Null Results in Brief

**CYP17 Genotype and Ovarian Cancer: A Null Case-Control Study**

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Introduction

Long-term differences in steroid hormone levels between women likely contribute to the individudal variation in ovarian cancer risk, although the precise biological mechanisms are unclear (1). The \( P450c17 \) (\( CYP17 \)) gene codes for 17α-hydroxylase and 17,20 lyase which catalyze the rate-limiting step in androgen biosynthesis, cleaving the \( C21 \) steroids to the \( C19 \) steroids, androstenedione and dihydroepiandrosterone. The 5′ untranslated region has a single bp polymorphism (T \( \rightarrow \) C transition) that creates an Sp-1 type (CCACC box) promoter site (2). The presence of the variant A2 allele has been associated with elevated transcription of progesterone and estradiol in premenopausal women (3), which might modulate the release of pituitary gonadotropin and increase the risk of ovarian cancer. The A2 allele has also been associated with polycystic ovarian syndrome, a condition resulting from high androgen levels (4). Polycystic ovarian syndrome was a significant risk factor for ovarian cancer in the Cancer and Steroid Hormone Study (5), and pre- and postmenopausal ovarian cancer cases had significantly higher prediagnostic levels of androstenedione and dehydroepiandrosterone than nested controls in the Washington County cohort (6). The association of the \( CYP17 \) polymorphism with the risk of breast cancer, another hormone-associated cancer, was shown in a multiethnic cohort study (7), but the analysis did find one containing main-effect terms only. Logistic regression was used to explore gene-environment interactions by modeling each level of interaction between the pairs of variables using subjects who had exposure to the environment of interest with case-control status by creating binary indicators (e.g., menstrual regularity) and tumor registry (e.g., histology) information to be included in the genotyping analysis. One hundred and forty-four controls were also selected to match the age and ethnicity of the cases. Laboratory personnel were blinded to the case-control status of the subjects. DNA was purified from peripheral blood leukocytes by SDS/proteinase K treatment and phenol/chloroform extraction. Genotyping for the \( CYP17 \) A2 polymorphism was evaluated as described by Fiegelson et al. (2).

Unconditional multiple logistic regression models were used to estimate the association (ORs and 95% CIs) of each genotype of interest with case-control status by creating binary indicator variables representing the levels of the exposure. Adjustment variables included age (as a continuous variable), ethnicity by indicator variables (Caucasian, Asian, other), education (<13 years, 13–14 years, ≥15 years), pregnancy history (ever versus never), oral contraceptive pill use (ever versus never), and history of tubal ligation (yes versus no). Gene dosage effects were modeled by assigning the value 1, 2, or 3 to a genotype trend variable according to the subject’s number of variant alleles (zero, one, or two variant alleles, respectively). Logistic regression was used to explore gene-environment interactions by modeling each level of interaction between the pairs of variables using subjects who had A1/A1 genotypes and who were “unexposed” as the reference category. The likelihood ratio test was used to compare this interaction model with one containing main-effect terms only.

Results

The overall and ethnic-specific genotype distributions of the genes under investigation were found to be in Hardy-Weinberg equilibrium and were similar to frequencies in other studies (2, 3).
and Ovarian Cancer but not with the results of Helzlsouer et al. which is in agreement with the findings of Feigelson et al. earlier age at menarche than women with the CYP17 controls in the frequency of the CYP17 variant A2 allele. The mean age at menarche among controls did not differ significantly (P = 0.10) by genotype (A1/A1, 12.8 years; A1/A2, 12.7 years; A2/A2, 12.2 years), but women with the A2 allele were more likely to have had an earlier age at menarche than women with the A1 genotype, which is in agreement with the findings of Feigelson et al. (2) but not with the results of Helzlsouer et al. (8). Stratification of cases and controls by age at menarche did not influence the risk of ovarian cancer associated with the CYP17 genotype. The two-way association of CYP17 genotype and age at menarche (<13 years versus ≥13 years) with the risk of ovarian cancer was also modeled, but we found only weak evidence for an age at menarche-CYP17 interaction (P = 0.06).

Discussion

Polymorphisms of alleles involved in steroid biosynthesis and excretion offer great potential as biomarkers of ovarian cancer risk because these genes regulate the concentrations of important hormones and their metabolites. Several lines of evidence, reviewed by Risch (1), support a positive association of androgen and, perhaps, progesterone activity with the risk of ovarian cancer. Because the CYP17 variant A2 allele appears to upregulate gene transcription, resulting in higher levels of androstenedione and dehydroepiandrosterone, we selected this polymorphism as a potential genetic marker for the risk of ovarian cancer. The observation that 17.20 lyase activity is high in the ovarian theca cells in women during the reproductive period (9), suggesting tissue-specific regulation of CYP17, lends biological plausibility to this hypothesis.

Our ability to examine the independent or joint association of CYP17 genotype and other variables with the risk of ovarian cancer was limited by a modest number of subjects. A conservative estimate of study power to examine the main effect of CYP17 genotype was 0.72, assuming a significance level of 0.05 and a minimum detectable relative risk of 2.0 (or 0.5, which was the lower confidence bound of the A1/A1 versus any A2 comparison). In conclusion, the results of our study suggest no substantial relation of the CYP17 variant A2 allele with the risk of ovarian cancer.

Acknowledgments

The authors thank the physicians, administrators, and cancer registrars at the following Honolulu, Hawaii institutions for their support of this study: Castle Memorial Hospital, Kaiser Foundation Hospital, Kapiolani Medical Center for Women and Children, Kuakini Medical Center, Queen’s Medical Center, Straub Clinic and Hospital, St. Francis Hospital, Tripler Army Hospital, and Wahiawa General Hospital. The findings and conclusions of this study do not necessarily represent the views of these physicians and institutions.

References


Table 1: Association of CYP17 genotype with the risk of ovarian cancer

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases (n = 125)</th>
<th>Controls (n = 144)</th>
<th>ORc</th>
<th>95% CI</th>
<th>Pd for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All study subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1/A1</td>
<td>45 (36.0)</td>
<td>51 (35.4)</td>
<td>1†</td>
<td>0.4–1.3</td>
<td></td>
</tr>
<tr>
<td>A1/A2</td>
<td>53 (42.4)</td>
<td>66 (45.8)</td>
<td>0.7</td>
<td>0.4–1.3</td>
<td></td>
</tr>
<tr>
<td>A2/A2</td>
<td>27 (21.6)</td>
<td>27 (18.8)</td>
<td>0.9</td>
<td>0.4–1.8</td>
<td>0.82</td>
</tr>
<tr>
<td>Age at menarche &lt;13 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1/A1</td>
<td>21 (33.9)</td>
<td>35 (44.3)</td>
<td>1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1/A2</td>
<td>29 (46.8)</td>
<td>32 (40.5)</td>
<td>1.2</td>
<td>0.6–2.7</td>
<td></td>
</tr>
<tr>
<td>A2/A2</td>
<td>10 (16.1)</td>
<td>12 (15.2)</td>
<td>1.4</td>
<td>0.5–4.2</td>
<td>0.54</td>
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<tr>
<td>Age at menarche ≥13 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1/A1</td>
<td>24 (35.8)</td>
<td>16 (24.6)</td>
<td>1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1/A2</td>
<td>24 (35.8)</td>
<td>34 (52.3)</td>
<td>0.3</td>
<td>0.1–0.8</td>
<td></td>
</tr>
<tr>
<td>A2/A2</td>
<td>17 (25.4)</td>
<td>15 (23.1)</td>
<td>0.4</td>
<td>0.1–1.3</td>
<td>0.13</td>
</tr>
</tbody>
</table>

a Adjusted by multiple unconditional logistic regression for age, ethnicity, education, pregnancy history, oral contraceptive pill use, and history of total ligation.

b Based on the likelihood ratio test comparing models with and without a trend variable; assigned values 1, 2 and 3.

c Reference category.
Cancer Epidemiology, Biomarkers & Prevention

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