Null Results in Brief

No Association between Polymorphisms in LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 and Postmenopausal Breast Cancer Risk

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Abstract

There is evidence that adipokines such as leptin and adiponectin may influence breast tumor development. We conducted a nested case-control study using women in the American Cancer Society Cancer Prevention Study II to examine the association between postmenopausal breast cancer and variability in the genes encoding leptin, the leptin receptor, adiponectin, adiponectin receptor 1, and adiponectin receptor 2. Using 648 cases and 659 controls, we found no statistically significant (P < 0.05) associations between breast cancer risk and any of the single nucleotide polymorphisms. Individual odds ratios ranged from 0.93 to 1.06. We found no evidence of effect modification by body mass index, adult weight gain, location of weight gain, or physical activity. Although we cannot rule out that these genes are involved in gene-gene or gene-environment interactions, our results suggest that individual single nucleotide polymorphisms in these genes do not substantially affect postmenopausal breast cancer risk. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2553–7)

Introduction

Adipokines (proteins secreted from adipose tissue) such as leptin and adiponectin may influence breast tumor development. In vitro studies have provided evidence that leptin promotes cell proliferation, cell survival, cell migration, and angiogenesis (4-11). Adiponectin, on the other hand, has been shown to suppress cell growth, induce apoptosis, and inhibit angiogenesis (12-16). Further, serum adiponectin levels have been consistently inversely associated with postmenopausal breast cancer risk (14, 17-21). Few previous publications have examined genetic variation in leptin and adiponectin in relation to breast cancer risk, and the results have been inconsistent (22-26). The purpose of this study was to examine the association between postmenopausal breast cancer and variability in the genes encoding leptin (LEP), the leptin receptor (LEPR), adiponectin (ADIPOQ), adiponectin receptor 1 (ADIPOR1), and adiponectin receptor 2 (ADIPOR2).

Materials and Methods

Study Population. We conducted a nested case-control study using women in the American Cancer Society Cancer Prevention Study II who provided a blood sample (n = 21,965 women) after giving informed consent (27). Cases included predominantly White, postmenopausal women diagnosed with breast cancer between 1992 and 2001. Cases were verified through medical records or linkage to state cancer registries. Controls were selected from cohort members who remained cancer-free through 2001 and were matched to cases on age (±6 months), race (White, Black, other), and blood draw date (±6 months). Questionnaire information was collected before the cases were diagnosed.

Single Nucleotide Polymorphism Selection and Genotyping. Single nucleotide polymorphisms (SNP) were selected using HapMap4 (Release 21, July 2006). All SNPs in HapMap that had a minor allele frequency of at least 5% and were within 10 kb of LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 were identified (n = 382 SNPs). Because genotyping this extensive list of SNPs was cost-prohibitive, we used the Tagger program within Haploview (version 3.32) to create linkage disequilibrium bins and chose tagging SNPs, which reduced the number of SNPs analyzed while maximizing capture of the genetic variability in the genes (28). SNPs in a large intronic region in LEPR (n = 134 SNPs), as well as singleton, intronic SNPs >1 kb from an exon of any of these genes (n = 21 SNPs), were excluded. Genotyping was done on the remaining 53 SNPs using the Beckman SNPstream genotyping system. Forty-eight of the 53 SNPs were successfully genotyped.

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4 International HapMap Project (http://www.hapmap.org/).
Table 1. Association between SNPs representing linkage disequilibrium bins in LEP, LEPR, ADIPOQ, ADIPOR1, and ADIPOR2 and odds of postmenopausal breast cancer in the American Cancer Society Cancer Prevention Study II

<table>
<thead>
<tr>
<th>Gene</th>
<th>Marker</th>
<th>Location*</th>
<th>Genotypes</th>
<th>Genotype frequencies</th>
<th>OR† (95% confidence interval)</th>
<th>Other SNPs in linkage disequilibrium bin‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEP</td>
<td>rs4731423</td>
<td>Regulatory</td>
<td>AA</td>
<td>187</td>
<td>202</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GA or GG</td>
<td>445</td>
<td>442</td>
<td>1.01 (0.93-1.10)</td>
</tr>
<tr>
<td>LEP</td>
<td>rs13245201</td>
<td>Intron</td>
<td>AA</td>
<td>198</td>
<td>211</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GA or GG</td>
<td>438</td>
<td>433</td>
<td>0.99 (0.91-1.08)</td>
</tr>
<tr>
<td>LEP</td>
<td>rs10244329</td>
<td>Intron</td>
<td>AT or TT</td>
<td>460</td>
<td>461</td>
<td>1.00 (0.93-1.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>551</td>
<td>571</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>LEP</td>
<td>rs7795794</td>
<td>Intron</td>
<td>GA or AA</td>
<td>84</td>
<td>78</td>
<td>1.04 (0.95-1.14)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Association between SNPs representing linkage disequilibrium bins in LEP, LEPR, ADIPOQ, ADIPOR1, and ADIPOR2 and odds of postmenopausal breast cancer in the American Cancer Society Cancer Prevention Study II (Cont’d)

<table>
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<th>OR† (95% confidence interval)</th>
<th>Other SNPs in linkage disequilibrium bin‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADIPOQ</td>
<td>rs17366568</td>
<td>Intron</td>
<td>GG</td>
<td>485</td>
<td>489</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>rs3821799</td>
<td>Intron</td>
<td>GA or AA</td>
<td>147</td>
<td>152</td>
<td>0.99 (0.92-1.07)</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>rs3774261</td>
<td>Intron</td>
<td>CC</td>
<td>179</td>
<td>174</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>rs17366743</td>
<td>Exon</td>
<td>TT</td>
<td>461</td>
<td>476</td>
<td>0.98 (0.88-1.09)</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>rs7639352</td>
<td>Intron</td>
<td>CC</td>
<td>227</td>
<td>214</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>ADIPOR1</td>
<td>rs4336908</td>
<td>Regulatory</td>
<td>GG</td>
<td>409</td>
<td>430</td>
<td>0.96 (0.88-1.05)</td>
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<tr>
<td>ADIPOR1</td>
<td>rs7539542</td>
<td>3’-Untranslated region</td>
<td>CC</td>
<td>349</td>
<td>341</td>
<td>1.00 (1.00-1.01)</td>
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<tr>
<td>ADIPOR1</td>
<td>rs1418445</td>
<td>Intron</td>
<td>GG</td>
<td>239</td>
<td>255</td>
<td>1.00 (1.00-1.01)</td>
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<td>ADIPOR1</td>
<td>rs16850799</td>
<td>Intron</td>
<td>GG</td>
<td>371</td>
<td>390</td>
<td>1.00 (0.99-1.01)</td>
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<tr>
<td>ADIPOR2</td>
<td>rs132033</td>
<td>Intron</td>
<td>CC</td>
<td>325</td>
<td>323</td>
<td>1.00 (1.00-1.01)</td>
</tr>
<tr>
<td>ADIPOR2</td>
<td>rs11061952</td>
<td>Intron</td>
<td>GG</td>
<td>545</td>
<td>545</td>
<td>1.00 (reference)</td>
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<tr>
<td>ADIPOR2</td>
<td>rs10773986</td>
<td>Intron</td>
<td>AA</td>
<td>85</td>
<td>94</td>
<td>0.99 (0.92-1.06)</td>
</tr>
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<td>ADIPOR2</td>
<td>rs2058112</td>
<td>Intron</td>
<td>CC</td>
<td>491</td>
<td>484</td>
<td>1.00 (0.96-1.04)</td>
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<tr>
<td>ADIPOR2</td>
<td>rs11061973</td>
<td>Intron</td>
<td>GG</td>
<td>471</td>
<td>466</td>
<td>1.00 (reference)</td>
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<td>ADIPOR2</td>
<td>rs2108642</td>
<td>Intron</td>
<td>GA or AA</td>
<td>173</td>
<td>185</td>
<td>0.93 (0.82-1.05)</td>
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<td>ADIPOR2</td>
<td>rs1044471</td>
<td>3’-Untranslated region</td>
<td>CC</td>
<td>163</td>
<td>166</td>
<td>1.00 (reference)</td>
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<tr>
<td>ADIPOR2</td>
<td>rs13219</td>
<td>Regulatory</td>
<td>AA</td>
<td>208</td>
<td>203</td>
<td>1.00 (0.97-1.08)</td>
</tr>
</tbody>
</table>

*Location of polymorphism within the gene. Regulatory region spans 10 kb upstream and downstream from the first and last exons.
†OR adjusted for age, race, and date of blood draw.
‡Coefficient of determination ($r^2$) between the marker SNP and the other SNPs in the linkage disequilibrium bin was at least 0.8 (mean $r^2 = 0.953$).

The final analysis.

Results

This study included 648 cases and 659 controls. Cases and controls were similar in terms of age at blood draw (mean, 69 years) and race (99% White); additional characteristics of the cases and controls have been reported elsewhere (27). We found no statistically significant ($P < 0.05$) associations between breast cancer risk and any of the SNPs in LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 using a dominant, genotypic, or additive genetic model (dominant models are shown in Table 1). Individual genotyped after two attempts. Positive and negative DNA controls and blind duplicates were randomly interspersed among the samples. Concordance among duplicate samples was >99%. Genotyping call rates ranged from 91.3% to 99.3%. One SNP (rs6660481) deviated from Hardy-Weinberg equilibrium at the $P = 0.01$ level and was excluded, leaving 47 SNPs in the final analysis.

Statistical Analysis. We used conditional logistic regression to estimate odds ratios (OR) for postmenopausal breast cancer. Models included body mass index, weight change, location of weight gain, and physical activity as potential confounders. Effect modification of the relationship between each SNP and postmenopausal breast cancer by these variables was evaluated.

Cancer Epidemiol Biomarkers Prev 2009;18(9). September 2009
Discussion

The results from this study do not support an association between postmenopausal breast cancer and individual SNPs in LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 in a population of predominately White U.S. women. Our results are consistent with a recent genome-wide association study\(^5\) of breast cancer that did not identify any SNPs in these gene regions as possible risk loci (29). The present study makes an important contribution to our understanding of these genes in relation to breast cancer because it is the first to comprehensively evaluate most of the known variation in these genes.

Five small breast cancer studies previously conducted in different countries (Korea, China, Taiwan, Tunisia, and United States) evaluated seven candidate LEP or LEPR SNPs with inconsistent results (22-26). Only one SNP was examined by more than one study (rs1137101). Two studies found ~2-fold statistically significant risk of breast cancer for rs1137101 (23, 26). However, two others found no association between this SNP and breast cancer (22, 25). Woo et al. also found no association between breast cancer and three other LEPR SNPs (rs8179183, rs805096, and rs1137100; ref. 25). Liu et al. reported a suggestion of an association between rs1137100 and breast tumor size but among premenopausal women only (24).

Only one previous study has looked at adiponectin SNPs and breast cancer. The authors found statistically significant associations between breast cancer and two ADIPOQ SNPs (rs2241766 and rs1501299) and two ADIPOR1 SNPs (rs2232853 and rs7539542) among U.S. women (30). The authors found no association with six SNPs (rs2232853 and rs7539542) among U.S. women (30). The authors found no association with six SNPs (rs2232853 and rs7539542) among U.S.

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