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The association between genetic polymorphisms in CYP19 and breast cancer risk in Korean women

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Abstract. Aromatase encoding by the CYP19 gene catalyzes the conversion of androgens to estrogens. In order to determine if polymorphisms of the CYP19 gene are associated with breast cancer risk, we analyzed the frequency of tetranucleotide (TTTA) tandem repeats and a 3-bp insertion (I)/deletion (D) polymorphism in intron 4 of the CYP19 gene in genomic DNA from 70 Korean breast cancer patients and 102 age-matched, healthy women. The 3-bp deletion allele was found more frequently in the breast cancer group than in the control group (p=0.001). Logistic regression analysis of the CYP 19 insertion/deletion (I/D) genotype showed a strong association between ID polymorphisms and breast cancer. The frequency of DD and ID alleles was significantly increased in the breast cancer group (DD genotype p=0.004, OR=12.81; and ID genotype p=0.005, OR=2.62). However, there were no differences in the genotype distributions of the (TTTA)n polymorphism of CYP19 between breast cancer patients and healthy controls. A positive association was noted between TTTA polymorphisms with 10 or more repeats and ER-negative tumors, as well as between lower repeat polymorphisms and ER-positive tumors (p=0.019). With respect to TTTA polymorphisms, we confirmed that the expression of aromatase in ER-positive MCF7 cells with 7-3 and 11 allele heterozygosity was significantly higher than in ER-negative MDA-MB231 cells with 11 allele homozygosity. These results suggest that 3-bp I/D polymorphisms of the CYP19 gene may be associated with breast cancer and that the (TTTA)n repeat genotype would be useful in selecting candidates for tamoxifen therapy, as well as predicting breast cancer risk in Korean women.

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Introduction

Breast cancer is the most common female cancer in the world (1). Breast cancer is the second most common cancer (16.8%) among Korean women, after stomach cancer. It is the 6th leading cause of cancer death in Korean women (2,3).

Estrogen plays an important role in carcinogenesis and the progression of breast cancer (4,5). Although the etiology of breast cancer is complex and involves lifestyle and environmental and genetic factors, increased and/or prolonged exposure to endogenous estrogens appears to play a major role in the development of the disease (6,7). Estrogen metabolites can give rise to the initial genetic damage (8). Furthermore, estrogens are thought to stimulate breast cell proliferation, promoting clonal expansion of initiated cells (9). About 25% of breast cancer cases are attributable to hereditary factors. Some genetic polymorphisms can affect a patient's predisposition to breast cancer, although they are not as highly penetrating as the BRCA1 and BRCA2 genes. The enzymes involved in the biosynthesis and metabolism of estrogens (CYP17, CYP19, CYP2D6, COMT, GSTM1, GSTT1, GSTP1 or CYP1A1) have been a major target in the identification of genetic polymorphisms associated with breast cancer risk (10,11).

CYP19 (aromatase), which is located on the q arm of chromosome 15, has 10 exons and encodes for the enzyme P450 aromatase (12). Aromatase converts androgens to estrogens and is one of the key enzymes involved in estrogen biosynthesis in the ovaries (13). Aromatase is present in the endoplasmic reticulum of the cells in which it is expressed, including the granulosa cells and corpus luteum of the ovary, the Leydig cells of the testis, the placenta, and various sites in the brain and in adipose tissue (14). Several mutations have been identified in the CYP19 gene. One of them, the tetranucleotide repeat polymorphism (TTTA)n, is located in intron 4 of the CYP19 gene (15,16). There have been many reports of different TTTA repeat alleles being associated with variations in breast cancer risk. Haiman *et al* (17), Yasuo *et al* (18) and Kristensen *et al* (19) reported that (TTTA)10 or more

was associated with an increased risk of breast cancer in their patient populations. Although (TTTA)n is the most widely studied repeat polymorphism in the CYP19 gene, there are many conflicting reports concerning the role of this polymorphism in different ethnic populations as it relates to breast cancer. Part of this disagreement seems to be due to the fact that different racial or ethnic groups differ with respect to risk of death or developing breast cancer. This might be related to wide racial variations in the distribution of various genetic polymorphisms.

In the present case-control study, we investigated the association between CYP19 polymorphisms and breast cancer risk in Korean women. In addition, we evaluated the usefulness of risk factors based on a combination of these polymorphisms. We confirmed these risk factors in a breast cancer cell line.

Materials and methods

Patients and control subjects. The present study included 70 women who were diagnosed with breast cancer between 2000 and 2004 in the Department of Pathology, Keimyung University Hospital, Daegu, Korea. The mean patient age was 50.3 years (range, 22-77 years). Breast cancer and paired normal tissue samples were collected from each patient at the time of hospitalization. Fresh tumor tissue and paired normal breast tissue were immediately processed for DNA extraction. A thorough histologic examination of the remaining tumor was made using H&E-stained tissue preparations. Histologically, 63 specimens were ductal invasive, 14 were ducal carcinoma *in situ*, 5 were lobular invasive, 3 were medullary, 1 was mucinous, 1 was apocrine, 1 was malignant phyllodes, and 2 were papillary invasive. Tumors were graded as grade I (n=16), II (n=18), or III (n=56). With respect to the TNM system, the group contained 31 T1, 40 T2, 5 T3 and 14 Tis tumors. There were 42 lymph node-negative and 48 lymph node-positive patients. Clinicopathological data included histological type, cancer grade, lymph node status and biomarker status (ER, PR, HER2, p53, BCl2, Ki-67).

One hundred and two case-matched, healthy women with the same ethnic background consented to have blood collected. The majority of the subjects attended the Kyung Hee Univer-sity Hospital for routine evaluation. They ranged from 25 to 59 years of age (mean, 49.3 years). Each subject donated up to 3 ml of whole blood, which was subsequently subjected to DNA extraction. All patients and control subjects agreed to genetic testing as approved by the hospital's Institutional Review Board.

Genomic DNA extraction and PCR amplification. Genomic DNA was extracted from solid tissue and blood samples so CYP19 polymorphisms could be assessed. The sliced tissue samples were lysed overnight at 56˚C in a solution containing 20 mM Tris-HCl (pH 8.0), 5 mM EDTA, 400 mM NaCl, 1% SDS, and 20 mg/ml proteinase K. DNA was extracted using phenol:chloroform:isoamyl alcohol (25:24:1). Core-One™ blood genomic DNA isolation kits (Core-Bio System, Seoul, Korea) were used for extracting DNA in case-matched, healthy, control blood samples according to the manufacturer's instructions.

The CYP19 STR in the intron 4 (TTTA)n alleles were determined by introducing 100 ng of genomic DNA in a PCR reaction mixture containing 1 U Taq polymerase, 250 μM dNTP, 10 mM Tris-HCl (pH 8.3), 40 mM KCl, and 1.5 mM $MgCl_2$ (Bioneer, Korea) to a 20 μl total reaction volume. In order to detect tetranucleotide (TTTA) repeat polymorphisms in intron 4 of the CYP19 gene [including the 3-bp I/D polymorphism region 50-bp upstream of the (TTTA)n tract], a set of the primers was utilized as previously described (12) (Forward: 5'-GCAGGTACTTAGTTAGCTAC-3; Reverse 5'-TTACAGTGAGCCAAGGTCGT-3'). Amplification conditions were as follows: 5 min for predenaturation at 95˚C; 30 sec at 95˚C, 30 sec at 60˚C, 30 sec at 72˚C, these steps were repeated for 35 cycles; and a final extension step at 72˚C for 5 min. All reactions were carried out in a GeneAmp PCR systems 9700 (Applied Biosystems, Foster City, CA, USA). The PCR products ranged in size from 168 to 191 bp, depending on the number of TTTA repeats.

Sequencing. PCR products were analyzed in 3% MetaPhor agarose gels with ethidium bromide stain and were visualized under ultraviolet irradiation. Target bands were extracted from gels using a mega-spin gel elution kit (iNtRON Biotech., Sungnam, S. Korea) and confirmed by direct sequencing with dideoxy nucleotide chain terminators in a cycle sequencing reaction with the BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems).

Statistical analysis. The χ^2 test (SPSS for Windows, version 11.5) was used to assess correlations between clinicopathological features (using grade, lymph node status and biomarkers) and CYP19 (using (TTTA)n and I/D polymorphisms). $P<0.05$ were regarded as statistically significant. All statistical tests were two-sided.

Cell culture and real-time PCR. The MCF7 and MDA-MB 231 cells were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum. Total RNA was extracted with TRI reagent (Invitrogen, USA), and cDNA was synthesized using 1 μg total RNA (Promega, USA). For real-time PCR analysis, 3 μg of total RNA was reverse transcribed with 100 U of MMLV reverse transcriptase (MBI Fermentase, USA) and a 10 mM dNTP mixture, in a 50 μl reaction mixture containing oligo dT (Bioneer, Korea). One microliter of cDNA mixture was then used as a DNA template in a 20 μl reaction mixture, including SYBG premix (Finzyme) and 10 pM of each primer, using a PTC-200 programmable thermal controller (MJ Research, Waltham, MA). Primers were designed using the web-based primer selection software, Primer3. The forward primer sequence of aromatase was 5'-ATTAGGGCCCTGTGTCTGCT-3', and the reverse primer sequence was 5'-GACTTTTCCTCCCC CAATCA-3'. The target PCR bands were normalized against the band intensity of GAPDH using the ΔCt analysis method.

Results

CYP19 polymorphisms in breast cancer patients and health controls. Analysis of CYP19 (TTTA)n polymorphisms in the Korean population resulted in PCR products with different

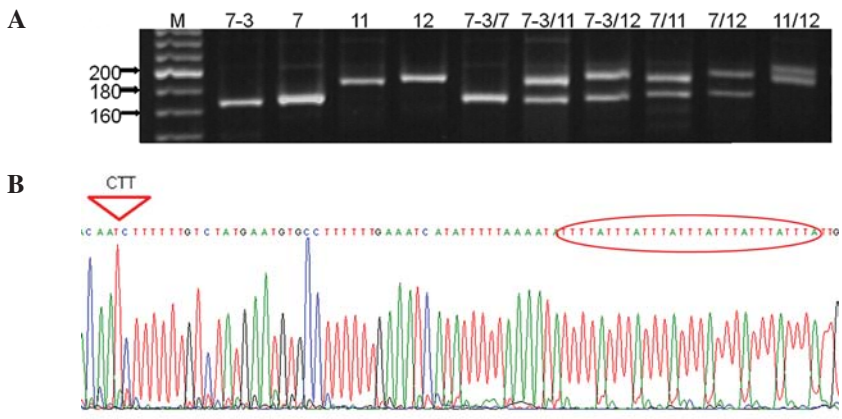

Figure 1. (A) Representative examples of CYP19 genotypes analyzed on a 3% MetaPhor agarose gel. Numbers indicate the number of (TTTA)n repetitions present in the respective CYP19 alleles (M, DNA size marker). (B) Sequence analysis of intron 4 in the CYP19 allele, containing 7 TTTA repeats and a 3-bp deletion.

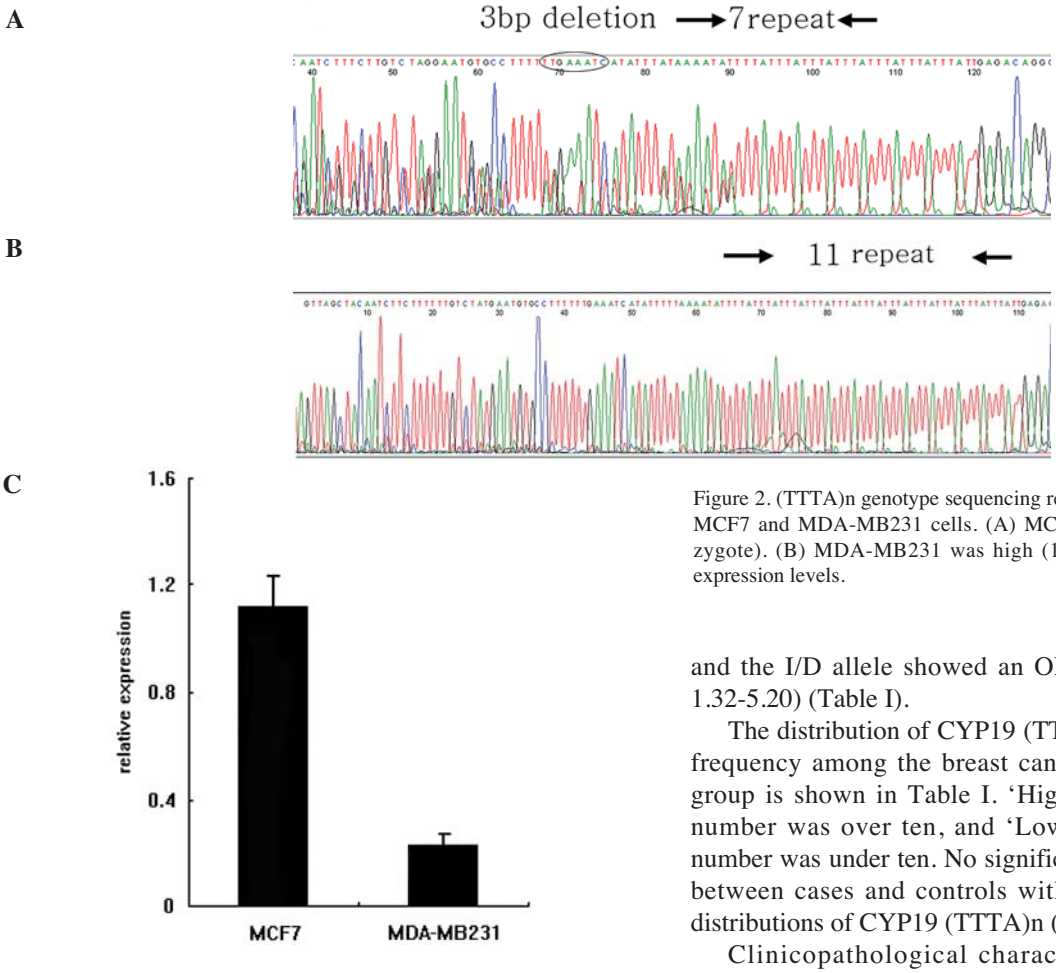

Figure 2. (TTTA)n genotype sequencing results and aromatase expression in MCF7 and MDA-MB231 cells. (A) MCF7 was low (7-3 and 11 heterozygote). (B) MDA-MB231 was high (11 homozygote). (C) Aromatase expression levels.

lengths corresponding to 4 alleles, combined into 10 genotypes, as shown in Fig. 1A. The PCR product with the smallest length was submitted to direct sequencing; it contained 7 (TTTA)n repeats and a 3-bp deletion allele, as shown in Fig. 1B.

The results of this case-control study of the association between the CYP19 genotype and breast cancer risk are shown in Table I. The 3-bp I/D polymorphisms in the CYP19 gene were associated with breast cancer risk in this case-control study (p=0.001). Moreover, the 3-bp deletion (D/D) allele showed an OR value of 12.81 (95% CI, 1.48-110.28), and the I/D allele showed an OR value of 2.62 (95% CI, 1.32-5.20) (Table I).

The distribution of CYP19 (TTTA)n genotypes and allele frequency among the breast cancer group and the control group is shown in Table I. 'High' means the TTTA copy number was over ten, and 'Low' means the TTTA copy number was under ten. No significant differences were noted between cases and controls with respect to the genotype distributions of CYP19 (TTTA)n (p=0.699).

Clinicopathological characteristic of breast cancer according to genetic polymorphisms are shown in Table II. The (TTTA)n polymorphisms with under 10 repeats (low type) were significantly more common in the ER-positive group (p=0.019, OR=4.16), but there was no association between I/D polymorphisms and clinicopathological characteristics.

Cell culture and aromatase expression. There was a significant difference in the (TTTA)n genotypes between the two groups, as they related to ER positivity and negativity. We confirmed this phenomenon in a stable ER-positive cell line

Table I. Logistic regression analysis of I/D and (TTTA)n genotype in the CYP19 gene.

Genotype	Case n (%)	Control n (%)	P-value	OR (95% CI)
I/D type				
DD	1 (1.0)	23 (22.5)	0.004	12.81 (1.48 110.28)
DI	22 (21.6)	27 (38.6)	0.005	2.62 (1.32-5.20)
II	79 (77.5)	37 (52.9)		Reference (1.0)
(TTTA)n type				
High (10 or more)	15 (21.4)	19 (18.6)		
n (%)		0.699		
Low (less 10)	55 (78.6)	83 (81.4)		
n (%)				

Table II. Association of (TTTA)n polymorphisms in the CYP19 gene with clinicopathological features and biomarkers in patients with breast cancer (n=67).

	Genotype of CYP19		
Factor	High n (%)	Hetero, low n (%)	P-value
Histological grade			
I	2 (14.3)	10 (19.2)	0.727
II	4 (28.6)	10 (19.2)	
III	8 (57.1)	32 (61.5)	
Lymph node status			
Negative	9 (64.3)	27 (50.9)	0.373
Positive	5 (35.7)	26 (49.1)	
ER			
Negative	9 (64.3)	16 (30.2)	0.019[a]
Positive	5 (35.7)	37 (69.8)	
PR			
Negative	9 (64.3)	29(54.7)	0.520
Positive	5 (35.7)	24 (45.3)	
HER2			
Negative	5 (35.7)	26 (50)	0.342
Positive	9 (64.3)	26 (50)	
p53			
≤10%	4 (28.6)	18 (34.6)	0.670
>10%	10 (71.4)	34 (65.4)	
BCl2			
Negative	2 (14.3)	11 (21.1)	0.566
Positive	12 (85.7)	41 (78.8)	

[a]P=0.019, OR=4.16, 95% Wald CI=1.2-14.39. ER, estrogen receptor; PR, progesterone receptor; HER2, epidermal growth factor receptor type 2.

(MCF7) and an ER-negative cell line (MDA-MB231). The MCF7 genotype was low, and the MDA-MB231 genotype was high (Fig. 2A and B). We also evaluated the aromatase expression in each cell type using real-time PCR. Aromatase expression was high in MCF7 cells and low in MDA-MB231 cells (Fig. 2C).

Summary of CYP19 (TTTA)n genotypes among controls.

Genotype	Ethnicity-allele frequency (%)				
	Norwegian, Swedish n=504	Caucasian n=284	British n=506	Japanese n=376	Korean n=102
High type	34.5	41.6	41.3	30.7	44.5
Low type[a]	65.5	58.4	58.7	69.3	55.5

[a]Additional 3-bp deletion.

Discussion

Many studies have addressed CYP19 polymorphisms as a risk factor in breast cancer (20). Several different CYP19 gene polymorphisms have been reported in relation to breast cancer risk, including tetranucleotide repeats in intron 4 (17,18,21-23), C-T substitutions in the 3' non-coding region of exon 10 (19), cytosine to thymine substitutions in codon 264 of exon 7 (resulting in conversion of arginine to cysteine) (24), silent G-A polymorphisms at codon 80 in exon 3 (25), and rare 3-bp changes within the promoter region of exon 1 (26). The tetranucleotide repeat polymorphism is the most widely studied of all these variants in the CYP19 gene.

Kristensen *et al* (19) reported an association between TTTA polymorphisms and breast cancer risk in a case-control study of a Norwegian and Swedish population and found a positive relationship between the 12-repeat allele and breast cancer risk (OR=2.42). In a case-control study, Siegelmann and Buetow (25) observed a lower frequency of the 12-repeat allele and a higher frequency of the 7-repeat allele in a Caucasian population (OR=1.47). In a study of Japanese women, 10 or more repeat alleles were observed at higher frequency in the breast cancer group (OR=1.8) (Table III).

In this study, we studied the association between (TTTA)n polymorphisms of the CYP19 gene and breast cancer risk in Korean women. However, we did not find any relationship between (TTTA) repeat polymorphisms and breast cancer.

All previous studies have reported that the most common allele is (TTTA)7 [including (TTTA)7-3], followed in frequency by (TTTA)11. The typical number of repeats in the TTTA polymorphism in the Korean control population is seven or eleven - never eight or ten. This phenomenon is also noted in Japanese control groups. However, Caucasian and British control populations do rarely manifest (TTTA)8 and (TTTA)10 alleles. It has been suggested that the repeat number differs according to race. Asian women have a lower breast cancer incidence than Caucasian women (27). Racial differences in the frequencies of alleles associated with breast cancer might play some role in this phenomenon (28).

The reason for the association of these polymorphisms with breast cancer risk is currently unknown. Haiman *et al* reported an association between the (TTTA) repeat number and serum estrogen levels in postmenopausal women and suggested that (TTTA) polymorphisms affect the expression of CYP19 mRNA, resulting in altered estrogen levels (17). In this study, we noted a significant association between a high TTTA polymorphism repeat number (over 10) and ER-negative breast cancer. A low TTTA allele repeat number (under 10) was significantly associated with an increased risk of ER-positive breast cancer. This genetic polymorphism associated with ER-positive and ER-negative breast cancer risk would be very useful in the selection of candidates for prophylactic tamoxifen therapy. Tamoxifen has been shown to reduce the risk of ER-positive, but not ER-negative, breast cancer.

We also evaluated the association between I/D polymorphisms in intron 4 of the CYP19 gene and breast cancer in a Korean population, and noted a highly significant association. The DD allele was significantly increased in the breast cancer patient group (DD genotype OR=12.81, DI genotype OR=2.62) compared to the control group. Miyoshi *et al* (28) reported that DD allele carriers showed a significantly ($p<0.05$) increased risk of ER-positive breast cancer. Kado *et al* suggested that 3-bp I/D polymorphisms of the CYP19 gene may be weakly associated with susceptibility to endometriosis, not breast cancer, in a Japanese population (12,29).

In conclusion, we demonstrated that high repeat CYP19 (TTTA) alleles are associated with ER negativity, and low repeat CYP19 (TTTA) alleles are associated with ER positivity in breast cancer. DD alleles of the CYP 19 gene are increased in the breast cancer group compared to the control group. Our data suggest that (TTTA)n and I/D polymorphisms of the CYP19 gene will be useful in the selection of candidates for tamoxifen therapy and prediction of breast cancer development.

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