Null Results in Brief

Polymorphisms in the ICAM Gene Locus are not Associated with Breast Cancer Risk

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Introduction

In a recent case-control study which examined >25,000 single nucleotide polymorphisms (SNP), the intercellular adhesion molecule (ICAM) locus was proposed as a susceptibility locus for breast and prostate cancer (1). The genes ICAM1, ICAM4, and ICAM5 are all located within a 20 kb region of high linkage disequilibrium of chromosome 19p13.2. We examined the association of three previously implicated polymorphisms (rs5030382, K469E in ICAM1; rs281439, 542 bp upstream of ICAM5; rs1056538, and V3011 in ICAM5) with breast cancer risk in a nested case control study within the Nurses’ Health Study.

Materials and Methods

Genotyping assays for the ICAM locus polymorphisms (rs5030382, K469E in ICAM1; rs281439, 542 bp upstream of ICAM5; rs1056538, V3011 in ICAM5) were done by the 5′-nuclease assay (TaqMan) on the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Information on TaqMan genotyping assays is available on request from the authors. Our study included a total of 1,264 incident breast cancer cases diagnosed after blood draw up to June 1, 2000, and 1,747 matched controls, all drawn from 32,826 women who gave a blood sample from 1989 to 1990. Controls were randomly selected participants who were free of diagnosed cancer (except non-melanoma skin cancer), and matched to cases based on age, menopausal status, recent postmenopausal hormone use, and time, day, and month of blood collection. A detailed description of this study population has been previously reported (2). Approximately 95% of the samples were successfully genotyped; samples that failed genotyping were removed from the analyses. Internal blinded quality control samples showed 100% concordance.

We used SAS v8.2 (SAS Institute, Cary, NC) for all statistical analyses. Odds ratios (OR) and 95% confidence intervals were calculated using unconditional logistic regression, controlling for matching factors, age at menopause, age at menarche, age at first birth and parity, history of benign breast disease, and family history of breast cancer using PROC LOGISTIC. We tested for departures from Hardy-Weinberg equilibrium using PROC ALLELE. Interactions were tested by likelihood ratio tests comparing the model with main effects for each variable of interest to the model additionally including the two variables cross-tabulated. All P values reported are two-sided. Power calculations were carried out using Quanto (3).

Results

No departure from Hardy-Weinberg equilibrium was observed at any of the SNPs examined in the control population. We observed no statistically significant differences in allele or genotype frequencies between cases and controls; conditional, unconditional and unconditional multivariate logistic regressions gave similar results, with ORs not significantly different from 1.00 (Table 1). No difference in genotype frequencies were observed between cases with estrogen or progesterone receptor–positive and estrogen or progesterone receptor–negative tumors or other tumor characteristic groups, such as tumor size and grade (data not shown). No statistically significant interactions were observed between family history of breast cancer or age at diagnosis and the polymorphisms assayed (data not shown).

Conclusions

ICAM1 has been proposed as a likely candidate for genetic susceptibility to breast cancer. Soluble levels of ICAM-1 in the sera of patients with stage IV breast cancer were higher than that of healthy controls (4) and patients with lower grade tumors (5). ICAM-1 is hypothesized to be involved in the adhesion of tumor cells to the vascular epithelium, and therefore, promote the development of metastases.

In a large-scale association study of >25,000 SNPs in ~16,000 genes, Kammerer et al. (1) identified the ICAM locus at chromosome 19p13.2 as a region of susceptibility to breast cancer. They used one small study of Germans (254 cases and 268 controls) as a “discovery” set, and two smaller studies for replication (188 cases and 150 controls from Germany, 180 cases and 180 controls from Australia). Only the ICAM5 V3011 polymorphism showed a statistically significant association (P = 0.001 for difference in allele frequency between cases and controls) with breast cancer risk in the discovery set, which was marginally supported by the replication sets (P = 0.07 and 0.03, respectively).

If the three studies reported by Kammerer et al. are combined, statistically significant associations between the ICAM5 V3011 and ICAM1 K469E polymorphisms exist. Using the data they report, an OR of 0.55 for the ICAM5 V3011 AA versus GG, and an OR of 0.63 for the ICAM1 K469E GG versus AA could be calculated. Our study has >93% power to detect log-additive OR < 0.81 with SNPs similar in allele
frequency to those reported here at the type 1 error rate of 1%. The allele frequencies between our study and those of Kammerer et al. were similar for all three SNPs among the control populations. The cost of genotyping is steadily declining, whereas the speed of genotyping is steadily increasing. This is making it more feasible to examine many loci in large sample sets. However, in order to avoid false-positive findings, both discovery and replication studies of sufficient size need to be carried out.

Table 1. Association between genotype and ICAM locus polymorphisms in the Nurses’ Health Study

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR (95% confidence intervals)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5030382, ICAM1 K469E</td>
<td>Lys/Lys</td>
<td>388 (33.2)</td>
<td>543 (33.2)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td></td>
<td>Lys/Glu</td>
<td>585 (50.0)</td>
<td>798 (48.8)</td>
<td>1.00 (0.84-1.20)</td>
</tr>
<tr>
<td></td>
<td>Glu/Glu</td>
<td>196 (16.8)</td>
<td>294 (18.0)</td>
<td>0.85 (0.67-1.08)</td>
</tr>
<tr>
<td>rs281439, 542 bp upstream of ICAM5</td>
<td>C/C</td>
<td>739 (60.6)</td>
<td>1,014 (60.1)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td></td>
<td>C/G</td>
<td>411 (33.7)</td>
<td>593 (35.2)</td>
<td>0.94 (0.80-1.12)</td>
</tr>
<tr>
<td></td>
<td>G/G</td>
<td>69 (5.7)</td>
<td>80 (4.7)</td>
<td>1.24 (0.87-1.77)</td>
</tr>
<tr>
<td>rs1056538, ICAM5 V301I</td>
<td>Val/Val</td>
<td>456 (37.7)</td>
<td>640 (38.6)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td></td>
<td>Val/Ile</td>
<td>581 (48.0)</td>
<td>749 (45.1)</td>
<td>1.06 (0.89-1.26)</td>
</tr>
<tr>
<td></td>
<td>Ile/Ile</td>
<td>173 (14.3)</td>
<td>271 (16.3)</td>
<td>0.83 (0.65-1.06)</td>
</tr>
</tbody>
</table>

*Unconditional logistic regression, controlled for fasting status, date and time of blood draw, age at blood draw (5 year categories), menopausal status, recent postmenopausal hormone use at blood draw, age at menopause, age at menarche, body mass index at age 18, weight gain since age 18, age at first birth/parity, history of benign breast disease, and family history of breast cancer.

References
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