Null Results in Brief

No Association between Genetic Polymorphisms in Insulin and Insulin Receptor Substrate-1 and Prostate Cancer

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Introduction

High levels of insulin and insulin-like growth factors have been associated with increased risk of prostate cancer (1, 2). Insulin regulates and stimulates cell growth, and inhibits apoptosis in cellular models, although mitogenicity seems to occur at supraphysiologic levels. Insulin also inhibits transcription of insulin-like growth factor binding protein-1 and decreases the synthesis of sex hormone binding proteins. Therefore, insulin may increase the unbound circulating insulin-like growth factors and the bioavailability of testosterone for hormone-dependent tissues such as the prostate. Insulin receptor substrate 1 (IRS1) is the primary docking molecule for the receptor and is required for activation of the phosphoinositol-3-kinase pathway, which regulates insulin-like growth factor–mediated survival, enhancement of cellular motility, and antiapoptosis; and for activation of the RAS-mitogen-activated protein kinase pathway, which regulates cell proliferation. Thus, genetic variations in insulin (INS) and IRS1 may affect an individual’s risk of prostate cancer.

A single nucleotide polymorphism (+1127 INS-PstI) located in the 3’ untranslated region of INS is hypothesized to have a functional effect on the expression of INS. This polymorphism is also in tight linkage disequilibrium with the variable number of tandem repeat polymorphism that is hypothesized to have a direct effect on insulin regulation. The CC genotype has been associated with a 3-fold increased risk of prostate cancer in one recent case-control study (3). Another study reported a statistically significant association of the IRS1 G972R (Gly—Arg) polymorphism and advanced prostate cancer, although there was no association for INS +1127 INS-PstI (4). The role of the INS +1127 INS-PstI and IRS1 G972R polymorphisms in the etiology of prostate cancer thus remains unclear. We present here the results from a sibling-matched case-control study to further clarify the potential relation of these two genetic polymorphisms with prostate cancer.

Materials and Methods

The design of our study has been described in detail elsewhere (5). Briefly, we recruited a study population of 918 brothers (439 cases and 479 controls) from 413 discordant families (i.e., with at least one unaffected sibling) from the major medical institutions in the greater Cleveland, Ohio area and from the Henry Ford Health System in Detroit, Michigan. Institutional Review Board approval was obtained from the participating institutions and all study participants gave informed consent. Sibling sets consisted of probands with prostate cancer diagnosed at age 73 or younger and at least one brother without prostate cancer who was either older or no more than 8 years younger than the proband’s age at diagnosis. The study population was composed of 91% Caucasian, 8% African American, and 1% Hispanic and Asian American. Genotyping was undertaken according to assays recently described elsewhere (3, 4).

We first calculated allele frequencies by disease status, and then estimated age-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) by conditional logistic regression (matched on family) for the association between the polymorphisms and prostate cancer. Due to rarity of homozygous INS +1127 TT and IRS1 972 Arg/Arg genotypes, we have combined them with those heterozygous for INS and IRS1, respectively, in the regression analyses.

To investigate the potential effect of these polymorphisms on prostate cancer aggressiveness, we undertook analyses stratified by the case’s tumor stage and grade at diagnosis; men with tumor stage ≥T2c or Gleason score >7 (and their control brothers) were categorized as having high stage/grade; others were considered low stage/grade. In our regression models, we investigated the potential confounding by age, height, and body mass index; the latter two did not materially alter our results, and all results reported here are adjusted for age only.

Results and Discussion

One control’s genotype was not amplified, leaving 478 controls available for our analyses. The allele frequencies of both INS +1127 INS-PstI and IRS1 G972R are comparable to reports from previous studies and conform to Hardy-Weinberg equilibrium. No noteworthy difference was observed between the case’s and control’s frequencies of INS or IRS1 polymorphism (Table 1). Conditional logistic regression analyses revealed no association with prostate cancer (Table 1). Specifically, we observed no association between INS +1127 TT/CT and IRS1 RR/GR as compared with INS +1127 CC and IRS1 GG, respectively. Stratifying these analyses by
the cases’ stage/grade of prostate cancer or age at diagnosis did not materially alter our null results (data not shown). Furthermore, restricting the analyses to Caucasians only did not affect our findings.

By using a sibling-based design, our results are not susceptible to population stratification bias. However, this design can be less efficient than a study of unrelated cases and controls. Nevertheless, our study had over 80% power to detect an OR ≥ 1.75 for the polymorphisms studied here. In conclusion, this moderately large case-control study did not detect an association between the INS +1127 INS-PstI or IRS1 G972R polymorphism and risk or aggressiveness of prostate cancer.

Table 1. Frequency of INS and IRS1 variants and ORs and 95% CIs for their association with prostate cancer in sibling-based study

<table>
<thead>
<tr>
<th>Gene variant</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS +1127 INS-PstI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>281 (64.0)</td>
<td>315 (65.9)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>CT</td>
<td>151 (34.4)</td>
<td>151 (31.6)</td>
<td>1.06 (0.71-1.58)</td>
</tr>
<tr>
<td>TT</td>
<td>7 (1.6)</td>
<td>12 (2.5)</td>
<td></td>
</tr>
<tr>
<td>IRS1 G972R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gly/Gly</td>
<td>386 (88.1)</td>
<td>422 (88.1)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Gly/Arg</td>
<td>50 (11.4)</td>
<td>56 (11.7)</td>
<td>1.14 (0.64-2.04)</td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>2 (0.5)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age.
†OR and 95% CI for TT/CT combined.
‡OR and 95% CI for Arg/Arg and Gly/Arg combined.

References
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