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

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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.

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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

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.

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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.

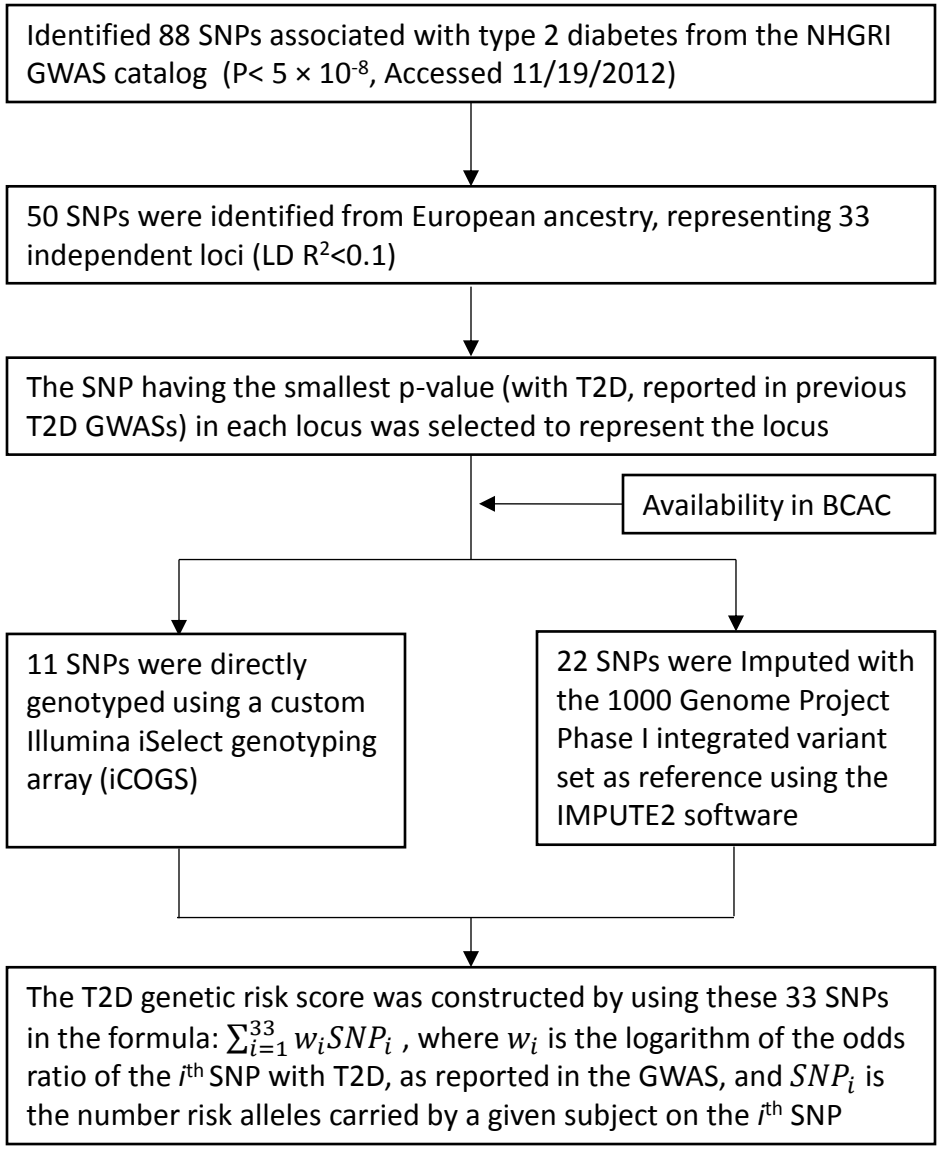
[c]: Risk/reference alleles. The risk allele is the allele that associated with increased risk of type 2 diabetes.

[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