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No association of risk variants for diabetes and obesity with breast cancer: the Multiethnic Cohort and PAGE studies

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Abstract

Body mass index is an established risk factor for post-menopausal breast cancer. Epidemiologic studies have also reported a positive association between type 2 diabetes (T2D) and breast cancer risk. To investigate a genetic basis linking these common phenotypes with breast cancer, we tested 31 common variants for T2D and obesity in a case-control study of 1,915 breast cancer cases and 2,884 controls nested within the Multiethnic Cohort (MEC) study. Following adjustment for multiple tests, we found no significant association between any variant and breast cancer risk. Summary scores comprised of the numbers of risk alleles for T2D and/or obesity were also not found to be significantly associated with breast cancer risk.

Keywords

type 2 diabetes; obesity; GWAS; SNPs; breast cancer

Introduction

Obesity is an important risk factor for many common chronic diseases, including breast cancer in postmenopausal women (1-4) and type 2 diabetes (T2D). Many epidemiologic studies have also reported diabetics to have a greater risk of breast cancer than non-diabetics, independent of body weight (5-8). Biological markers of obesity and diabetes, such as insulin and insulin-like growth factors (IGFs), have been associated with breast cancer risk (9-13), which suggests that there may be shared biological processes and pathways involved in the etiology of these common phenotypes. In this study, we further explored the hypothesis that there are shared etiologic pathways for obesity, T2D and breast cancer, by testing for pleiotropic effects of 31 established risk variants for T2D (n=18) and obesity (n=13) in a study of 1,915 breast cancer cases and 2,884 breast cancer controls from the Multiethnic Cohort (MEC).

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Methods

Study subjects

The MEC study is a prospective cohort study consisting of 215,251 adult men and women living in Hawaii and California (mainly Los Angeles county)(14) predominantly composed of five populations: European Americans, African Americans, Native Hawaiians, Japanese and Latinos. Through 2005, the breast cancer case-control study in the MEC included 1,915 invasive cases with a diagnosis after cohort entry and 2,014 controls with no history of breast cancer. Cases were identified through cohort linkage to population-based cancer Surveillance, Epidemiology and End Results (SEER) registries in California and Hawaii(14). We also included an additional 870 controls with no history of breast cancer from a colorectal cancer (CRC) case-control study in the MEC.

Genotyping

Genotyping of the 31 SNPs was performed using the allelic discrimination assay on whole genome amplified DNA samples, except for the additional CRC controls which used genomic DNA(15). The genotype completion rate for each SNP was >95.0% among both cases and controls in each racial/ethnic group, with an average completion rate of 99.1% in both cases and controls. Hardy-Weinberg Equilibrium (HWE) was assessed for each allele in each racial/ethnic group using a chi-square test (1df). Among the 155 tests for HWE, 8 significant departures were expected by chance while 7 were observed.

Statistical analysis

In each of the five populations in the MEC as well as in the pooled sample, we tested for log-additive effects of the 31 variants with odds ratios estimated using unconditional logistic regression adjusted for age (quartiles), body mass index (quartiles), self-reported diabetes and race/ethnicity (in pooled analysis). To account for multiple hypothesis testing, an $\alpha \leq 0.0016$ (0.05/31 tests) was used. To examine the combined contribution of all variants on breast cancer risk, we constructed three summary risk scores, taken as the number of risk alleles for the 18 validated T2D SNPs, for the 13 validated obesity SNPs and for the total of 31 T2D/obesity SNPs respectively. Individuals missing genotypes were given the mean score for that locus within each population of the same ethnicity/race. We excluded from the analysis 32 (1.7%) cases and 78 (2.7%) controls with missing genotypes for ≥ 10 SNPs. Analysis for overall breast cancer risk was conducted on 1,883 cases and 2,806 controls. We also conducted analyses stratified by ER status (ER+ cases, n=1,217; ER- cases, n=299). The statistical analysis was performed using the SAS 9.2 package, SAS Institute Inc., Cary, North Carolina.

Results

The mean age of the breast cancer cases (65.3 years at diagnosis) was only slightly higher than that of controls (64.9 years at the time of blood draw).

We observed a nominally significant association ($p<0.05$) with only 1 variant in the pooled analysis (Table 1) whereas 1.6 were expected by chance. The most significant findings

included inverse associations with rs5219 (*KCNJ11)* among all cases, (OR=0.89, P=0.012) and ER- cases (OR=0.73, P=0.0031), as well as with rs864745 (*JAZF)* in ER- cases (OR=0.75, P=0.0020). These associations, however, were no longer significant after adjusting for multiple comparisons (Table 1, Supplemental Table 1-3). Results were similar when limiting the analysis to postmenopausal women (n=1,197 cases and 1,731 controls; Supplemental Table 4).

We also did not find any significant association of the aggregate risk scores comprised of the T2D, obesity or T2D/obesity risk alleles with breast cancer risk (T2D SNPs: OR=1.01; 95% CI=0.99-1.04; P=0.31; obesity SNPs: OR=1.02; 95% CI=0.99-1.04; P=0.24; All SNPs: OR=1.01; 95% CI=1.00-1.03; P=0.14)(Supplemental Table 5).

Discussion

We found no strong evidence that the validated risk variants for T2D and obesity are associated with breast cancer risk among women of various ethnicities. Neither did we find any significant association between a summary risk score comprised of the risk alleles for these variants and breast cancer risk. We had adequate statistical power (80%) to detect an OR of 1.21 for SNPs with a MAF of 0.10, and an OR of 1.15 for SNPs with a MAF of 0.20. However, power may be lower as most of these markers of T2D and obesity risk were identified in GWAS among men and women of European ancestry and may not be strongly correlated with the functional alleles in all populations.

In conclusion, while obesity and, to a lesser extent, T2D are risk factors for breast cancer, we found no evidence that the known risk variants for T2D or obesity are associated with breast cancer risk in a multiethnic population. These data suggest that the potential for a shared biology between T2D/obesity and breast cancer is not due to pleiotropic effects of these risk loci.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

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

SNP/ Allele tested[b]	Chr./ Nearest gene	OR(95%CI)[a] Risk allele frequency in controls						P for trend pooled	P_{het}[c]
		European Americans 503 cases 633 controls	African Americans 381 cases 542 controls	Native Hawaiians 135 cases 344 controls	Japanese Americans 509 cases 782 controls	Latinos 355 cases 505 controls	Pooled 1,883 cases 2,806 controls		
Type 2 Diabetes SNPs									
rs10923931 T	1 *NOTCH2*	1.13(0.85-1.49) 0.097	0.87(0.71-1.07) 0.33	0.96(0.49-1.86) 0.055	0.97(0.58-1.63) 0.025	1.28(0.93-1.76) 0.095	1.01(0.88-1.15) 0.12	0.94	0.32
rs7578597 T	2 *THADA*	1.05(0.88-1.48) 0.89	1.13(0.90-1.41) 0.75	1.04(0.54-2.00) 0.95	1.47(0.69-3.15) 0.99	0.71(0.48-1.03) 0.94	1.03(0.89-1.20) 0.90	0.69	0.27
rs1801282 C	3 *PPARG*	1.14(0.88-1.48) 0.87	0.70(0.39-1.26) 0.98	1.06(0.55-2.04) 0.94	0.83(0.54-1.28) 0.97	1.15(0.84-1.57) 0.89	1.04(0.88-1.23) 0.93	0.63	0.41
rs4607103 C	3 *ADAMTS9*	0.86(0.71-1.04) 0.74	0.99(0.81-1.22) 0.71	0.89(0.64-1.22) 0.74	0.95(0.80-1.13) 0.65	0.99(0.80-1.22) 0.68	0.94(0.86-1.03) 0.70	0.20	0.81
rs4402960 T	3 *IGF2BP2*	0.91(0.76-1.08) 0.34	1.07(0.88-1.30) 0.49	0.89(0.64-1.23) 0.28	0.91(0.76-1.08) 0.33	1.16(0.92-1.45) 0.26	0.98(0.89-1.07) 0.34	0.61	0.30
rs10010131 G	4 *WFS1*	1.01(0.86-1.20) 0.59	0.91(0.74-1.12) 0.67	0.86(0.60-1.23) 0.80	1.14(0.68-1.89) 0.98	0.96(0.78-1.19) 0.70	0.97(0.87-1.07) 0.76	0.55	0.82
rs7754840 C	6 *CDKAL1*	1.02(0.85-1.20) 0.31	1.10(0.91-1.34) 0.54	1.04(0.78-1.38) 0.52	1.06(0.90-1.25) 0.43	1.00(0.81-1.23) 0.32	1.05(0.96-1.14) 0.42	0.29	0.97
rs864745 A	7 *JAZF1*	0.93(0.78-1.09) 0.53	0.87(0.71-1.07) 0.74	0.81(0.59-1.10) 0.72	1.02(0.84-1.23) 0.78	1.01(0.83-1.24) 0.62	0.94(0.86-1.03) 0.68	0.17	0.68
rs13266634 C	8 *SLC30A8*	1.00(0.83-1.20) 0.71	0.78(0.57-1.07) 0.90	0.95(0.70-1.28) 0.63	1.05(0.89-1.24) 0.63	1.04(0.82-1.31) 0.75	1.00(0.90-1.10) 0.72	0.91	0.60
rs2383208 A	9 *CDKN2B*	1.01(0.81-1.25) 0.81	1.06(0.83-1.34) 0.80	0.98(0.71-1.35) 0.74	1.07(0.91-1.26) 0.57	0.96(0.73-1.27) 0.86	1.03(0.93-1.13) 0.74	0.62	0.92
rs1111875 G	10 *HHEX*	1.01(0.85-1.20) 0.60	1.16(0.93-1.46) 0.75	1.09(0.79-1.52) 0.30	1.20(1.00-1.44) 0.26	0.94(0.76-1.16) 0.63	1.07(0.98-1.18) 0.50	0.15	0.48
rs7903146 T	10 *TCF7L2*	1.06(0.89-1.28) 0.29	1.00(0.81-1.23) 0.27	1.16(0.77-1.73) 0.14	1.05(0.72-1.55) 0.045	1.00(0.79-1.27) 0.22	1.03(0.92-1.15) 0.19	0.59	0.98
rs12779790 C	10 *CDC123*	0.88(0.71-1.10) 0.17	0.97(0.74-1.26) 0.14	1.15(0.80-1.64) 0.18	1.21(0.97-1.49) 0.16	0.98(0.76-1.27) 0.17	1.03(0.92-1.15) 0.16	0.63	0.33
rs2237895[d] C	11 *KCNQ1*	0.99(0.83-1.18) 0.42	0.98(0.77-1.25) 0.21	0.94(0.68-1.31) 0.36	1.06(0.88-1.32) 0.35	1.00(0.80-1.27) 0.42	1.00(0.90-1.10) 0.35	0.93	0.96
rs2237897[d] C	11 *KCNQ1*	1.01(0.68-1.49) 0.95	1.13(0.80-1.59) 0.92	1.13(0.77-1.67) 0.78	0.92(0.75-1.13) 0.62	0.97(0.74-1.26) 0.78	1.00(0.89-1.13) 0.80	1.00	0.016
rs5219 T	11 *KCNJ11*	1.07(0.90-1.28) 0.35	0.77(0.55-1.08) 0.10	1.01(0.75-1.37) 0.38	0.81(0.68-0.95) 0.39	0.77(0.63-0.96) 0.39	0.89(0.81-0.97) 0.32	0.012	0.082
rs7961581 C	12 *TSPAN8*	0.96(0.79-1.17) 0.27	0.95(0.75-1.20) 0.21	1.10(0.80-1.51) 0.28	1.01(0.82-1.24) 0.20	1.27(1.00-1.60) 0.20	0.94(0.76-1.15) 0.23	0.60	0.39
rs8050136 A	16 *FTO*	0.86(0.72-1.02) 0.42	0.89(0.73-1.08) 0.44	0.63(0.43-0.93) 0.24	1.07(0.88-1.30) 0.21	0.96(0.77-1.19) 0.28	0.91(0.83-1.00) 0.32	0.055	0.21
Obesity SNPs									
rs2815752 A	1 *NEGR1*	1.00(0.85-1.19) 0.63	1.10(0.90-1.34) 0.54	1.04(0.70-1.56) 0.83	0.85(0.64-1.14) 0.93	1.06(0.85-1.31) 0.71	1.02(0.92-1.13) 0.73	0.70	0.63

		OR(95%CI)[a] Risk allele frequency in controls							
SNP/ Allele tested[b]	**Chr./ Nearest gene**	**European Americans 503 cases 633 controls**	**African Americans 381 cases 542 controls**	**Native Hawaiians 135 cases 344 controls**	**Japanese Americans 509 cases 782 controls**	**Latinos 355 cases 505 controls**	**Pooled 1,883 cases 2,806 controls**	**P for trend pooled**	**P_{het}[c]**
rs10913469 C	1 *SEC16B*	0.99(0.80-1.23) 0.18	0.87(0.70-1.08) 0.28	0.57(0.38-0.85) 0.21	1.20(1.00-1.44) 0.23	0.89(0.70-1.14) 0.20	0.96(0.86-1.06) 0.22	0.38	0.016
rs6548238 T	2 *TMEM18*	1.08(0.87-1.34) 0.17	1.07(0.80-1.44) 0.11	0.59(0.31-1.13) 0.079	1.15(0.89-1.49) 0.10	1.17(0.88-1.56) 0.13	1.08(0.95-1.22) 0.12	0.23	0.40
rs10938397 G	4 *GNPDA2*	0.93(0.78-1.10) 0.42	0.81(0.64-1.02) 0.25	1.14(0.83-1.55) 0.28	0.97(0.81-1.16) 0.29	1.08(0.88-1.32) 0.35	0.97(0.89-1.06) 0.32	0.50	0.34
rs925946[e] T	11 *BDNF*	0.92(0.76-1.12) 0.29	1.01(0.81-1.26) 0.28	1.73(1.19-2.53) 0.18	1.12(0.70-1.77) 0.030	0.90(0.70-1.15) 0.23	1.02(0.91-1.14) 0.19	0.78	0.24
rs6265[e] C	11 *BDNF*	1.33(1.06-1.68) 0.79	1.32(0.85-2.05) 0.94	0.70(0.51-0.97) 0.68	0.92(0.78-1.09) 0.60	0.91(0.70-1.19) 0.85	1.01(0.91-1.12) 0.76	0.88	0.049
rs10838738 G	11 *MTCH2*	0.99(0.83-1.19) 0.34	1.16(0.86-1.56) 0.11	0.96(0.70-1.33) 0.32	0.99(0.83-1.17) 0.34	1.17(0.96-1.43) 0.35	1.05(0.95-1.15) 0.29	0.36	0.58
rs7138803 A	12 *BCDIN3D*	0.93(0.78-1.10) 0.39	0.97(0.77-1.23) 0.19	0.97(0.68-1.38) 0.19	1.06(0.90-1.26) 0.34	0.97(0.78-1.21) 0.26	0.99(0.90-1.09) 0.29	0.83	0.90
rs7498665 G	16 *SH2B1*	0.82(0.69-0.97) 0.40	1.03(0.84-1.26) 0.27	1.03(0.75-1.41) 0.28	1.00(0.79-1.27) 0.13	0.87(0.72-1.06) 0.45	0.92(0.83-1.01) 0.30	0.073	0.47
rs8050136 A	16 *FTO*	0.87(0.74-1.03) 0.42	0.91(0.75-1.10) 0.44	0.60(0.41-0.86) 0.24	1.04(0.86-1.26) 0.21	0.96(0.78-1.19) 0.28	0.92(0.84-1.00) 0.32	0.055	0.21
rs17782313 C	18 *MC4R*	0.97(0.80-1.19) 0.22	0.98(0.80-1.20) 0.29	1.00(0.65-1.52) 0.13	0.95(0.79-1.15) 0.23	0.92(0.68-1.23) 0.13	0.98(0.88-1.08) 0.21	0.63	0.98
rs11084753 G	19 *KCTD15*	0.89(0.75-1.07) 0.68	1.12(0.92-1.36) 0.64	1.04(0.78-1.39) 0.42	1.03(0.87-1.22) 0.29	0.96(0.79-1.18) 0.67	1.00(0.91-1.09) 0.53	0.97	0.53
rs29941 G	19 *KCTD15*	0.90(0.75-1.08) 0.69	1.11(0.86-1.42) 0.82	0.87(0.65-1.17) 0.40	1.05(0.87-1.27) 0.21	0.81(0.66-1.00) 0.66	0.94(0.85-1.03) 0.54	0.18	0.26

[a] OR adjusted for age(quartiles), BMI(quartiles), diabetes status (self-report) and ethnicity (in pooled analysis).

[b] NCBI build 36 (forward strand).

[c] P value for heterogeneity between risk allele and ethnic groups (4-df).

[d] Rs2237895 and rs2237897 adjusted for each other.

[e] Rs925946 and rs6265 adjusted for each other.