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Variants in hormone biosynthesis genes and risk of endometrial cancer

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Abstract

We investigated the risk associated with variants in three genes involved in estrogen biosynthesis, *CYP11A1*, *CYP17A1*, and *CYP19A1*, in the population-based case control study of Estrogen, Diet, Genetics, and Endometrial Cancer. This study was conducted in New Jersey in 2001–2006 with 417 cases and 402 controls. For *CYP11A1*, there was no association between the number of [TTTTA]_n repeats (D15S520) and risk. For *CYP17A1*, risk was somewhat lower among women with the C/C genotype at T-34C (rs743572) (adjusted OR=0.65, 95% CI 0.41–1.02). For *CYP19A1*, risk was lower among women homozygous for the 3-base pair deletion (rs11575899) in exon 4 (adjusted OR=0.44, 95% CI 0.26–0.76), while the number of [TTTA]_n repeats was not significantly related to risk: the adjusted OR for n=7/7 repeats vs n>7/>7 repeats was 0.81 (95% CI 0.54–1.23). In stratified analyses, results for *CYP19A1* were stronger among women with higher (>27.4) body mass index: for the homozygous deletion, OR=0.30 (95% CI 0.15–0.62); for the n=7/7 genotype, OR=0.49 (95% CI 0.26–0.93). The interaction between the n=7/7 genotype and BMI was statistically significant (p=0.01). The insertion/deletion variant in *CYP19A1* appears to be related to risk of endometrial cancer; risk associated with variants in this gene may vary according to BMI.

Keywords

endometrial cancer; epidemiology; *CYP11A1*; *CYP17A1*; *CYP19A1*

Introduction

Endometrial cancer, the most common gynecologic cancer in the U.S. [1], is largely related to sex steroid hormones. A unifying hypothesis for the etiology of endometrial cancer is the presence of excessive or prolonged exposure to estrogens unopposed by progesterone [2,3]. The major risk factor, obesity, is thought to increase risk mainly through its association with estrogen and progesterone levels: in premenopausal women, estrogen levels are high regardless of weight but obesity is associated with anovulation and low levels of progesterone [4–6]; in postmenopausal women, the main source of circulating estrogen is conversion from androgens in adipose tissue, and progesterone levels are low [7–9]. Use of unopposed estrogen replacement therapy also increases risk [10,11]. Both case-control and prospective studies have

shown that higher levels of circulating estradiol and estrone increase risk of developing endometrial cancer [12,13]. The link between obesity and endometrial cancer may also be related to other aspects of excess weight, such as through a pathway involving insulin resistance, chronic hyperinsulinemia, and increased availability of IGF-1, leading to increased cell proliferation and decreased apoptosis [14].

One approach to understanding hormonal carcinogenesis is through investigation of genes involved in the pathway of estrogen biosynthesis. Our objective in this study was to investigate risk associated with variants in *CYP11A1*, *CYP17A1* and *CYP19A1*. As shown in Figure 1, estrogens and other steroid hormones are derived from cholesterol, with the first step consisting of the formation of pregnenolone from cholesterol through the activity of *CYP11A1* (15q23–24). We studied a pentanucleotide [TTTA]_n repeat (D15S520) at the –528 position in the promoter region. *CYP17A1* (10q24.3) converts pregnenolone and progesterone to 17 α -hydroxypregnenolone and 17 α -hydroxyprogesterone, respectively, and these intermediates to DHEA (dehydroepiandrosterone) and androstenedione, respectively. Androstenedione and its metabolite, testosterone, are the precursors of estrone and estradiol, respectively. We tested the T/C change (rs743572, also referred to as A1/A2) at the –34 position relative to the start codon in the 5' promoter region of *CYP17A1*. *CYP19A1* (15q21.1) codes for aromatase, which confers the rate limiting step in the production of estrogen. In addition to converting testosterone to estradiol in ovarian granulosa cells, aromatase converts androstenedione to estrone in adipose and other peripheral tissue. We studied two variants in *CYP19A1*, a tetranucleotide repeat [TTTA]_n in intron 4 and a nearby deletion of 3 base pairs [–/TCT] (rs11575899) thought to be found only in conjunction with the seven repeat [15,16].

Materials and Methods

Study Population

The EDGE Study (Estrogen, Diet, Genetics, and Endometrial Cancer) is a population-based case-control study. Cases were eligible if they were age 21 and over, lived in one of six counties in northern NJ (Bergen, Essex, Hudson, Middlesex, Morris, Union), and spoke English or Spanish. They were diagnosed with epithelial endometrial cancer between July 1, 2001 and June 30, 2005 and interviewed between January 2002 and April 2006. Cases were identified by the NJDHSS (New Jersey Department of Health and Senior Services) using rapid case ascertainment. During the four years of the study, 1559 eligible women were identified, of whom 1104 could be contacted within one year of diagnosis. Four hundred sixty-nine (42%) completed the interview. Of those who completed the interview, 417 (89%) provided a buccal sample and are included in this analysis. Pathology reports and slides were obtained for cases in the study and reviewed by the study pathologist.

Controls had the same eligibility requirements as cases and, in addition, could not have had a hysterectomy. They were interviewed between January 2002 and December 2005. Women aged <65 were initially located through RDD (random digit dialing) conducted by a commercial research service. One hundred seventy-five of the 355 eligible women (49%) completed the interview. For women aged ≥ 65 , we initially identified potential controls by random selection from lists purchased from the CMS (Centers for Medicare and Medicaid Services). We identified 316 women, of whom 68 (22%) completed the interview, while the remainder declined; for 40% of those who declined, eligibility was unknown. Beginning in August 2003, we undertook area sampling for controls. In randomly chosen areas, households were contacted by mail followed by home visits. Initially we sought women aged ≥ 65 ; later, we included women aged ≥ 55 . We identified 524 eligible women, of whom 224 (43%) completed the interview. In total, 467 controls completed the interview, of whom 402 (86%) provided a buccal sample and are included in this analysis. Informed consent was obtained from all participants

and the study was approved by the Institutional Review Boards at Memorial Sloan-Kettering Cancer Center and NJDHSS.

Data and Biospecimen Collection

Interviews were conducted by telephone for most respondents (93%) and covered established and possible risk factors for endometrial cancer. We sent respondents a kit with instructions for providing buccal specimens using a mouthwash rinse and waist and hip circumference measurements and the Block 98 diet questionnaire.

Laboratory methods

DNA was obtained from buccal cells collected with mouthwashes using the Puregene DNA isolation kit (Gentra Systems Inc, Minneapolis, MN), replacing glycogen with tRNA (10µg/µl) for the DNA precipitation step. DNA concentration was measured by spectrophotometry at 260 nm in a Spectramax Plus 384 (Molecular Devices, Sunnyvale, USA). The DNA quality was determined by the ratio A260/A280.

Genotyping was undertaken for variants in *CYP11A1* (D15S520), *CYP17A1* (T-34C, rs743572), and *CYP19A1* (3bp insertion/deletion (Ins/Del), rs11575899, and intron 4 [TTTA]_n repeat polymorphism). All genotyping was done with PCR-based methods and included pyrosequencing for *CYP17A1* [17] with the PSQ™ 96 MA or PSQ™ HS 96A instruments (Biotage AB, Uppsala, Sweden) and fragment size analysis [18] by an ABI PRISM® 3100 Genetic Analyzer (Applied Biosystems, Foster City, USA) for *CYP11A1* and *CYP19A1*. The PCR primers and PCR annealing temperatures are available on request. PCR fragments were amplified in a reaction containing 0.2µM each of the specific forward and reverse primers, 1.5 to 3.0mM MgCl₂, 200 to 250µM dNTP and 0.05 U/µl Taq Polymerase, and PCR buffer. The cycling consisted of a denaturation at 95°C for 5 minutes followed by 40 to 45 cycles of 95°C for 30 seconds, primer-specific annealing temperature (Ta) for 30 seconds, 72°C for 30 seconds, with a final extension at 72°C for 7 minutes. Products were immobilized and denatured at 80°C for 2 minutes. For the pyrosequencing reaction, the corresponding sequencing primer was added to the single stranded DNA and nucleotides dispensed automatically by a Pyrosequencing AB PSQ96MA or HS instrument and software (Uppsala, Sweden).

All genotyping included known internal laboratory controls consisting of sequenced DNA from healthy donors (homozygous wild type and variant, and heterozygous DNAs) and blanks (water). Results are included if: (i) all the control and water samples tested showed the expected genotype or no signal, respectively; (ii) there was 100% agreement in the genotyping calls between 2 independent laboratory members, each of whom read all results; and (iii) there was 100% agreement in two independent assays of genotypes in randomly selected samples. The number of randomly selected samples ranged from 6% for the T-34C polymorphism in *CYP17A1* to 14% for the 3bp Ins/Del polymorphism in *CYP19A1*. For *CYP17A1* and the *CYP19A1* Ins/Del, genotyping was successful for 99.8% of samples; for the *CYP11A1* and *CYP19A1* repeat polymorphisms, the success rate was 99.4%.

Statistical Analysis

Logistic regression was used to determine associations of genotype with case-control status. Potential confounding variables that we investigated were those related to case-control status in this and other studies: age; BMI (wt(kg)/ht(m²)), classified as normal (<25), overweight (25–29.9), obese (30–34.9), very obese (≥35); education (high school or less, college, graduate school); smoking (current, past/never); parity (0–1, 2, ≥3); age at menarche (≥13, <13); OC (oral contraceptive) use (ever, never used); history of endometrial cancer in a first degree relative (yes, no); menopausal status/age at menopause (premenopausal, age at menopause

<50, age at menopause ≥ 50 , postmenopausal with age at menopause unknown); and use of hormone replacement therapy (HRT) (never used any HRT, used unopposed estrogen only, used combined therapy, i.e., estrogen and progesterone). To investigate whether population stratification could have influenced our genotyping results, we also considered race, Hispanic ethnicity, and grandparents' European origins, based on questionnaire data. For the repeat polymorphisms in *CYP11A1* and *CYP19A1*, we grouped the genotypes according to the number of copies (0, 1, or 2) of the most common number of repeats (4 for the former and 7 for the latter). These are also the categories most commonly reported in the literature. We also investigated the number of copies of 8 repeats for *CYP19A1* since some studies have reported this. Since we studied only four variants in this pathway, we did not adjust for multiple comparisons.

We investigated effect modification by BMI using as the cut-point the median value of 27.4 in cases and controls combined in order to avoid small numbers in individual cells. We evaluated genotype associations separately in cases with endometrioid tumors or adenocarcinomas (not further specified) and those with other types. There were not sufficient numbers of users of estrogen replacement therapy only or premenopausal women to stratify on these factors.

For RDD and CMS controls, we frequency matched controls to the expected distribution of cases by 5-year age groups; however, in area sampling this would have required a complex sampling scheme that would have been difficult to execute in the field. Instead, we included all age-eligible women who were willing to take part in the study. We were able to enroll more older controls, leading to an imbalance in age between the cases and controls. In logistic regression, we used a spline technique that modeled the association between age and case-control status separately according to three age categories: <65; 65 to 79; and ≥ 80 [19]. Including all eligible women in a neighborhood has the potential to introduce bias because women living in the same neighborhoods are likely to have similar characteristics. The 224 women recruited through area sampling lived in 150 neighborhoods, with the number from any one neighborhood ranging from 1 (in 90 neighborhoods) to 7 (in one neighborhood). To determine whether clustering by neighborhood affected the results, we compared results from the logistic models with those obtained by fitting generalized estimating equations [20], which account for the clustering of subjects. Differences in parameter estimates and standard errors were trivial, indicating that the clustering does not affect the analysis and that logistic models perform similar to general estimating equations. SAS version 9.1 (SAS Institute, Cary NC) was used for analysis.

Results

Characteristics of cases and controls

The 819 women who provided a mouthwash sample (88% of all respondents) were significantly older than the 117 women who did not (mean age (SD) 63.4 (10.4) vs 59.7 (11.8), $p < 0.01$) and, after adjustment for age, less likely to be current smokers ($p < 0.01$). Those who gave a sample were somewhat more likely to have normal BMI and a family history of endometrial cancer ($0.05 < p < 0.10$, adjusted for age) (data not shown).

As shown in Table 1, controls were older than cases, with mean ages (SD) of 64.8 (± 11.0) and 62.0 (± 9.5), respectively ($p < 0.001$). Cases and controls were similar in education and most were white. Other results are shown adjusted for age. Cases had much higher BMI than controls. Controls had higher parity, were more likely to be current smokers, and were more likely to have used oral contraceptives and combined HRT. Cases were somewhat more likely than controls to have early age at menarche, later age at menopause, and to report endometrial cancer in a first degree relative. Although using only unopposed ERT (estrogen replacement therapy)

did not increase risk in our study, we did find increased risk for those who used ERT within two years of the reference date (OR=2.35, 95% CI 0.84–6.6, adjusted for age and BMI). Cases and controls were similar in the proportion with any grandparent born in or with ancestry from: the British Isles (35% of cases and 31% of controls); Germany (29% and 26%, respectively); Italy or France (24% and 26%); Poland or Czechoslovakia (23% and 25%); Russia or the countries of the former Soviet Union (12% and 13%); Belgium or the Netherlands (6% and 3%); and Scandinavia (3% and 4%).

Genotype results

All polymorphisms were in Hardy-Weinberg equilibrium among the controls ($p>0.05$). Table 2 shows associations of genetic variants with risk, unadjusted, adjusted for age, and adjusted for age and BMI. For the [TTTA]_n repeat in *CYP11A1*, compared to the reference category, $n=4/4$, we found no association of risk with longer repeats: the OR (adjusted for age and BMI) was 0.87 (95% CI 0.62–1.24) for those with 4/>4 genotypes and OR=1.07 (95% CI 0.71–1.60) for those >4/>4 genotypes. For *CYP17A1*, there was moderately decreased risk associated with carrying one or two C alleles, with adjusted ORs of 0.77 (95% CI 0.55–1.07) for the heterozygote and OR=0.65 (95% CI 0.41–1.02) for the homozygous CC genotype (p for trend, 0.04).

For *CYP19A1*, we found reduced risk among women who were homozygous for the intronic 3bp deletion, with an age- and BMI- adjusted OR of 0.44 (95% CI, 0.26–0.76) but no reduced risk for heterozygotes (OR=1.13, 95% CI, 0.83–1.55). We did not find the number of TTTA repeats in intron 4 of *CYP19A1* to be associated with risk. Although the 3bp deletion is linked to the 7 repeat allele, women homozygous for 7 repeats had only slightly reduced risk (OR=0.81, 95% CI 0.54–1.23). Adjustment for BMI strongly influenced the OR for the *CYP19A1* genotypes, since it was related to genotype in our data: obese and very obese controls were more likely to have the homozygous 3bp deletion (22% compared to 11% in normal or overweight women, $p<0.05$) and to have [TTTA]_n=7/7 (38% compared to 26%, $p<0.01$). We also investigated the [TTTA]₈ repeat: carrying any $n=8$ allele was not associated with risk (adjusted OR=1.05, 95% CI 0.74–1.49). There were too few participants with any 10 or 12 repeat alleles ($n=24$ and 48, respectively) for analysis. Although it has been reported that the 3bp deletion is found only in women with 7 repeats, we observed two women who were homozygous for both the 3bp deletion and [TTTA]₈ alleles.

Adjustment for other known risk factors did not affect these results. To assess the possibility of population stratification, in models including age and BMI, we added variables for race, Hispanic ethnicity, and specific region of origin within Europe (any grandparent from the British Isles, Germany, Italy or France, Poland or Czechoslovakia, and Russia or the former USSR), individually and as a group. Results were nearly identical to those reported.

We investigated associations of genotypes with risk according to strata based on BMI (Table 3) using the median (27.4 kg/m²) in the cases and controls combined. For *CYP11A1* and *CYP17A1*, results did not differ substantially according to BMI. For *CYP19A1*, in heavier women, we noted significantly reduced risk for the homozygous 3bp deletion (OR=0.30, 95% CI 0.15–0.62) and for those homozygous for the [TTTA]₇ alleles (OR=0.49, 95% CI 0.26–0.93). For the analysis of the microsatellite repeat, the interaction between BMI and the $n=7/7$ genotype was statistically significant ($p=0.01$). Comparison of cases with endometrioid ($n=338$) or other histology ($n=70$) separately to all controls did not provide clear associations of genotypes with risk according to tumor type (data not shown).

Discussion

To our knowledge, this is the first report of a polymorphism in *CYP11A1* and risk of endometrial cancer. We found no association with the [TTTTA]_n repeat in the promoter region that we tested. This polymorphism has been studied mainly in relation to PCOS (polycystic ovarian syndrome), a condition marked by high levels of androgens. While genotypes with more than 4 repeats have been found to be associated with risk of PCOS and with androgen levels in women with PCOS, other studies have not supported these results [21]. No functional differences have been reported for repeats of different lengths and no associations with hormone levels have been found in normal women [21]. There are other polymorphisms in this gene that may be functional [22] and may be candidates for future study in relation to risk of endometrial cancer.

For *CYP17A1*, results from earlier studies have been mixed. Some smaller studies (with the number of cases ranging from 51 to 184) reported reduced risk associated with the C/C genotype (reviewed in [22]), consistent with our results, while a larger study in Poland (497 cases, 1,024 controls) found no association [23]. The study by Gaudet et al [23] found, as we did, no difference in results according to levels of BMI, while Haiman et al [24] found a stronger effect in obese women. The C allele was originally thought to be associated with an Sp-1 binding site that would lead to higher expression [25]; however, a later study did not support this [26]. Several studies have examined the relationship between *CYP17A1* genotype and serum levels of androgens, estrogens, or progesterone. While there is some evidence that the variant allele is associated with higher levels of serum estrogens, other studies have not supported these findings and overall the evidence for an association of genotypes with estrogens is weak (reviewed in [21]). In addition, there is no evidence of association of genotype with serum levels of androgens, the precursors of estrogens (Figure 1). Higher levels of estrogens in women with the C allele have been reported in saliva [27], urine [28], and follicular fluid [29]. The association of the variant with higher levels of estrogen found in some studies would lead to the hypothesis that it would increase risk of endometrial cancer, in contrast to the reductions in risk noted in this and some other studies. Haplotypes have been described [30,31] but the only study to evaluate them in endometrial cancer found no associations with risk [23].

We found a strong reduction in risk for the 3bp [-/TCT] polymorphism in *CYP19A1*; the one other study of this variant also reported reduced risk, but the effect was smaller and not statistically significant (OR=0.71, 95% CI 0.39–1.27) [32]. Earlier studies [32,33] reported higher risk associated with longer repeats in the intronic [TTTA]_n polymorphism; while results for the n=7/7 genotype compared to the n>7/>7 genotype in the present study are in the same direction, the association is weak and not statistically significant (OR=0.79, 95% CI 0.52–1.19). A number of other variants in *CYP19A1* have been studied in relation to endometrial cancer [32,34] and several have been found to be related to risk, particularly in postmenopausal women. Most of those related to endometrial cancer are in an area of linkage disequilibrium (designated as Block 4 [35]) which includes the Ins/Del and the [TTTA]_n repeat reported here. A study in China [36] found associations between BMI and variants in genotypes in Block 4 in healthy women, although different polymorphisms were studied and the association was found only in premenopausal women in that study.

There is little information on the functional relevance of the variants we studied in these genes. Our finding of reduced risk for women homozygous for the 3bp deletion in *CYP19A1* is consistent with reports of lower ratios of estrogens to androgens in serum of unaffected women with this genotype. However, this is based on only two studies, and studies of associations between genotype and androgens and estrogens individually are inconsistent (reviewed in [21]). Associations between the [TTTA]_n repeat and these measures are conflicting and

inconsistent. There is, however, growing evidence that variants in *CYP19A1* influence hormone levels in blood. A recent analysis of three cohort studies [37] found 7 of the 19 tag SNPs (single nucleotide polymorphisms) studied to be strongly associated with serum levels of estrone and estradiol in postmenopausal women. Four of these 7 SNPs are located in Block 4.

We selected the variants for this study based on reports in the literature at the time we undertook genotyping; however, a tagging approach using HapMap data would have been a preferable alternative. For each of the variants studied, the distributions of genotypes in controls reported in Table 2 are similar to those reported in other studies and, for *CYP17A1*, among Europeans in HapMap [38]. The EDGE Study includes a reasonably large number of cases and controls chosen from the population of northern New Jersey, a state with high incidence of endometrial cancer [39,40]. Although our response rate was less than optimal for both cases and controls, the differences between cases and controls shown in Table 1 are similar to those reported in other studies [41–44], somewhat reducing concerns about non-response bias; in addition, participation is unlikely to be influenced by genotype. Our study included a large proportion of cases with BMI ≥ 30 , perhaps reflecting national trends in obesity through 2000 [45]. In addition, we had relatively few women who had ever used HRT compared to other recent studies [11]. We had only moderate power to investigate gene-environment interactions. Our genotyping was limited to a small number of SNPs in these genes; studies using a larger number of markers are warranted, particularly for *CYP19A1*. We did not use genetic methods to control for the influence of race or ethnicity; however, the similar distributions between cases and controls and the lack of change in the ORs when ancestry was included in logistic regression models make it unlikely that population stratification affected the results.

Overall, we conclude that the -34 T/C change in *CYP17A1* may be related to somewhat reduced risk of endometrial cancer, although results from other studies are inconsistent. Functional studies and investigation of additional variants in this gene will further understanding of this relationship. For *CYP19A1*, there is growing evidence that some SNPs are related to estrogen levels and to risk; however, additional studies are needed to determine the specific changes that affect estrogen levels and risk of endometrial cancer.

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Figure 1.

Steroid hormone biosynthesis.

DHEAS, dehydroepiandrosterone sulfate; *CYP11A1*, cytochrome P-450 11A1 gene; *CYP17A1*, cytochrome P-450 17A1 gene; *CYP19A1*, cytochrome P-450 19A1 gene; *HSD3β*, 3β-hydroxysteroid dehydrogenase; *HSD17β*, 17β-hydroxysteroid dehydrogenase genes

Table 1

Characteristics of cases and controls

	Cases <i>n</i> =417		Controls <i>n</i> =402		Adjusted ^d OR (95% CI)
	<i>n</i>	%	<i>n</i>	%	
Age					
<55	87	(21)	65	(16)	
55–64	181	(43)	139	(35)	
65–74	99	(24)	114	(28)	
≥75	50	(12)	84	(21)	
Mean age (SD) P-value	62.0	(9.5)	64.8	(11.0)	P<0.001
Education					
High school or less	152	(36)	138	(34)	
College	180	(43)	162	(40)	
Graduate school	85	(20)	102	(25)	
Race/ethnicity ^b					
White	371	(89)	368	(92)	
Black	35	(8)	18	(4)	
Other	10	(2)	16	(4)	
Hispanic (any race)	18	(4)	20	(5)	
BMI ^c					
Normal (<25)	108	(26)	190	(47)	1.00 Reference
Overweight (25–29.9)	116	(28)	123	(31)	1.68 (1.18–2.39)
Obese (30–34.9)	66	(16)	63	(16)	1.83 (1.20–2.79)
Very obese (≥35)	126	(30)	26	(6)	7.79 (4.79–12.7)
Mean BMI (SD) P-value	31.6	(8.8)	26.5	(5.4)	P<0.0001
Parity					
0–1	148	(35)	92	(23)	1.00 Reference
2	143	(34)	145	(36)	0.61 (0.43–0.87)
≥3	126	(30)	165	(41)	0.51 (0.36–0.73)
Smoking					
Never	231	(55)	209	(52)	1.00 Reference
Past	161	(39)	155	(39)	0.94 (0.70–1.26)
Current	25	(6)	38	(9)	0.53 (0.31–0.91)

	Cases <i>n</i> =417		Controls <i>n</i> =402		Adjusted ^d OR (95% CI)
	<i>n</i>	%	<i>n</i>	%	
Oral contraceptive use					
Never	223	(53)	202	(50)	1.00 Reference
Ever	194	(47)	200	(50)	0.67 (0.50–0.91)
Use of HRT					
Never	334	(80)	296	(74)	1.00 Reference
Unopposed E only	34	(8)	32	(8)	0.93 (0.55–1.56)
Any combined HRT	49	(12)	74	(18)	0.52 (0.35–0.77)
Age at menarche					
≥13	180	(43)	204	(51)	1.00 Reference
<13	237	(57)	198	(49)	1.27 (0.96–1.67)
Menopause status ^d					
Postmenopausal					
Age at menopause					
<50	107	(26)	126	(31)	1.00 Reference
≥50	198	(47)	171	(43)	1.39 (0.99–1.94)
Unknown	48	(12)	54	(13)	1.05 (0.66–1.69)
Premenopausal	57	(14)	48	(12)	0.98 (0.56–1.71)
Endometrial cancer in first degree relative					
No	392	(94)	387	(96)	1.00 Reference
Yes	25	(6)	15	(4)	1.67 (0.85–3.28)

^a adjusted for age (see Methods)

^b one case missing race; one case and three controls missing ethnicity

^c one case missing BMI

^d menopausal status could not be determined for 7 cases and 3 controls

Table 2
Association of variants in *CYP11A1*, *CYP17A1*, and *CYP19A1* with risk of endometrial cancer

	Cases <i>n</i> =417 <i>n</i>	%	Controls <i>n</i> =402 <i>n</i>	%	OR (95% CI)	Adjusted ^a OR (95% CI)	Adjusted ^b OR (95% CI)
<i>CYP11A1</i>							
-528 [TTTTA] _n							
D15S520							
4/4	119	(29)	112	(28)	1.00 Reference	1.00 Reference	1.00 Reference
4/>4	191	(46)	199	(50)	0.90 (0.65–1.25)	0.92 (0.66–1.28)	0.87 (0.62–1.24)
>4/>4	103	(25)	90	(22)	1.08 (0.73–1.58)	1.04 (0.70–1.53)	1.07 (0.71–1.60)
<i>P</i> _{trend}					0.75	0.89	0.81
<i>CYP17A1</i>							
T-34C rs743572							
T/T	148	(35)	122	(30)	1.00 Reference	1.00 Reference	1.00 Reference
T/C	210	(50)	207	(52)	0.84 (0.62–1.14)	0.80 (0.58–1.09)	0.77 (0.55–1.07)
C/C	59	(14)	71	(18)	0.69 (0.45–1.04)	0.68 (0.44–1.04)	0.65 (0.41–1.02)
<i>P</i> _{trend}					0.07	0.06	0.04
<i>CYP19A1</i>							
3bp Ins/Del							
rs11575899							
3bp Ins/Ins	185	(44)	177	(44)	1.00 Reference	1.00 Reference	1.00 Reference
3bp Ins/Del	199	(48)	171	(43)	1.11 (0.83–1.49)	1.11 (0.83–1.49)	1.13 (0.83–1.55)
3bp Del/Del	32	(8)	53	(13)	0.58 (0.36–0.94)	0.55 (0.34–0.90)	0.44 (0.26–0.76)
<i>P</i> _{trend}					0.20	0.15	0.07
[TTTA] _n							
>7/>7	99	(24)	99	(25)	1.00 Reference	1.00 Reference	1.00 Reference
>7/7	207	(50)	186	(47)	1.11 (0.79–1.57)	1.11 (0.78–1.57)	1.04 (0.72–1.50)
7/7	109	(26)	114	(29)	0.96 (0.65–1.40)	0.93 (0.63–1.37)	0.81 (0.54–1.23)
<i>P</i> _{trend}					0.79	0.69	0.30

NOTE: Numbers for genotypes may not add to total number of cases and controls because of missing genotype data.

^a Adjusted for age (see Methods).

^b Adjusted for age and BMI (normal weight, overweight, obese, very obese).

Table 3
Association of variants in *CYP11A1*, *CYP17A1*, and *CYP19A1* with risk of endometrial cancer according to strata of body mass index

	BMI <27.4 (n=159 cases, 253 controls)	BMI ≥27.4 (n=257 cases, 149 controls)	
	Adjusted ^a OR (95% CI)	Adjusted ^a OR (95% CI)	P _{interaction}
<i>CYP11A1</i>			
-528			
[TTTTA] _n			
D15S520			
4/4	1.00 Reference	1.00 Reference	
4/other	1.03 (0.63–1.69)	0.77 (0.46–1.27)	0.37
other/other	1.20 (0.68–2.12)	1.02 (0.56–1.85)	0.68
<i>CYP17A1</i>			
T-34C			
rs743572			
T/T	1.00 Reference	1.00 Reference	
T/C	0.85 (0.54–1.32)	0.73 (0.45–1.21)	0.60
C/C	0.58 (0.30–1.12)	0.74 (0.39–1.41)	0.93
<i>CYP19A1</i>			
3bp Ins/Del			
rs11575899			
Ins/Ins	1.00 Reference	1.00 Reference	
Ins/Del	1.38 (0.90–2.12)	0.93 (0.59–1.49)	0.29
Del/Del	0.67 (0.31–1.45)	0.30 (0.15–0.62)	0.24
[TTTA] _n			
>7/>7	1.00 Reference	1.00 Reference	
>7/7	1.30 (0.79–2.12)	0.73 (0.41–1.31)	0.07
7/7	1.18 (0.68–2.06)	0.49 (0.26–0.93)	0.01

^a Adjusted for age (see Methods) and BMI (continuous).