henderson BE, Stram DO, Haiman CA, Le Marchand L (2011) Type 2 diabetes risk variants and colorectal cancer risk: the Multiethnic Cohort and PAGE studies. Gut 60 (12):1703-1711. doi:10.1136/gut.2011.237727
18. Sainz J, Rudolph A, Hoffmeister M, Frank B, Brenner H, Chang-Claude J, Hemminki K, Forsti A (2012) Effect of type 2 diabetes predisposing genetic variants on colorectal cancer risk. The Journal of clinical endocrinology and metabolism 97 (5):E845-851. doi:10.1210/jc.2011-2565

19. Machiela MJ, Lindstrom S, Allen NE, Haiman CA, Albanes D, Barricarte A, Berndt SI, Bueno-de-Mesquita HB, Chanock S, Gaziano JM, Gapstur SM, Giovannucci E, Henderson BE, Jacobs EJ, Kolonel LN, Krogh V, Ma J, Stampfer MJ, Stevens VL, Stram DO, Tjonneland A, Travis R, Willett WC, Hunter DJ, Le Marchand L, Kraft P (2012) Association of type 2 diabetes susceptibility variants with advanced prostate cancer risk in the Breast and Prostate Cancer Cohort Consortium. American journal of epidemiology 176 (12):1121-1129. doi:10.1093/aje/kws191
20. Chen F, Wilkens LR, Monroe KR, Stram DO, Kolonel LN, Henderson BE, Le Marchand L, Haiman CA (2011) No association of risk variants for diabetes and obesity with breast cancer: the Multiethnic Cohort and PAGE studies. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 20 (5):1039-1042. doi:10.1158/1055-9965.EPI-11-0135
21. Hou N, Zheng Y, Gamazon ER, Ogundiran TO, Adebamowo C, Nathanson KL, Domchek SM, Rebbeck TR, Simon MS, John EM, Hennis A, Nemesure B, Wu SY, Leske MC, Ambs S, Niu Q, Zhang J, Pierce B, Cox NJ, Olopade OI, Huo D (2012) Genetic susceptibility to type 2 diabetes and breast cancer risk in women of European and African ancestry. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 21 (3):552-556. doi:10.1158/1055-9965.EPI-11-0979
22. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, Schmidt MK, Chang-Claude J, Bojesen SE, Bolla MK, Wang Q, Dicks E, Lee A, Turnbull C, Rahman N, Breast, Ovarian Cancer Susceptibility C, Fletcher O, Peto J, Gibson L, Dos Santos Silva I, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Czene K, Irwanto A, Liu J, Waisfisz Q, Meijers-Heijboer H, Adank M, Hereditary B, Ovarian Cancer Research Group N, van der Luijt RB, Hein R, Dahmen N, Beckman L, Meindl A, Schmutzler RK, Muller-Myhsok B, Lichtner P, Hopper JL, Southey MC, Makalic E, Schmidt DF, Uitterlinden AG, Hofman A, Hunter DJ, Chanock SJ, Vincent D, Bacot F, Tessier DC, Canisius S, Wessels LF, Haiman CA, Shah M, Luben R, Brown J, Luccarini C, Schoof N, Humphreys K, Li J, Nordestgaard BG, Nielsen SF, Flyger H, Couch FJ, Wang X, Vachon C, Stevens KN, Lambrechts D, Moisse M, Paridaens R, Christiaens MR, Rudolph A, Nickels S, Flesch-Janys D, Johnson N, Aitken Z, Aaltonen K, Heikkinen T, Broeks A, Veer LJ, van der Schoot CE, Guenel P, Truong T, Laurent-Puig P, Menegaux F, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Zamora MP, Perez JI, Pita G, Alonso MR, Cox A, Brock IW, Cross SS, Reed MW, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Henderson BE, Schumacher F, Le Marchand L, Andrulis IL, Knight JA, Glendon G, Mulligan AM, kConFab I, Australian Ovarian Cancer Study G, Lindblom A, Margolin S, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Bui QM, Stone J, Dite GS, Apicella C, Tsimiklis H, Giles GG, Severi G, Baglietto L, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Brenner H, Muller H, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Jones M, Figueroa J, Lissowska J, Brinton L, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Bruning T, Network G, Radice P, Peterlongo P, Manoukian S, Bonanni B, Devilee P, Tollenaar RA, Seynaeve C, van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Durda K, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Bogdanova NV, Antonenkova NN, Dork T, Kristensen VN, Anton-Culver H, Slager S, Toland AE, Edge S, Fostira F, Kang D, Yoo KY, Noh DY, Matsuo K, Ito H, Iwata H, Sueta A, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Shu XO, Lu W, Gao YT, Cai H, Teo SH, Yip CH, Phuah SY, Cornes BK, Hartman M, Miao H, Lim WY, Sng JH, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Shen CY, Hsiung CN, Wu PE, Ding SL, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Blot WJ, Signorello LB, Cai Q, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Simard J, Garcia-Closas M, Pharoah PD, Chenevix-Trench G, Dunning AM, Benitez J, Easton DF (2013) Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nature genetics 45 (4):353-361, 361e351-352. doi:10.1038/ng.2563
23. Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, Maranian MJ, Bolla MK, Wang Q, Shah M, Perkins BJ, Czene K, Eriksson M, Darabi H, Brand JS, Bojesen SE, Nordestgaard BG, Flyger H, Nielsen SF, Rahman N, Turnbull C, Bocs, Fletcher O, Peto J, Gibson L, Dos-Santos-Silva I, Chang-Claude J, Flesch-Janys D, Rudolph A, Eilber U, Behrens S, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Khan S, Aaltonen K, Ahsan H, Kibriya MG, Whittemore AS, John EM, Malone KE, Gammon MD, Santella RM, Ursin G, Makalic E, Schmidt DF, Casey G, Hunter DJ, Gapstur SM, Gaudet MM, Diver WR, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Berg CD, Chanock SJ, Figueroa J, Hoover RN, Lambrechts D, Neven P, Wildiers H, van Limbergen E, Schmidt MK, Broeks A, Verhoef S, Cornelissen S, Couch FJ, Olson JE, Hallberg E, Vachon C, Waisfisz Q, Meijers-Heijboer H, Adank MA, van der Luijt RB, Li J, Liu J, Humphreys K, Kang D, Choi JY, Park SK, Yoo KY, Matsuo K, Ito H, Iwata H, Tajima K, Guenel P, Truong T, Mulot C, Sanchez M, Burwinkel B, Marme F, Surowy H, Sohn C, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Gonzalez-Neira A, Benitez J, Zamora MP, Perez JI, Shu XO, Lu W, Gao YT, Cai H, Cox A, Cross SS, Reed MW, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, kConFab I, Group A, Lindblom A, Margolin S, Teo SH, Yip CH, Taib NA, Tan GH, Hooning

MJ, Hollestelle A, Martens JW, Collee JM, Blot W, Signorello LB, Cai Q, Hopper JL, Southey MC, Tsimiklis H, Apicella C, Shen CY, Hsiung CN, Wu PE, Hou MF, Kristensen VN, Nord S, Alnaes GI, Nbcs, Giles GG, Milne RL, McLean C, Canzian F, Trichopoulos D, Peeters P, Lund E, Sund M, Khaw KT, Gunter MJ, Palli D, Mortensen LM, Dossus L, Huerta JM, Meindl A, Schmutzler RK, Sutter C, Yang R, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Hartman M, Miao H, Chia KS, Chan CW, Fasching PA, Hein A, Beckmann MW, Haeberle L, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Ashworth A, Orr N, Schoemaker MJ, Swerdlow AJ, Brinton L, Garcia-Closas M, Zheng W, Halverson SL, Shrubsole M, Long J, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Bruning T, Network G, Radice P, Peterlongo P, Manoukian S, Bernard L, Bogdanova NV, Dork T, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Devilee P, Tollenaar RA, Seynaeve C, Van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Huzarski T, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Slager S, Toland AE, Ambrosone CB, Yannoukakos D, Kabisch M, Torres D, Neuhausen SL, Anton-Culver H, Luccarini C, Baynes C, Ahmed S, Healey CS, Tessier DC, Vincent D, Bacot F, Pita G, Alonso MR, Alvarez N, Herrero D, Simard J, Pharoah PP, Kraft P, Dunning AM, Chenevix-Trench G, Hall P, Easton DF (2015) Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nature genetics 47 (4):373-380. doi:10.1038/ng.3242

24. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR (2012) Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nature genetics 44 (8):955-959. doi:10.1038/ng.2354

25. Garcia-Closas M, Couch FJ, Lindstrom S, Michailidou K, Schmidt MK, Brook MN, Orr N, Rhie SK, Riboli E, Feigelson HS, Le Marchand L, Buring JE, Eccles D, Miron P, Fasching PA, Brauch H, Chang-Claude J, Carpenter J, Godwin AK, Nevanlinna H, Giles GG, Cox A, Hopper JL, Bolla MK, Wang Q, Dennis J, Dicks E, Howat WJ, Schoof N, Bojesen SE, Lambrechts D, Broeks A, Andrulis IL, Guenel P, Burwinkel B, Sawyer EJ, Hollestelle A, Fletcher O, Winqvist R, Brenner H, Mannermaa A, Hamann U, Meindl A, Lindblom A, Zheng W, Devillee P, Goldberg MS, Lubinski J, Kristensen V, Swerdlow A, Anton-Culver H, Dork T, Muir K, Matsuo K, Wu AH, Radice P, Teo SH, Shu XO, Blot W, Kang D, Hartman M, Sangrajrang S, Shen CY, Southey MC, Park DJ, Hammet F, Stone J, Veer LJ, Rutgers EJ, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Peto J, Schrauder MG, Ekici AB, Beckmann MW, Dos Santos Silva I, Johnson N, Warren H, Tomlinson I, Kerin MJ, Miller N, Marme F, Schneeweiss A, Sohn C, Truong T, Laurent-Puig P, Kerbrat P, Nordestgaard BG, Nielsen SF, Flyger H, Milne RL, Perez JI, Menendez P, Muller H, Arndt V, Stegmaier C, Lichtner P, Lochmann M, Justenhoven C, Ko YD, Gene EI, breast CN, Muranen TA, Aittomaki K, Blomqvist C, Greco D, Heikkinen T, Ito H, Iwata H, Yatabe Y, Antonenkova NN, Margolin S, Kataja V, Kosma VM, Hartikainen JM, Balleine R, kConFab I, Tseng CC, Berg DV, Stram DO, Neven P, Dieudonne AS, Leunen K, Rudolph A, Nickels S, Flesch-Janys D, Peterlongo P, Peissel B, Bernard L, Olson JE, Wang X, Stevens K, Severi G, Baglietto L, McLean C, Coetzee GA, Feng Y, Henderson BE, Schumacher F, Bogdanova NV, Labreche F, Dumont M, Yip CH, Taib NA, Cheng CY, Shrubsole M, Long J, Pylkas K, Jukkola-Vuorinen A, Kauppila S, Knight JA, Glendon G, Mulligan AM, Tollenaar RA, Seynaeve CM, Kriege M, Hooning MJ, van den Ouweland AM, van Deurzen CH, Lu W, Gao YT, Cai H, Balasubramanian SP, Cross SS, Reed MW, Signorello L, Cai Q, Shah M, Miao H, Chan CW, Chia KS, Jakubowska A, Jaworska K, Durda K, Hsiung CN, Wu PE, Yu JC, Ashworth A, Jones M, Tessier DC, Gonzalez-Neira A, Pita G, Alonso MR, Vincent D, Bacot F, Ambrosone CB, Bandera EV, John EM, Chen GK, Hu JJ, Rodriguez-Gil JL, Bernstein L, Press MF, Ziegler RG, Millikan RM, Deming-Halverson SL, Nyante S, Ingles SA, Waisfisz Q, Tsimiklis H, Makalic E, Schmidt D, Bui M, Gibson L, Muller-Myhsok B, Schmutzler RK, Hein R, Dahmen N, Beckmann L, Aaltonen K, Czene K, Irwanto A, Liu J, Turnbull C, Familial Breast Cancer S, Rahman N, Meijers-Heijboer H, Uitterlinden AG, Rivadeneira F, Australian Breast Cancer Tissue Bank I, Olswold C, Slager S, Pilarski R, Ademuyiwa F, Konstantopoulou I, Martin NG, Montgomery GW, Slamon DJ, Rauh C, Lux MP, Jud SM, Bruning T, Weaver J, Sharma P, Pathak H, Tapper W, Gerty S, Durcan L, Trichopoulos D, Tumino R, Peeters PH, Kaaks R, Campa D, Canzian F, Weiderpass E, Johansson M, Khaw KT, Travis R, Clavel-Chapelon F, Kolonel LN, Chen C, Beck A, Hankinson SE, Berg CD, Hoover RN, Lissowska J, Figueroa JD, Chasman DI, Gaudet MM, Diver WR, Willett WC, Hunter DJ, Simard J, Benitez J, Dunning AM, Sherman ME, Chenevix-Trench G, Chanock SJ, Hall P, Pharoah PD, Vachon C, Easton DF, Haiman CA, Kraft P (2013) Genome-wide association studies identify four ER negative-specific breast cancer risk loci. Nature genetics 45 (4):392-398, 398e391-392. doi:10.1038/ng.2561

26. Ghoussaini M, Fletcher O, Michailidou K, Turnbull C, Schmidt MK, Dicks E, Dennis J, Wang Q, Humphreys MK, Luccarini C, Baynes C, Conroy D, Maranian M, Ahmed S, Driver K, Johnson N, Orr N, dos Santos Silva I, Waisfisz Q, Meijers-Heijboer H, Uitterlinden AG, Rivadeneira F, Netherlands Collaborative Group on Hereditary B, Ovarian C, Hall P, Czene K, Irwanto A, Liu J, Nevanlinna H, Aittomaki K, Blomqvist C, Meindl A, Schmutzler RK, Muller-Myhsok B, Lichtner P, Chang-Claude J, Hein R, Nickels S, Flesch-Janys D, Tsimiklis H, Makalic E, Schmidt D, Bui M, Hopper JL, Apicella C, Park DJ, Southey M, Hunter DJ, Chanock SJ, Broeks A, Verhoef S, Hogervorst FB, Fasching PA, Lux MP, Beckmann MW, Ekici AB,

Sawyer E, Tomlinson I, Kerin M, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Guenel P, Truong T, Cordina-Duverger E, Menegaux F, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Milne RL, Alonso MR, Gonzalez-Neira A, Benitez J, Anton-Culver H, Ziogas A, Bernstein L, Dur CC, Brenner H, Muller H, Arndt V, Stegmaier C, Familial Breast Cancer S, Justenhoven C, Brauch H, Bruning T, Gene Environment Interaction of Breast Cancer in Germany N, Wang-Gohrke S, Eilber U, Dork T, Schurmann P, Bremer M, Hillemanns P, Bogdanova NV, Antonenkova NN, Rogov YI, Karstens JH, Bermisheva M, Prokofieva D, Khusnutdinova E, Lindblom A, Margolin S, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Lambrechts D, Yesilyurt BT, Floris G, Leunen K, Manoukian S, Bonanni B, Fortuzzi S, Peterlongo P, Couch FJ, Wang X, Stevens K, Lee A, Giles GG, Baglietto L, Severi G, McLean C, Alnaes GG, Kristensen V, Borrensen-Dale AL, John EM, Miron A, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Kauppila S, Andrulis IL, Glendon G, Mulligan AM, Devilee P, van Asperen CJ, Tollenaar RA, Seynaeve C, Figueroa JD, Garcia-Closas M, Brinton L, Lissowska J, Hooning MJ, Hollestelle A, Oldenburg RA, van den Ouweland AM, Cox A, Reed MW, Shah M, Jakubowska A, Lubinski J, Jaworska K, Durda K, Jones M, Schoemaker M, Ashworth A, Swerdlow A, Beesley J, Chen X, kConFab I, Australian Ovarian Cancer Study G, Muir KR, Lophatananon A, Rattanamongkongul S, Chaiwerawattana A, Kang D, Yoo KY, Noh DY, Shen CY, Yu JC, Wu PE, Hsiung CN, Perkins A, Swann R, Velentzis L, Eccles DM, Tapper WJ, Gerty SM, Graham NJ, Ponder BA, Chenevix-Trench G, Pharoah PD, Lathrop M, Dunning AM, Rahman N, Peto J, Easton DF (2012) Genome-wide association analysis identifies three new breast cancer susceptibility loci. Nature genetics 44 (3):312-318. doi:10.1038/ng.1049

27. Siddiq A, Couch FJ, Chen GK, Lindstrom S, Eccles D, Millikan RC, Michailidou K, Stram DO, Beckmann L, Rhie SK, Ambrosone CB, Aittomaki K, Amiano P, Apicella C, Australian Breast Cancer Tissue Bank I, Baglietto L, Bandera EV, Beckmann MW, Berg CD, Bernstein L, Blomqvist C, Brauch H, Brinton L, Bui QM, Buring JE, Buys SS, Campa D, Carpenter JE, Chasman DI, Chang-Claude J, Chen C, Clavel-Chapelon F, Cox A, Cross SS, Czene K, Deming SL, Diasio RB, Diver WR, Dunning AM, Durcan L, Ekici AB, Fasching PA, Familial Breast Cancer S, Feigelson HS, Fejerman L, Figueroa JD, Fletcher O, Flesch-Janys D, Gaudet MM, Consortium G, Gerty SM, Rodriguez-Gil JL, Giles GG, van Gils CH, Godwin AK, Graham N, Greco D, Hall P, Hankinson SE, Hartmann A, Hein R, Heinz J, Hoover RN, Hopper JL, Hu JJ, Huntsman S, Ingles SA, Irwanto A, Isaacs C, Jacobs KB, John EM, Justenhoven C, Kaaks R, Kolonel LN, Coetzee GA, Lathrop M, Le Marchand L, Lee AM, Lee IM, Lesnick T, Lichtner P, Liu J, Lund E, Makalic E, Martin NG, McLean CA, Meijers-Heijboer H, Meindl A, Miron P, Monroe KR, Montgomery GW, Muller-Myhsok B, Nickels S, Nyante SJ, Olswold C, Overvad K, Palli D, Park DJ, Palmer JR, Pathak H, Peto J, Pharoah P, Rahman N, Rivadeneira F, Schmidt DF, Schmutzler RK, Slager S, Southey MC, Stevens KN, Sinn HP, Press MF, Ross E, Riboli E, Ridker PM, Schumacher FR, Severi G, Dos Santos Silva I, Stone J, Sund M, Tapper WJ, Thun MJ, Travis RC, Turnbull C, Uitterlinden AG, Waisfisz Q, Wang X, Wang Z, Weaver J, Schulz-Wendtland R, Wilkens LR, Van Den Berg D, Zheng W, Ziegler RG, Ziv E, Nevanlinna H, Easton DF, Hunter DJ, Henderson BE, Chanock SJ, Garcia-Closas M, Kraft P, Haiman CA, Vachon CM (2012) A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. Human molecular genetics 21 (24):5373-5384. doi:10.1093/hmg/dds381

28. Ahsan H, Halpern J, Kibriya MG, Pierce BL, Tong L, Gamazon E, McGuire V, Felberg A, Shi J, Jasmine F, Roy S, Brutus R, Argos M, Melkonian S, Chang-Claude J, Andrulis I, Hopper JL, John EM, Malone K, Ursin G, Gammon MD, Thomas DC, Seminara D, Casey G, Knight JA, Southey MC, Giles GG, Santella RM, Lee E, Conti D, Duggan D, Gallinger S, Haile R, Jenkins M, Lindor NM, Newcomb P, Michailidou K, Apicella C, Park DJ, Peto J, Fletcher O, dos Santos Silva I, Lathrop M, Hunter DJ, Chanock SJ, Meindl A, Schmutzler RK, Muller-Myhsok B, Lochmann M, Beckmann L, Hein R, Makalic E, Schmidt DF, Bui QM, Stone J, Flesch-Janys D, Dahmen N, Nevanlinna H, Aittomaki K, Blomqvist C, Hall P, Czene K, Irwanto A, Liu J, Rahman N, Turnbull C, Familial Breast Cancer S, Dunning AM, Pharoah P, Waisfisz Q, Meijers-Heijboer H, Uitterlinden AG, Rivadeneira F, Nicolae D, Easton DF, Cox NJ, Whittemore AS (2014) A genome-wide association study of early-onset breast cancer identifies PFKM as a novel breast cancer gene and supports a common genetic spectrum for breast cancer at any age. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 23 (4):658-669. doi:10.1158/1055-9965.EPI-13-0340

29. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D (2006) Principal components analysis corrects for stratification in genome-wide association studies. Nature genetics 38 (8):904-909. doi:10.1038/ng1847

30. Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin X (2010) Powerful SNP-set analysis for case-control genome-wide association studies. American journal of human genetics 86 (6):929-942. doi:10.1016/j.ajhg.2010.05.002

31. Team RC (2014) R: A Language and Environment for Statistical Computing. R foundation for Statistical computing, Vienna, Austria
32. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D (2010) Diabetes and cancer: a consensus report. Diabetes care 33 (7):1674-1685. doi:10.2337/dc10-0666
33. La Vecchia C, Giordano SH, Hortobagyi GN, Chabner B (2011) Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. The oncologist 16 (6):726-729. doi:10.1634/theoncologist.2011-0050
34. Cai Q, Zhang B, Sung H, Low SK, Kweon SS, Lu W, Shi J, Long J, Wen W, Choi JY, Noh DY, Shen CY, Matsuo K, Teo SH, Kim MK, Khoo US, Iwasaki M, Hartman M, Takahashi A, Ashikawa K, Matsuda K, Shin MH, Park MH, Zheng Y, Xiang YB, Ji BT, Park SK, Wu PE, Hsiung CN, Ito H, Kasuga Y, Kang P, Mariapun S, Ahn SH, Kang HS, Chan KY, Man EP, Iwata H, Tsugane S, Miao H, Liao J, Nakamura Y, Kubo M, Consortium DG-O, Delahanty RJ, Zhang Y, Li B, Li C, Gao YT, Shu XO, Kang D, Zheng W (2014) Genome-wide association analysis in East Asians identifies breast cancer susceptibility loci at 1q32.1, 5q14.3 and 15q26.1. Nature genetics 46 (8):886-890. doi:10.1038/ng.3041
35. Brown AM (2001) Wnt signaling in breast cancer: have we come full circle? Breast Cancer Res 3 (6):351-355
36. Howe LR, Brown AM (2004) Wnt signaling and breast cancer. Cancer Biol Ther 3 (1):36-41
37. Fu Z, Deming SL, Fair AM, Shrubsole MJ, Wujcik DM, Shu XO, Kelley M, Zheng W (2011) Well-done meat intake and meat-derived mutagen exposures in relation to breast cancer risk: the Nashville Breast Health Study. Breast cancer research and treatment 129 (3):919-928. doi:10.1007/s10549-011-1538-7

FIGURE LEGENDS

Fig. 1 Overview of the T2D genetic risk score construction

TABLES

Table 1 The associations between T2D genetic risk score and breast cancer risk in Breast Cancer Association Consortium

Table 2 Selected T2D risk variants associated with breast cancer risk in BCAC at *P* < 0.05 and their associations in GAME-ON DRIVE project

Table 1: The associations between T2D genetic risk score and breast cancer risk in Breast Cancer Association Consortium

	T2D GRS by Quintiles					Linear Trend
	Q_1 (low)	Q_2	Q_3	Q_4	Q_5	
Overall Breast Cancer						
$N_{cases}/N_{controls}$	9148/8497	9519/8496	9175/8496	9227/8496	9256/8497	
OR[a] [95% CI]	1 (reference)	1.03 (0.98,1.08)	1.00 (0.95,1.04)	1.00 (0.96,1.05)	1.00 (0.96,1.05)	0.69
ER+ Breast Cancer						
$N_{cases}/N_{controls}$	5473/8497	5616/8496	5259/8496	5351/8496	5375/8497	
OR[a] [95% CI]	1 (reference)	1.03 (0.98,1.09)	0.98 (0.93,1.03)	1.00 (0.95,1.05)	1.01 (0.96,1.06)	0.74
ER- Breast Cancer						
$N_{cases}/N_{controls}$	1402/8497	1490/8496	1451/8496	1451/8496	1494/8497	
OR[a] [95% CI]	1 (reference)	1.03 (0.95,1.12)	1.00 (0.92,1.10)	0.97 (0.89,1.06)	0.99 (0.91,1.08)	0.47
Among Pre-menopausal Women						
$N_{cases}/N_{controls}$	1971/1881	2152/1770	2023/1796	2018/1824	2045/1782	
OR[a] [95% CI]	1 (reference)	1.11 (1.00,1.24)	1.06 (0.95,1.18)	1.06 (0.95,1.17)	1.05 (0.94,1.17)	0.74
Among Post-menopausal Women						
$N_{cases}/N_{controls}$	4751/3909	4817/3874	4514/3909	4455/3821	4532/3842	
OR[a] [95% CI]	1 (reference)	1.03 (0.97,1.10)	0.99 (0.93,1.06)	0.98 (0.92,1.05)	1.02 (0.96,1.09)	0.93
Among Age<50 Women						
$N_{cases}/N_{controls}$	1757/2389	1941/2375	1919/2372	1843/2363	1926/2393	
OR[a] [95% CI]	1 (reference)	1.07 (0.97,1.18)	1.07 (0.97,1.19)	1.04 (0.94,1.15)	1.04 (0.94,1.15)	0.74
Among Age≥50 Women						
$N_{cases}/N_{controls}$	7391/6108	7578/6121	7256/6124	7384/6133	7330/6104	
OR[a] [95% CI]	1 (reference)	1.01 (0.96,1.07)	0.98 (0.93,1.03)	1.00 (0.95,1.05)	1.00 (0.95,1.05)	0.62
Among BMI<25 Women						
$N_{cases}/N_{controls}$	2420/2150	2526/2103	2418/2146	2321/2187	2485/2168	
OR[a] [95% CI]	1 (reference)	1.05 (0.96,1.15)	0.99 (0.90,1.09)	0.94 (0.86,1.03)	1.04 (0.95,1.14)	0.64
Among BMI≥25 Women						
$N_{cases}/N_{controls}$	2499/2154	2652/2308	2552/2282	2611/2229	2651/2359	
OR[a] [95% CI]	1 (reference)	1.00 (0.92,1.09)	0.97 (0.89,1.06)	1.03 (0.94,1.12)	0.96 (0.88,1.05)	0.64

T2D GRS: Weighted type 2 diabetes related genetic variants risk score

[a]: All associations were assessed individually by each study and then combined by fixed-effect inverse-variance weighted meta-analysis. All models adjusted for age and top eight principal components for population stratification. Study specific principal component was further adjusted for LMBC study.

Table 2: Selected T2D risk variants associated with breast cancer risk in BCAC at *P* < 0.05 and their associations in GAME-ON DRIVE project

						BCAC (Cases N=46325/ Controls N=42482)				GAME-ON DRIVE (Cases N=16003/ Controls N=41335)				Combined (Cases N=62328/ Controls N=83817)		
SNPs	Chr	Position[a]	Gene[b]	Alleles[c]	R-square[d]	RAF[e]	OR[f]	95% CI[f]	P-Value[f]	RAF	OR	95% CI	P-Value	OR[g]	95% CI[g]	P-Value[g]
rs243021	2	60584819	BCL11A	A/G	-	0.46	1.02	(1.00,1.04)	0.03	0.46	1.01	(0.98,1.05)	0.45	1.02	(1.00,1.04)	0.02
rs4402960	3	185511687	IGF2BP2	T/G	-	0.31	0.98	(0.96,1.00)	0.05	0.32	0.97	(0.94,1.01)	0.13	0.98	(0.96,1.00)	0.01
rs13292136	9	81952128	CHCHD9	C/T	0.926	0.92	1.05	(1.01,1.09)	0.02	0.94	0.98	(0.92,1.05)	0.62	1.03	(0.99,1.06)	0.08
rs7903146	10	114758349	TCF7L2	T/C	-	0.28	1.04	(1.02,1.07)	1.20E-4	0.30	1.04	(1.00,1.08)	0.04	1.04	(1.02,1.06)	1.26E-05
rs7961581	12	71663102	TSPAN8,LGR5	C/T	0.981	0.28	0.97	(0.94,0.99)	2.48E-3	0.26	1.00	(0.96,1.04)	0.96	0.97	(0.95,0.99)	9.01E-03
rs8042680	15	91521337	PRC1	A/C	-	0.31	0.98	(0.95,1.00)	0.02	0.30	0.95	(0.92,0.99)	6.18E-3	0.97	(0.95,0.99)	8.05E-04
rs9939609	16	53820527	FTO	A/T	1.000	0.40	0.93	(0.91,0.95)	3.63E-12	0.38	0.96	(0.93,0.99)	0.01	0.94	(0.92,0.95)	4.13E-13

SNP: single nucleotide polymorphism; Chr: Chromosome; BCAC: Breast Cancer Association Consortium; GAME-ON: Genetic Associations and Mechanisms in Oncology; DRIVE: Discovery, Biology, and Risk of Inherited Variants in Breast Cancer; RAF: risk allele frequency; OR: odds ratio; CI: confidence interval;

[a]: The chromosome physical position is based on the National Center for Biotechnology Information (NCBI) database, Build 36.3.

[b]: The closest gene.

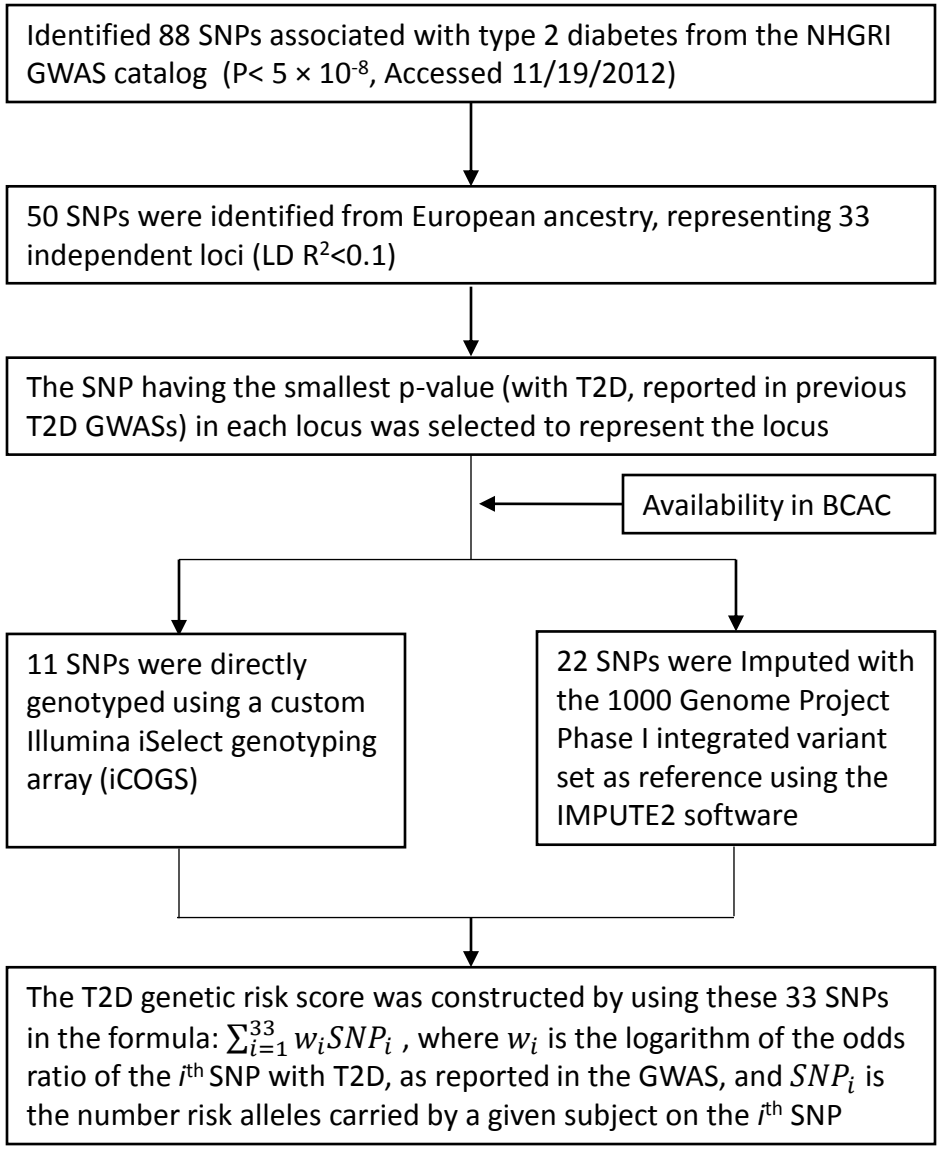
[c]: Risk/reference alleles. The risk allele is the allele that associated with increased risk of type 2 diabetes.

[d]: Imputation quality in BCAC; - indicates directly genotyped SNPs.

[e]: Among controls.

[f]: All associations were assessed individually by each study and then combined by a fixed-effects inverse-variance weighted meta-analysis. All models adjusted for first eight principal components for population stratification. Study specific principal component was further adjusted for LMBC study.

[g]: Combined BCAC and GAME-ON DRIVE results by fixed-effects inverse-variance weighted meta-analysis.


Identified 88 SNPs associated with type 2 diabetes from the NHGRI GWAS catalog (P< 5 × 10-8, Accessed 11/19/2012)
50 SNPs were identified from European ancestry, representing 33 independent loci (LD R2<0.1)
The SNP having the smallest p-value (with T2D, reported in previous T2D GWASs) in each locus was selected to represent the locus
Availability in BCAC
11 SNPs were directly genotyped using a custom Illumina iSelect genotyping array (iCOGS)
22 SNPs were Imputed with the 1000 Genome Project Phase I integrated variant set as reference using the IMPUTE2 software
The T2D genetic risk score was constructed by using these 33 SNPs in the formula: $\sum_{i=1}^{33} w_i SNP_i$, where w_i is the logarithm of the odds ratio of the i^{th} SNP with T2D, as reported in the GWAS, and SNP_i is the number risk alleles carried by a given subject on the i^{th} SNP

Association of Genetic Susceptibility Variants for Type 2 Diabetes with Breast Cancer Risk in Women of European Ancestry

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SUPPLEMENTAL MATERIALS

Supplemental Table 1 Studies participating in the Breast Cancer Association Consortium (BCAC) that contributed to this project

Supplemental Table 2 Breast Cancer GWAS included in the GAME-ON DRIVE Meta-analysis

Supplemental Table 3 Associations of 33 independent T2D related SNPs with breast cancer risk in BCAC, GAME-ON DRIVE, and combined

Supplemental Table 4 Subject characteristics by case-control status and their associations with weighted type 2 diabetes genetic risk score in Breast Cancer Association Consortium

Supplemental Table 5 Sensitivity analysis of the associations between T2D GRS and breast cancer risk in Breast Cancer Association Consortium using genotyped SNPs and imputed SNPs with a $R^2 > 0.9$.

Supplemental Table 6 Validation of the developed T2D GRS with prior history of diabetes among controls from the Nashville Breast Health Study, 2001-2011

Supplemental Table 1 Studies participating in the Breast Cancer Association Consortium (BCAC) that contributed to this project

Study (reference)	Abbreviation	Country	Study design	Recruitment base	
				Cases	**Controls**
Australian Breast Cancer Family Study [1]	ABCFS	Australia	Population-based case-control study	Cancer registries in Victoria and New South Wales (1992-1999): all cases from Melbourne and Sydney diagnosed before age 40 plus a random sample of those diagnosed at ages 40-59.	Identified between 1992 and 1999 from the electoral rolls in Melbourne and Sydney (enrolling to vote is compulsory); frequency matched to cases by age in 5-year categories.
Amsterdam Breast Cancer Study [2]	ABCS	Netherlands	Hospital-based consecutive cases; population-based controls	Breast cancer patients diagnosed before age 50 in 2003-2009 at the NKI-AVL; and (ABCS-F) All non-BRCA1/2 breast cancer cases from the family cancer clinic of the NKI-AVL tested in the period 1995-2009; all ages and diagnosed with breast cancer in 1965-2008.	Population-based cohort of women recruited through the Sanquin blood bank, all ages.

Bavarian Breast Cancer Cases and Controls [3]	BBCC	Germany	Hospital based cases; population based controls	Consecutive, unselected cases with invasive breast cancer recruited at the University Breast Centre, Franconia in Northern Bavaria from 2002-2010.	Healthy women aged 55 or older with no diagnosis of cancer. Invited by a newspaper advertisement in Northern Bavaria from 2002-2010.
British Breast Cancer Study [4]	BBCS	UK	Cancer registry and National Cancer Research network (NCRN) based cases; population based controls	(i) English & Scottish Cancer Registries: all breast cancer cases who developed a first primary before age 66 in 1971 or later and who subsequently developed a second primary cancer. (ii) Breast Cancer Clinics: all breast cancer cases who developed a first primary before age 71 in 1967 or later and who either subsequently developed a second primary or had at least two affected female first-degree relatives. All recruited from 2001-2008.	A friend, sister-in-law, daughter-in-law or other non-blood relative of cases, recruited from 2001-2008.
Breast Cancer in Galway Genetic Study [5]	BIGGS	Ireland	Hospital based cases; population based controls	Unselected cases recruited from University College Hospital Galway and surrounding hospitals in the West of Ireland since 2001.	Women > 60 years with no personal history of any cancer and no family history of breast or ovarian cancer identified from retirement groups in the West of Ireland during 2001-2008.
Breast Cancer Study of the University of Heidelberg [6]	BSUCH	Germany	Hospital based cases; healthy blood donor controls	All cases diagnosed with breast cancer in 2007-2009 at the University Women`s Clinic Heidelberg.	Female blood donors recruited in 2007- 2009 at the Institute of Transfusion Medicine & Immunology, Mannheim.
CECILE Breast Cancer Study [7]	CECILE	France	Population-based case-control	All cases diagnosed with breast cancer in 2005-2007 among women <75 years of age residing in the départements of Ille-et-Vilaine and Côte d'Or. Cases were recruited from the main cancer treatment center (Centre Eugène-Marquis in Rennes and Centre Georges-François-Leclerc in Dijon) and from other private or public hospitals in each area.	General population control women residing in the same areas as the cases (Ille-et-Vilaine and Côte d'Or). Controls were frequency-matched to the cases by 5-year age groups. They were recruited in 2005-2007 using a random digit dialing procedure and quotas by socioeconomic status to reflect the distribution by SES of the population in each area.
Copenhagen General Population Study [8]	CGPS	Denmark	Population-based	Consecutive, incident cases from one hospital with centralized care for a population of 400,000 women in Copenhagen (2001-present).	Women with no history of breast cancer residing in the same region as cases identified from the Copenhagen General Population

					Study (2003-2007).
Spanish National Cancer Centre Breast Cancer Study [9]	CNIO-BCS	Spain	Case-control study	(i) consecutive breast cancer patients from three public hospitals, two in Madrid and one in Oviedo; (ii) cases with at least one affected first degree relative recruited through the CNIO family cancer clinic in Madrid (2000-2005).	Women attending the Menopause Research Centre, Madrid and female members of the College of Lawyers attending medical check-up in Madrid between 2000 and 2005, all free of breast cancer.
California Teachers Study [10]	CTS*	USA	Prospective cohort study: nested case-control	Nested case-control study conducted within a cohort of California teachers (113,590) who were under age 80 years at baseline, had no prior history of invasive or *in situ* breast cancer. Cases are women newly diagnosed with a histologically confirmed invasive primary adenocarcinoma of the breast at age 80 years or younger from 1998 to 2008.	Controls are a probability sample of at-risk cohort members, frequency matched to cases on age at baseline (5-year age groups), self-reported race/ethnicity (white, African American, Latina, Asian, other), and broad geographic region within California Controls were selected without replacement, using an assigned reference date.
ESTHER Breast Cancer Study [11]	ESTHER	Germany	Population-based case-control study	Breast cancer cases in all hospitals in the state of Saarland, from 2001-2003 (ESTHER) and 1996-1998 (VERDI).	Random sample of women undergoing a routine health check-up in Saarland, in 2000-2002; frequency matched to cases by age in-5 year categories.
German Consortium for Hereditary Breast & Ovarian Cancer [12]	GC-HBOC	Germany	Population-based familial case-control study	Index patients from German breast cancer families; *BRCA1/2* mutation free, collected 1996-2007 via Institute of Human Genetics, University Heidelberg & Department of Gynaecology & Obstetrics, Cologne & Department of Gynaecology and Obstetrics at the Ludwig-Maximilians-University, Munich; Germany.	Healthy, unrelated, ethnically matched female blood donors recruited in 2004 & 2007 by German Red Cross Blood Service of Baden-Württemberg-Hessen, Institute of Transfusion Medicine & Immunology, Mannheim.
Gene Environment Interaction and Breast Cancer in Germany [13]	GENICA*	Germany	Population-based case-control study	Incident breast cancer cases were enrolled at hospitals in the Greater Bonn area during 2000-2004.	Random address sample selected in 2001-2004 from 31 population registries in the greater Bonn area; frequency matched to cases on year of birth in 5-year categories.

Helsinki Breast Cancer Study [14]	HEBCS	Finland	Hospital-based case-control study + additional familial cases	(i) Consecutive cases (883) from the Department of Oncology, Helsinki University Central Hospital 1997-8 and 2000, (ii) Consecutive cases (986) from the Department of Surgery, Helsinki University Central Hospital 2001-2004, (iii) Familial breast cancer patients (536) from the Helsinki University Central Hospital, Departments of Oncology and Clinical Genetics (1995-).	Healthy females from the same geographical region in Southern Finland in 2003.
Hannover-Minsk Breast Cancer Study [15]	HMBCS	Belarus	Hospital based cases; population based controls	Cases from the Byelorussian Institute for Oncology and Medical Radiology Aleksandrov N.N. in Minsk or at one of 5 regional oncology centers in Gomel, Mogilev, Grodno, Brest or Vitebsk (2002-2008).	Women attending general medical examination at gynecology clinics in Gomel, Mogilev, Grodno, Brest or Vitebsk; women attending the Institute for Inherited Diseases in Minsk; female blood donors in Minsk; healthy relatives of cases (2002-2008).
Karolinska Breast Cancer Study [16]	KARBAC	Sweden	Population and hospital-based cases; geographically matched controls	(i) Familial cases from Department of Clinical Genetics, Karolinska University Hospital, Stockholm. (ii) Consecutive cases from Department of Oncology, Huddinge & Söder Hospital, Stockholm 1998-2000.	Blood donors of mixed gender from same geographical region. Excess material was received from all blood donors over a 3 month period in 2004 (approximately 3000) and DNA was extracted from a random sample of 1500.
Kuopio Breast Cancer Project [17]	KBCP	Finland	Population-based prospective clinical cohort	Women seen at Kuopio University Hospital between 1990-1995 because of a breast lump, mammographic abnormality, or other breast symptom and who were found to have breast cancer.	Selected from the National Population Register during 1990-1995; age and long-term area-of-residence matched to cases.
Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study [18]	KConFab/AOCS	Australia and New Zealand	Clinic-based recruitment of familial breast cancer patients (cases); population-based case-control study of ovarian cancer (controls only)	Index (youngest affected) cases from *BRCA1*- and *BRCA2*-mutation-negative multiple-case breast and breast-ovarian families recruited though family cancer clinics from across Australia and New Zealand from 1998-present.	Identified from the electoral rolls from across Australia as part of the Australian Ovarian Cancer Study in 2002-2006.

Leuven Multidisciplinary Breast Centre [19]	LMBC	Belgium	Hospital-based case-control study	All patients diagnosed with breast cancer and seen in the Multidisciplinary Breast Center in Leuven (Gashuisberg) since June 2007 plus retrospective collection of cases diagnosed since 2000.	Blood donors at Gasthuisberg Hospital (2007-2008).
Mammary Carcinoma Risk Factor Investigation [20]	MARIE	Germany	Population-based case-control study	Incident cases diagnosed from 2001-2005 in the study region Hamburg in Northern Germany, and from 2002-2005 in the study region Rhein-Neckar-Karlsruhe in Southern Germany.	Two controls per case were randomly drawn from population registries and frequency matched by birth year and study region to the case. Controls were recruited from 2002 to 2006.
Milan Breast Cancer Study Group [21]	MBCSG	Italy	Clinic-based recruitment of familial/early onset breast cancer patients (cases); population-based controls	Familial and/or early onset breast cancer patients (aged 22-87) negative for mutations in *BRCA1* and *BRCA2*, ascertained at two large cancer centers in Milan from 2000-present.	Female blood donors recruited at two centres in Milan from 2004-present and 2007-present.
Mayo Clinic Breast Cancer Study [22]	MCBCS	USA	Hospital-based case-control study	Incident cases residing in 6 states (MN, WI, IA, IL, ND, SD) seen at the Mayo Clinic in Rochester, MN from 2002-2010.	Women presenting for general medical examination at the Mayo Clinic from 2002-2010; frequency matched to cases on age, ethnicity and county/state.
Melbourne Collaborative Cohort Study [23]	MCCS	Australia	Population-based prospective cohort study	Incident cases from the cohort of 24,469 women, diagnosed during the follow-up from baseline (1990-1994) to 2008.	Random sample of the initial cohort.
Multi-ethnic Cohort [24]	MEC	USA	Prospective cohort study: nested case-control	Incident cases identified from SEER cancer registries in Los Angeles County & State registries in California & Hawaii, USA from 1993-2002. Grouped by self-reported ethnicity.	Women without cancer from the same States, recruited concurrently with cases & frequency matched to cases by age at blood-draw & self-reported ethnicity.
Montreal Gene-Environment Breast Cancer Study [25]	MTLGEBCS	Canada	Population-based case-control study design	All cases are postmenopausal women (47-75 years) living in Montreal with a primary invasive breast cancer and with no previous occurrence of any type of cancer. All cases were identified from 2007 to 2010 in 15 of 16 Montreal hospitals that treat breast cancer.	Random sample from the universal Provincial Voter Registration List, approximately frequency-matched to cases on age (5-year bins) and living in Montreal.

Norwegian Breast Cancer Study [26]	NBCS*	Norway	Hospital-based case-control study	Incidence cases from three different hospitals: Ullevål Univ. Hospital 1990-94, Norwegian Radium Hospital 1975-1986 and 1995-1998, Haukeland University Hospital 1992-2001.	Women residing in Tromsø and Bergen who attended the Norwegian Breast Cancer Screening Program.
Oulu Breast Cancer Study [27]	OBCS	Finland	Hospital-based case-control study	Consecutive incident cases diagnosed at the Oulu University Hospital during 2000-2004.	Female blood donors recruited in 2002 from the same geographical region in Northern Finland.
Ontario Familial Breast Cancer Registry [28]	OFBCR	Canada	Population-based familial case-control study	Invasive cases aged 20-54 and a random sample aged 55-69 years identified from the Ontario Cancer Registry from 1996-1998. All those at high genetic risk were eligible; random samples of women not meeting these criteria were also asked to participate. During 2001-2005, enrollment was limited to minority and high-risk families.	Identified by calling randomly selected residential telephone numbers in the same geographical region from 1998-2001; frequency matched to cases by age in 5 year categories.
Leiden University Medical Centre Breast Cancer Study [29]	ORIGO	Netherlands	Hospital-based prospective cohort study	Consecutive case patients diagnosed 1996-2006 in 2 hospitals in South-West Netherlands (Leiden & Rotterdam). No selection for family history; Rotterdam case patients selected for diagnosis aged <70. Case patients with in situ carcinomas eligible.	(1) Blood bank healthy donors from Southwest Netherlands recruited in 1996, 2000 or 2007; (2) People who married a person who was part of a family with high breast cancer risk (*BRCA1/2/X*). From the Southwest of the Netherlands, recruited 1990-1996; (3) Females tested at the local clinical genetics department for familial diseases, excluding familial cancer syndromes (no mutation found in gene(s) related to the disease being tested), recruited 1995-2007.
NCI Polish Breast Cancer Study [30]	PBCS	Poland	Population-based case-control study	Incident cases identified through a rapid identification system in participating hospitals covering ~ 90% of all eligible cases, and cancer registries in Warsaw and Łódź covering 100% of all eligible cases (2000-2003).	Randomly selected from population lists of all residents of Poland from 2000-2003, stratified and frequency matched to cases on city and age in 5-year categories.
Karolinska Mammography Project for Risk	pKARMA	Sweden	Case-control study	Incident cases from Jan 2001 - Dec 2008 from the Stockholm/Gotland area. Identified through the Stockholm breast	Unmatched participants of the KARMA mammography screening study recruited between 2010 and

Prediction of Breast Cancer - prevalent cases [25]				cancer registry.	2011 from Southern Sweden and Stockholm.
Rotterdam Breast Cancer Study [31]	RBCS	Netherlands	Hospital based case-control study, Rotterdam area	Familial breast cancer patients selected from the clinical genetics center at Erasmus Medical Center during 1994-2005.	Spouses or mutation-negative siblings of heterozygous Cystic Fibrosis mutation carriers selected from the clinical genetics center at Erasmus Medical Center during 1996-2006.
Singapore and Sweden Breast Cancer Study [32]	SASBAC	Sweden	Population-based case-control study	Women diagnosed in Sweden aged 50-74 in 1993-1995.	Population-based controls frequency matched by age to the cases.
Sheffield Breast Cancer Study [33]	SBCS	UK	Hospital-based case-control study	Women with breast cancer recruited in 1998-2005 at surgical outpatient clinics at the Royal Hallamshire Hospital, Sheffield.	Unselected women attending the Sheffield Mammography Screening Service in 2000-2004 with no evidence of a breast lesion.
Study of Epidemiology and Risk factors in Cancer Heredity [34]	SEARCH	UK	Population-based case-control study	Identified through the Eastern Cancer Registration and Information Centre: (i) prevalent cases; diagnosed 1991-1996; under 55 years of age at diagnosis; recruited 1996-2002 (ii) incident cases; diagnosed since 1996; under 70 years of age at diagnosis; recruited 1996-present.	(a) Women from the same geographic region selected from the EPIC-Norfolk cohort study, 1992-1994 (b) women attending GP practices, frequency matched to cases by age and geographic region (2003-2010) (c) women attending for breast screening as part of the NHSBSP participating in the Sisters in Breast Screening (SIBS) study
Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study [35]	SKKDKFZS*	Germany	Hospital-based breast cancer cohort	Women diagnosed with primary *in situ* or invasive breast cancer at the Städtisches Klinikum Karlsruhe from March 1993 to July 2005. Cases were 21-93 years of age.	Controls for triple negative cases were from an unselected series of unaffected women from the same geographical region.
IHCC-Szczecin Breast Cancer Study [36]	SZBCS	Poland	Hospital based case-control study	Prospectively ascertained cases of invasive breast cancer patients diagnosed at the Regional Oncology Hospital (2002-2003 and 2006-2007) or the University Hospital (2002-2007), both in Szczecin, West Pomerania, Poland.	Selected from a population-based study of the 1.3 million inhabitants of West Pomerania (2003-2004); matched to cases for year of birth, sex and region.
Triple Negative Breast Cancer Consortium Study	TNBCC*	Multiple	Multiple	Triple negative invasive breast cancer cases from multiple countries	Women free of breast cancer from the same geographic regions as cases

[37]					
UK Breakthrough Generations Study [38]	UKBGS	UK	Prospective cohort study: nested case-control study of women who had not had breast cancer prior to entry into the cohort	Cohort members who developed breast cancer or in situ breast cancer after entry into the Breakthrough Generations Study (cohort of >100,000 women followed up for breast cancer, recruited from the UK during 2003-2010).	Women who had not had breast cancer or in situ breast cancer selected by 1:1 matching to cases on date of birth, year of entry in to the study (2003-2010), source of recruitment, availability of blood sample and ethnicity.

*CTS, NBCS and SKKDKFZ are studies in BCAC but were genotyped as part of the triple negative consortium (TNBCC). Part of GENICA was also genotyped as part of TNBCC. Samples in all studies included in our analysis were unique.

Supplemental Table 2 Breast Cancer GWAS included in the GAME-ON DRIVE Meta-analysis

Study	Country	Case Ascertainment	Control Ascertainment	Genotyping platform	Cases	Controls
ABCFS/kConFab [1]	Australia	Recruitment through cancer registries in Victoria and New South Wales	Recruitment from the electoral rolls in Melbourne and Sydney matched to cases by age in 5-year categories	Illumina 610k	282	285
BBCS [4]	UK	Recruitment through cancer registries and clinics in the UK, predominantly bilateral cases	WTCCC2: 1958 Birth Cohort + UK National Blood Service	Illumina 370k (cases) Illumina 1.2M (controls)	1609	5190
GC-HBOC [12]	Germany	BRCA1/2 mutation negative cases from University Clinics in Cologne and Munich	KORA (Cooperative Health Research in the Region Augsburg)	Affymetrix 5.0k (cases) Affymetrix 6.0k (controls)	634	477
MARIE [20]	Germany	Random sample of cases from the MARIE study, but restricted to ductal and lobular carcinomas and oversampled for lobular (about 2:1)	KORA (Cooperative Health Research in the Region Augsburg)	Illumina 370k (cases) Illumina 550k (controls)	708	470
HEBCS [14,39]	Finland	Unselected cases plus additional familial cases from Helsinki University Central Hospital	Population Controls from from the NordicDB, a Nordic pool and portal for genome-wide control data	llumina 550k + 610k (cases) Illumina 370k (controls)	810	1012
SASBAC [14]	Sweden	Population- based case control study of postmenopausal women	Population-based controls frequency matched by age to cases	Illumina 317k+240k (cases) Illumina 550k (controls)	790	756
UK2 [40]	UK	UK cancer genetics clinics + oncology clinics	WTCCC2: 1958 Birth Cohort + UK National Blood Service	Illumina 670k (cases) Illumina 1.2M (controls)	3628	5190

DFBBCS [41]	Netherlands	BRCA1/2 mutation negative familial bilateral breast cancer patients selected from five clinical genetics centers; Erasmus University Medical Center/Daniel den Hoed, The Netherlands Cancer Institute, Leiden University Medical Center, University Medical Center Utrecht, and VU University Medical Center.	Controls were from the Rotterdam study, and are 55 years or older at the time of inclusion. For this study females were selected and breast cancer cases were excluded.	Illumina 610k (cases) Illumina 550k (controls)	464	3265
BPC3 [42]	US/Europe	Estrogen Receptor negative cases from population based cohorts within the Breast and Prostate cancer cohort consortium (BPC3)	Individually matched within cohorts in BPC3	Illumina 660k+550K+317k	2188	25519
Early-onset Breast Cancer GWAS [43]	US/Europe/Australia	Population-based subjects were recruited from eight sites, some of which oversampled cases with a personal or family history. Eligible cases were non-Hispanic White women diagnosed with invasive breast cancer when 51 years or younger and not known to carry pathogenic mutations in BRCA1 or BRCA2.	Eligible controls were non-hispanic white women aged 20-51 years without a history of breast cancer, who were identified largely by random-digit dialing.	Illumina 610k + Cyto 12)	3523	2702
SardiNIA (N/A)	Italy	N/A	N/A	Affymetrix 500k (cases) Affymetrix 6.0k (controls)	1367	1659

GAME-ON=Genetic Associations and Mechanisms in Oncology. DRIVE=Discovery, Biology, and Risk of Inherited Variants in Breast Cancer. N/A=no data were available.

Supplemental Table 3 Associations of the 33 T2D related SNPs with breast cancer risk in the BCAC, GAME-ON DRIVE, and combined.

							BCAC (Cases N=46325/ Controls N=42482)				GAME-ON DRIVE (Cases N=16003/ Controls N=41335)				Combined (Cases N=62328/ Controls N=83817)		
SNPs	Chr	Position[a]	Region	Gene[b]	Alleles[c]	R[2 d]	RAF[e]	OR[f]	95% CI[f]	P[f]	RAF	OR	95% CI	P	OR	95% CI	P
rs10923931	1	120517959	1p12	NOTCH2, ADAM30	T/G	-	0.11	1.02	(0.99,1.06)	0.17	0.11	1.03	(0.98,1.09)	0.292	1.02	(1.00,1.05)	0.09
rs7578597	2	43732823	2p21	THADA	T/C	0.998	0.9	1.00	(0.97,1.03)	0.92	0.89	0.99	(0.94,1.05)	0.744	1.00	(0.97,1.02)	0.80
rs243021	2	60584819	2p16.1	BCL11A	A/G	-	0.46	1.02	(1.00,1.04)	0.03	0.46	1.01	(0.98,1.05)	0.448	1.02	(1.00,1.04)	0.02
rs7593730	2	161171454	2q24.2	RBMS1, ITGB6	C/T	0.994	0.79	0.99	(0.97,1.01)	0.44	0.77	1.01	(0.97,1.05)	0.66	1.00	(0.97,1.02)	0.66
rs2943641	2	227093745	2q36.3	LOC64673, IRS1	C/T	-	0.64	1.00	(0.98,1.02)	0.72	0.65	1.02	(0.98,1.05)	0.347	1.01	(0.99,1.03)	0.43
rs4607103	3	64711904	3p14.1	ADAMTS9	C/T	0.947	0.75	0.99	(0.97,1.02)	0.60	0.77	1.02	(0.98,1.06)	0.377	1.00	(0.98,1.02)	1.00
rs4402960	3	185511687	3q27.2	IGF2BP2	T/G	-	0.31	0.98	(0.96,1.00)	0.05	0.32	0.97	(0.94,1.01)	0.129	0.98	(0.96,1.00)	0.01
rs4689388	4	6270056	4p16.1	WFS1, PPP2R2C	A/G	-	0.58	1.00	(0.98,1.02)	0.96	0.58	1.01	(0.98,1.05)	0.584	1.00	(0.99,1.02)	0.75
rs4457053	5	76424949	5q13.3	ZBED3	G/A	0.855	0.29	0.99	(0.97,1.02)	0.66	0.32	1.00	(0.96,1.04)	0.971	1.00	(0.98,1.02)	0.71
rs10440833	6	20688121	6p22.3	CDKAL1	A/T	0.984	0.27	1.01	(0.99,1.03)	0.42	0.27	1.05	(1.02,1.1)	0.006	1.02	(1.00,1.04)	0.04
rs864745	7	28180556	7p15.1	JAZF1	T/C	0.997	0.5	0.98	(0.96,1.00)	0.08	0.49	0.95	(0.92,0.98)	0.004	0.97	(0.96,0.99)	3.11E-03
rs972283	7	130466854	7q32.3	KLF14	G/A	0.546	0.54	1.01	(0.98,1.04)	0.51	0.51	1.01	(0.97,1.05)	0.704	1.01	(0.99,1.03)	0.45
rs896854	8	95960511	8q22.1	TP53INP1	T/C	0.953	0.52	1.00	(0.98,1.02)	0.90	0.48	1.01	(0.97,1.04)	0.662	1.00	(0.99,1.02)	0.74
rs3802177	8	118185025	8q24.11	SLC30A8	G/A	0.997	0.69	1.01	(0.99,1.03)	0.56	0.69	1.01	(0.98,1.05)	0.438	1.01	(0.99,1.03)	0.37
rs10811661	9	22134094	9p21.3	CDKN2A, CDKN2B	T/C	-	0.83	0.98	(0.96,1.01)	0.21	0.81	0.96	(0.92,1.01)	0.108	0.98	(0.96,1.00)	0.06
rs7018475	9	22137685	9p21.3	CDKN2B	T/G	-	0.74	1.00	(0.97,1.02)	0.71	-	-	-	-	1.00	(0.97,1.02)	0.71
rs13292136	9	81952128	9q21.31	CHCHD9	C/T	0.926	0.92	1.05	(1.01,1.09)	0.02	0.94	0.98	(0.92,1.05)	0.621	1.03	(1.00,1.07)	0.08
rs12779790	10	12328010	10p13	CDC123, CAMK1D	G/A	0.697	0.18	1.00	(0.97,1.03)	0.93	0.19	0.99	(0.94,1.03)	0.597	1.00	(0.97,1.02)	0.83
rs5015480	10	94465559	10q23.33	HHEX,IDE	C/T	0.979	0.58	0.99	(0.97,1.01)	0.36	0.59	1.00	(0.96,1.03)	0.794	0.99	(0.97,1.01)	0.35
rs7903146	10	114758349	10q25.2	TCF7L2	T/C	-	0.28	1.04	(1.02,1.07)	1.20E-04	0.3	1.04	(1.00,1.08)	0.038	1.04	(1.02,1.06)	1.26E-05
rs231362	11	2691471	11p15.5	KCNQ1	G/A	0.705	0.52	1.01	(0.99,1.04)	0.22	0.5	1.00	(0.97,1.04)	0.815	1.01	(0.99,1.03)	0.25
rs5215	11	17408630	11p15.1	KCNJ11	C/T	-	0.38	0.99	(0.97,1.01)	0.17	0.36	0.99	(0.96,1.03)	0.599	0.99	(0.97,1.00)	0.15
rs1552224	11	72433098	11q13.4	CENTD2	A/C	0.859	0.83	0.99	(0.96,1.01)	0.34	0.84	1.01	(0.96,1.06)	0.667	0.99	(0.97,1.02)	0.55
rs1387153	11	92673828	11q14.3	MTNR1B	T/C	0.581	0.28	1.02	(0.99,1.05)	0.22	0.3	0.98	(0.94,1.02)	0.375	1.01	(0.98,1.03)	0.63
rs1531343	12	66174894	12q14.3	HMGA2	C/G	0.943	0.09	1.02	(0.99,1.06)	0.23	0.1	1.01	(0.95,1.07)	0.782	1.02	(0.99,1.05)	0.25
rs7961581	12	71663102	12q21.1	TSPAN8, LGR5	C/T	0.981	0.28	0.97	(0.94,0.99)	2.48E-03	0.26	1.00	(0.96,1.04)	0.962	0.97	(0.96,0.99)	9.01E-03

rs7957197	12	121460686	12q24.31	HNF1A	T/A	0.981	0.8	1.00	(0.98,1.03)	0.72	0.81	1.03	(0.98,1.07)	0.21	1.01	(0.99,1.03)	0.35
rs7178572	15	77747190	15q24.3	HMG20A	G/A	-	0.71	1.02	(0.99,1.04)	0.14	0.71	1.04	(1.00,1.08)	0.048	1.02	(1.00,1.04)	0.02
rs11634397	15	80432222	15q25.1	ZFAND6	G/A	0.938	0.65	1.01	(0.99,1.04)	0.21	0.66	1.04	(1.00,1.09)	0.035	1.02	(1.00,1.04)	0.04
rs8042680	15	91521337	15q26.1	PRC1	A/C	-	0.31	0.98	(0.95,1.00)	0.02	0.3	0.95	(0.92,0.99)	0.006	0.97	(0.95,0.99)	8.05E-04
rs9939609	16	53820527	16q12.2	FTO	A/T	1.000	0.4	0.93	(0.91,0.95)	3.63E-12	0.38	0.96	(0.93,0.99)	0.013	0.94	(0.92,0.95)	4.13E-13
rs8090011	18	7068462	18p11.31	LAMA1	G/C	0.864	0.39	1.00	(0.98,1.02)	0.80	0.38	1.03	(0.99,1.07)	0.111	1.01	(0.99,1.03)	0.30
rs5945326	23	152899922	Xq28	DUSP9	A/G	0.698	0.79	1.00	(0.97,1.02)	0.84	0.77	0.98	(0.92,1.03)	0.391	0.99	(0.97,1.02)	0.58

SNP: single nucleotide polymorphism; Chr: Chromosome; BCAC: Breast Cancer Association Consortium; GAME-ON: Genetic Associations and Mechanisms in Oncology; DRIVE: Discovery, Biology, and Risk of Inherited Variants in Breast Cancer; RAF: risk allele frequency; OR: odds ratio; CI: confidence interval;

[a]: The chromosome physical position is based on the National Center for Biotechnology Information (NCBI) database, Build 36.3.

[b]: The closest gene.

[c]: Alleles risk/reference alleles. Risk allele associated with increased risk of type 2 diabetes.

[d]: Imputation quality in BCAC; - indicates directly genotyped SNPs.

[e]: Among controls.

[f]: All associations were assessed individually by study and then combined by a fixed-effects inverse-variance weighted meta-analysis. All models adjusted for top eight principal components for population stratification. Study specific principal component was further adjusted for LMBC study.

Supplemental Table 4 Subject characteristics by case-control status and their associations with weighted type 2 diabetes genetic risk score in Breast Cancer Association Consortium

		Breast cancer			T2D GRS[e]	
Breast cancer risk factors	**N**	**Case[a] (N=46325)**	**Control[a] (N=42482)**	**P-Value[b]**	**Association/ Summary[c]**	**P-Value[d]**
Age (years)	80455	57.8 ± 11.2	54.9 ± 11.9	<0.01	0.006	0.26
Age at menarche (years)	53990	13.1 ± 1.6	13.1 ± 1.6	0.30	-0.021	<0.01
Age at menopause (years)	26921	48.5 ± 5.8	48.7 ± 5.9	<0.01	-0.004	0.71
Age at first live birth (years)	44735	25.1 ± 4.9	25.4 ± 4.8	<0.01	-0.014	0.05
Body mass index[f] (kg/m[b])	31514	26.4 ± 4.9	26.4 ± 4.8	0.62	0.018	0.03
Parity (numbers)	61837	1.9 ± 1.3	2.0 ± 1.3	<0.01	-0.0005	0.93
Family history of breast cancer	47417			<0.01		0.12
No		21425 (72.3)	15781 (88.8)		4.60 ± 0.52	
Yes		8221 (27.7)	1990 (11.2)		4.62 ± 0.52	
Menopausal status	61686			<0.01		0.69
Pre		10209 (30.7)	9053 (31.9)		4.58 ± 0.52	
Post		23069 (69.3)	19355 (68.1)		4.58 ± 0.51	
Parous	62683			<0.01		0.74
Nulliparous		5205 (15.7)	4305 (14.6)		4.58 ± 0.52	
Parous		27986 (84.3)	25187 (85.4)		4.58 ± 0.52	
Breastfeeding[g]	34778			<0.01		<0.01
Never		3409 (17.0)	2731 (18.5)		4.62 ± 0.51	
Ever		16632 (83.0)	12006 (81.5)		4.56 ± 0.52	
Use of oral contraceptives	28941			<0.01		0.91
Never		6553 (39.9)	4297 (34.3)		4.58 ± 0.52	
Ever		9852 (60.1)	8239 (65.7)		4.58 ± 0.52	
Use of hormone replacement therapy	30983			0.87		0.32
Never		10463 (61.0)	8429 (60.9)		4.58 ± 0.51	
Ever		6685 (39.0)	5406 (39.1)		4.58 ± 0.52	
Smoking status	39562			<0.01		0.21
Never		10104 (50.1)	10386 (53.5)		4.57 ± 0.52	
Past		6331 (31.4)	6529 (33.6)		4.58 ± 0.52	
Current		3719 (18.5)	2493 (12.8)		4.55 ± 0.51	

T2D GRS: Weighted type 2 diabetes related genetic variants risk score

[a]: Mean±sd for continuous variables and frequency (percentage) for categorical variables

[b]: Wilcoxon's test for continuous variables and Pearson's test for categorical variables

[c]: For continuous variables, Pearson's correlations(r) between each risk factor and T2D GRS are presented; For categorical variables, T2D GRS summary statistics (mean±sd) by risk factor categories are presented

[d]: Test for correlation for continuous variables, and Wilcoxon's test for categorical variables.

[e]: Among breast cancer controls

[f]: Among postmenopausal women

[g]: Among parous women

Supplemental Table 5 Sensitivity analysis of the associations between T2D GRS and breast cancer risk in Breast Cancer Association Consortium using genotyped SNPs and imputed SNPs with a $R^2 > 0.9$.

	T2D GRS by Quintiles					
	Q_1 (low)	Q_2	Q_3	Q_4	Q_5	Linear Trend
Overall Breast Cancer						
$N_{cases}/N_{controls}$	9196/8497	9459/8496	9209/8496	9326/8496	9135/8497	
OR[a] [95% CI]	1 (reference)	1.02 (0.98,1.07)	1.00 (0.95,1.04)	1.01 (0.96,1.05)	0.99 (0.95,1.03)	
P-Value[a]		0.3	0.83	0.69	0.64	0.45
ER+ Breast Cancer						
$N_{cases}/N_{controls}$	5439/8497	5544/8496	5368/8496	5397/8496	5326/8497	
OR[a] [95% CI]	1 (reference)	1.02 (0.97,1.08)	0.99 (0.94,1.05)	1.01 (0.96,1.07)	0.99 (0.94,1.04)	
P-Value[a]		0.37	0.83	0.59	0.72	0.61
ER- Breast Cancer						
$N_{cases}/N_{controls}$	1407/8497	1501/8496	1437/8496	1493/8496	1450/8497	
OR[a] [95% CI]	1 (reference)	1.05 (0.96,1.14)	0.98 (0.90,1.07)	1.01 (0.93,1.10)	0.97 (0.89,1.06)	
P-Value[a]		0.31	0.68	0.82	0.49	0.38
Among Pre-menopausal Women						
$N_{cases}/N_{controls}$	2022/1824	2119/1849	1972/1770	2032/1815	2064/1795	
OR[a] [95% CI]	1 (reference)	1.06 (0.96,1.18)	1.00 (0.90,1.12)	1.00 (0.90,1.11)	1.06 (0.95,1.18)	
P-Value[a]		0.25	0.94	0.97	0.29	0.71
Among Post-menopausal Women						
$N_{cases}/N_{controls}$	4702/3887	4751/3903	4604/3863	4553/3852	4459/3850	
OR[a] [95% CI]	1 (reference)	1.02 (0.95,1.09)	1.00 (0.94,1.07)	1.00 (0.93,1.07)	0.99 (0.92,1.06)	
P-Value[a]		0.61	0.99	0.94	0.73	0.6
Among Age<50 Women						
$N_{cases}/N_{controls}$	1823/2365	1919/2387	1852/2388	1890/2364	1902/2388	
OR[a] [95% CI]	1 (reference)	1.05 (0.95,1.16)	0.99 (0.89,1.10)	1.01 (0.91,1.12)	1.02 (0.92,1.13)	
P-Value[a]		0.34	0.84	0.85	0.68	0.94
Among Age≥50 Women						
$N_{cases}/N_{controls}$	7373/6132	7540/6109	7357/6108	7436/6132	7233/6109	
OR[a] [95% CI]	1 (reference)	1.02 (0.97,1.07)	1.00 (0.95,1.06)	1.01 (0.96,1.06)	0.98 (0.93,1.03)	
P-Value[a]		0.47	0.93	0.78	0.46	0.37
Among BMI<25 Women						
$N_{cases}/N_{controls}$	2431/2189	2546/2103	2348/2136	2391/2160	2454/2166	
OR[a] [95% CI]	1 (reference)	1.07 (0.98,1.18)	0.98 (0.89,1.07)	0.97 (0.88,1.06)	1.05 (0.96,1.15)	
P-Value[a]		0.12	0.67	0.49	0.27	0.94
Among BMI≥25 Women						
$N_{cases}/N_{controls}$	2517/2156	2589/2280	2603/2294	2605/2263	2651/2339	
OR[a] [95% CI]	1 (reference)	0.99 (0.91,1.08)	0.96 (0.88,1.05)	1.00 (0.91,1.09)	0.96 (0.88,1.05)	
P-Value[a]		0.82	0.42	0.95	0.34	0.43

T2D GRS: Weighted type 2 diabetes related genetic variants risk score

[a]: All associations were assessed individually by each study and then combined by fixed-effect inverse-variance weighted meta-analysis. All models adjusted for age and top eight principal components for population stratification. Study specific principal component was further adjusted for LMBC study.

Supplemental Table 6 Validation of the developed T2D GRS with prior history of diabetes among controls from the Nashville Breast Health Study, 2001-2011[44]

History of diabetes	T2D GRS by Quintiles					Linear Trend
	Q_1 (low)	Q_2	Q_3	Q_4	Q_5	
Yes/No	13/277	19/272	17/272	24/267	35/254	
OR[a] [95% CI]	1	1.58 (0.76,3.28)	1.38 (0.65,2.92)	2.08 (1.02,4.21)	2.95 (1.51,5.75)	<0.01

T2D GRS: Weighted type 2 diabetes related genetic variants risk score
[a]: All models adjusted for age and top four principal components.

Supplemental References

1. Dite GS, Jenkins MA, Southey MC, Hocking JS, Giles GG, McCredie MR, Venter DJ, Hopper JL (2003) Familial risks, early-onset breast cancer, and BRCA1 and BRCA2 germline mutations. J Natl Cancer Inst 95 (6):448-457
2. Schmidt MK, Tollenaar RA, de Kemp SR, Broeks A, Cornelisse CJ, Smit VT, Peterse JL, van Leeuwen FE, Van't Veer LJ (2007) Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2*1100delC germline mutation. J Clin Oncol 25 (1):64-69. doi:10.1200/JCO.2006.06.3024
3. Schrauder M, Frank S, Strissel PL, Lux MP, Bani MR, Rauh C, Sieber CC, Heusinger K, Hartmann A, Schulz-Wendtland R, Strick R, Beckmann MW, Fasching PA (2008) Single nucleotide polymorphism D1853N of the ATM gene may alter the risk for breast cancer. J Cancer Res Clin Oncol 134 (8):873-882. doi:10.1007/s00432-008-0355-9
4. Fletcher O, Johnson N, Palles C, dos Santos Silva I, McCormack V, Whittaker J, Ashworth A, Peto J (2006) Inconsistent association between the STK15 F31I genetic polymorphism and breast cancer risk. J Natl Cancer Inst 98 (14):1014-1018. doi:10.1093/jnci/djj268
5. Colleran G, McInerney N, Rowan A, Barclay E, Jones AM, Curran C, Miller N, Kerin M, Tomlinson I, Sawyer E (2010) The TGFBR1*6A/9A polymorphism is not associated with differential risk of breast cancer. Breast Cancer Res Treat 119 (2):437-442. doi:10.1007/s10549-009-0395-0
6. Yang R, Dick M, Marme F, Schneeweiss A, Langheinz A, Hemminki K, Sutter C, Bugert P, Wappenschmidt B, Varon R, Schott S, Weber BH, Niederacher D, Arnold N, Meindl A, Bartram CR, Schmutzler RK, Muller H, Arndt V, Brenner H, Sohn C, Burwinkel B (2011) Genetic variants within miR-126 and miR-335 are not associated with breast cancer risk. Breast Cancer Res Treat 127 (2):549-554. doi:10.1007/s10549-010-1244-x
7. Villeneuve S, Fevotte J, Anger A, Truong T, Lamkarkach F, Gaye O, Kerbrat P, Arveux P, Miglianico L, Imbernon E, Guenel P (2011) Breast cancer risk by occupation and industry: analysis of the CECILE study, a population-based case-control study in France. Am J Ind Med 54 (7):499-509. doi:10.1002/ajim.20952
8. Weischer M, Bojesen SE, Tybjaerg-Hansen A, Axelsson CK, Nordestgaard BG (2007) Increased risk of breast cancer associated with CHEK2*1100delC. J Clin Oncol 25 (1):57-63. doi:10.1200/JCO.2005.05.5160
9. Milne RL, Ribas G, Gonzalez-Neira A, Fagerholm R, Salas A, Gonzalez E, Dopazo J, Nevanlinna H, Robledo M, Benitez J (2006) ERCC4 associated with breast cancer risk: a two-stage case-control study using high-throughput genotyping. Cancer Res 66 (19):9420-9427. doi:10.1158/0008-5472.CAN-06-1418
10. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, Pinder R, Reynolds P, Sullivan-Halley J, West D, Wright W, Ziogas A, Ross RK (2002) High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). Cancer Causes Control 13 (7):625-635

11. Widschwendter M, Apostolidou S, Raum E, Rothenbacher D, Fiegl H, Menon U, Stegmaier C, Jacobs IJ, Brenner H (2008) Epigenotyping in peripheral blood cell DNA and breast cancer risk: a proof of principle study. PLoS One 3 (7):e2656. doi:10.1371/journal.pone.0002656
12. Frank B, Hemminki K, Wappenschmidt B, Meindl A, Klaes R, Schmutzler RK, Bugert P, Untch M, Bartram CR, Burwinkel B (2006) Association of the CASP10 V410I variant with reduced familial breast cancer risk and interaction with the CASP8 D302H variant. Carcinogenesis 27 (3):606-609. doi:10.1093/carcin/bgi248
13. Justenhoven C, Pierl CB, Haas S, Fischer HP, Baisch C, Hamann U, Harth V, Pesch B, Bruning T, Vollmert C, Illig T, Dippon J, Ko YD, Brauch H (2008) The CYP1B1_1358_GG genotype is associated with estrogen receptor-negative breast cancer. Breast Cancer Res Treat 111 (1):171-177. doi:10.1007/s10549-007-9762-x
14. Li J, Humphreys K, Heikkinen T, Aittomaki K, Blomqvist C, Pharoah PD, Dunning AM, Ahmed S, Hooning MJ, Martens JW, van den Ouweland AM, Alfredsson L, Palotie A, Peltonen-Palotie L, Irwanto A, Low HQ, Teoh GH, Thalamuthu A, Easton DF, Nevanlinna H, Liu J, Czene K, Hall P (2011) A combined analysis of genome-wide association studies in breast cancer. Breast Cancer Res Treat 126 (3):717-727. doi:10.1007/s10549-010-1172-9
15. Bogdanova NV, Antonenkova NN, Rogov YI, Karstens JH, Hillemanns P, Dork T (2010) High frequency and allele-specific differences of BRCA1 founder mutations in breast cancer and ovarian cancer patients from Belarus. Clin Genet 78 (4):364-372. doi:10.1111/j.1399-0004.2010.01473.x
16. Margolin S, Werelius B, Fornander T, Lindblom A (2004) BRCA1 mutations in a population-based study of breast cancer in Stockholm County. Genet Test 8 (2):127-132. doi:10.1089/1090657041797365
17. Hartikainen JM, Tuhkanen H, Kataja V, Dunning AM, Antoniou A, Smith P, Arffman A, Pirskanen M, Easton DF, Eskelinen M, Uusitupa M, Kosma VM, Mannermaa A (2005) An autosome-wide scan for linkage disequilibrium-based association in sporadic breast cancer cases in eastern Finland: three candidate regions found. Cancer Epidemiol Biomarkers Prev 14 (1):75-80
18. Beesley J, Jordan SJ, Spurdle AB, Song H, Ramus SJ, Kjaer SK, Hogdall E, DiCioccio RA, McGuire V, Whittemore AS, Gayther SA, Pharoah PD, Webb PM, Chenevix-Trench G, Australian Ovarian Cancer Study G, Australian Cancer S, Australian Breast Cancer Family S (2007) Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: results from two Australian studies and an additional validation set. Cancer Epidemiol Biomarkers Prev 16 (12):2557-2565. doi:10.1158/1055-9965.EPI-07-0542
19. De Maeyer L, Van Limbergen E, De Nys K, Moerman P, Pochet N, Hendrickx W, Wildiers H, Paridaens R, Smeets A, Christiaens MR, Vergote I, Leunen K, Amant F, Neven P (2008) Does estrogen receptor negative/progesterone receptor positive breast carcinoma exist? J Clin Oncol 26 (2):335-336; author reply 336-338. doi:10.1200/JCO.2007.14.8411
20. Flesch-Janys D, Slanger T, Mutschelknauss E, Kropp S, Obi N, Vettorazzi E, Braendle W, Bastert G, Hentschel S, Berger J, Chang-Claude J (2008) Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. Int J Cancer 123 (4):933-941. doi:10.1002/ijc.23655
21. Catucci I, Verderio P, Pizzamiglio S, Manoukian S, Peissel B, Barile M, Tizzoni L, Bernard L, Ravagnani F, Galastri L, Pierotti MA, Radice P, Peterlongo P (2009) SNPs in ultraconserved elements and familial breast cancer risk. Carcinogenesis 30 (3):544-545; author reply 546. doi:10.1093/carcin/bgn289
22. Olson JE, Ingle JN, Ma CX, Pelleymounter LL, Schaid DJ, Pankratz VS, Vierkant RA, Fredericksen ZS, Wu Y, Couch FJ, Vachon CM, Sellers TA, Weinshilboum RM (2007) A comprehensive examination of CYP19 variation and risk of breast cancer using two haplotype-tagging approaches. Breast Cancer Res Treat 102 (2):237-247. doi:10.1007/s10549-006-9324-7
23. Giles GG, English DR (2002) The Melbourne Collaborative Cohort Study. IARC Sci Publ 156:69-70
24. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, Stram DO, Monroe KR, Earle ME, Nagamine FS (2000) A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 151 (4):346-357
25. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, Schmidt MK, Chang-Claude J, Bojesen SE, Bolla MK, Wang Q, Dicks E, Lee A, Turnbull C, Rahman N, Breast, Ovarian Cancer Susceptibility C, Fletcher O, Peto J, Gibson L, Dos Santos Silva I, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Czene K, Irwanto A, Liu J, Waisfisz Q, Meijers-Heijboer H, Adank M, Hereditary B, Ovarian Cancer Research Group N, van der Luijt RB, Hein R, Dahmen N, Beckman L, Meindl A, Schmutzler RK, Muller-Myhsok B, Lichtner P, Hopper JL, Southey MC, Makalic E, Schmidt DF, Uitterlinden AG, Hofman A, Hunter DJ, Chanock SJ, Vincent D, Bacot F, Tessier DC, Canisius S, Wessels LF, Haiman CA, Shah M, Luben R, Brown J, Luccarini C, Schoof N, Humphreys K, Li J, Nordestgaard BG, Nielsen SF, Flyger H, Couch FJ,

Wang X, Vachon C, Stevens KN, Lambrechts D, Moisse M, Paridaens R, Christiaens MR, Rudolph A, Nickels S, Flesch-Janys D, Johnson N, Aitken Z, Aaltonen K, Heikkinen T, Broeks A, Veer LJ, van der Schoot CE, Guenel P, Truong T, Laurent-Puig P, Menegaux F, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Zamora MP, Perez JI, Pita G, Alonso MR, Cox A, Brock IW, Cross SS, Reed MW, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Henderson BE, Schumacher F, Le Marchand L, Andrulis IL, Knight JA, Glendon G, Mulligan AM, kConFab I, Australian Ovarian Cancer Study G, Lindblom A, Margolin S, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Bui QM, Stone J, Dite GS, Apicella C, Tsimiklis H, Giles GG, Severi G, Baglietto L, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Brenner H, Muller H, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Jones M, Figueroa J, Lissowska J, Brinton L, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Bruning T, Network G, Radice P, Peterlongo P, Manoukian S, Bonanni B, Devilee P, Tollenaar RA, Seynaeve C, van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Durda K, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Bogdanova NV, Antonenkova NN, Dork T, Kristensen VN, Anton-Culver H, Slager S, Toland AE, Edge S, Fostira F, Kang D, Yoo KY, Noh DY, Matsuo K, Ito H, Iwata H, Sueta A, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Shu XO, Lu W, Gao YT, Cai H, Teo SH, Yip CH, Phuah SY, Cornes BK, Hartman M, Miao H, Lim WY, Sng JH, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Shen CY, Hsiung CN, Wu PE, Ding SL, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Blot WJ, Signorello LB, Cai Q, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Simard J, Garcia-Closas M, Pharoah PD, Chenevix-Trench G, Dunning AM, Benitez J, Easton DF (2013) Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 45 (4):353-361, 361e351-352. doi:10.1038/ng.2563

26. Nordgard SH, Johansen FE, Alnaes GI, Bucher E, Syvanen AC, Naume B, Borresen-Dale AL, Kristensen VN (2008) Genome-wide analysis identifies 16q deletion associated with survival, molecular subtypes, mRNA expression, and germline haplotypes in breast cancer patients. Genes Chromosomes Cancer 47 (8):680-696. doi:10.1002/gcc.20569

27. Erkko H, Xia B, Nikkila J, Schleutker J, Syrjakoski K, Mannermaa A, Kallioniemi A, Pylkas K, Karppinen SM, Rapakko K, Miron A, Sheng Q, Li G, Mattila H, Bell DW, Haber DA, Grip M, Reiman M, Jukkola-Vuorinen A, Mustonen A, Kere J, Aaltonen LA, Kosma VM, Kataja V, Soini Y, Drapkin RI, Livingston DM, Winqvist R (2007) A recurrent mutation in PALB2 in Finnish cancer families. Nature 446 (7133):316-319. doi:10.1038/nature05609

28. John EM, Hopper JL, Beck JC, Knight JA, Neuhausen SL, Senie RT, Ziogas A, Andrulis IL, Anton-Culver H, Boyd N, Buys SS, Daly MB, O'Malley FP, Santella RM, Southey MC, Venne VL, Venter DJ, West DW, Whittemore AS, Seminara D, Breast Cancer Family R (2004) The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast Cancer Res 6 (4):R375-389. doi:10.1186/bcr801

29. Huijts PE, Vreeswijk MP, Kroeze-Jansema KH, Jacobi CE, Seynaeve C, Krol-Warmerdam EM, Wijers-Koster PM, Blom JC, Pooley KA, Klijn JG, Tollenaar RA, Devilee P, van Asperen CJ (2007) Clinical correlates of low-risk variants in FGFR2, TNRC9, MAP3K1, LSP1 and 8q24 in a Dutch cohort of incident breast cancer cases. Breast Cancer Res 9 (6):R78. doi:10.1186/bcr1793

30. Garcia-Closas M, Brinton LA, Lissowska J, Chatterjee N, Peplonska B, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Blair A, Kalaylioglu Z, Rymkiewicz G, Mazepa-Sikora D, Kordek R, Lukaszek S, Sherman ME (2006) Established breast cancer risk factors by clinically important tumour characteristics. Br J Cancer 95 (1):123-129. doi:10.1038/sj.bjc.6603207

31. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, Healey CS, Bowman R, collaborators S, Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odefrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, Fletcher O, Johnson N, Seal S, Stratton MR, Rahman N, Chenevix-Trench G, Bojesen SE, Nordestgaard BG, Axelsson CK, Garcia-Closas M, Brinton L, Chanock S, Lissowska J, Peplonska B, Nevanlinna H, Fagerholm R, Eerola H, Kang D, Yoo KY, Noh DY, Ahn SH, Hunter DJ, Hankinson SE, Cox DG, Hall P, Wedren S, Liu J, Low YL, Bogdanova N, Schurmann P, Dork T, Tollenaar RA, Jacobi CE, Devilee P, Klijn JG, Sigurdson AJ, Doody MM, Alexander BH, Zhang J, Cox A, Brock IW, MacPherson G, Reed MW, Couch FJ, Goode EL, Olson JE, Meijers-Heijboer H, van den Ouweland A, Uitterlinden A, Rivadeneira F, Milne RL, Ribas G, Gonzalez-Neira A, Benitez J, Hopper JL, McCredie M, Southey M, Giles GG, Schroen C, Justenhoven C, Brauch H, Hamann U, Ko YD, Spurdle AB, Beesley J, Chen X, kConFab, Group AM, Mannermaa A, Kosma VM, Kataja V, Hartikainen J, Day NE, Cox DR, Ponder BA (2007) Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 447 (7148):1087-1093. doi:10.1038/nature05887

32. Wedren S, Lovmar L, Humphreys K, Magnusson C, Melhus H, Syvanen AC, Kindmark A, Landegren U, Fermer ML, Stiger F, Persson I, Baron J, Weiderpass E (2004) Oestrogen receptor alpha gene haplotype and postmenopausal breast cancer risk: a case control study. Breast Cancer Res 6 (4):R437-449. doi:10.1186/bcr811
33. MacPherson G, Healey CS, Teare MD, Balasubramanian SP, Reed MW, Pharoah PD, Ponder BA, Meuth M, Bhattacharyya NP, Cox A (2004) Association of a common variant of the CASP8 gene with reduced risk of breast cancer. J Natl Cancer Inst 96 (24):1866-1869. doi:10.1093/jnci/dji001
34. Lesueur F, Pharoah PD, Laing S, Ahmed S, Jordan C, Smith PL, Luben R, Wareham NJ, Easton DF, Dunning AM, Ponder BA (2005) Allelic association of the human homologue of the mouse modifier Ptprj with breast cancer. Hum Mol Genet 14 (16):2349-2356. doi:10.1093/hmg/ddi237
35. Rashid MU, Jakubowska A, Justenhoven C, Harth V, Pesch B, Baisch C, Pierl CB, Bruning T, Ko Y, Benner A, Wichmann HE, Brauch H, Hamann U, Network G (2005) German populations with infrequent CHEK2*1100delC and minor associations with early-onset and familial breast cancer. Eur J Cancer 41 (18):2896-2903. doi:10.1016/j.ejca.2005.04.049
36. Jakubowska A, Jaworska K, Cybulski C, Janicka A, Szymanska-Pasternak J, Lener M, Narod SA, Lubinski J, Group IH-BCS (2009) Do BRCA1 modifiers also affect the risk of breast cancer in non-carriers? Eur J Cancer 45 (5):837-842. doi:10.1016/j.ejca.2008.10.021
37. Stevens KN, Vachon CM, Lee AM, Slager S, Lesnick T, Olswold C, Fasching PA, Miron P, Eccles D, Carpenter JE, Godwin AK, Ambrosone C, Winqvist R, Brauch H, consortium G, Schmidt MK, Cox A, Cross SS, Sawyer E, Hartmann A, Beckmann MW, Schulz-Wendtland R, Ekici AB, Tapper WJ, Gerty SM, Durcan L, Graham N, Hein R, Nickels S, Flesch-Janys D, Heinz J, Sinn HP, Konstantopoulou I, Fostira F, Pectasides D, Dimopoulos AM, Fountzilas G, Clarke CL, Balleine R, Olson JE, Fredericksen Z, Diasio RB, Pathak H, Ross E, Weaver J, Rudiger T, Forsti A, Dunnebier T, Ademuyiwa F, Kulkarni S, Pylkas K, Jukkola-Vuorinen A, Ko YD, Van Limbergen E, Janssen H, Peto J, Fletcher O, Giles GG, Baglietto L, Verhoef S, Tomlinson I, Kosma VM, Beesley J, Greco D, Blomqvist C, Irwanto A, Liu J, Blows FM, Dawson SJ, Margolin S, Mannermaa A, Martin NG, Montgomery GW, Lambrechts D, dos Santos Silva I, Severi G, Hamann U, Pharoah P, Easton DF, Chang-Claude J, Yannoukakos D, Nevanlinna H, Wang X, Couch FJ (2011) Common breast cancer susceptibility loci are associated with triple-negative breast cancer. Cancer Res 71 (19):6240-6249. doi:10.1158/0008-5472.CAN-11-1266
38. Swerdlow AJ, Jones ME, Schoemaker MJ, Hemming J, Thomas D, Williamson J, Ashworth A (2011) The Breakthrough Generations Study: design of a long-term UK cohort study to investigate breast cancer aetiology. Br J Cancer 105 (7):911-917. doi:10.1038/bjc.2011.337
39. Leu M, Humphreys K, Surakka I, Rehnberg E, Muilu J, Rosenstrom P, Almgren P, Jaaskelainen J, Lifton RP, Kyvik KO, Kaprio J, Pedersen NL, Palotie A, Hall P, Gronberg H, Groop L, Peltonen L, Palmgren J, Ripatti S (2010) NordicDB: a Nordic pool and portal for genome-wide control data. Eur J Hum Genet 18 (12):1322-1326. doi:10.1038/ejhg.2010.112
40. Turnbull C, Ahmed S, Morrison J, Pernet D, Renwick A, Maranian M, Seal S, Ghoussaini M, Hines S, Healey CS, Hughes D, Warren-Perry M, Tapper W, Eccles D, Evans DG, Breast Cancer Susceptibility C, Hooning M, Schutte M, van den Ouweland A, Houlston R, Ross G, Langford C, Pharoah PD, Stratton MR, Dunning AM, Rahman N, Easton DF (2010) Genome-wide association study identifies five new breast cancer susceptibility loci. Nat Genet 42 (6):504-507. doi:10.1038/ng.586
41. Hofman A, Breteler MM, van Duijn CM, Janssen HL, Krestin GP, Kuipers EJ, Stricker BH, Tiemeier H, Uitterlinden AG, Vingerling JR, Witteman JC (2009) The Rotterdam Study: 2010 objectives and design update. Eur J Epidemiol 24 (9):553-572. doi:10.1007/s10654-009-9386-z
42. Siddiq A, Couch FJ, Chen GK, Lindstrom S, Eccles D, Millikan RC, Michailidou K, Stram DO, Beckmann L, Rhie SK, Ambrosone CB, Aittomaki K, Amiano P, Apicella C, Australian Breast Cancer Tissue Bank I, Baglietto L, Bandera EV, Beckmann MW, Berg CD, Bernstein L, Blomqvist C, Brauch H, Brinton L, Bui QM, Buring JE, Buys SS, Campa D, Carpenter JE, Chasman DI, Chang-Claude J, Chen C, Clavel-Chapelon F, Cox A, Cross SS, Czene K, Deming SL, Diasio RB, Diver WR, Dunning AM, Durcan L, Ekici AB, Fasching PA, Familial Breast Cancer S, Feigelson HS, Fejerman L, Figueroa JD, Fletcher O, Flesch-Janys D, Gaudet MM, Consortium G, Gerty SM, Rodriguez-Gil JL, Giles GG, van Gils CH, Godwin AK, Graham N, Greco D, Hall P, Hankinson SE, Hartmann A, Hein R, Heinz J, Hoover RN, Hopper JL, Hu JJ, Huntsman S, Ingles SA, Irwanto A, Isaacs C, Jacobs KB, John EM, Justenhoven C, Kaaks R, Kolonel LN, Coetzee GA, Lathrop M, Le Marchand L, Lee AM, Lee IM, Lesnick T, Lichtner P, Liu J, Lund E, Makalic E, Martin NG, McLean CA, Meijers-Heijboer H, Meindl A, Miron P, Monroe KR, Montgomery GW, Muller-Myhsok B, Nickels S, Nyante SJ, Olswold C, Overvad K, Palli D, Park DJ, Palmer JR, Pathak H, Peto J, Pharoah P, Rahman N, Rivadeneira F, Schmidt DF, Schmutzler RK, Slager S, Southey MC, Stevens KN,

Sinn HP, Press MF, Ross E, Riboli E, Ridker PM, Schumacher FR, Severi G, Dos Santos Silva I, Stone J, Sund M, Tapper WJ, Thun MJ, Travis RC, Turnbull C, Uitterlinden AG, Waisfisz Q, Wang X, Wang Z, Weaver J, Schulz-Wendtland R, Wilkens LR, Van Den Berg D, Zheng W, Ziegler RG, Ziv E, Nevanlinna H, Easton DF, Hunter DJ, Henderson BE, Chanock SJ, Garcia-Closas M, Kraft P, Haiman CA, Vachon CM (2012) A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. Hum Mol Genet 21 (24):5373-5384. doi:10.1093/hmg/dds381
43. Ahsan H, Halpern J, Kibriya MG, Pierce BL, Tong L, Gamazon E, McGuire V, Felberg A, Shi J, Jasmine F, Roy S, Brutus R, Argos M, Melkonian S, Chang-Claude J, Andrulis I, Hopper JL, John EM, Malone K, Ursin G, Gammon MD, Thomas DC, Seminara D, Casey G, Knight JA, Southey MC, Giles GG, Santella RM, Lee E, Conti D, Duggan D, Gallinger S, Haile R, Jenkins M, Lindor NM, Newcomb P, Michailidou K, Apicella C, Park DJ, Peto J, Fletcher O, dos Santos Silva I, Lathrop M, Hunter DJ, Chanock SJ, Meindl A, Schmutzler RK, Muller-Myhsok B, Lochmann M, Beckmann L, Hein R, Makalic E, Schmidt DF, Bui QM, Stone J, Flesch-Janys D, Dahmen N, Nevanlinna H, Aittomaki K, Blomqvist C, Hall P, Czene K, Irwanto A, Liu J, Rahman N, Turnbull C, Familial Breast Cancer S, Dunning AM, Pharoah P, Waisfisz Q, Meijers-Heijboer H, Uitterlinden AG, Rivadeneira F, Nicolae D, Easton DF, Cox NJ, Whittemore AS (2014) A genome-wide association study of early-onset breast cancer identifies PFKM as a novel breast cancer gene and supports a common genetic spectrum for breast cancer at any age. Cancer Epidemiol Biomarkers Prev 23 (4):658-669. doi:10.1158/1055-9965.EPI-13-0340
44. Fu Z, Deming SL, Fair AM, Shrubsole MJ, Wujcik DM, Shu XO, Kelley M, Zheng W (2011) Well-done meat intake and meat-derived mutagen exposures in relation to breast cancer risk: the Nashville Breast Health Study. Breast Cancer Res Treat 129 (3):919-928. doi:10.1007/s10549-011-1538-7