Null Results in Brief

No Association between a Single Nucleotide Polymorphism in CYP19 and Breast Cancer Risk1

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Introduction
Genetic polymorphisms in CYP19 have been hypothesized to alter aromatase activity and have been examined in relationship with breast cancer risk (1–4). A greater frequency of tetranucleotide (TTTA)n repeat alleles in intron 4 have been reported among affected women (1,2). In a Scandinavian case-control study (cases/controls, 481/236) Kristensen (3) observed a positive association between a SNP (C → T) in the untranslated region of exon 10 and risk of breast cancer (TT versus CC genotypes; OR, 2.00; 95% CI, 1.28–3.11), and a greater frequency of the TT genotype among women with larger and more advanced tumors. We assessed the association between CYP19 genotype, breast cancer risk, and endogenous steroid hormone levels in the prospective Nurses’ Health Study.

Materials and Methods
Detailed information regarding the design of this nested case-control study (cases, n = 461; controls, n = 619) has been published previously (2). CYP19 genotyping analysis was performed by the Taqman Allelic Discrimination method (Applied Biosystems, Foster City, CA). ORs and 95% CIs were calculated using conditional and unconditional logistic regression and were adjusted for established breast cancer risk factors (2). Linear regression models were used to evaluate associations between genotype and circulating hormone levels among controls, controlling for age, body mass index, and laboratory batch.

Results
No association was observed between CYP19 genotype and breast cancer risk (Table 1), or between genotype and established breast cancer risk factors. We did not observe the TT genotype to be overrepresented among cases with more advanced disease (4+ involved nodes; CT: OR, 0.7; 95% CI, 0.3–1.8; TT: OR, 1.0; 95% CI, 0.4–2.5). In addition, the TT genotype was not significantly overrepresented among larger tumors (>2 versus ≤2 cm, 32 versus 25%; P = 0.2) or tumors positive for the estrogen or progesterone receptor (data not shown). Linkage disequilibrium was observed between the T nucleotide and (TTTA)n repeats 8–13 (P < 0.001). We observed no significant interactions between the T allele and established breast cancer risk factors. Among postmenopausal controls, estrogen levels were not elevated among T allele carriers (Table 1). However, compared to noncarriers, women with the T allele had significantly lower levels of testosterone, androstenedione, DHEA, and DHEAS, and a significantly greater E1:A ratio.

Discussion
We did not observe an association between the C → T SNP in exon 10 of CYP19 and breast cancer risk among Caucasian women. We had 86% power to detect a significant relative risk as low as 1.75 for homozygous carriers of the C allele compared with women with the CC genotype. In addition, our results do not provide support for the previous observation that the T allele is associated with larger, more advanced tumors. We were unable to demonstrate that the positive associations reported between rare tetranucleotide repeat alleles and breast cancer risk previously described by us (2) and Kristensen et al. (1) can be accounted for by this SNP in exon 10. However, the decrease in androgen levels and greater E1:A ratio support the hypothesis that the T allele may have elevated aromatase activity.

Table 1 The relationship between CYP19 genotype, breast cancer risk, and steroid hormone levels

<table>
<thead>
<tr>
<th>CYP19 genotype, n (%)</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>CT</td>
</tr>
<tr>
<td>103 (22)</td>
<td>240 (52)</td>
</tr>
<tr>
<td>Controls</td>
<td>134 (22)</td>
</tr>
<tr>
<td>OR (95% CI)a</td>
<td>1.0</td>
</tr>
<tr>
<td>(0.69–1.34)</td>
<td>(0.60–1.27)</td>
</tr>
<tr>
<td>Hormone</td>
<td>(n = 51–60)</td>
</tr>
<tr>
<td>Estrone sulfate (pg/ml)</td>
<td>208.8</td>
</tr>
<tr>
<td>Estrone (pg/ml)</td>
<td>29.0</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>7.2</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>23.5</td>
</tr>
<tr>
<td>Androstenedione (ng/dl)</td>
<td>63.7</td>
</tr>
<tr>
<td>DHEA (ng/dl)</td>
<td>226.2</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>89.3</td>
</tr>
<tr>
<td>E1:A × 10</td>
<td>4.6</td>
</tr>
</tbody>
</table>

a Estimated by conditional logistic regression and adjusted for established breast cancer risk factors.
b P ≤ 0.05.
c P ≤ 0.10.
d P ≤ 0.01.

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2 To whom requests for reprints should be addressed, at Channing Laboratory, 181 Longwood Avenue, Boston, Massachusetts 02115.
3 The abbreviations used are: SNP, single nucleotide polymorphism; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; OR, odds ratio; CI, confidence interval; E1:A, estrone:androstenedione (ratio).
Acknowledgments
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References


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