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Genetic Susceptibility to Type 2 Diabetes and Breast Cancer Risk in Women of European and African Ancestry

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Abstract

Background—Epidemiologic studies have reported a positive association between type 2 diabetes (T2D) and breast cancer risk, independent of body weight.

Methods—We investigated 40 genetic variants known to be associated with T2D in relation to breast cancer risk among 2651 breast cancer cases and 2520 controls of African or European ancestry that were pooled from seven studies.

Results—We found that two T2D risk alleles in Caucasian women (rs5945326-G, rs12518099-C) and one in women of African ancestry (rs7578597-T) were positively associated with breast cancer risk at a nominal significance level of 0.05, whereas two T2D risk alleles were inversely associated with breast cancer risk in Caucasian women (rs1111875-C, rs10923931-T). The composite T2D susceptibility score (the number of risk allele) was not significantly associated with breast cancer risk.

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Conclusion—The association between established T2D genetic susceptibility variants and breast cancer risk in women of African or European ancestry is likely weak, if it does exist.

Impact—The pleiotropic effects of known T2D risk alleles cannot explain the association between T2D and breast cancer risk.

Introduction

Epidemiologic studies have reported a positive moderate association between type 2 diabetes (T2D) and breast cancer risk, independent of obesity (1). Two meta-analyses indicated relative risks of 1.15 and 1.20 for breast cancer in T2D patients compared to women without T2D (1, 2) . T2D may lead to breast cancer through the effects of insulin and insulin-like growth factor (IGF) in addition to the dysregulation of sex hormones (3). However, the exact mechanisms underlying the association between the two diseases remain unclear. Unmeasured confounding could be an alternative explanation. Here, using data from 2651 breast cancer cases and 2520 controls, we further examined whether genetic susceptibility to T2D is related to breast cancer risk, which is less subject to environmental confounders because of Mendelian randomization (4). We also tested for pleiotropic effect of each of 40 established T2D risk variants.

Methods

Study subjects

We pooled data from seven studies to compose a large biracial sample, with 2,279 Caucasian women (1142 cases and 1,137 controls) from the Cancer Genetic Markers of Susceptibility (CGEMS) breast cancer project (5), and a total of 2,892 women of African ancestry from the Nigerian Breast Cancer Study (681 cases and 282 controls), the Baltimore Breast Cancer Study (117 cases and 111 controls), the Barbados National Cancer Study (93 cases and 244 controls), the Northern California site of the Breast Cancer Family Registry (199 cases and 213 controls), the Racial Variability in Genotypic Determinants of Breast Cancer Risk Study (151 cases and 272 controls), and the Chicago Cancer Prone Study (268 cases and 261 controls).

Genotyping

Using the catalog of genome-wide association studies (6), we chose 40 single nucleotide polymorphisms (SNPs) from 40 T2D susceptibility loci. For loci with multiple index SNPs, we picked the most reproducible SNP for each locus. For Caucasian women, 25 of 40 SNPs were genotyped using Illumina HumanHap500 array in the CGEMS breast cancer project (5) and downloaded from the Database of Genotypes and Phenotypes (dbGaP). The remaining 15 SNPs were imputed using MACH (7). The imputation quality is excellent with average R^2 being 0.93 (ranging from 0.71-1.00). For women of African ancestry, we genotyped the 40 T2D SNPs and 29 ancestry informative markers using Illumina GoldenGate platform; one SNP (rs13266634) failed. The genotyping successful rate was 99.8% for the remaining SNPs. Hardy-Weinberg equilibrium was assessed for each allele, separately for each study; 18 out of the 274 tests were significant compared to 14 expected.

Statistical analysis

For each individual, a composite susceptibility score was constructed as the total count of risk alleles of the 39 successfully genotyped T2D SNPs. Both continuous and categorical risk scores (quartile in controls) were examined in relation to breast cancer risk using logistic regression, stratified by race and adjusted for age group (5-year interval), study site, and genetic ancestry estimate from ancestry informative markers. Additionally, we tested

each of the 40 T2D variants for association with breast cancer under log-additive genetic models for the two racial groups separately and together. The statistical analysis was conducted using SAS 9.2 package (SAS Institute, Cary, NC).

Results

Three T2D SNPs were positively associated with breast cancer risk at a nominal significance level, consistent with a positive association between T2D and breast cancer: rs5945326 (*DUSP9*) and rs12518099 (*CETN3*) in Caucasian women and rs7578597 (*THADA*) in women of African ancestry (Table 1). However, two T2D risk alleles (rs1111875 and rs10923931) were inversely associated with breast cancer risk in Caucasian women. Two SNPs remained nominally significant in the pooled analysis (rs7578597 and rs12518099). After Bonferroni correction, none of the above variants remained significant. Table 2 shows that the composite T2D susceptibility score was not significantly associated with breast cancer. In the pooled analysis, the odds ratio for the fourth quartile was 1.13 compared with quartile 1 (p-trend=0.09).

Discussion

We found that the established risk variants for T2D did not have a strong association with breast cancer risk among women of African and European ancestry. This finding is in line with a previously published study, wherein 18 common variants for T2D were examined (8). Three of the five nominally significant SNPs in the present study were also examined by Chen et al., but none were statistically significant in their study (8). A GWAS found an association between breast cancer risk and SNP rs1011970 on 9p21 (9), which is 67kb upstream of SNP rs7020996 examined in the present study. However, these two SNPs are not in linkage disequilibrium. Another study, based on moderate sample size, found that SNPs in the *FTO* gene were associated with breast cancer risk (10). Our study found no association with rs8050136 *(FTO).* In conclusion, this study provides no evidence that the association between T2D and breast cancer risk (if it does exist) can be explained by the pleiotropic effects of known T2D risk alleles.

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Table 1

Association of known T2D risk alleles with breast cancer risk by race/ethnicity

		OR (95% CI)* Risk allele frequency in controls		P for trend pooled	P for heterogeneity
SNP reference/risk allele	**Region reported gene(s)**	**European descent 1,142 cases 1,137 controls**	**African descent 1,509 cases 1,383 controls**		
rs10923931 G/T	1p12 *NOTCH2, ADAM30*	**0.81 (0.67 – 0.98)** 0.115	1.02 (0.91 – 1.14) 0.333	0.38	0.046
rs6712932 C/T	2q12.1 Intergenic	0.96 (0.85 – 1.08) 0.664	1.08 (0.96 – 1.23) 0.717	0.67	0.13
rs243021 G/A	2p16.1 *BCL11A*	1.04 (0.93 – 1.17) 0.643	0.92 (0.82 – 1.03) 0.376	0.57	0.13
rs7578597 C/T	2p21 *THADA*	1.06 (0.88 – 1.27) 0.890	**1.17 (1.04 – 1.33)** 0.713	**0.017**	0.37
rs2943641 T/C	2q36.3 *LOC64673, IRS1*	0.95 (0.84 – 1.07) 0.653	1.04 (0.92 – 1.17) 0.706	0.87	0.32
rs358806 C/A	3p14 *CACNA2D3, WNT5A*	0.92 (0.80 – 1.07) 0.204	0.97 (0.81 – 1.16) 0.108	0.27	0.74
rs4607103 T/C	3p14.1 *ADAMTS9*	0.91 (0.80 – 1.04) 0.748	0.96 (0.85 – 1.07) 0.700	0.20	0.46
rs6780569 A/G	3p24.3 *UBE2E2*	0.93 (0.76 – 1.13) 0.910	1.04 (0.93 – 1.16) 0.414	0.71	0.29
rs4402960 G/T	3q27.2 *IGF2BP2*	0.99 (0.88 – 1.12) 0.327	1.03 (0.92 – 1.15) 0.531	0.69	0.59
rs4689388 C/T	4p16.1 *WFS1, PPP2R2C*	1.06 (0.95 – 1.20) 0.577	1.09 (0.96 – 1.23) 0.715	0.11	0.87
rs7659604 C/T	4q27 TMEM155	1.06 (0.94 – 1.19) 0.394	0.95 (0.84 – 1.07) 0.674	0.93	0.20
rs4457053 A/G	5q13.3 *ZBED3*	1.04 (0.91 – 1.19) 0.305	1.04 (0.91 – 1.20) 0.169	0.41	0.95
rs12518099 T/C	5q14.3 *LOC72901, CETN3*	**1.17 (1.02 – 1.34)** 0.219	1.04 (0.91 – 1.19) 0.485	**0.044**	0.25
rs9472138 C/T	6p21.1 *VEGFA*	0.99 (0.87 – 1.13) 0.285	0.89 (0.77 – 1.02) 0.186	0.24	0.30
rs10946398 A/C	6p22.3 *CDKAL*	1.02 (0.90 – 1.15) 0.327	0.98 (0.88 – 1.08) 0.540	0.86	0.65
rs849134 G/A	7p15.1 *JAZF1*	1.07 (0.95 – 1.21)	0.94 (0.83 – 1.07)	0.91	0.14

SNP reference/risk allele	Region reported gene(s)	OR (95% CI)* Risk allele frequency in controls		P for trend pooled	P for heterogeneity
		European descent 1,142 cases 1,137 controls	African descent 1,509 cases 1,383 controls		
		0.510	0.755		
rs972283 A/G	7q32.3 *KLF14*	0.99 (0.87 – 1.13) 0.511	0.93 (0.79 – 1.10) 0.862	0.49	0.56
rs896854 C/T	8q22.1 *TP53INP1*	1.09 (0.97 – 1.22) 0.478	1.02 (0.91 – 1.16) 0.706	0.20	0.49
rs13266634 T/C	8q24.11 *SLC30A8*	1.05 (0.93 – 1.19) 0.686	NA; genotyping failed		
rs7020996 T/C	9p21.3 *CDKN2A, CDKN2B*	1.04 (0.86 – 1.26) 0.840	0.99 (0.88 – 1.11) 0.924	0.96	0.63
rs13292136 T/C	9q21.31 *CHCHD9*	0.98 (0.77 – 1.25) 0.940	0.99 (0.81 – 1.22) 0.924	0.76	0.98
rs17584499 C/T	9p24.1 *PTPRD*	0.95 (0.82 – 1.11) 0.193	1.17 (0.91 – 1.52) 0.046	0.89	0.17
rs12779790 A/G	10p13 *CDC123, CAMK1D*	0.94 (0.81 – 1.10) 0.189	1.01 (0.86 – 1.18) 0.146	0.58	0.56
rs1111875 T/C	10q23.33 *HHEX*	**0.88 (0.78 – 0.99)** 0.602	1.10 (0.97 – 1.25) 0.762	0.47	0.01
rs7903146 C/T	10q25.2 *TCF7L2*	1.02 (0.90 – 1.16) 0.287	1.05 (0.93 – 1.19) 0.282	0.48	0.80
rs9300039 A/C	11p12 Intergenic	1.04 (0.85 – 1.27) 0.905	0.97 (0.81 – 1.15) 0.889	0.98	0.59
rs1387153 C/T	11q14.3 *MTNR1B*	1.01 (0.89 – 1.15) 0.297	1.07 (0.95 – 1.20) 0.354	0.34	0.49
rs5215 T/C	11p15.1 *KCNJ11*	0.94 (0.83 – 1.05) 0.365	0.90 (0.73 – 1.12) 0.078	0.16	0.82
rs2237892 T/C	11p15.5 *KCNQ1*	0.87 (0.68 – 1.10) 0.941	1.08 (0.90 – 1.30) 0.897	0.92	0.16
rs12304921 A/G	12q13.13 *HIGD1C*	0.99 (0.85 – 1.17) 0.156	1.02 (0.89 – 1.18) 0.174	0.90	0.79
rs1531343 G/C	12q14.3 *HMGA2*	0.85 (0.69 – 1.04) 0.100	1.004 (0.90 – 1.12) 0.380	0.53	0.14
rs4760790 G/A	12q21.1 *TSPAN8, LGR5*	0.98 (0.87 – 1.12) 0.279	1.05 (0.91 – 1.22) 0.154	0.84	0.60
rs7957197 A/T	12q24.31 *HNF1A*	1.02 (0.88 – 1.18) 0.799	1.04 (0.90 – 1.20) 0.827	0.68	0.96

		OR (95% CI)* Risk allele frequency in controls		P for trend pooled	P for heterogeneity
SNP reference/risk allele	**Region reported gene(s)**	**European descent 1,142 cases 1,137 controls**	**African descent 1,509 cases 1,383 controls**		
rs7172432 G/A	15q22.2 *C2CD4A, C2CD4B*	1.06 (0.94 – 1.19) 0.574	1.07 (0.95 – 1.21) 0.308	0.11	0.79
rs11634397 A/G	15q25.1 *ZFAND6*	1.01 (0.88 – 1.15) 0.657	1.05 (0.94 – 1.18) 0.430	0.50	0.65
rs8042680 C/A	15q26.1 *PRC1*	0.95 (0.84 – 1.08) 0.325	0.99 (0.82 – 1.19) 0.893	0.44	0.74
rs8050136 C/A	16q12.2 *FTO*	0.97 (0.86 – 1.10) 0.407	0.94 (0.84 – 1.05) 0.437	0.26	0.69
rs4430796 A/G	17q12 *HNF1B, TCF2*	1.05 (0.94 – 1.18) 0.477	1.03 (0.92 – 1.16) 0.658	0.27	0.84
rs391300 A/G	17p13.3 *SRR*	1.02 (0.90 – 1.15) 0.630	1.10 (0.98 – 1.23) 0.455	0.16	0.30
rs5945326 A/G	Xq26 *DUSP9*	**1.15 (1.003 – 1.32)** 0.218	0.99 (0.87 – 1.13) 0.214	0.18	0.12

*Odds ratio (95% confidence interval) adjusted for age, study, and genetic ancestry.

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Table 2

Association of T2D risk score and breast cancer risk

	European descent			African descent			Pooled
Risk allele count	**Cases (n=1142)**	**Controls (n=1137)**	**OR (95% CI)***	**Cases (n=1509)**	**Controls (n=1383)**	**OR (95% CI)***	**OR (95% CI)***
Categorical							
25-36	452	449	1 (ref.)	370	393	1 (ref.)	1 (ref.)
37-38	213	244	0.87 (0.69-1.09)	277	252	1.11 (0.88-1.40)	0.98 (0.83-1.15)
39-41	292	265	1.09 (0.88-1.35)	486	425	1.11 (0.90-1.36)	1.09 (0.94-1.26)
42-50	185	176	1.02 (0.80-1.31)	376	313	1.21 (0.97-1.51)	1.13 (0.96-1.32)
P-trend			0.53			0.10	0.09
Continuous							
Mean ± SD	37.5± 4.0	37.5± 3.8		39.1± 3.6	38.7± 3.7		
Per 4 risk alleles			1.00 (0.92-1.09)			1.08 (0.99-1.17)	1.04 (0.98-1.10)

*Odds ratio (95% confidence interval) adjusted for age, study, and genetic ancestry.