Polymorphisms of the Estrogen-metabolizing Genes CYP17 and Catechol-0-methyltransferase and Risk of Epithelial Ovarian Cancer

Elizabeth I. O. Garner,1 Erika E. Stokes, Ross S. Berkowitz, Samuel C. Mok, and Daniel W. Cramer

ABSTRACT

Because some studies have linked polymorphic variants of the estrogen-metabolizing genes CYP17 and catechol O-methyl transferase (COMT) with risk for hormonally related cancers, we sought to determine whether selected polymorphisms of these genes differed between women with and without ovarian cancer. From a population-based study of ovarian cancer, we analyzed DNA from a total of 480 cases and controls. PCR amplification was performed using primers that amplify restriction sites for MspAI (A2 polymorphism-CYP17) and NalIII (Val/Met polymorphism-COMT). Digestion of the PCR products was performed. Genotypes identified by gel electrophoresis were assigned as homozygous wild type (WW), heterozygous variant (Wv), and homozygous variant (vv). Frequencies were compared using χ2 or Fisher’s exact tests. Logistic regression was used to calculate crude and adjusted relative risks (RRs) for ovarian cancer associated with possession of any variant allele overall, and within demographic, weight, and smoking history categories, and by histological subtype of ovarian cancer. A portion (68.9%) of cases either carried or was homozygous for the A2 variant of CYP17 compared with 53.9% of controls, for a RR (and 95% confidence interval) of 1.86 (1.26, 2.75; P = 0.003), adjusted for age, parity, oral contraceptive use, site of study, and family history of breast or ovarian cancer. The increased risk was most apparent for women >50 and women with invasive serous cancers. A portion (71.9%) of cases either carried or was homozygous for the Val/Met variant of COMT, compared with 76.9% of controls (P = 0.27). Although the inverse association of ovarian cancer with possession of a Val/Met variant was not significant overall, it was for mucinous tumors of the ovary, with an adjusted RR of 0.28 (0.13, 0.61; P = 0.0012). Possession of the A2 variant of CYP17 appears to increase risk for ovarian cancer, whereas possession of the Val/Met variant of COMT decreases the risk for mucinous tumors. Confirmation in other populations and further exploration of potential pathogenic mechanisms will be necessary.

INTRODUCTION

The observation that breast and ovarian cancers tend to cluster in certain families led ultimately to the identification of the BRCA1 and BRCA2 genes as key factors determining susceptibility to both of these cancers in many, but not all, families. Other genetic factors are likely involved, however, and interest has recently focused on genes that are involved in the production and metabolism of estrogen. The hypothesis is that the activity of the products of such genes may affect long-term levels of estrogen and/or its potentially carcinogenic metabolites and influence the risk of breast and ovarian cancer, which are likely to have a hormonal basis (1).

Polymorphisms of the cytochrome P450 gene, CYP17, as well as COMT, have been of particular interest and have been studied likely to have a hormonal basis (1). Metabolites and influence the risk of breast and ovarian cancer, which are involved in the conversion of pregnenolone and progesterone to their respective 17-hydroxy metabolites, as well as the subsequent conversion of these intermediates to dehydroepiandrosterone or androstenedione, the precursors of estrone and testosterone. A polymorphism in CYP17, known as A2, leads to the substitution of C for T in the promoter region of the gene and introduces a restriction site for MspAI (2). The variant of this polymorphism has been hypothesized to alter the promoter activity, possibly increasing CYP17 transcription and theoretically increasing estrogen or androgen production (3). Ovarian cancers have been shown to possess receptors for estrogen, as well as progesterone (4), suggesting a role of these hormones in tumor cell proliferation. CYP17 activity could thus influence risk for ovarian cancer development.

COMT is an important enzyme in the inactivation of catechol estrogens, which are believed to be contributors to estrogen-induced cancer development through the formation of reactive adducts with DNA (5). In addition, the intermediate products of catechol estrogen metabolism, including 2- and 4-methoxyestradiol, may themselves have antiestrogenic properties and have been shown to inhibit tumor cell growth, stimulate apoptosis, and inhibit angiogenesis (6). A G-A transition in exon 4, which results in a valine to methionine substitution, introduces a restriction site for NalIII. The resultant variant form of COMT is believed to have low activity and heat instability (7). It has been hypothesized that this COMT polymorphism may modulate risk of hormonally responsive cancers because of a decreased ability of COMT to methylate and thereby inactivate catechol estrogens, as well as through decreased production of the intermediate products of catechol estrogen metabolism (8).

Although the A2 polymorphism of CYP17 and the VAL/MET polymorphism of COMT have been the topics of a number of studies of breast cancer, they are less well studied in ovarian cancer. At the time this study was undertaken, there was only a single study of the CYP17 polymorphism, and no published studies existed on the role of the COMT polymorphism in ovarian cancer risk. Here, we present the results of a case control study of epithelial ovarian cancer in association with the A2 polymorphism of CYP17 and the VAL/MET polymorphism of COMT.

MATERIALS AND METHODS

Details of the study have been provided elsewhere (9). Briefly, over a 5-year period from May 1992 to March 1997, 1080 incident cases of ovarian cancer of women residing in eastern Massachusetts or New Hampshire were identified through hospital tumor boards and statewide cancer registries. A group of 203 cases was excluded because they had died or moved, had no telephone, did not speak English, or had a nonovarian primary tumor after review, so that 877 eligible women remained. Physicians declined permission to contact 126 (14%) of these women, and an additional 136 cases (16%) declined to participate. The original case population consisted of 563 women with epithelial ovarian cancer, including those with tumors of borderline malignancy.

Population-based controls were identified using RDD, supplemented by the use of population rosters for older cases. On the basis of the telephone exchanges for the cases, phone numbers were generated and called to screen households for potential controls who were within 4 years of the age of the case. Approximately 5400 calls (not including businesses or nonworking
numbers) yielded 10% of households in which the answerer declined to provide a household census and 80% of households in which an age and sex matched control for a case could not be made or was ineligible because of a prior oophorectomy. Of the remaining 10% of households screened with a potential eligible control, 72% agreed to participate. RDD proved inefficient for identifying controls over age 60 in MA, so we chose to identify older controls in MA by randomly selecting women from lists (townbooks) of all residents in towns by name, age, and address according to precinct. Older controls were matched to cases by community and age within 4 years based on the townbooks. Of 328 sampled townbook controls, 21% could not be reached, 18% were ineligible, and 30% declined to participate. The final control population included 523 women selected through either RDD or the townbooks.

After written informed consent, an in-person interview was used to assess demographic information, menstrual and reproductive history, medical and family history, and personal habits for each woman. All exposures were assessed before a “reference date,” defined as 1 year before the date of diagnosis for cases and the date of interview for controls. Blood was drawn, and plasma, red cell, and buffy coat components were saved.

We chose to use a random sample of the total case and control populations with the goal of being able to detect a 2-fold increase (or a 50% decrease) in the risk for ovarian cancer associated with heterozygosity or homozygosity of the polymorphic variant. On the basis of studies published previously, for both the risk for ovarian cancer associated with heterozygosity or homozygosity of these estimates, we chose a sample size of 50% of the population and homozygosity between 15 and 25%. On the basis of these estimates, we chose a sample size of ~240 cases and 240 controls.

From buffy coat samples obtained previously from the sampled subjects, genomic DNA was extracted by overnight treatment with digestion buffer containing 0.1 mg/ml proteinase K, followed by phenol-chloroform extraction and precipitation with ethanol. DNA samples were stored at 4°C until use. Genotyping of the respective polymorphisms was performed using PCR and subsequent restriction fragment length polymorphism techniques. Technicians were blinded to case control status of the DNA samples. The respective gene fragments containing the polymorphisms of interest were amplified with the following primers: CYP17A2: forward: 5’-CATTCCGACCTTCTGGAGTC-3’ reverse: 5’-GGCTCTTGGGTACCTTG-3’

or forward: 5’-TTCTCCAAAGGCGAAGAGA-3’ reverse: 5’-TTGGCCCTAAACAATTAAGC-3’ COMT Val/Met: forward: 5’-TACTGTTGGCTACTACGTTGC-3’ reverse: 5’-GTTGAACTTGTGTTGAAACC-3’

For analysis of the CYP17 polymorphism, a 25-μl PCR reaction mix was used: 1 μl of genomic DNA (50–100 ng/μl), 2.5-μl reaction buffer II with MgCl2 (PE Biosystems), 2.5 μl of deoxynucleotide triphosphates, 0.15 μl of Taq polymerase (Promega), and 2 μl of each primer (forward and reverse). The reaction was performed in a Perkin-Elmer 9600 Thermal Cycler, and DNA was denatured at 94°C for 5 min and amplified during 30 cycles of 94°C for 1 min, 57°C for 1 min, and 72°C for 1 min, with extension at 72°C for 5 min. For the COMT polymorphism, a 20-μl PCR reaction mix was used: 2 μl of genomic DNA (50–100 ng/μl), 1.6 μl of MgCl2, 1.6 μl of deoxynucleotide triphosphates, 2 μl of reaction buffer (Applied Biosystems), 0.2 μl of Taq polymerase (AmpliTaq Gold, Applied Biosystems), and 0.4 μl of each primer (forward and reverse). The reaction was performed in a Perkin-Elmer 480 Thermal Cycler;

DNA was denatured at 95°C for 10 min and then amplified during 35 cycles of 95°C for 30 s, 55°C for 30 s, and 72°C for 1 min, with extension at 72°C for 10 min.

The PCR products were digested with the respective restriction endonucleases (CYP17 A2-MspAl, COMT VAL/MET-NalII) in a 25 or 20 μl, respectively, reaction mixture as follows: 15 or 10 μl of PCR product, 2.5 or 2 μl of digestion buffer, and 0.5 or 1 μl of restriction enzyme (in addition to 0.25 μl of BSA for CYP17 mix). Digestion was carried out at 37°C overnight (CYP17) or for 1 h (COMT). The digested PCR products were then separated by agarose gel electrophoresis, and restriction patterns were analyzed as described by Feigelson et al. (10) and Lavigne et al. (11). Predicted restriction patterns were known from previous studies of these polymorphisms and are easily distinguishable using these techniques. Patterns were analyzed without knowledge of subject status, and subjects were categorized as homozygous wild-type, heterozygous, or homozygous variants for each polymorphism. Blank DNA controls were used to rule out PCR contamination, and ambiguous results were repeated until a clear result was obtained.

Because matching was performed for convenience, rather than for control of confounding, matching was not preserved in the analysis. Analyses were performed using the SAS system (SAS institute, Inc., Cary, NC). The RR for ovarian cancer associated with possession of a variant allele was calculated relative to wild types without the allele. Adjusted RRs were calculated using logistic regression with age (continuous), site (MA or New Hampshire), parity (nulliparous, one live birth, two live births, more than or equal to three live births), OC use (never, <3 months, or ≥3 months), and family history of breast or ovarian cancer (no or yes). Analyses were repeated for subgroups of the population: e.g., age above or <50, BMI above or below the control median, and ever or never smoked. RRs were calculated for all epithelial ovarian cancer and the histological subtypes (serous invasive, serous borderline, mucinous, endometrioid, clear cell, and other or undifferentiated).

RESULTS

There were no significant differences between the sampled cases and controls compared with the entire series of cases and controls (data not shown). Sampled cases differed from sampled controls by the same features that distinguished all cases and all controls, including a greater frequency of women among cases who had never married, never had children, and never used OCs.

Table 1 shows the frequency of the two polymorphic variants studied and associated RRs, adjusted for age, study center, parity, OC use, and family history of breast or ovarian cancer. One hundred twenty (53.3%) cases were heterozygous, and 35 (15.6%) were homozygous for the A2 variant of CYP17, compared with 96 (39.8%) and 34 (14.1%) controls. The adjusted RR (and 95% confidence limits) for ovarian cancer associated with heterozygosity for the A2 variant was 1.96 (1.29, 2.96), P = 0.002, and the RR for homozygosity of the A2 variant was 1.58 (0.89, 2.82), P = 0.12. One hundred three (49.0%) cases were heterozygous, and 48 (22.9%) were homozygous for the low activity (MET) variant of COMT, compared with 119 (52.9%) and 54 (14.1%) controls. The adjusted RR (and 95% confidence limits) for ovarian cancer associated with heterozygosity

<table>
<thead>
<tr>
<th>Gene/variant</th>
<th>Genotype</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>Crude RR (95% CL)</th>
<th>Adj. RR (95% CL)</th>
<th>p^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17A2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>70 (31.1)</td>
<td>111 (46.1)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>120 (53.3)</td>
<td>96 (39.8)</td>
<td>1.98 (1.33, 2.96)</td>
<td>1.96 (1.29, 2.96)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Homozygous</td>
<td>35 (15.6)</td>
<td>34 (14.1)</td>
<td>1.63 (0.93, 2.85)</td>
<td>1.58 (0.89, 2.82)</td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td>Any variant</td>
<td>155 (68.9)</td>
<td>130 (53.9)</td>
<td>1.89 (1.29, 2.76)</td>
<td>1.86 (1.26, 2.75)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>COMT val/met</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>59 (28.1)</td>
<td>52 (23.1)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>103 (49.0)</td>
<td>119 (52.9)</td>
<td>0.76 (0.48, 1.21)</td>
<td>0.74 (0.46, 1.18)</td>
<td>0.198</td>
<td></td>
</tr>
<tr>
<td>Homozygous</td>
<td>48 (22.9)</td>
<td>54 (24.0)</td>
<td>0.78 (0.46, 1.34)</td>
<td>0.72 (0.42, 1.27)</td>
<td>0.252</td>
<td></td>
</tr>
<tr>
<td>Any variant</td>
<td>151 (71.9)</td>
<td>173 (76.9)</td>
<td>0.77 (0.50, 1.19)</td>
<td>0.73 (0.47, 1.14)</td>
<td>0.167</td>
<td></td>
</tr>
</tbody>
</table>

^1 CI, confidence limit.

^2 Adjusted for age (continuous), site, parity, OC use, and family history of breast or ovarian cancer.

Table 1: Frequency of polymorphic variants among all cases and controls and associated RRs for ovarian cancer.
for the MET variant was 0.74 (0.46, 1.18), $P = 0.198$, and the RR for homozygosity of the MET variant was 0.72 (0.42, 1.27), $P = 0.252$.

Table 2 shows the adjusted risk for ovarian cancer associated with possession of a variant allele (either heterozygosity or homozygosity) within demographic and weight categories, as well as categories defined by smoking history. The increased risk for ovarian cancer associated with the possession of the A2 variant was found to be most apparent in women $>50$, those below the median BMI (23.9), and women who had ever smoked. The null association between the low activity (MET) variant of COMT and ovarian cancer overall persisted in the various subgroups examined. Too few non-Caucasians were included in this study to examine the effect of race on risk associated with either variant. We did, however, examine the polymorphisms by Jewish or non-Jewish background. The point estimate for risk for ovarian cancer associated with the A2 allele was higher for Jewish women compared with non-Jewish women, but the confidence interval on this RR was wide and included 1, RR = 3.48 (0.74, 16.31).

Table 3 shows the proportion of women with any variant allele (either heterozygosity or homozygosity) within specific histological subtypes of ovarian cancer and associated RRs compared with all controls. Possession of the A2 variant was most likely to be associated with an undifferentiated cancer. Mucinous tumors of the ovary were significantly less likely to be associated with possession of the low activity (MET) variant of COMT, RR = 0.28 (0.13, 0.61).

Table 2. Risk for ovarian cancer by possession of a variant allele within age, weight, smoking, and ethnic categories

<table>
<thead>
<tr>
<th>Age</th>
<th>CYP17 A2</th>
<th>RR (95% CL)</th>
<th>P</th>
<th>COMT Val/Met</th>
<th>RR (95% CL)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 50$</td>
<td>No. (%) WT cases</td>
<td>41 (33.9%)</td>
<td>38 (33.3%)</td>
<td>No. (%) WT controls</td>
<td>62 (45.3%)</td>
<td>30 (23.4%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>1.61 (0.97, 2.67)</td>
<td>0.61 (0.35, 1.08)</td>
<td>Adj. RR</td>
<td>1.61 (0.94, 2.75)</td>
<td>0.012</td>
</tr>
<tr>
<td>$&gt;50$</td>
<td>No. (%) WT cases</td>
<td>29 (27.9%)</td>
<td>21 (21.9%)</td>
<td>No. (%) WT controls</td>
<td>49 (47.2%)</td>
<td>22 (22.7%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>2.30 (1.30, 4.10)</td>
<td>1.05 (0.53, 2.06)</td>
<td>Adj. RR</td>
<td>2.29 (1.27, 4.14)</td>
<td>0.006</td>
</tr>
<tr>
<td>Weight ≤ Median BMI</td>
<td>No. (%) WT cases</td>
<td>31 (29.5%)</td>
<td>29 (27.9%)</td>
<td>No. (%) WT controls</td>
<td>61 (48.4%)</td>
<td>24 (20.3%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>2.24 (1.30, 3.87)</td>
<td>0.66 (0.36, 1.23)</td>
<td>Adj. RR</td>
<td>2.33 (1.32, 4.12)</td>
<td>0.004</td>
</tr>
<tr>
<td>&gt; Median BMI</td>
<td>No. (%) WT cases</td>
<td>39 (32.5%)</td>
<td>30 (28.3%)</td>
<td>No. (%) WT controls</td>
<td>50 (43.5%)</td>
<td>28 (26.7%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>1.60 (0.94, 2.72)</td>
<td>0.90 (0.49, 1.64)</td>
<td>Adj. RR</td>
<td>1.53 (0.89, 2.64)</td>
<td>0.126</td>
</tr>
<tr>
<td>Smoking</td>
<td>Never smoked</td>
<td>No. (%) WT cases</td>
<td>34 (37.8%)</td>
<td>26 (31.3%)</td>
<td>No. (%) WT controls</td>
<td>49 (45.8%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>1.39 (0.79, 2.46)</td>
<td>0.69 (0.36, 1.33)</td>
<td>Adj. RR</td>
<td>1.55 (0.84, 2.89)</td>
<td>0.163</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>No. (%) WT cases</td>
<td>36 (26.7%)</td>
<td>33 (26.0%)</td>
<td>No. (%) WT controls</td>
<td>62 (46.3%)</td>
<td>28 (22.4%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>2.37 (1.42, 3.95)</td>
<td>0.82 (0.46, 1.47)</td>
<td>Adj. RR</td>
<td>2.12 (1.25, 3.60)</td>
<td>0.005</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Non-Jewish</td>
<td>No. (%) WT cases</td>
<td>63 (30.4%)</td>
<td>54 (26.0%)</td>
<td>No. (%) WT controls</td>
<td>99 (45.0%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>1.87 (1.26, 2.78)</td>
<td>0.79 (0.50, 1.24)</td>
<td>Adj. RR</td>
<td>1.86 (1.23, 2.81)</td>
<td>0.003</td>
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<tr>
<td>Jewish</td>
<td>No. (%) WT cases</td>
<td>7 (38.9%)</td>
<td>5 (29.4%)</td>
<td>No. (%) WT controls</td>
<td>12 (57.1%)</td>
<td>4 (20.0%)</td>
</tr>
<tr>
<td></td>
<td>Crude RR</td>
<td>2.10 (0.58, 7.56)</td>
<td>0.60 (0.13, 2.72)</td>
<td>Adj. RR</td>
<td>3.48 (0.74, 16.31)</td>
<td>0.114</td>
</tr>
</tbody>
</table>

* Adjusted for age (continuous), site, parity, OC use, and family history of breast or ovarian cancer.
* WT, wild type.
* Median BMI 23.9.
DISCUSSION

Although it is an appealing hypothesis that genes affecting the production or metabolism of estrogen may affect the risk of hormonally related cancers, the evidence from the literature is inconsistent. Early reports suggested an association with an increased risk of breast cancer for the A2 variant allele of the CYP17 gene (10, 12), especially for breast cancer arising premenopausally or presenting at an advanced stage. Subsequent studies, however, failed to show this association (3, 13), even within these subgroups. With regard to ovarian cancer risk, Spurdle et al. (14) reported no evidence for an association. Because of a lack of epidemiological information on cases, subgroup analysis was not possible in their study. Goodman et al., in a smaller study, also reported no significant association between CYP17 polymorphisms and ovarian cancer risk. The authors of this study do point to a lack of power as a possible explanation (15). In our study, we found that both heterozygotes and homozygotes for the A2 variant were not at higher risk than heterozygotes.

Results on the COMT VAL/MET polymorphism have also been conflicting, with an increased risk for premenopausal breast cancer associated with the low activity variant in one study (16), an increased risk for postmenopausal breast cancer in another study (11), and a null association in a third study (8). In papers published after we began our investigation, no association between the COMT polymorphism and ovarian cancer was found (17, 18). The investigators did not, however, examine the association by histological subtype of ovarian cancer. We also found no overall association of the low activity variant with ovarian cancer in our study, except in the subgroup of women with mucinous tumors, where an inverse association was noted.

In published reports about the CYP17 and COMT genes, there has been interest in the interaction between the polymorphic variants and cancer risk by age, weight, menarchal or menopausal status, and smoking categories. As already noted, the A2 allele of CYP17 has been postulated to increase the risk for premenopausal breast cancer and its presence to negate the usual protective effect of late age at menarche on breast cancer risk (3, 10). We chose to use 50 years of age as a surrogate for menopausal status, and, in our analyses, the effect of the CYP17 A2 allele was more apparent in the older (largely postmenopausal) women. The association was also more apparent in leaner women. The low-activity COMT variant has been reported to affect the risk for postmenopausal breast cancer, especially in women with a greater BMI (11). In our study, neither age nor BMI affected the risk associated with the low-activity COMT variant. We did, however, find an inverse association for women with mucinous tumors. Thus, COMT may be one more of a number of molecular genetic markers that differ between mucinous and nonmucinous cancers. Although these subgroup analyses provide interesting hypotheses, it should be appreciated that most of these associations, including the ones reported here, are the results of post-hoc analyses without compelling a priori biological arguments for the interaction or effect modification. Thus, confirmation in other studies and exploration of potential pathogenetic mechanisms will be necessary. As mentioned, the existing studies on COMT and ovarian cancer did not examine the association separately for mucinous tumors.

In studying genetic risk factors for breast and ovarian cancers, it must be considered that a potential genetic factor might appear to be linked with the disease simply because it may cosegregate with a BRCA1 or BRCA2 mutation. Neither of the genes examined are located on the same chromosomes as BRCA1 or BRCA2. In addition, cases were drawn from the general population and largely consisted of sporadic cases, only 10% of whom are estimated to carry a BRCA1 and BRCA2 mutation. However, this figure does not pertain to Jewish women with ovarian cancer, 25–40% of whom may carry one of the unique founder mutations of BRCA1 or BRCA2 (19). Thus, some estimate of the interaction between BRCA1 or BRCA2 mutations and the polymorphisms studied might be obtained by examining associations among Jewish women. No difference was observed for the COMT variant, but the point estimate of risk associated with the CYP17 A2 allele was greater (although not significant) for Jewish women (Table 2). Thus, it may be worthwhile to look for potential interaction between BRCA1 or BRCA2 mutations and the A2 allele in future studies.
General limitations of case control studies include selection and recall biases. Because it is possible that women with very rapidly progressing ovarian cancers may not have been studied, our results could be biased if cases with polymorphic variants had differential survival. Such a pattern has not been described, however. Selection factors among controls also have the potential to bias results, although our estimates of the prevalence of the variants appear to be consistent with those found in other studies of largely Caucasian populations (10, 11). The tendency for exposures to be differentially reported by cases would not pertain to the measurement of germ-line mutations.

The role of estrogen and its metabolites in the pathogenesis of epithelial ovarian cancers has yet to be clarified, although the key risk factors for ovarian cancer, nulliparity, and lack of OC use suggest hormonal pathways. In vitro studies provide evidence of estrogen responsiveness of ovarian epithelium (20), and estrogen antagonists have been used in the treatment of chemotherapy-resistant tumors. Recent evidence of an increased risk of ovarian cancer with post-menopausal estrogen replacement therapy further suggests a role of estrogen in the pathogenesis of this disease (21).

This study now provides some evidence that genetic factors related to estrogen synthesis and metabolism may also affect ovarian cancer risk. Additional molecular epidemiological studies need to be performed to more clearly elucidate the role of variant forms of CYP17, COMT, and other estrogen-metabolizing genes. In addition, investigation is needed into interactions of polymorphic changes in these genes with other potential carcinogenic exposures. Additional study will also be required to determine the mechanisms by which genetic polymorphisms may modify the risk of ovarian cancer.

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Polymorphisms of the Estrogen-metabolizing Genes CYP17 and Catechol- O-methyltransferase and Risk of Epithelial Ovarian Cancer


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