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

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Running Title: No Association of T2D/Obesity SNPs with Breast Cancer

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Abstract:

Background: 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.

Methods: 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.

Results: 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.

Conclusions: Our findings provide no evidence for association between established T2D and/or obesity risk variants and breast cancer risk among women of various ethnicities.

Impact: These results suggest that the potential for a shared biology between T2D/obesity and breast cancer is not due to pleiotropic effects of these risk variants.
**Introduction:**

Obesity is a risk factor for many common chronic diseases, including breast cancer in postmenopausal women (1, 2) 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 (3, 4). Biological markers of obesity and diabetes, such as insulin and insulin-like growth factors (IGFs), have been associated with breast cancer risk (5-7), which suggests that there may be shared biological processes in the etiology of these common phenotypes. We further explored the hypothesis of 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).

**Methods:**

**Study subjects:**

The MEC is a prospective cohort study consisting of 215,251 adult men and women living in Hawaii and California (8) predominantly 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 and 2,014 controls. Cases were identified through cohort linkage to population-based cancer Surveillance, Epidemiology and End Results (SEER) registries in California and Hawaii. 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. The genotype completion rate for each SNP was >95.0% for cases and controls (average 99.1%). Hardy-Weinberg Equilibrium (HWE) was assessed for each allele in each racial/ethnic group and of the 155 tests, 7 were significant while 8 were expected.

Statistical analysis:

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 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 variant within each population of the same race/ethnicity. We excluded from the analysis 32 (1.7%) cases and 78 (2.7%) controls with missing genotypes for $\geq$ 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. 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). Results were similar when limiting the 
analysis to postmenopausal women (n=1,197 cases and 1,731 controls).

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, P=0.31; obesity SNPs: OR=1.02, P=0.24; All SNPs: OR=1.01, P=0.14).

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 variants.
Acknowledgements:

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Assistance with phenotype harmonization, SNP selection and annotation, data cleaning, data management, integration and dissemination, and general study coordination was provided by the PAGE Coordinating Center (U01HG004801-01). The National Institutes of Mental Health also contributes to the support for the Coordinating Center.

We thank the participants of the Multiethnic Cohort who have contributed to a better understanding of the genetic contributions to breast cancer.
References:


Table 1. Association of known T2D and obesity risk alleles with breast cancer risk by race/ethnicity.

<table>
<thead>
<tr>
<th>SNP/Allele tested</th>
<th>Chr./Nearest gene</th>
<th>European Americans</th>
<th>OR(95%CI)a</th>
<th>OR(95%CI)b</th>
<th>OR(95%CI)c</th>
<th>OR(95%CI)d</th>
<th>OR(95%CI)e</th>
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<tbody>
<tr>
<td>rs10923931</td>
<td>1 NOTCH2</td>
<td>1.13(0.85-1.49)</td>
<td>0.97(0.64-1.48)</td>
<td>0.97(0.58-1.63)</td>
<td>1.28(0.93-1.76)</td>
<td>1.01(0.88-1.15)</td>
<td>0.94</td>
</tr>
<tr>
<td>rs7578597</td>
<td>2 THADA</td>
<td>1.05(0.88-1.25)</td>
<td>1.04(0.54-2.00)</td>
<td>1.47(0.69-3.15)</td>
<td>0.71(0.48-1.03)</td>
<td>1.03(0.89-1.20)</td>
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<tr>
<td>rs1801282</td>
<td>3 PPARC</td>
<td>1.14(0.88-1.48)</td>
<td>1.06(0.55-2.04)</td>
<td>0.83(0.54-1.28)</td>
<td>0.87(0.50-1.54)</td>
<td>1.04(0.88-1.23)</td>
<td>0.63</td>
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<tr>
<td>rs4607103</td>
<td>3 ADAMTS9</td>
<td>0.86(0.71-1.04)</td>
<td>0.89(0.63-1.22)</td>
<td>0.95(0.80-1.13)</td>
<td>0.99(0.80-1.22)</td>
<td>0.94(0.86-1.03)</td>
<td>0.20</td>
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<tr>
<td>rs4402960</td>
<td>3 IGFBP2</td>
<td>0.91(0.76-1.08)</td>
<td>0.89(0.64-1.23)</td>
<td>0.91(0.76-1.08)</td>
<td>1.16(0.92-1.45)</td>
<td>0.98(0.89-1.07)</td>
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<td>rs10010131</td>
<td>4 WFSI</td>
<td>1.01(0.86-1.20)</td>
<td>0.86(0.60-1.23)</td>
<td>1.14(0.68-1.89)</td>
<td>0.96(0.78-1.21)</td>
<td>0.97(0.87-1.07)</td>
<td>0.55</td>
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<tr>
<td>rs7754840</td>
<td>6 CDKAL1</td>
<td>1.02(0.85-1.20)</td>
<td>1.04(0.78-1.38)</td>
<td>1.06(0.90-1.25)</td>
<td>1.00(0.81-1.23)</td>
<td>1.05(0.96-1.14)</td>
<td>0.29</td>
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<tr>
<td>rs664745</td>
<td>7 JAZF1</td>
<td>0.93(0.78-1.09)</td>
<td>0.81(0.59-1.10)</td>
<td>1.02(0.84-1.23)</td>
<td>1.01(0.83-1.24)</td>
<td>0.94(0.86-1.03)</td>
<td>0.17</td>
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<tr>
<td>rs13266634</td>
<td>8 SLC30A4</td>
<td>1.00(0.83-1.20)</td>
<td>0.95(0.70-1.28)</td>
<td>1.05(0.89-1.24)</td>
<td>1.04(0.82-1.31)</td>
<td>1.00(0.90-1.10)</td>
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<td>rs2383208</td>
<td>9 CDK2B2</td>
<td>1.01(0.81-1.25)</td>
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<td>1.07(0.91-1.26)</td>
<td>0.96(0.73-1.27)</td>
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<td>rs1111875</td>
<td>10 HHEX</td>
<td>1.01(0.85-1.20)</td>
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<td>1.20(1.00-1.44)</td>
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<td>rs7803146</td>
<td>10 TCFTL2</td>
<td>1.06(0.89-1.28)</td>
<td>1.16(0.77-1.73)</td>
<td>1.05(0.72-1.55)</td>
<td>1.00(0.79-1.27)</td>
<td>1.03(0.92-1.15)</td>
<td>0.59</td>
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<td>rs12779790</td>
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<td>0.88(0.71-1.10)</td>
<td>0.91(0.69-1.24)</td>
<td>1.21(0.97-1.54)</td>
<td>0.98(0.76-1.27)</td>
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<td>0.63</td>
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<tr>
<td>rs2237895</td>
<td>11 KCNQ1</td>
<td>0.99(0.83-1.18)</td>
<td>0.94(0.68-1.31)</td>
<td>1.06(0.88-1.32)</td>
<td>1.00(0.80-1.27)</td>
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<tr>
<td>rs2237897</td>
<td>11 KCNQ1</td>
<td>1.01(0.68-1.49)</td>
<td>1.13(0.80-1.59)</td>
<td>0.92(0.75-1.12)</td>
<td>0.97(0.74-1.26)</td>
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<td>1.00</td>
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<td>rs5219</td>
<td>11 KCN11</td>
<td>1.07(0.90-1.28)</td>
<td>0.77(0.55-1.08)</td>
<td>1.01(0.75-1.37)</td>
<td>0.81(0.68-0.95)</td>
<td>0.78(0.63-0.96)</td>
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<tr>
<td>rs7961581</td>
<td>12 TSPAN8</td>
<td>0.96(0.79-1.17)</td>
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<td>1.10(0.80-1.51)</td>
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<td>0.96(0.74-1.25)</td>
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<tr>
<td>rs8050136</td>
<td>16 FTO</td>
<td>0.86(0.72-1.02)</td>
<td>0.89(0.73-1.08)</td>
<td>0.63(0.43-0.93)</td>
<td>1.07(0.88-1.30)</td>
<td>0.96(0.77-1.19)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Risk allele frequency in controls

Type 2 Diabetes SNPs

- rs10923931 (rs10010131): 0.97 (0.96-1.08)
- rs7578597 (rs109231): 1.04 (1.03-1.06)
- rs1801282 (rs7578597): 1.05 (1.04-1.06)
- rs4607103 (rs10010131): 1.01 (1.00-1.02)
- rs4402960 (rs10010131): 1.00 (0.99-1.01)
- rs10010131 (rs10010131): 1.00 (0.99-1.01)

Obesity SNPs

- rs2215752 (rs2215752): 1.05 (1.04-1.06)
- rs10913409 (rs10913409): 1.04 (1.03-1.05)
- rs6548238 (rs6548238): 1.09 (1.08-1.10)
- rs10938397 (rs10938397): 1.10 (1.09-1.11)
- rs925946 (rs925946): 1.09 (1.08-1.10)
- rs6265 (rs6265): 1.11 (1.10-1.12)
- rs10838378 (rs10838378): 1.10 (1.09-1.11)
- rs7138803 (rs7138803): 1.10 (1.09-1.11)
- rs7498665 (rs7498665): 1.11 (1.10-1.12)
- rs8050136 (rs8050136): 1.12 (1.11-1.13)
- rs17782313 (rs17782313): 1.13 (1.12-1.14)
<table>
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<tr>
<th>rs11084753</th>
<th>19</th>
<th>KCTD15</th>
<th>0.89(0.75-1.07)</th>
<th>1.12(0.92-1.36)</th>
<th>1.04(0.78-1.39)</th>
<th>1.03(0.87-1.22)</th>
<th>0.96(0.79-1.18)</th>
<th>0.99(0.91-1.09)</th>
<th>0.97</th>
<th>0.53</th>
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<tr>
<td>rs29941</td>
<td>19</td>
<td>KCTD15</td>
<td>0.90(0.75-1.08)</td>
<td>1.11(0.86-1.42)</td>
<td>0.87(0.65-1.17)</td>
<td>1.05(0.87-1.27)</td>
<td>0.81(0.66-1.00)</td>
<td>0.94(0.85-1.03)</td>
<td>0.18</td>
<td>0.26</td>
</tr>
</tbody>
</table>

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

**NCBI build 36 (forward strand).**

*P value for interaction between risk allele and ethnic groups (4-df).

*Rs2237895 and rs2237897 adjusted for each other.

*Rs925946 and rs6265 adjusted for each other.
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