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Association of two common single-nucleotide polymorphisms in the *CYP19A1* locus and ovarian cancer risk

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Abstract

Although the role of estrogen in the etiology of ovarian cancer is uncertain, there is increasing evidence that hormone replacement therapy is a risk factor for ovarian malignancy. The production of estrogen involves the conversion of androgens via P450 aromatase, encoded by the *CYP19A1* gene. Genetic variation in two *CYP19A1* single-nucleotide polymorphisms (SNPs), rs749292 and rs727479, has been found to produce 10–20% increases in estrogen levels among postmenopausal women. We tested the hypothesis that these SNPs were associated with the risk of ovarian cancer in a population-based case–control study in Hawaii, including 367 histologically confirmed epithelial ovarian cancer cases and 602 age- and ethnicity-matched controls. The *A* allele of rs749292 was positively associated with ovarian cancer risk in a codominant model for all races combined (*AG* versus *AA* genotype: odds ratio (OR), 1.48 and 95% confidence interval (CI, 1.07–2.04); *GG* versus *AA*: OR, 1.87 (CI, 1.24–2.82); P_{trend}=0.002). Similar significant associations of the rs749292 *A* allele on the risk of ovarian cancer were found among Caucasian and Japanese women. No relation of the rs727479 SNP to ovarian cancer risk was observed overall, although Caucasian women carrying the variant *A* allele compared with women with an *CC* genotype had an OR of 2.91 (CI, 1.15–7.37). These data suggest *CYP19A1* variants may influence susceptibility to ovarian cancer.

Introduction

Although the precise role of steroid hormones in ovarian cancer risk is unclear (Risch 1998, Lukanova & Kaaks 2005), there is growing evidence for a positive association of hormone replacement therapy with ovarian cancer incidence that is evident for estrogen-only and estrogen plus progestin formulations (Lacey *et al.* 2002, 2006, Riman *et al.* 2002, Folsom *et al.* 2004, Beral *et al.* 2007). Oral contraceptives, which suppress the ovarian production of estrogen, are strongly protective against ovarian cancer (Lurie *et al.* 2007). Breast feeding is also inversely associated with ovarian cancer, perhaps through reduced serum concentrations of estradiol (Risch 1998). Hypotheses regarding the hormonal etiology of ovarian cancer have focused on the proliferative effect of estrogens on the ovarian surface epithelium (Lukanova & Kaaks 2005). However, in addition to their growth promotion, estrogens can be activated to form catechol intermediates that cause oxidative DNA damage, lipid peroxidation, and (indirectly) DNA adducts (Yager & Liehr 1996, Goodman *et al.* 2001).

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Several enzymes are involved in the biosynthesis of estrogen from cholesterol, including the P450 enzyme, aromatase, coded by the *CYP19A1* gene (Kado *et al.* 2002, Arvanitis *et al.* 2003, Haiman *et al.* 2003, 2007, Paynter *et al.* 2005, Tao *et al.* 2007, Cai *et al.* 2008). Aromatase catalyzes the aromatization of androstenedione to estrone and testosterone to estradiol. A variety of polymorphisms have been described in *CYP19A1*, and these have been evaluated in association with breast cancer (Haiman *et al.* 2003, 2007, Cai *et al.* 2008), endometrial cancer (Paynter *et al.* 2005, Tao *et al.* 2007), and endometriosis (Kado *et al.* 2002, Arvanitis *et al.* 2003) risk with inconsistent results. Haiman *et al.* (2007) used a high-density single-nucleotide polymorphism (SNP) map of 103 common SNPs with a mean allele frequency ≥5% to identify the linkage disequilibrium and haplotype patterns across the *CYP19A1* locus at 15q21.1 (Haiman *et al.* 2007). Two modestly correlated (r^2=0.46) SNPs, rs749292 (A allele) and rs727479 (A allele), were the strongest independent predictors of an increase in circulating estrone and estradiol levels among women in three prospective studies. In this pooled analysis, women with the rs749292 *AA* genotype had 14.4% higher levels of estradiol versus women with the *GG* genotype and women with the rs727479 *AA* genotype had 15.7% higher levels of estradiol compared with women with the *CC* genotype. A two SNP haplotype (*A*-*A*) comprising these common alleles was associated with a 10–20% increase in estrogen levels among more than 3000 postmenopausal women who were not on hormone replacement therapy. In the present analysis, we examined the hypothesis that the *A* alleles of these two common SNPs in *CYP19A1* are associated with an increased risk of ovarian cancer in a multiethnic case–control study in Hawaii.

Materials and methods

Study design and population

Eligible cases for this population-based, case–control study in Hawaii comprised all patients, 18 years of age and older, with histologically confirmed, primary, epithelial ovarian cancer diagnosed between 1993 and 2006 (Goodman *et al.* 2001, Lurie *et al.* 2007). Incident cases were identified through the rapid-reporting system of the Hawaii Tumor Registry, which is part of the Surveillance, Epidemiology, and End-Results Program of the National Cancer Institute. Information on tumor histology was obtained from pathology and surgical reports. Interview information and DNA samples were obtained from 367 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. Potential controls were randomly selected from the pool so that the ethnic (e.g., Japanese) and 5-year age group distribution would match that of the case group with an approximate 1:1.6 ratio. Eligibility criteria for controls included age 18 years or older, residency in Hawaii for a minimum of 1 year, no prior history of ovarian cancer, and having at least one intact ovary. Interviews and DNA samples were obtained from 602 of the eligible women. The response rate was 65% for cases and 68% for controls. The study protocol was approved by the Institutional Review Board of the University of Hawaii. All study participants provided written informed consent.

Data collection

Socio-demographic, life style, and health-related information were collected during a ~2.5 h interview using a structured pre-tested questionnaire. Interviewers were uniformly trained and supervised to standardize interviewing and coding techniques. Quality control and performance of the interviewers was monitored by the project coordinator through a repeat interview of a random sample of 15% of subjects on a random 5% of the interview questions.

Genotyping

DNA was purified from whole blood using Qiagen Midi Kits (Qiagen).

Genotyping of *CYP19A1* rs749292 and rs727479 was performed with the 5′ nuclease discrimination assay using TaqMan (Applied Biosystems, Foster City, CA, USA). Samples from cases and controls were intermixed on each plate. Each 384-well plate included 48 randomly selected blinded samples and 8 non-DNA controls to evaluate accuracy and reproducibility. The call rates were 98.5% for rs749292 and 98.0% for rs727479. The concordance rates among duplicates were 100% for both SNPs.

Statistical analysis

Fisher's goodness of fit test was used to assess whether allele frequency distributions among controls overall and in each ethnic group were consistent with Hardy–Weinberg equilibrium. Unconditional multiple logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of genotype with ovarian cancer risk. The genotype for each SNP was treated as a non-ordered categorical variable to test for heterogeneity and as an ordered categorical variable (with three levels: 0, 1, and 2; one assigned to each genotype) to test for a gene-dose effect. Pairwise linkage disequilibrium (D′) and correlation coefficients (r^2) were estimated using the HAPLOVIEW program (Barrett *et al.* 2005). Haplotypes for each subject were created using PHASE (Stephens *et al.* 2001).

Subjects with undetermined genotypes were excluded. All models were adjusted for age, ethnicity (except for ethnic-specific analyses), gravidity, use of contraceptive and menopausal hormones, tubal ligation, hysterectomy, menopausal status, and body mass index (BMI kg/m^2; BMI≥30; BMI<30).

Results

The mean age of cases (55.3 years: range 18–87) and controls (56.2: range 19–88) was similar. The majority of cases were Japanese, followed by Caucasian, Hawaiian, Filipino, and other (Table 1). A family history of ovarian cancer in first-degree relatives was positively associated with ovarian cancer risk, whereas gravidity, use of contraceptive steroids, and menopausal estrogen in combination with progesterone, tubal ligation, and premenopausal status were associated with a decreased ovarian cancer risk.

Both *CYP19A1* SNPs were consistent with Hardy–Weinberg equilibrium among controls in each ethnic group and in all ethnic groups combined (*P* value >0.05). The minor allele frequency was 0.40 for rs749292 (ethnic-specific range: 0.34–0.50; $P_{heterogeneity}$=0.34) and 0.36 for rs727479 (ethnic-specific range: 0.26–0.50; $P_{heterogeneity}$=0.0003).

The *A* allele of rs749292 (Table 2) was positively associated with ovarian cancer risk in a codominant model for all races combined (*AG* versus *AA* genotype: OR, 1.48 (CI, 1.07–2.04); *GG* versus *AA*: OR, 1.87 (CI, 1.24–2.82); P_{trend}=0.002). The OR for women with one or two copies of the *A* allele was 1.59 (CI, 1.17–2.16). Similar significant associations of the *A* allele on the risk of ovarian cancer were found among Caucasian and Japanese women. No relation of the rs727479 SNP to ovarian cancer risk was observed for all races combined, although Caucasian women carrying an *A* allele compared with women with a *CC* genotype had an OR of 2.91 (CI, 1.15–7.37). The linkage disequilibrium (LD) between these two SNPs was not strong (*D′*=0.90; r^2=0.34). The *A-A* haplotype homozygotes were at increased ovarian cancer risk (OR, 1.46; CI, 1.01–2.13); however, heterozygous carriers of the *A-A* haplotype had significantly increased risk only among Caucasian women (OR, 2.21; CI, 1.11–4.39). No significant differences were found in the association of the rs749292 variant with the risk of ovarian cancer by obesity, menopausal status, or histological type of cancer (data not shown).

Discussion

In this study, we found that a common polymorphism in the *CYP19A1* gene (rs749292) that has been shown to influence circulating estrogen levels in postmenopausal women was associated with the risk of ovarian cancer. The variant *A* allele of rs727479 was also associated with risk, but only among Caucasian women. Although these two SNPs were only in modest LD, the *A*-*A* haplotype was found to be a strong predictor of circulating estrogen in postmenopausal women (Haiman *et al.* 2007). Homozygous *A*-*A* allele carriers were at significantly higher risk of ovarian cancer among all women combined, and heterozygous carriers of this haplotype had significantly higher ovarian cancer risk among Caucasian women.

Aromatase is a key enzyme in sex steroid biology, catalyzing the conversion of aromatic estrogens from androgens (Stocco 2008). Aromatase is expressed in a number of tissues, including the ovarian granulosa cell and adipose tissue fibroblasts (Bulun *et al.* 2007, Stocco 2008). Among premenopausal women, the principal source of aromatase is in the granulosa cells where estradiol is produced abundantly during the follicular phase. However, among postmenopausal women, the highest level of aromatase production is in adipose tissue where estrone is produced peripherally from adrenal androstenedione.

Several prospective studies have reported an increased risk of ovarian cancer among long-term users of estrogen replacement therapy (Rodriguez *et al.* 2001, Lacey *et al.* 2002, 2006, Folsom *et al.* 2004, Beral *et al.* 2007) and combination estrogen plus progestin therapy (Lacey *et al.* 2006, Beral *et al.* 2007), although the results have been null in some investigations (Sit *et al.* 2002, Pike *et al.* 2004). It is difficult to reconcile an inverse association of oral contraceptive pill use and a positive association of postmenopausal estrogen plus progestin therapy with the risk of ovarian cancer given that both preparations contain a similar combination of compounds (Beral *et al.* 2007). A possible explanation for this apparent inconsistency is that the majority of women exposed to postmenopausal estrogen plus progestin previously used unopposed estrogen (Pike *et al.* 2004). Alternatively, Narod (2007) has suggested that differences in formulations or in the biological effects of oral contraceptives and hormone replacement therapy in pre- and postmenopausal women may accommodate these seemingly contradictory observations. Postmenopausal estrogen exposure to the ovary may enhance cell proliferation and tumor growth, whereas premenopausal estrogens may reduce the number of healthy cells susceptible to transformation.

Several theories suggest that malignant transformation of the ovary is associated with excessive gonadotropin secretion and increased estrogenic stimulation of the ovarian surface epithelium (Cramer & Welch 1983). Increased mitotic activity of the ovarian surface epithelium during menstruation, when mutation is most likely, occurs in the presence of elevated estrogen concentrations. A number of estrogen-regulated proteins have been identified in ovarian normal ovarian epithelium and cancer that influence cell proliferation, motility, invasion, and metastasis (Zheng *et al.* 2007). If the local production of estrogen is critical to ovarian carcinogenesis, aromatase may be involved through its role in mediating local estrogen synthesis (Li *et al.* 2008).

Endometriosis, an estrogen-dependent disease that is characterized by the presence of endometrium-like tissue in ectopic sites outside the uterus, may be a risk factor for ovarian cancer (Ness 2003). Endometriosis in postmenopausal women leads to progesterone resistance and local estrogen formation via high levels of aromatase expression. Although aromatase expression may be more strongly associated with endometrioid and clear cell histologic types of ovarian cancer that arise from endometriotic foci (Ness 2003), we found no difference in the association of *CYP19A1* rs749292 or rs727479 variants with the risk of these histologic subtypes.

The present analysis suggests that aromatase excess may be linked to the development of ovarian cancer. An association of aromatase with the risk of ovarian cancer is biologically plausible through an influence of estrogen on the etiology of this lethal malignancy (Bulun *et al.* 2007). Furthermore, aromatase inhibitors may be effective in the treatment of advanced ovarian cancer (Li *et al.* 2008). Future consortium-based studies will be needed to replicate this novel finding.

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References

Arvanitis DA, Koumantakis GE, Goumenou AG, Matalliotakis IM, Koumantakis EE, Spandidos DA. CYP1A1, CYP19, and GSTM1 polymorphisms increase the risk of endometriosis. Fertility and Sterility 2003;79(Suppl 1):702–709. [PubMed: 12620480]

Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263–265. [PubMed: 15297300]

Beral V, Million Women Study Collaborators. Bull D, Green J, Reeves G. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet 2007;369:1703–1710. [PubMed: 17512855]

Bulun SE, Chen D, Lu M, Zhao H, Cheng Y, Demura M, Yilmaz B, Martin R, Utsunomiya H, Thung S, et al. Aromatase excess in cancers of breast, endometrium and ovary. Journal of Steroid Biochemistry and Molecular Biology 2007;106:81–96. [PubMed: 17590327]

Cai Q, Kataoka N, Li C, Wen W, Smith JR, Gao YT, Shu XO, Zheng W. Haplotype analyses of CYP19A1 gene variants and breast cancer risk: results from the Shanghai Breast Cancer Study. Cancer Epidemiology, Biomarkers and Prevention 2008;17:27–32.

Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inference regarding pathogenesis. Journal of the National Cancer Institute 1983;71:717–721. [PubMed: 6578367]

Folsom AR, Anderson JP, Ross JA. Estrogen replacement therapy and ovarian cancer. Epidemiology 2004;15:100–104. [PubMed: 14712153]

Goodman MT, McDuffie K, Kolonel LN, Terada K, Donlon TA, Wilkens LR, Guo C, Le Marchand L. Case–control study of ovarian cancer and polymorphisms in genes involved in catecholestrogen formation and metabolism. Cancer Epidemiology, Biomarkers and Prevention 2001;10:209–216.

Haiman CA, Stram DO, Pike MC, Kolonel LN, Burtt NP, Altshuler D, Hirschhorn J, Henderson BE. A comprehensive haplotype analysis of CYP19 and breast cancer risk: the Multiethnic Cohort. Human Molecular Genetics 2003;12:2679–2692. [PubMed: 12944421]

Haiman CA, Dossus L, Setiawan VW, Stram DO, Dunning AM, Thomas G, Thun MJ, Albanes D, Altshuler D, Ardanaz E, et al. Genetic variation at the CYP19A1 locus predicts circulating estrogen levels but not breast cancer risk in postmenopausal women. Cancer Research 2007;67:1893–1897. [PubMed: 17325027]

Kado N, Kitawaki J, Obayashi H, Ishihara H, Koshiba H, Kusuki I, Tsukamoto K, Hasegawa G, Nakamura N, Yoshikawa T, et al. Association of the CYP17 gene and CYP19 gene polymorphisms with risk of endometriosis in Japanese women. Human Reproduction 2002;17:897–902. [PubMed: 11925378]

Lacey JV Jr, Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, Schatzkin A, Schairer C. Menopausal hormone replacement therapy and risk of ovarian cancer. Journal of the American Medical Association 2002;288:334–341. [PubMed: 12117398]

Lacey JV Jr, Brinton LA, Leitzmann MF, Mouw T, Hollenbeck A, Schatzkin A, Hartge P. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health – AARP Diet and Health Study Cohort. Journal of the National Cancer Institute 2006;98:1397–1405. [PubMed: 17018786]

Li YF, Hu W, Fu SQ, Li JD, Liu JH, Kavanagh JJ. Aromatase inhibitors in ovarian cancer: is there a role? International Journal of Gynecological Cancer 2008;18:600–614. [PubMed: 17894799]

Lukanova A, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. Cancer Epidemiology, Biomarkers and Prevention 2005;14:98–107.

Lurie G, Thompson P, McDuffie KE, Carney ME, Terada KY, Goodman MT. Association of estrogen and progestin potency of oral contraceptives with ovarian carcinoma risk. Obstetrics and Gynecology 2007;109:597–607. [PubMed: 17329510]

Narod SA. Ovarian cancer and HRT in the Million Women Study. Lancet 2007;369:1667–1668. [PubMed: 17512836]

Ness RB. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. American Journal of Obstetrics and Gynecology 2003;189:280–294. [PubMed: 12861175]

Paynter RA, Hankinson SE, Colditz GA, Kraft P, Hunter DJ, De Vivo I. CYP19 (aromatase) haplotypes and endometrial cancer risk. International Journal of Cancer 2005;116:267–274.

Pike MC, Pearce CL, Peters R, Cozen W, Wan P, Wu AH. Hormonal factors and the risk of invasive ovarian cancer: a population-based case–control study. Fertility and Sterility 2004;82:186–195. [PubMed: 15237010]

Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM, Weiderpass E, Persson IR. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. Journal of the National Cancer Institute 2002;94:497–504. [PubMed: 11929950]

Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. Journal of the National Cancer Institute 1998;90:1774–1786. [PubMed: 9839517]

Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. Journal of the American Medical Association 2001;285:1460–1465. [PubMed: 11255422]

Sit AS, Modugno F, Weissfeld JL, Berga SL, Ness RB. Hormone replacement therapy formulations and risk of epithelial ovarian carcinoma. Gynecologic Oncology 2002;86:118–123. [PubMed: 12144815]

Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. American Journal of Human Genetics 2001;68:978–989. [PubMed: 11254454]

Stocco C. Aromatase expression in the ovary: hormonal and molecular regulation. Steroids 2008;73:473–487. [PubMed: 18321551]

Tao MH, Cai Q, Zhang ZF, Xu WH, Kataoka N, Wen W, Xiang YB, Zheng W, Shu XO. Polymorphisms in the CYP19A1 (aromatase) gene and endometrial cancer risk in Chinese women. Cancer Epidemiology, Bio-markers and Prevention 2007;16:943–949.

Yager JD, Liehr JG. Molecular mechanisms of estrogen carcinogenesis. Annual Review of Pharmacology and Toxicology 1996;36:203–232.

Zheng H, Kavanagh JJ, Hu W, Liao Q, Fu S. Hormonal therapy in ovarian cancer. International Journal of Gynecological Cancer 2007;17:325–338. [PubMed: 17362310]

Table 1

Participant characteristics

Characteristics	Number (%) of participants		ORs (95% CIs)[a]
	Cases (*n*=367)	Controls (*n*=602)	
Age (years)			Matching factor
<45	78 (21)	124 (21)	
45–54	107 (29)	176 (29)	
55–64	90 (25)	157 (26)	
>64	92 (25)	105 (24)	
Ethnicity			Matching factor
Caucasian	90 (25)	158 (26)	
Japanese	102 (28)	175 (29)	
Hawaiian	82 (24)	119 (20)	
Filipino	43 (12)	80 (13)	
Other	40 (11)	70 (12)	
Family history of ovarian cancer			
No	350 (95)	593 (99)	1.00 (reference)
Yes	17 (5)	9 (1)	3.74 (1.55–9.03)
Gravidity			
Nulligravid	90 (25)	62 (10)	1.00 (reference)
1	46 (13)	70 (12)	0.55 (0.33–0.93)
2–3	138 (38)	256 (42)	0.49 (0.33–0.75)
≥4	93 (25)	214 (36)	0.38 (0.24–0.60)
Used oral contraceptives			
No	197 (54)	190 (32)	1.00 (reference)
Yes	170 (46)	412 (68)	0.35 (0.25–0.49)
Had tubal ligation			
No	304 (83)	413 (69)	1.00 (reference)
Yes	63 (17)	189 (31)	0.60 (0.42–0.86)
Menopausal status			
Postmenopausal	239 (65)	378 (63)	1.00 (reference)
Premenopausal	128 (35)	224 (37)	0.51 (0.25–1.05)
Type of menopause			
Natural menopause	203 (55)	329 (55)	1.00 (reference)
Hysterectomy	164 (45)	273 (45)	1.13 (0.66–1.97)
Use of menopausal hormones			
Never used	265 (72)	392 (65)	1.00 (reference)
Estrogen only	34 (9)	50 (8)	0.85 (0.48–1.52)
Progesterone only	13 (4)	19 (3)	0.80 (0.36–1.77)
Combined estrogen and progesterone	55 (15)	141 (24)	0.55 (0.36–0.84)
BMI			
Underweight (BMI≤18.5)	6 (2)	18 (4)	1.00 (reference)

Characteristics	Number (%) of participants		ORs (95% CIs)[a]
	Cases (*n*=367)	Controls (*n*=602)	
Normal (18.5<BMI<25)	141 (52)	218 (48)	1.23 (0.49–3.04)
Overweight (25≤BMI<30)	63 (23)	126 (28)	1.18 (0.62–4.08)
Obese (BMI≥30)	64 (23)	90 (20)	1.59 (0.57–4.71)

[a] Odds ratios (ORs) and 95% confidence intervals (CIs) based on unconditional logistic regression models including all listed variables.

Table 2

Association of *CYP19A1* rs749292S and rs727479 single-nucleotide polymorphisms (SNPs), and the *A-A* haplotype with the risk of epithelial ovarian cancer

	All			Caucasian			Japanese		
SNPs	**Cases**	**Controls**	**OR (95% CI)[a]**	**Cases**	**Controls**	**OR (95% CI)[b]**	**Cases**	**Controls**	**OR (95% CI)[b]**
rs749292									
GG	102	211	1.00	22	54	1.00	25	71	1.00
GA	183	287	1.48 (1.07–2.04)	45	69	2.03 (1.03–3.99)	53	78	1.93 (1.04–3.59)
AA	76	95	1.87 (1.24–2.82)	22	33	2.14 (0.97–4.73)	24	23	2.62 (1.20–5.76)
P for trend			0.002			0.04			0.01
Any *A* versus *GG*	159	382	1.59 (1.17–2.16)	67	102	2.07 (1.10–3.90)			2.18 (1.21–3.93)
rs727479									
AA	151	250	1.00	39	64	1.00	54	94	1.00
AC	170	251	1.11 (0.82–1.50)	43	64	1.04 (0.57–1.88)	42	63	1.54 (0.50–4.67)
CC	40	87	0.72 (0.46–1.14)	7	26	0.34 (0.13–0.90)	6	14	1.22 (0.41–3.63)
P for trend			0.41			0.09			0.78
Any *A* versus *CC*	321	501	1.51 (0.98–1.32)	82	128	2.91 (1.15–7.37)	96	157	1.49 (0.52–4.29)
A-A haplotype									
0 Copies	222	371	1.00	22	55	1.00	53	100	1.00
1 Copy	64	125	0.91 (0.63–1.31)	44	67	2.21 (1.11–4.39)	25	47	1.02 (0.54–1.92)
2 Copies	73	86	1.46 (1.01–2.13)	22	30	2.52 (1.13–5.63)	24	22	1.79 (0.87–3.66)

[a] Adjusted for age, ethnicity, gravidity, tubal ligation, hysterectomy, menopausal status, use of contraceptive and menopausal hormones, and obesity.

[b] Adjusted for the same variables except ethnicity.