Original Article

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The Relationship between Adiponectin and Breast Cancer

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ABSTRACT

Objective: Breast cancer is the most common type of cancer in women worldwide. It is indicated that increased body mass index elevates the risk of developing breast cancer, worsens prognosis, and decreases survival. Several polymorphisms of adiponectin have been shown to affect serum levels of adiponectin and their association with breast cancer. The aim of this study was to investigate the relationship between the adiponectin 45T/G and 276 G/T gene polymorphism and breast cancer in the East Marmara region.

Materials and Methods: A case-control study was performed in 97 patients with breast cancer and 101 controls in East Marmara in order to evaluate the prevalence of adiponectin gene polymorphism at positions 45 and 276. Patients with familial breast cancer and those who had received chemotherapy or radiotherapy were excluded from the study. Adiponectin gene polymorphisms were investigated using polymerase chain reaction - restriction fragment length polymorphism (PCR- RFLP).

Results: Adiponectin 45T/G gene genotype frequencies of TT, TG, and GG were 61.9%, 37.1%, and 1% in patients with breast cancer, and 67.3%, 30.7%, and 2% in the control group, respectively. Adiponectin 276G/T gene genotype frequencies of GG, GT, and TT were 45.4%, 45.4%, and 9.3% in patients with breast cancer and 55.4%, 39.6%, and 5.0% in the control group, respectively.

Conclusion: Our study showed that adiponectin 45T/G and 276 G/T gene polymorphism is not associated with breast cancer risk in patients from the East Marmara region.

Keywords: Breast cancer, adiponectin, genetic polymorphism

Introduction

Obesity is an important health issue, and it is positively correlated with the incidence and mortality of breast cancer (1). Obese patients with breast cancer are known to have a higher risk of lymph node metastasis, larger tumors, and higher mortality rates compared with non-obese patients (2). Estrogen levels raised due to aromatization in adipose tissues increase mitogenic agents such as insulin associated with obesity-metabolic syndrome and insulin-like growth factor (IGF), and adipokines released from adipose tissues are considered responsible for this (3-5).

Adiponectin is an adipocytokine secreted by adipocytes. The adiponectin gene is located on chromosome 3q27 (6). Decreased adiponectin levels in obese patients have been discovered to be an increased risk factor for breast cancer (7). Some single nucleotide polymorphisms (SNP) in the adiponectin gene have been proven to be associated with breast cancer. Of these polymorphisms, which are located on exon 2 of the adiponectin gene, 45T/G has been found responsible for the relationship between breast cancer and obesity. 276G/T, on the other hand, is located at intron 2 of the adiponectin gene, and has no discovered effects (8). The distribution of gene polymorphisms can differ based on the population.

Before our study, the adiponectin gene polymorphism had never been studied in Turkey. We aimed to demonstrate the relationship between SNP and breast cancer within the East Marmara region of Turkey.

Materials and Methods

A total of 97 patients with breast cancer wo underwent surgery in our clinic and 101 healthy controls with no family history of breast cancer were enrolled into this study. Those who had a body mass index less than 20 and patients with renal or liver failure were excluded from

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the study. The patients with a family history of breast cancer and those who underwent chemotherapy or radiotherapy were also not included in this study. The study was approved by the Local Ethics Committee. Consent was obtained from all patients for the study.

For the amplification the area of DNA containing adiponectin 276G/T [BsmI (rs1501299)] polymorphism, the primaries F: 5′-CTG AGA TGG ACG GAG TC TTT-3′ and R: 5′-CCA AAT CAC TTC AGG TTG CTT-3′ were used. After denaturation at 95°C for 5 min, the polymerase chain reaction (PCR) was performed in the following order: 95°C for 30 s, 60°C for 45 s, and 72°C for 50 s, for 35 rounds and finally 72°C for 10 min. The PCR mix with a total amount of 20 µL was prepared including 10 mM Tris-Cl (pH 8.8), 50 mM KCl, 0.08% Nonidet P-40, and 1.5 mM $MgCl_2$, 200 µM deoxyribonucleotide triphosphate (dNTP), and 1.0 U Taq DNA polymerase (MBI Fermentas).

The primaries F: 5′-GCA GCT CCT AGA AGT AGA CTC TGC TG-3′ and R: 5′-GCA GGT CTG TGA TGA AAG AGG CC-3′ were used to amplify the area of DNA containing adiponectin 45T/G [SmaI (rs2241766)]. The PRC was performed at 95°C for 45 s, 61°C for 45 s, and 72°C for 1 min for 35 rounds, and finally 72°C for 60 s after denaturation at 94°C for 5 min. The PCR mix with a total volume of 20 µL included 10 mM Tris-Cl (pH 8.8), 50 mM KCl, 0.08% Nonidet P40 and 1.5 mM $MgCl_2$, 200 µM dNTP, and 1.0 U Taq DNA polymerase (MBI Fermentas).

BsmI restriction enzyme digestion with a total volume of 15 µL was prepared with 1X BsmI buffer (NE buffer), 1 U BsmI enzyme, 5 µL PCR product and 6 µL sterile distilled water for drinking, and was kept at 37°C overnight. The digestion products were separated in 8% polyacrylamide gel, and scanned after being stained using silver nitrate. All scans were saved on a computer with the aid of a scanner. Genotyping was performed and read at 456 bp GG, 456bp, 374bp and 82bp GT, 374bp and 82bp TT. The SmaI restriction enzyme digestion was 15 µL in total including 1X SmaI buffer (NE Buffer), 1U SmaI enzyme, 5 µL PCR product and 6 µL sterile distilled water for drinking, and was kept at 37°C overnight before the procedure. The digestion products were separated in 8% polyacrylamide gel and scanned after being stained using silver nitrate. All scans were saved on a computer. Genotyping was performed and read at 372bp TT, 372bp, 209bp and 163bp TG, 209bp and 163bp GG.

Statistical analysis

The Statistical Package for the Social Sciences version 13.0 (SPSS Inc.; Chicago, IL, USA) was used to analyze the statistical data. After observing the normal distribution of data, a post hoc test was conducted after one-way analysis of variance, and a group test was evaluated using the χ^2 test. The results are presented with mean ± standard deviation.

Results

For the gene polymorphism 276G/T rs1501299, the genotype frequencies were 45.4%, 55.4% of GG genotype, 45.4%, 39.6% of GG genotype, and 9.3%, 5.0% for TT genotype for the patients and controls, respectively. There was no statistical difference between the case and control genotypes (χ2=2.694, p= 0.260) (Table 1). The allele frequency was 68.1% in the patients and 75.24% in the controls for allele G, and 32.0% in the patients and 24.75% in the controls for allele T. These findings were not statistically significant (allele G: p= 0.235,

Table 1. The genotype and allele frequencies of SNP 276G/T [BsmI (rs1501299)] and 45T/G [SmaI (rs2241766)] in the breast cancer and control groups

Genotype	Breast Cancer Patients	Control Patients	x^2	p	OR; 95% CI
BsmI (rs1501299)	97 (100.0)	101 (100.0)	2.694	0.260	
GG	44 (45.4)	56 (55.4)	2.013	0.156	0.667 (0.381 - 1.168)
GT	44 (45.4)	40 (39.6)	0.671	0.413	1.266 (0.720 - 2.227)
TT	9 (9.3)	5 (5.0)	1.410	0.235	1.964 (0.634 - 6.084)
Allele frequency					
G	132 (68.1)	152 (75.24)	1.410	0.235	0.509 (0.164-1.578)
T	62 (32.0)	50 (24.75)	2.013	0.156	1.499 (0.856-2.625)
HWE (p)	0.816	0.789			
SmaI (rs2241766)	97 (100.0)	101 (100.0)	1.126	0.569	
TT	60 (61.9)	68 (67.3)	0.648	0.421	0.787 (0.439-1.411)
TG	36 (37.1)	31 (30.7)	0.911	0.340	1.333 (0.738-2.405)
GG	1 (1.0)	2 (2.0)	0.299	0.585	0.516 (0.046-5.780)
Allele frequency					
T	156 (80.4)	167 (82.7)	0.299	0.585	1.939 (0.173-21.741)
G	38 (19.6)	35 (17.3)	0.648	0.421	1.271 (0.709-2.278)
HWE (p)	0.110	0.730			

HWE: Hardy-Weinberg Equation; OR: odds ratio; CI: confidence interval

allele T: p=0.156). The genotype distribution of 276 G/T rs1501299 was found stable for the patient and control population according to the Hardy-Weinberg Equation (p>0.05) (Table 1).

For the gene polymorphism 45T/G rs2241766, the genotype frequencies were 61.9%, 67.3% of TT genotype, 37.1%, 30.7% of TG genotype, and 1.0%, 2.0% for GG genotype for the patients and controls, respectively. There was no statistical difference found between the patient and control genotypes ($\chi 2=1.126$, p= 0.569) (Table 1). The allele frequency was 80.4% in the patients and 82.7% in the controls for allele T, and 19.6% in the patients and 17.3% in the controls for allele G. These findings were not statistically significant (allele T: p=0.585, allele G: p=0.421). The genotype distribution of 45T/G rs2241766 was found stable for the patient and control population according to the Hardy-Weinberg Equation (p>0.05) (Table 1).

Discussion and Conclusion

In our study of patients with breast cancer and healthy controls who were studied for adiponectin 45T/G and 276T/G gene polymorphisms in East Marmara Region, we discovered that these genes did not pose a risk for patients with breast cancer.

Adipose tissues are a source of energy for the body and also a source for various biologic molecules (9). Adipokines, cytokines, and many mediators such as leptin, adiponectin, visfatin, and apelin have a role in energy metabolism, insulin sensitivity, and in immunologic pathways (9, 10). Secreted by adipose tissues, adiponectin is inversely proportional to body mass index. Decreased adiponectin levels increase insulin resistance in peripheral tissues and the amount of insulin in circulation (11). Increased insulin levels contribute to the development of breast cancer by enhancing the release of vascular endothelial growth factor (VEGF) from breast tissues through insulin-like growth factor (IGF-1) receptors (12). Inversely proportional to adiponectin, increased insulin extends the mitogenic effect of estrogen (13). Furthermore, adiponectin suppresses endothelial cell proliferation and migration, and causes cell death with caspase pathways (14). Adiponectin also inhibits nuclear factor-Kβ activation, which is effective in the development of breast cancer (15). For these reasons, various studies have shown the relationship between decreased adiponectin levels and breast cancer (16, 17). Although the relationship between plasma adiponectin levels and breast cancer in postmenopausal patients has been demonstrated, the relationship between adiponectin levels and cancer in premenopausal women has not been clearly displayed (18-20). There are more studies regarding the effects of adiponectin on tissue levels and adiponectin polymorphism due to the fact that results were different with plasma adiponectin levels (21).

Elevated serum adiponectin levels possess a protective role against breast cancer. The Mediterranean diet, which is high in grains, glycemic control, and exercise increase serum adiponectin levels (22, 23). As for adiponectin gene polymorphism, adiponectin polymorphisms 276 G/T (rs1501299) and 45T/G (rs2241766) showed increased adiponectin levels (24, 25). In an adiponectin gene polymorphism study in patients with breast cancer, an increased adiponectin level and 39% less breast cancer risk in the adiponectin 45T/G (rs2241766) genotype, and a decreased adiponectin level and 59% less breast cancer risk in the adiponectin 276 G/T and GG (rs1501299) genotypes were found (26). However, the age differences between the patient and the control group, and family histories of breast cancer were not analyzed in this study.

Adiponectin 45T/G and 276T/G gene polymorphisms are of gene polymorphisms associated with breast cancer (8, 27, 28). In a study by Al Khaldi et al. (27), the adiponectin gene 45T>G was found more frequently in patients with breast cancer in Kuwait, and the adiponectin gene was considered to predispose for breast cancer. Adiponectin 45T/G and 276 T/G polymorphisms were demonstrated to be associated with breast cancer in a study conducted in India. Mohan Reddi et al. (8) showed 1.7 times more breast cancer risk in 45T/G and 1.6 times more breast cancer risk in 276 T/G in their study, which was not the case in our study. The most extensive study on gene polymorphism in the literature reported no relationship between breast cancer and adiponectin polymorphism (29). Kaklamani et al. (26) detected increased breast cancer risk only in the adiponectin 276 T/G (rs 1501294) of African-American patients in the one-way analysis in their study. On the other hand, there was no difference in the frequency of adiponectin 45 (rs2241766) and 276 (rs1501294) of Hispanic American patients. In a study by Menzaghi et al. (30), weight gain increased and insulin resistance improved in 276 G/T polymorphism, which could be related to high adiponectin levels. In another study conducted in China, it was reported that adiponectin 45 (rs2241766) gene polymorphism had no relationship with any metabolic state (31). Studies on different races in the United States of America (USA) gathered different results of adiponectin and breast cancer (32). Circumstances such as different results of 276G/T polymorphism in different races within the USA, obesity increasing breast cancer in the Caucasian race while decreasing it in Hispanic Americans led to the authors to believe that the relationship between breast cancer and adiponectin could vary in different populations (33, 34). In addition to the findings of adiponectin gene polymorphism from different geographic locations, the adiponectin gene polymorphism results from the Anatolian region in our study did not form a significant relationship.

The role of serum adiponectin in the mechanism of breast cancer, adiponectin gene polymorphism, and adiponectin level in breast tissue still has not been adequately explained. Fibroblast growth factor receptor 2 polymorphism except adiponectin was found significant in breast cancer, whereas there was no significant difference in the literature regarding the Rho-kinase 1 (ROCK1) gene (35, 36). This proves that breast cancer is not only genetic or affected by environmental factors, and it has a much more complex mechanism. This research on the adiponectin gene polymorphism performed for the first time in breast cancer in Turkey is significant in putting forth the related data from Turkey.

Although we aimed to compare the adiponectin gene polymorphisms in patients with breast cancer with those of the control group in our study, not having access to clinical data was a limitation of the study. Unfortunately, this limitation is also apparent in other studies of this subject (26, 37). To better explain the mechanism of breast cancer, it would be beneficial if adiponectin receptor levels in tissue along with gene polymorphism were investigated in further studies the roles of IGF-1 and VEGF were analyzed.

Consequently, despite the fact that adiponectin gene polymorphism is believed to be hormonally and genetically effective in the complex mechanism of breast cancer, there was no relationship found in that regard in our study. Recommendations for further research may include factors of geographic differences, patients' clinical conditions, and the effect of tissue receptors on the role of adiponectin in the mechanism of breast cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from Local Ethics Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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