No Relationship between Ovarian Cancer Risk and Progesterone Receptor Gene Polymorphism in a Population-based, Case-Control Study in North Carolina

Johnathan M. Lancaster, Robert M. Wenham, Susan Halabi, Brian Calingaert, Jeffrey R. Marks, Patricia G. Moorman, Rex C. Bentley, Andrew Berchuck, and Joellen M. Schildkraut

Introduction
The protective effects of pregnancy and OC use on ovarian cancer risk may be attributable to the action of progestins on the ovarian epithelium (1). It has been hypothesized that a PROGINS polymorphism has functional significance (2) and is associated with ovarian cancer in a pooled German/Irish population (3). A study of BRCA1 and BRCA2 mutation carriers found that the PROGINS allele was associated with a 2.4-times increased risk of ovarian cancer among the subgroup that had never used OCs (4). In contrast, no association between PROGINS and sporadic ovarian cancer risk has been identified in several studies with ORs ranging from 0.85 to 0.95 (5, 6). In light of these conflicting reports, we sought to investigate the hypothesis that the PROGINS allele is associated with increased ovarian cancer risk.

Materials and Methods
Study subjects included 309 epithelial ovarian cancer cases and 397 age- and race-matched controls enrolled through a population-based, case-control study in a 48 county region in North Carolina. Cases were 20–74 years of age at diagnosis and were identified using a rapid case ascertainment system in conjunction with the population-based North Carolina Central Cancer Registry. Controls were identified through random digit dialing and Health Care Financing Administration phone lists. The response rates for cases and controls were ~85% and 52%, respectively. Epidemiological and medical information was obtained from an in-person interview. This study has been described in more detail elsewhere (7).

Leukocyte DNA was extracted and subjected to PROGINS allelotyping using a PCR-based assay as described previously (5). Unadjusted and multivariable adjusted ORs and 95% CIs were calculated using unconditional logistic regression.

Results
Cases and controls were similar in age, race, education, and income. Among cases, 57% were diagnosed with stage III/IV cancer, 75% had invasive tumors, and 59% were serous.

The study had 80% power to detect an OR of ≥1.6 for carriers heterozygous for the PROGINS allele and an OR of ≥2.6 for carriers homozygous for the PROGINS allele compared with noncarriers, for risk of ovarian cancer at an α = 0.05 level. Crude ORs for being heterozygous and homozygous for the rare allele compared with the reference group of noncarriers were 1.1 (95% CI, 0.8–1.5) and 0.8 (95% CI, 0.3–1.7), respectively (Table 1). These results remained unchanged when limiting the cases to invasive cancers only or to invasive cancers of the serous histological subtype. Adjusting for age, race, and menopause did not significantly change any of these ORs.

Within the subgroup of women who had never used OCs, we found ovarian cancer cases were more likely to have the PROGINS allele than controls (Table 1). When we combined homozygote and heterozygote carriers, a borderline significant increased risk was observed (adjusted OR, 1.8; 95% CI, 1.0–3.3). Among women who ever used OCs, carriers had similar risk to noncarriers (adjusted OR, 0.8; 95% CI, 0.5–1.2), although there was some suggestion of a protective effect among the subgroup homozygous for the PROGINS allele (adjusted OR, 0.4; 95% CI, 0.2–1.2). A statistically significant interaction between OC use and having at least one PROGINS allele was detected in a multivariable logistic regression model (P = 0.04).

Stratifying by age, parity, or race revealed no association between the PROGINS allele and ovarian cancer. The PROGINS allele was distributed similarly among those with stage I/II disease and those with stage III/IV. The PROGINS distribution was also similar between invasive cases with undifferentiated/poorly-differentiated cancer and those with moderately/well-differentiated tumors.

Discussion
This study supports previous negative studies and is the first population-based, case-control study to examine the relationship between the PROGINS allele and ovarian cancer risk. The existence of epidemiological data, as well as information on cancer stage and histology, allowed us to examine the significance of PROGINS within specific subgroups while controlling for potential confounding factors. The sample size of our study provides sufficient statistical power to detect an association of the level observed previously (3), but we did not observe a significant association between the PROGINS allele and ovarian cancer risk.
Consistent with a previous report (4) there appeared to be some increased risk associated with the PROGINS allele among nonusers of OCs. However, this increased risk should be interpreted cautiously, because the PROGINS distribution among cases who were OC nonusers exactly matches the PROGINS distribution among controls who are OC users.

Acknowledgments
We thank Robin Berger, Lantoya Harris, and Nancy Fisher for conducting the interviews.

References

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases (n = 309)</th>
<th>Controls (n = 397)</th>
<th>Crude OR (95% CI)</th>
<th>ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>T1T1 219 (71)</td>
<td>285 (72)</td>
<td>1.0 referent</td>
<td>1.0 referent</td>
</tr>
<tr>
<td></td>
<td>T1T2 80 (26)</td>
<td>95 (24)</td>
<td>1.1 (0.8-1.5)</td>
<td>1.1 (0.7-1.5)</td>
</tr>
<tr>
<td></td>
<td>T2T2 10 (3)</td>
<td>17 (4)</td>
<td>0.8 (0.3-1.7)</td>
<td>0.7 (0.3-1.6)</td>
</tr>
<tr>
<td></td>
<td>T1T2/T2T2 90 (29)</td>
<td>112 (28)</td>
<td>1.0 (0.8-1.5)</td>
<td>1.0 (0.7-1.4)</td>
</tr>
<tr>
<td>OC users</td>
<td>T1T1 146 (72)</td>
<td>180 (68)</td>
<td>1.0 referent</td>
<td>1.0 referent</td>
</tr>
<tr>
<td></td>
<td>T1T2 51 (26)</td>
<td>70 (27)</td>
<td>0.9 (0.6-1.4)</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td></td>
<td>T2T2 5 (2)</td>
<td>14 (5)</td>
<td>0.4 (0.2-1.3)</td>
<td>0.4 (0.2-1.2)</td>
</tr>
<tr>
<td></td>
<td>T1T2/T2T2 56 (28)</td>
<td>84 (32)</td>
<td>0.8 (0.6-1.2)</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>OC users</td>
<td>T1T1 73 (68)</td>
<td>105 (79)</td>
<td>1.0 referent</td>
<td>1.0 referent</td>
</tr>
<tr>
<td></td>
<td>T1T2 29 (27)</td>
<td>25 (19)</td>
<td>1.7 (0.9-3.1)</td>
<td>1.7 (0.9-3.4)</td>
</tr>
<tr>
<td></td>
<td>T2T2 5 (5)</td>
<td>3 (2)</td>
<td>2.4 (0.6-10.3)</td>
<td>2.2 (0.5-9.9)</td>
</tr>
<tr>
<td></td>
<td>T1T2/T2T2 34 (32)</td>
<td>28 (21)</td>
<td>1.7 (1.0-3.1)</td>
<td>1.8 (1.0-3.3)</td>
</tr>
</tbody>
</table>

a ORs for the overall association are adjusted for age, race, and menopausal status. The ORs for OC use, yes or no, are adjusted for age, race, and tubal ligation.
No Relationship between Ovarian Cancer Risk and Progesterone Receptor Gene Polymorphism in a Population-based, Case-Control Study in North Carolina


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/12/3/226

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.