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Evaluation of *CYP17A1* and *LEP* Gene Polymorphisms in Breast Cancer

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Keywords

Breast cancer · Leptin · *CYP17A1* · Genetic susceptibility · Polymorphism

Summary

Background: Polymorphisms of estrogen synthesis- and adiposity-related genes can contribute to the development of breast cancer. The purpose of the current study was to analyze the association between *CYP17A1* T27C (rs743572) and *LEP* -2548G>A (rs7799039) gene polymorphisms and breast cancer. **Material and Methods:** 199 breast cancer patients and 197 healthy controls were included in the study. The *CYP17A1* and *LEP* gene polymorphisms were determined using polymerase chain reaction-based restriction fragment length polymorphism analysis. **Results:** No statistically significant association was found between these polymorphisms and breast cancer risk among a Turkish population. However, stratified analysis of these polymorphisms in relation to different clinicopathological characteristics of breast cancer revealed an association between breast cancer diagnosis and the *CYP17A1* T27C polymorphism (p = 0.024). **Conclusion:** Our study suggests no strong association between the *CYP17A1* T27C and *LEP* -2548G>A polymorphisms and the incidence of breast cancer in Turkish women. The potential association between *CYP17A1* T27C and the type of breast cancer deserves further consideration.

Introduction

Breast cancer is the most common cancer among women and responsible for approximately 458,400 deaths each year [1]. Today, more than 2.9 million breast cancer cases exist in the United States [2]. Common risk factors explain only a small part of the cases, and susceptibility to breast cancer is determined by a combination of lifestyle and environmental and genetic factors [3].

Polymorphisms which are observed in estrogen biosynthesis- and adiposity-related genes could affect circulating estrogen and adipokine levels and influence a woman's susceptibility to breast cancer [4]. Our study included 2 of the candidate genes: cytochrome P450, family 17, subfamily A, polypeptide 1 (*CYP17A1*) and leptin (*LEP*).

The human *CYP17A1* gene, located on chromosome 10q24.3, encodes the cytochrome P450c17α enzyme involved in the early stages of endogenous estrogen biosynthesis [5]. A common polymorphism (T27C, -34 T>C) in the 5' untranslated region (5'-UTR) of *CYP17A1* was first thought to create an SP1 promoter site [6]; however, this was disproved by a later study [7]. For this reason, the functional effect of a T>C change is unknown today. The rare C allele was demonstrated to be associated with higher serum levels of different sex steroids [6, 8, 9], and was shown to increase breast cancer risk in conjunction with long-term hormone replacement therapy and high body mass index in postmenopausal women [10]. To date, several studies have reported on the association between the *CYP17A1* T27C polymorphism and breast cancer with conflicting results [11, 12].

Leptin is an adipose tissue-derived hormone whose primary role is to modulate appetite and energy balance. Cell-based and

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Table 1. Clinical and pathological characteristics of breast cancer patients stratified according to *CYP17A1* T27C and *LEP* -2548G>A polymorphisms (data analyzed with χ^2 test)

		CYP17A1 T27C, n (%)				*LEP* -2548G>A, n (%)			
Characteristics	Total, n (%)	TT	TC	CC	p value	GG	GA	AA	p value
Age at onset (n = 190)					0.946				0.980
< 50 years	101 (53.2)	53 (54.1)	39 (52.7)	9 (50.0)		23 (52.3)	53 (53.0)	25 (54.3)	
≥ 50 years	89 (46.8)	45 (45.9)	35 (47.3)	9 (50.0)		21 (47.7)	47 (47.0)	21 (45.7)	
Family history of cancer (n = 192)					0.910				0.093
Breast cancer	28 (14.6)	13 (13.3)	13 (13.3)	2 (11.1)		5 (11.4)	18 (18.0)	5 (10.4)	
Other cancer	59 (30.7)	30 (30.6)	24 (31.6)	5 (27.8)		18 (40.9)	22 (22.0)	19 (39.6)	
None	105 (54.7)	55 (56.1)	39 (51.3)	11 (61.1)		21 (47.7)	60 (30.0)	24 (50.0)	
Diagnosis type (n = 179)					0.024				0.561
Bilateral breast cancer	11 (6.1)	10 (10.9)	1 (1.4)	0		5 (11.4)	4 (4.4)	2 (4.5)	
Left breast cancer	84 (46.9)	47 (51.1)	29 (40.8)	8 (50.0)		19 (43.2)	45 (49.5)	20 (45.5)	
Right breast cancer	84 (46.9)	35 (38.0)	41 (57.7)	8 (50.0)		20 (45.5)	42 (46.2)	22 (50.0)	
Tumor histology (n = 189)					0.343				0.972
Ductal carcinoma	168 (88.9)	89 (91.8)	64 (86.5)	15 (83.3)		36 (87.8)	90 (89.1)	42 (89.4)	
Lobular carcinoma	11 (5.8)	3 (3.1)	7 (9.5)	1 (5.6)		3 (7.3)	5 (5.0)	3 (6.4)	
Other	10 (5.3)	5 (5.2)	3 (4.1)	2 (11.1)		2 (4.9)	6 (5.9)	2 (4.3)	
Tumor stage (n = 157)					0.476				0.433
I	18 (11.4)	10 (12.2)	7 (11.7)	1 (6.7)		5 (13.2)	5 (6.3)	8 (20.0)	
II	61 (38.9)	28 (34.1)	24 (40.0)	9 (60.0)		14 (36.8)	31 (39.2)	16 (40.0)	
III	72 (45.9)	39 (47.6)	28 (46.7)	5 (33.3)		17 (44.7)	40 (50.6)	15 (37.5)	
IV	6 (3.8)	5 (6.1)	1 (1.7)	0		2 (5.3)	3 (3.8)	1 (2.5)	
Age at menarche (n = 173)					0.524				0.125
< 15 years	138 (79.8)	74 (82.2)	55 (78.6)	9 (69.2)		27 (71.1)	77 (85.6)	34 (75.6)	
≥ 15 years	35 (20.2)	16 (17.8)	15 (21.4)	4 (30.8)		11 (28.9)	13 (14.4)	11 (24.4)	
Menopause (n = 186)					0.671				0.828
Menstruation ongoing	70 (37.6)	36 (36.7)	29 (39.7)	5 (33.3)		16 (37.2)	36 (37.1)	18 (39.1)	
At age < 40 years	11 (5.9)	8 (8.2)	2 (2.7)	1 (6.7)		3 (7.0)	4 (4.1)	4 (8.7)	
At age ≥ 40 years	105 (56.5)	54 (55.1)	42 (57.5)	9 (60.0)		24 (55.8)	57 (58.8)	24 (52.2)	
Number of births (n = 184)					0.259				0.618
0	20 (10.9)	8 (8.5)	11 (15.1)	1 (5.9)		2 (4.9)	12 (12.4)	6 (13.0)	
1	18 (9.8)	12 (12.8)	6 (8.2)	0		5 (12.2)	10 (10.3)	3 (6.5)	
≥ 2	146 (79.3)	74 (78.7)	56 (76.7)	16 (94.1)		34 (82.9)	75 (77.3)	37 (80.4)	
Duration of breastfeeding (n = 186)					0.387				0.312
None	28 (15.1)	11 (11.6)	15 (20.3)	2 (11.8)		4 (9.3)	16 (16.5)	8 (17.4)	
< 6 months	41 (22.0)	22 (23.2)	17 (23.0)	2 (11.8)		14 (32.6)	20 (20.6)	7 (15.2)	
≥ 6 months	117 (62.9)	62 (65.3)	42 (56.8)	13 (76.5)		25 (58.1)	61 (62.9)	31 (67.4)	
ER status (n = 152)					0.090				0.455
Positive	106 (69.7)	54 (66.7)	48 (77.4)	4 (44.4)		23 (65.7)	60 (74.1)	23 (63.9)	
Negative	46 (30.3)	27 (33.3)	14 (22.6)	5 (55.6)		12 (34.3)	21 (25.9)	13 (36.1)	
PR status (n = 122)					0.248				0.949
Positive	69 (56.6)	39 (60.9)	28 (54.9)	2 (28.6)		16 (59.3)	38 (55.9)	15 (55.6)	
Negative	53 (43.4)	25 (39.1)	23 (45.1)	5 (71.4)		11 (40.7)	30 (44.1)	12 (44.4)	

ER = Estrogen receptor; PR = progesterone receptor.

animal studies have provided strong evidence that leptin could be involved in neoplastic processes [13–15], and it plays an important role in increasing breast cancer cell proliferation by amplifying estrogen signaling [16]. These observations suggest that leptin may be involved in breast tumorigenesis. The *LEP* gene promoter includes many binding sites for a variety of transcription factors [17]. The common *LEP* -2548G>A polymorphism is associated with obesity and variations in serum leptin levels and leptin synthesis [18]. Few previous publications have examined the *LEP* -2548G>A polymorphism in relation to breast cancer risk, and the results were inconsistent [19].

The relationship between the *CYP17A1* T27C and *LEP* -2548G>A polymorphisms and the risk of breast cancer have been investigated in different populations. To our knowledge, only 1 study with a smaller sample size has reported an association between breast cancer and the *CYP17A1* T27C polymorphism so far; however, no study has reported on the association between the *LEP* -2548G>A polymorphism and breast cancer in Turkish popula-

Table 2. Genotype and allele frequencies of *CYP17A1* and *LEP* gene polymorphisms in patients and controls (data analyzed with χ^2 test)

Polymorphism	Patients (n = 199) n (%)	Controls (n = 197) n (%)	p	OR (CI 95%)
CYP17A1 T27C				
Genotypes				
TT	102 (51.3)	104 (52.8)	0.866	
TC	79 (39.7)	78 (39.6)		
CC	18 (9.0)	15 (7.6)		
TT : TC+CC	102 (51.3) : 97 (48.7)	104 (52.8) : 93 (47.2)	0.764	1.06 (0.72–1.58)
TT+TC : CC	181 (91.0) : 18 (9.0)	182 (92.4) : 15 (7.6)	0.717	1.21 (0.59–2.47)
Alleles				
T	283 (71.1)	286 (72.6)	0.693	1.08 (0.79–1.47)
C	115 (28.9)	108 (27.4)		
LEP -2548G>A				
Genotypes				
GG	45 (22.6)	40 (21.6)	0.967	
GA	105 (52.8)	98 (53.0)		
AA	49 (24.6)	47 (25.4)		
GG : GA+AA	45 (22.6) : 154 (77.4)	40 (21.6) : 145 (78.4)	0.902	0.94 (0.58–1.53)
GG+GA : AA	150 (75.4) : 49 (24.6)	138 (74.6) : 47 (25.4)	0.906	0.96 (0.60–1.52)
Alleles				
G	195 (49.0)	178 (48.1)	0.829	0.96 (0.73–1.28)
A	203 (51.0)	192 (51.9)		

OR = Odds ratio; CI = confidence interval.

tions. The present study aimed to investigate *CYP17A1* and *LEP* gene polymorphisms in relation to breast cancer risk in a Turkish population.

Materials and Methods

Patients

Included in this population-based, case-control study were 199 female breast cancer patients treated at the Research Hospital of Ondokuz Mayis University, Samsun (113 patients) and the Oncology Training and Research Hospital, Ankara (86 patients), Turkey, during a 5-year period from 2002 to 2007. All subjects were diagnosed histologically using specimens obtained by surgical resection or biopsy. Clinical data were obtained from the patients' medical records. The mean age of patients and controls was 52.44 ± 11.297 years and 50.34 ± 10.480 years, respectively. The control group comprised healthy women who were older than 35 years and did not have a family history of any cancer or other serious diseases. All controls came from the same subpopulation as the patients. The breast cancer patients and healthy controls signed an informed consent form for genetic analysis after receiving information about the study. This study was approved by the local ethics committee of Ondokuz Mayis University, Faculty of Medicine.

Genotyping

Genomic DNA was extracted from whole blood of both patients and controls using the salting-out method [20]. All DNA samples were stored at -20 °C until further analysis. The *CYP17A1* T27C (-34T>C) (rs743572) and *LEP* -2548G>A (rs7799039) polymorphisms were analyzed by polymerase chain reaction (PCR)-based restriction fragment length polymorphism assay. The primers for the *LEP* -2548G>A polymorphism were (F) 5'-TTT CCT GTA ATT TTC CCG TGA G-3' and (R) 5'-AAA GCA AAG ACA GGC ATA AAA A-3'. The 241 bp PCR product was digested with HhaI restriction enzyme at 37 °C overnight and analyzed on 3% agarose gel stained with ethidium bromide. 205 and 36 bp fragments were observed in the presence of G nucleotide. The PCR primers of the *CYP17A1* T27C polymorphism were (F) 5'-CAT TCG CAC TCT GGA GTC-3' and (R) 5'-GGC TCT TGG GGT ACT TG-3'. The 413 bp PCR product was digested with MspA1I restriction enzyme at 37 °C for 16 h. The C allele was digested into 290 and 123 bp fragments.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software program (IBM SPSS Statistics), version 20.0 (IBM Corp., Armonk, NY, USA). The chi-square (χ^2) test was used to evaluate the Hardy-Weinberg equilibrium (HWE) for the distribution of genotypes in patients and controls. Genotypes and alleles were compared between cases and controls using the χ^2 test, and odds ratio and 95% confidence interval were used for the assessment of risk factors. The relationships between *CYP17A1* and *LEP* gene polymorphisms and the clinical and pathological characteristics of patients were analyzed using the χ^2 test. All p values were 2-tailed, and p values less than 0.05 were considered significant.

Results

The clinical and pathological characteristics of the breast cancer patients stratified according to the *LEP* -2548G>A and *CYP17A1* T27C polymorphisms are shown in table 1. No association was observed between *LEP* -2548G>A and *CYP17A1* T27C genotypes and clinical and pathological characteristics, except for *CYP17A1* T27C and type of breast cancer. Among the bilateral breast cancer patients, there were no women with a CC genotype and only 1 woman with a TC genotype (p = 0.024) (table 1).

Allelic and genotypic distributions of *LEP* -2548G>A and *CYP17A1* T27C are shown in table 2. Genotype and allele frequencies of *LEP* -2548G>A (p = 0.967 and p = 0.829, respectively) and *CYP17A1* T27C (p = 0.866 and p = 0.693, respectively) were not

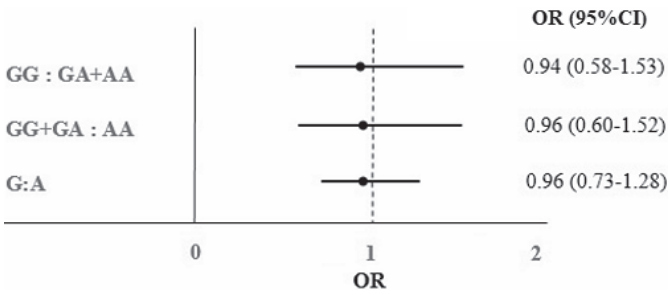

Fig. 1. Forest plot of breast cancer associated with the -2548G>A polymorphism in the *LEP* gene.

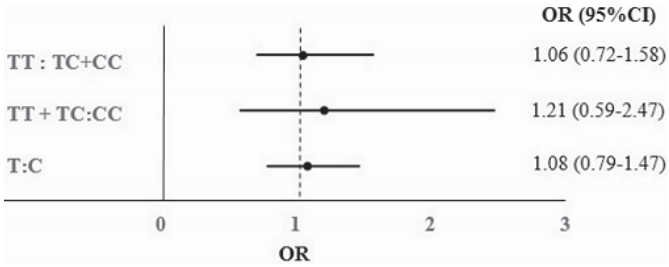

Fig. 2. Forest plot of breast cancer associated with the T27C polymorphism in the *CYP17A1* gene.

statistically different between patients and controls (table 2, figs. 1 and 2). The distribution of the *LEP* -2548G>A and *CYP17A1* T27C genotypes in patients and controls did not deviate from the HWE.

Discussion

An increase in estrogen signaling plays an important role in breast cancer development [21]. For this reason, variants which can change the levels of estrogen have been examined in association with breast cancer in different populations, and different results were reported [12, 19]. CYP17A1 is one of the important enzymes involved in estrogen biosynthesis. The common T27C polymorphism of the *CYP17A1* gene has been studied for its association with breast cancer in many studies [11, 12]. The C allele of this polymorphism was suggested to increase estrogen biosynthesis [8, 9].

There are 3 meta-analyses that have reported an association between the *CYP17A1* T27C polymorphism and breast cancer risk, all published in 2010 [12, 22, 23]. These meta-analyses included 24–43 studies from different populations and showed no association between the *CYP17A1* T27C polymorphism and breast cancer, which is in line with our results. There were no studies pertaining to Turkish populations, even within the widest meta-analysis including 43 studies [12]. Subsequently, a study based on a Turkish population was reported with a relatively small sample size of 55 cases and 91 controls, which similar to our results did not find any association between the *CYP17A1* T27C polymorphism and breast cancer in this population [24].

In later studies, Chattopadhyay et al. [25], in their case-control study comprising 360 patients and 360 controls, found that a joint TC and CC genotype of the *CYP17A1* T27C polymorphism was significantly associated with elevated risk of breast cancer in premenopausal women in an Indian population; and among the Greenlandic Inuit women, the *CYP17A1* variant C allele was associated with a decreased risk of breast cancer [26]. A borderline association of locus *CYP17A1* T27C with an increasing risk of breast cancer during the premenopausal period was demonstrated in a Russian population ($p = 0.04$) [27]. In contrast, the T27C polymorphism in *CYP17A1* was not associated with a general increase in breast cancer risk in a Canadian population, similar to our results [28]. However, the *CYP17A1* CC genotype was only observed in women with estrogen receptor (ER)-positive breast cancer but not in those with ER-negative breast cancer in the same study [28].

Cell-based and animal studies have suggested that high levels of leptin might increase breast tumorigenesis [14]. It was reported that the *LEP* -2548G>A polymorphism could cause leptin overexpression in breast cancer cells [29]. A meta-analysis including 3 studies that examined the association between *LEP* -2548G>A and breast cancer risk failed to show a significant association [19]. After this meta-analysis, single-nucleotide polymorphisms of the *LEP/LEPR* genes were analyzed in 405 premenopausal Caucasian breast cancer patients and 810 Caucasian controls, and no strong association between the *LEP* -2458G>C polymorphism and premenopausal breast cancer risk was observed [30]. In concordance with these results, we did not observe any association between breast cancer risk and the *LEP* -2548G>A polymorphism in our Turkish population.

We hypothesized that the -2548G>A polymorphism in the *LEP* gene and the T27C polymorphism in *CYP17A1* gene may be associated with breast cancer risk. While our data failed to reveal any associations between these polymorphisms and breast cancer risk in the study population, we detected for the first time an association between the type of breast cancer and *CYP17A1* T27C. Among the bilateral breast cancer patients, there were no women with a CC genotype and only 1 woman with a TC genotype.

Conclusion

Our study suggests no association between common genetic variants in the *LEP* and *CYP17A1* genes and the incidence of breast cancer in Turkish women. The potential association between the *CYP17A1* T27C polymorphism and the type of breast cancer deserves further consideration.

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Disclosure Statement

The authors have no conflict of interest to declare.

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