Genetic polymorphism of *CYP17* and breast cancer risk in Korean women

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Abbreviations: aOR, age-adjusted OR; BMI, body mass index; CI, confidence interval; CYP17, cytochrome P450C17 α ; mOR, multivariate OR; UTR, untranslated region

Abstract

***CYP17* gene is involved in steroidogenesis and steroid metabolism. Epidemiologic results on**

the association between the *CYP17* polymorphism and breast cancer risk have been inconsistent. We examined the association between the *Msp*AI polymorphism at +27 relative to the start of transcription in the 5'-untranslated region of *CYP17* gene and breast cancer risk in Korean women. Four hundred and sixty-two incident cases and 337 controls were recruited from three teaching hospitals in Seoul during 1994-2001. Polymorphism of the *CYP17* gene was determined by a single base extension assay. Demographic and lifestyle characteristics were identified using structured questionnaire. Age-adjusted (aOR) and multivariate odds ratios (mOR) and 95% confidence intervals (CI) were estimated by unconditional logistic regression. The proportions of A1/A1, A1/A2 and A2/A2 genotypes among controls were 20.8%, 45.1% and 34.1%, respectively. Compared to the A1/A1 genotype, A1/A2 or A2/A2 genotype was not statistically significantly associated with overall breast cancer risk (i.e., mOR = 1.01, 95% CI = 0.69-1.47 and mOR = 0.76, 95% CI = 0.51-1.14, respectively). However, a significant association between *CYP17* A2/A2 genotype and breast cancer was observed among women aged 50 years or less (mOR = 0.58, 95% CI = 0.34-0.99, $P=0.04$) and leaner women (body mass index < 22 kg/m²) (mOR = 0.48, 95% CI = 0.23-0.97, $P=0.04$). Our results suggest that genetic polymorphism in 5'-untranslated region of *CYP17* might play a role in breast cancer development in Korean women among younger women aged less than 50 or leaner women with body mass index less than 22 kg/m².

Keywords: breast neoplasms; estrogens; genotype; genetic polymorphism; steroid hydroxylases

Introduction

Higher level of endogenous estrogens is strongly associated with the risk of breast cancer (Hankinson *et al.*, 1998), and the level of endogenous estrogens is known to be regulated by the pathway of steroidogenesis in which many enzymes are involved. Recent interest has been focused on polymorphisms in genes that control the metabolism or intracellular transport

of sex hormones (Dunning *et al.*, 1999).

CYP17 gene codes for one of the key enzymes, cytochrome P450c17 α (*CYP17*) which catalyzes the conversion of 17-hydroxypregnenolone to 17-hydroxyprogesterone or dehydroepiandrosterone (DHEA) to androstenedione in the synthesis of estrogen. Thus, genetic polymorphism of *CYP17* could change the expression levels or activities of the cytochrome P450c17 α and, in turn, the risk of breast cancer in relation with the changes in estrogen biosynthesis. A polymorphism of T $\rightarrow$ C substitution in 5'-untranslated region (UTR) of *CYP17* gene creates *Msp*AI restriction site (denoted as A1/A2) and has also been suggested to create a promoter motif to transcription factor, Sp-1 (CCACC box) (Carey *et al.*, 1994). This polymorphism at +27 relative to the start of transcription, has a potential to enhance the promoter activity and production rate of *CYP17*, and eventually the levels of endogenous steroid hormones (Feigelson *et al.*, 1998; Haiman *et al.*, 1999).

A number of epidemiological studies have evaluated the potential role of *CYP17* polymorphism in breast cancer development (Feigelson *et al.*, 1997; Dunning *et al.*, 1998; Helzlsouer *et al.*, 1998; Weston *et al.*, 1998; Bergman-Jungstrom *et al.*, 1999; Huang *et al.*, 1999; Hamajima *et al.*, 2000; Kuligina *et al.*, 2000; Mitrinen *et al.*, 2000; Miyoshi *et al.*, 2000; Spurdle *et al.*, 2000; Ambrosone *et al.*, 2003; Cui *et al.*, 2003; Wu *et al.*, 2003; Hefler *et al.*, 2004) since the first association study (Feigelson *et al.*, 1997) reported that A2 carriers had 2.5-fold higher risk of advanced breast cancer in a nested case-control study of multiethnic cohort. However, the results for the association between *CYP17* polymorphism and breast cancer risk have been inconsistent. Several studies have found a positive association between A2/A2 genotype and the risk of breast cancer in the subgroups such as younger (22-36 years old) Sweden (Bergman-Jungstrom *et al.*, 1999), younger (<40) Australian (Spurdle *et al.*, 2000) and older ($\geq$ 55) Japanese (Miyoshi *et al.*, 2000). However, most other studies could not reproduce the positive association between A2/A2 genotype and breast cancer risk; e.g., no association was found in studies conducted for Caucasians in UK (Dunning *et al.*, 1998), US (Weston *et al.*, 1998; Haiman *et al.*, 1999; Ambrosone *et al.*, 2003), Finland (Mitrinen *et al.*, 2000), hispanics and African-Americans in US (Weston *et al.*, 1998), Japanese (Hamajima *et al.*, 2000), Chinese in Singapore (Wu *et al.*, 2003) and Taiwanese (Huang *et al.*, 1999).

These inconsistent results might be due to relatively small sample size, and ethnic diversity which comprises the difference in allele frequency, exposure to risk factor of breast cancer risk and the others. It is known that Asian women have higher variant allele (A2) than Caucasians (Miyoshi *et al.*, 2000). Those studies investigating the relationship between A2/A2 genotype and breast cancer risk for Asian population included less than two hundred breast cancer cases and showed inconsistent results (Huang *et al.*, 1999; Hamajima *et al.*, 2000; Miyoshi *et al.*, 2000; Wu *et al.*, 2003). Additionally, most association studies

have been conducted for Caucasian population, so far.

Therefore, in this study, the association between the T $\rightarrow$ C polymorphism in the 5'-UTR of the *CYP17* gene and breast cancer risk was evaluated in Korean population in a larger case-control study.

Materials and Methods

Subjects

Subjects were recruited from three teaching hospitals in Seoul during 1994-2001. Eligible subjects consisted of incident breast cancer cases with histological confirmation ($n = 577$) and controls with non-cancer diseases ($n = 507$) in the same hospitals from whom blood samples were available. After women with previous history of cancer, hysterectomy or oophorectomy and whose DNA samples with small amount were excluded, a total of 462 cases and 337 control subjects were included in the final analysis. The diseases of controls included infection or stone of gall bladder/bile duct, benign breast disease, acute appendicitis, hemorrhoid, hernia/ perforation, lipoma, and the others.

The study design was approved by the Committee on Human Research of Seoul National University Hospital, and the subjects provided their informed consents prior to participation in the study. Information on demographic characteristics and other known risk factors of breast cancer was obtained using a structured questionnaire administered by trained interviewers as described in detail previously (Lee *et al.*, 2004).

Genotyping

DNA was extracted using standard methods from blood drawn into 10 ml heparinized tubes and stored at -20°C until use. A1/A2 polymorphism of the *CYP17* was determined by the single base extension assay (SnapShot). The PCR products were obtained by using 500 nM of oligonucleotide primers (P1: 5'-TTT CCA CAA GGC AAG AGA TAA CA-3' and P2: 5'-GGA GGC TCT TGG GGT ACT-3') in a total volume of 20 μ l of reaction mixture. The amplification profile consisted of initial denaturation at 95°C for 5 min followed by 35 cycles of 30 s at 94°C, 60 s of 54°C and 120 s at 72°C.

Primer extension reaction was performed by combining 1 μ l of exonuclease I and alkaline phosphatase treated PCR product with 5 μ l SNaPshot kit (including DNA polymerase, fluorescently labeled ddNTPs, and control primers), 0.15 pmol extension primer (5'-TTGCCACAGCTCTTCTACTCCAC-3') and 3 μ l water. The reaction mixture was incubated at 94°C for 2 min and followed by 25 cycles of 95°C for 5 s, 50°C for 5 s and 60°C for 5 s. Aliquots of 1 μ l single base extension product and 9 μ l Hi-Di formamide were combined in a 96-well 3100 optical microamp plate, which was loaded onto a 3100 DNA sequencer (Applied Biosystems, Foster City, CA). Electrophoresis data were processed by Genescan Analysis version 3.7 (Applied Biosystems, Foster City, CA).

Statistical analysis

Age-adjusted (aOR) and multivariate odds ratios (mOR) and 95% confidence intervals (CI) were estimated by unconditional logistic regression. In the multivariate analysis, the ORs were adjusted for age at diagnosis, family history of breast cancer, history of benign disease, history of hypertension, breast feeding for 12 months or more, and the duration of education for more than 9 years.

Hardy-Weinberg equilibrium test was performed for the genotype distribution in the controls for evaluating possible selection bias and genotyping errors.

To evaluate the dominant effect of gene variation, heterozygous and homozygous variants were combined into one genotype group. Possible effect modification by other risk factors such as age, body mass index (BMI), and family history of breast cancer was evaluated by stratified analyses.

Results

The mean age of the 462 breast cancer cases and 337 controls was 47.6 (± 10.5) and 47.3 (± 14.5), respectively (t -test: $P = 0.63$). Cases and controls were significantly different in terms of the family history of breast cancer, past history of benign breast disease, history of hypertension, history of breast feeding for 12 months or more, and the duration of education for nine or more years (Table 1).

Among controls, the proportions of CYP17 A1/A1, A1/A2 and A2/A2 genotypes were 20.8%, 45.1% and 34.1%, respectively (Table 2). This genotype distribution did not diverge significantly from Hardy-Weinberg equilibrium ($P = 0.14$). There was no difference among the genotype distributions by the hospitals from which the subjects were recruited (χ^2 -test: $P = 0.22$).

Compared with the A1/A1 genotype, A1/A2 or A2/A2 genotype was not statistically significantly as-

Table 1. Characteristics of breast cancer cases ($n = 462$) and controls ($n = 337$).

	Cases		Controls		OR (95% CI) ^a	P-value
	N	%	N	%		
Age ≤ 50 yrs old	303	65.6	207	61.4	0.84 (0.62-1.12)	0.23
Postmenopausal	181	39.2	147	43.6	0.83 (0.63-1.11)	0.21
Age at menarche ≤ 13 yrs old	57	12.3	45	13.5	0.90 (0.59-1.37)	0.64
Family history of breast cancer	44	9.5	11	3.3	3.08 (1.57-6.06)	<0.01
History of benign breast disease	19	4.1	1	0.3	14.4 (1.9-107.9)	<0.01
History of hypertension	26	5.6	35	10.4	0.52 (0.30-0.87)	0.01
Number of full term pregnancy ≤ 1	98	21.2	86	25.5	0.79 (0.56-1.09)	0.15
Breast feeding ≥ 12 months	251	54.7	209	62.2	0.73 (0.55-0.98)	0.03
Body mass index ≥ 25 kg/m ²	109	23.8	68	20.9	1.19 (0.84-1.67)	0.33
Duration of education ≥ 9 yrs	307	66.5	180	53.4	1.73 (1.03-2.31)	<0.01

^aCrude odds ratio (95% confidence interval).

Table 2. The association between CYP17 genotypes and breast cancer risk.

Genotypes of	Cases		Controls		aOR (95% CI) ^a	P-value	mOR (95% CI) ^b	P-value
	N	%	N	%				
A1/A1	112	24.2	70	20.8	1.00 (reference)		1.00 (reference)	
A1/A2	223	48.3	152	45.1	0.92 (0.64-1.32)	0.85	1.01 (0.69-1.47)	0.97
A2/A2	127	27.5	115	34.1	0.69 (0.47-1.02)	0.05	0.76 (0.51-1.14)	0.19
P_{trend}					0.05		0.15	
A1/A2+A2/A2	350	75.8	267	79.2	0.82 (0.59-1.15)	0.25	0.90 (0.63-1.28)	0.56

^aAdjusted for age. ^bAdjusted for age at diagnosis, family history of breast cancer, history of benign disease, history of hypertension, breast feeding for 12 months or more, and the duration of education for more than 9 yrs.

sociated with overall breast cancer risk (*i.e.*, mOR = 1.01, 95% CI = 0.69-1.47, $P = 0.97$ for A1/A2 genotype, and mOR = 0.76, 95% CI = 0.51-1.14, $P = 0.19$ for A2/A2 genotype).

However, the inverse association was mildly strengthened among younger women. Compared to A1/A1 genotype, A2/A2 genotype had an inverse association among women aged 50 years or less (A2/A2 vs. A1/A1, aOR=0.54, 95% CI = 0.32-0.90, mOR = 0.58, 95% CI = 0.34-0.99, $P = 0.04$), and the risk decreased as the number of A2 allele increased ($P_{\text{trend}} = 0.04$) (Table 3). Among women aged more than 50, there was no association between A2/A2 genotype and breast cancer risk. The inverse association was also mildly pronounced in leaner women (BMI < 22 kg/m²) (A2/A2 vs. A1/A1, aOR = 0.44, 95% CI = 0.23-0.83 and mOR = 0.48, 95% CI = 0.23-0.97), and the decreasing trend of breast cancer risk was significant in that group ($P_{\text{trend}} = 0.03$) (Table 4).

The presence of A2 allele was not associated with other hormone related risk factors for breast cancer, such as age at menarche and age at menopause

(Table 5).

Discussion

Our results suggest that genetic polymorphism of *CYP17* might play a role in breast cancer development in Korean women especially among the subgroup of younger women (≤ 50) or leaner women (BMI < 22 kg/m²).

In agreement with the majority of the previous epidemiological studies on the association between *CYP17* polymorphism and breast cancer risk, this study did not reveal significant association between the *CYP17* A2 allele and overall risk of breast cancer. However, an inverse association between A2/A2 genotype and breast cancer risk among women aged 50 years or less was observed in this study. Although earlier studies reported a positive association between A2 allele and breast cancer risk, an inverse, though not significant, association was suggested in the studies conducted by Weston *et al.* (1998), Hamajima *et*

Table 3. The association between *CYP17* genotypes and breast cancer risk by age group.

Genotypes	Age ≤ 50 yrs old $n = 510$				Age > 50 yrs old $n = 289$			
	Case/ Control	aOR (95% CI) ^a	mOR (95% CI) ^b	P -value ^c	Case/ Control	aOR (95% CI) ^a	mOR (95% CI) ^b	P -value ^c
A1/A1	77/37	1.00 (reference)	1.00 (reference)		35/33	1.00 (reference)	1.00 (reference)	
A1/A2	142/94	0.77 (0.48-1.25)	0.81 (0.49-1.33)	0.40	81/58	1.34 (0.74-2.42)	1.51 (0.82-2.81)	0.19
A2/A2	84/76	0.54 (0.32-0.90)	0.58 (0.34-0.97)	0.04	43/39	1.07 (0.56-2.06)	1.12 (0.57-2.22)	0.74
P_{trend}		0.01	0.04			0.89	0.83	
A1/A2+A2/A2	226/170	0.67 (0.43-1.04)	0.71 (0.44-1.13)	0.14	124/97	1.23 (0.71-2.14)	1.35 (0.76-2.41)	0.31

^aAdjusted for age. ^bAdjusted for age at diagnosis, family history of breast cancer, history of benign disease, history of hypertension, breast feeding for 12 months or more, and the duration of education for more than 9 yrs. ^c P -value for mOR.

Table 4. The association between *CYP17* genotypes and breast cancer risk by body mass index (BMI).

Genotypes	BMI < 22 kg/m ² $n = 303$				BMI ≥ 22 kg/m ² $n = 496$			
	Case/ Control	aOR (95% CI) ^a	mOR (95% CI) ^b	P -value ^c	Case/ Control	aOR (95% CI) ^a	mOR (95% CI) ^b	P -value ^c
A1/A1	47/25	1.00 (reference)	1.00 (reference)		65/45	1.00 (reference)	1.00 (reference)	
A1/A2	86/52	0.88 (0.48-1.59)	0.89 (0.46-1.73)	0.72	137/100	0.95 (0.60-1.50)	1.04 (0.65-1.67)	0.87
A2/A2	42/51	0.44 (0.23-0.83)	0.48 (0.23-0.97)	0.04	85/64	0.92 (0.56-1.52)	1.02 (0.61-1.71)	0.94
P_{trend}		0.007	0.03			0.76	0.96	
A1/A2+A2/A2	128/103	0.66 (0.38-1.14)	0.70 (0.37-1.30)	0.25	222/164	0.94 (0.61-1.45)	1.03 (0.66-1.61)	0.89

^aAdjusted for age. ^bAdjusted for age at diagnosis, family history of breast cancer, history of benign disease, history of hypertension, breast feeding for 12 months or more, and the duration of education for more than 9 yrs. ^c P -value for mOR.

Table 5. The association between selective risk factors for breast cancer and CYP17 genotypes among controls.

Selective risk factors		Frequency (%)		P-value ^a
		A1/A1(%)	A1/A2+A2/A2(%)	
Age	≤50	37 (52.9)	170 (63.7)	0.10
	>50	33 (47.1)	97 (36.3)	
Family history of breast cancer	No	69 (98.6)	253 (96.2)	0.47 ^b
	Yes	1 (1.4)	10 (3.8)	
Duration of education	<9 yrs	37 (52.9)	120 (44.9)	0.24
	≥9 yrs	33 (47.1)	147 (55.1)	
Duration of breast feeding	<12 months	24 (34.3)	103 (38.7)	0.50
	≥12 months	46 (65.7)	163 (61.3)	
Age at first full term pregnancy	≤25 yrs old	36 (59.0)	109 (46.6)	0.08
	>25 yrs old	25 (41.0)	125 (53.4)	
Number of full term pregnancy	≤1	59 (84.3)	192 (71.9)	0.03
	>1	11 (15.7)	75 (28.1)	
Age at menarche	>13 yrs old	62 (88.6)	227 (86.0)	0.57
	≤13 yrs old	8 (11.4)	37 (14.0)	
Menopause	No	34 (48.6)	156 (58.4)	0.14
	Yes	36 (51.4)	111 (41.6)	
Body mass index	<22 kg/m ²	23 (33.8)	94 (36.4)	0.69
	≥22 kg/m ²	45 (66.2)	164 (63.6)	

^aFrom Pearson's χ^2 -test; ^bFrom Fisher's exact test.

al. (2000) and Mitrinen *et al.* (2000). The trend of inverse association has also been reported among Asian women in a recent meta-analysis for 15 case-control studies (Ye *et al.*, 2002).

The associations between A2/A2 genotype and the breast cancer risk in younger women and leaner women in this study suggest the possibility of hormonal involvement in the development of breast cancer. Most subjects under the age of 50 were premenopausal women whose baseline level of exposure to estrogen is higher than postmenopausal women. It is speculated that obese women have more anovulatory menstrual cycles, which in turn results in lower circulatory progesterone and estradiol levels (Cleary *et al.*, 1997).

Several studies suggested that T→C polymorphism of CYP17 gene would increase the hormonal production and thus the risk of breast cancer: the level of circulating estrogens was higher in women with A2 allele than A1 allele (Feigelson *et al.*, 1998; Haiman *et al.*, 1999; Miyoshi *et al.*, 2003). However, the effect of this polymorphism on the level of estrogen is still controversial. Kristensen *et al.* (1999) could not verify this hypothesis, *i.e.*, a recombinant Sp-1 protein which combined with human embryonic ϵ -globin gene did not combine with the created site of the CC-genotype *in vitro*. Likewise, Tworoger *et al.*, (2004) found no association between CYP17 genotype and estrogen concentrations in serum and urine.

In present study, hormone related factors, such as age at menarche or age at menopause was not related to A2 allele. Whether A2 allele is associated with lower level of estrogens in Korean women remains to be investigated in future studies.

One of other findings is the ethnic diversity of genotype distributions of CYP17 gene. Proportion of A2/A2 among Korean women in this study (34.1%) was higher than that of Caucasian population (8-17%) (Dunning *et al.*, 1998; Helzlsouer *et al.*, 1998; Weston *et al.*, 1998; Bergman-Jungstrom *et al.*, 1999; Haiman *et al.*, 1999; Young *et al.*, 1999; Ambrosone *et al.*, 2000; Kuliginal *et al.*, 2000; Mitrinen *et al.*, 2000; Spurdle *et al.*, 2000; Feigelson *et al.*, 2001; Cui *et al.*, 2003; Hefler *et al.*, 2004). The frequencies of A2/A2 among other Asian populations were 28% for Taiwanese (Huang *et al.*, 1999), 16-21% for Japanese (Hamajima *et al.*, 2000; Miyoshi *et al.*, 2000) and 34% for Singapore Chinese (Wu *et al.*, 2003).

Our study has several limitations such as hospital based study, relatively small sample sizes in subgroup analysis, and evaluation for only one polymorphism in CYP17 without evident genotype-phenotype relationship etc. Thus, the results of this study should be interpreted with caution and suggestive effect of CYP17 A2/A2 genotype observed in this study need to be evaluated in a well designed study with more statistical power.

In conclusion, in this study, a suggestive effect of

A2/A2 genotype of *CYP17* gene was observed only among the subgroup of younger and leaner women in Korean population. However, further studies with more comprehensive genotyping and evaluation of genotype-phenotype relationship need to be conducted.

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