

Null Results in Brief

CYP17 Genotype and Ovarian Cancer: A Null Case-Control Study¹

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Introduction

Long-term differences in steroid hormone levels between women likely contribute to the interindividual variation in ovarian cancer risk, although the precise biological mechanisms are unclear (1). The *P450c17α* (*CYP17*³) gene codes for 17 α -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→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 conducted in Hawaii and Los Angeles (2), although results from other studies have been inconsistent (7, 8). A recent report from the Nurses' Health Cohort did not find an association of breast cancer with the *CYP17* gene (7), but the analysis did find an inverse association of late age at menarche with breast cancer that was absent among women with the A2 allele, suggesting that *CYP17* influences early ovulatory events and perhaps the risk of ovarian cancer. Blood samples from a case-control study in Hawaii were used to test the hypothesis that women with the *CYP17* variant A2 allele are at increased risk of ovarian cancer.

Materials and Methods

Eligible cases for this population-based, case-control study in Hawaii comprised all patients with histologically confirmed, primary, epithelial ovarian cancer diagnosed between July 1, 1993, and June 30, 1999, in any of the major hospital centers on Oahu. Eligible women were 18 to 84 years of age and were residents of Oahu. Interview information was obtained from 218 (75%) of 291 ovarian cancer cases eligible for participation in the study. The control pool consisted of population-based lists of female Oahu residents who were interviewed by the Health Surveillance Program of the Hawaii Department of Health. This source was supplemented with women 65 years of age and older who were Health Care Financing Administration participants on Oahu. Potential controls were randomly selected from the pool so that the ethnic (*e.g.*, Chinese) and 5-year age-group distribution would match that of the case group with a 1:1 ratio. Four hundred and sixteen women meeting these eligibility criteria were contacted to participate in the study. Interviews were obtained for 284 (68%) of these women, with 132 (32%) eligible women refusing to participate.

We were able to draw blood from 146 (67%) of the interviewed cases and 192 (68%) of the interviewed controls. We selected 129 cases with complete questionnaire (*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, \geq 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,

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³ The abbreviations used are: *CYP17*, cytochrome P450c17 α ; OR, odds ratio; and CI, confidence interval.

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

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

^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.

7, 8). We found no significant differences between cases and controls in the frequency of the *CYP17* variant A2 allele after adjustment for covariates (Table 1). The OR for ovarian cancer was 0.8 (95% CI, 0.5–1.5) among women with at least one *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 up-regulate 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.

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