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*Original Article*

# Polymorphism in the second intron of the *FGFR2* gene rs1219648 associated with the early-onset breast cancer in Turkish population

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**Abstract:** The incidence of early-onset breast cancer has been increased up to 25% in the developing countries. Several studies reported that breast cancer cases in younger women have different biological characteristics than others. These patients should be studied separately. Lack of the necessary information about the younger patients prevents significant improvements about diagnosis and treatment strategies targeting these patients. Polymorphisms within intron 2 of the *FGFR2* gene have been associated with postmenopausal breast cancer patients in many populations. However, there exists no research on the impact of rs1219648 on early-onset breast cancer in Turkish population. In this study, the association of rs1219648 with early-onset breast cancer in Turkish women has been investigated. A total of 171 subjects, including 75 female breast cancer patients who were less than or equal to 40 years of age and 96 age-matched healthy controls were recruited. Our results indicate that G allele of the rs1219648 is statistically correlated with early-onset breast cancer (OR 2.0098, 95% CI 1.3016-3.1032, P=0.002). When rs1219648 was examined as a categorical variable where the reference category related to the wild-type genotype (AA), the calculated OR was [2.112 (95% CI 0.9904-4.5058), P=0.053], and [5.2308 (95% CI 1.9391-14.1102), P=0.001], for genotypes AG and GG, respectively. We present the first report on *FGFR2* rs1219648 polymorphism in early-onset breast cancer in Turkish women. Our results propose that rs1219648 polymorphism individually confers susceptibility for development of early-onset breast cancer in the Turkish populations.

**Keywords:** rs1219648, *FGFR2* gene, early-onset breast cancer, cancer susceptibility, Turkish women

## Introduction

Breast cancer is the primary cause of the death in industrialized countries and has the most noteworthy occurrence of malignancy in women around the world. It was estimated that 1.7 million women were diagnosed with breast cancer as new cases in 2012, and more than 521,900 of these cases resulted with death [1]. In statistical analyses which were performed by T.R Ministry of Health in 2008, it was determined that breast cancer is the most common cancer in women in Turkey. According to the estimation of World Health Organization (WHO) GLOBOCAN 2012 database, the number of new patients with breast cancer will be 19205 in Turkey in 2020 [2].

It is believed that breast cancer cases are associated with genetic and epigenetic alterations. In addition, the incidence of early-onset breast cancer in these cases in the developing countries reached up to 25% [3-6]. Previous studies have shown that early-onset breast cancers have different gene expression profiles [7]. In addition, it has been determined that they have more aggressive features compared to other types of breast cancer [8] and early-onset breast cancers are more unlikely to respond to the treatment [9, 10]. On the other hand, when compared to elder patients, a couple of specific issues such as chemotherapy-related infertility [11], the risk of early menopause [12], recurrence in ones who have had breast-conserving therapy or mastectomy are encountered [13, 14]. This situation reveals that breast cancer cases in young women might have different biological features compared to normal breast cancer cases. Thereby, it is required to understand the pathogenesis of the disease in a bet-

ter way in order to increase the likelihood of success in the treatment of such type of the cancers and develop emergent specific diagnostic and treatment strategies intended for such patients.

Genome-wide association studies (GWAS) is one of the most effective methods used in the detection of new genetic variants which participate in breast cancer within populations with various ethnic groups [15]. Fibroblast growth factor receptor 2 (*FGFR2*) gene is among the first genes which have been determined to be associated with the predisposition for breast cancer in GWAS studies [15-17]. *FGFR2* gene encodes tyrosine-kinase receptor localized into chromosome 10q26, which participates in various cellular events such as cell proliferation, invasion, motility and angiogenesis [18]. Previous studies have demonstrated that polymorphisms detected on the second intron of *FGFR2* gene increase predisposition for breast cancer by increasing FGFR2 gene expression via causing alterations in OCT1, RUNX2 and C/EBPβ transcription-binding affinities [19]. One of the most notable polymorphisms in the second intron of *FGFR2* is rs1219648 (IVS2 ± 7033A> G), which has been studied in postmenopausal breast cancer in details [16]. Studies concerning early-onset breast cancer are quite limited. Therefore, in this study, we aimed to investigate the correlation between rs1219648 polymorphism and early-onset breast cancer cases in Turkey. To our knowledge, this is the first study oriented at the investigation of early-onset breast cancer cases in Turkish population. Revealing the association of rs1219648 polymorphism in the *FGFR2* gene with early-onset breast cancer and setting out the risk factors will enable the development of new strategies and appropriate treatment methods intended for reduction of risk for breast cancer in young individuals.

## Materials and methods

### *Patient features and clinicopathological classification*

A total of 75 patients with breast cancer, who were admitted to Dicle University Faculty of Medicine, Department of Medical Pathology, were included in the study. The control group was comprised of 96 women younger than 40 years of age who did not have history or family history for any type of cancer. The age restriction was applied in patient selection and the ones under 40 years of age, who were diagnosed histopathologically with breast cancer between 2010 and 2015 were included in the study. The age range of the women included in the breast cancer study group was 18-40 years with a mean age of 33.56 ± 5.08 years. The 96 healthy women were at the same age range, in the population with breast cancer patients. All patients and controls were women in the premenopausal period. Required information about patients such as age, type of tumor, estrogen/progesterone receptor status, and Her-2 status was gathered via patient follow-up form. Selected patients and control populations were similar in terms of features like ethnicity and age. Written informed consents were signed by all the participants whose blood samples were collected for genetic testing and this study was approved by Firat University Ethics Committee.

### *DNA isolation*

The DNA isolation from patient's samples was performed from paraffin-embedded tissue blocks using Cobas DNA Sample Preparation Kit FFPET (Roche, USA) in accordance with the instructions of the producing company. However, the DNA isolation was performed from peripheral blood taken from healthy women using Qiamp blood kit (Qiagene). The DNA concentrations and quality were measured spectrophotometrically by using nanodrop (BioDrop ULITE, UK).

### *Determination of* rs1219648 *polymorphism in FGFR2 Gene*

For determination of single nucleotide polymorphism in intron number 2 (rs1219648) of the *FGFR2* gene, the DNA obtained from both tissue samples of 75 patients with breast cancer and 96 individuals in the control group were genotyped by using hybridization probe system (TIB MOLBIOL, Germany) on LightCycler 480 device (Roche Diagnostics, Penzberg, Germany). 15 µl reaction mixture containing 1.6 µl (3 mM) $MgCl_2$, 10.4 µl DNaz-free water, 1.0 µl reagentmix (lightSNiP), 2.0 µl FastStart DNA master and 5 µl DNA (50 ng), totally 20 µl volume, were inserted in 96 well LC 480 plates

**Table 1.** Sociodemographic and tumor characteristics of patients

| Variables | Total patients (n)=75 | Percent (%) |
|---|---|---|
| Tumor size | | |
| ≤2 cm | 21 | 28 |
| >2 cm to ≤5 cm | 34 | 45.3 |
| >5 cm | 20 | 26.6 |
| Grade | | |
| 1 | 12 | 16 |
| 2 | 36 | 48 |
| 3 | 27 | 36 |
| Node Status | | |
| Negative | 35 | 46.6 |
| Positive | 40 | 53.3 |
| Menopausal status | | |
| Pre-menopausal | 75 | 100 |
| Post-menopausal | 0 | 0 |

Due to missing values, percentages may not be totally 100%.

(Roche Diagnostics). The PCR reaction was performed via LightCycler 480 II under following conditions: Initial denaturation at 95°C for 10 min, followed by 45 cycles at 95°C for 10 sec, at 60°C for 10 sec, at 72°C for 15 sec and followed by one cycle each at 95°C for 30 sec, at 40°C for 2 min and cooling from 75°C to 40°C. The isolated DNAs were assayed with melting curve analysis. The melting curve analysis was performed by LightCycler 480 software in LightCycler 480 II. After dissociation curves were normalized, normal and mutant genotypes in patients and controls were determined by evaluating temperature deviations.

*Statistical analysis*

All statistical tests were performed with SPSS for Windows computing program, Version 16 (SPSS Inc. Chicago IL USA). Compliance of genetic distribution to Hardy-Weinberg equilibrium was analyzed with the chi-square test. The differences in the genotypic distributions among patients and controls were evaluated with the chi-square test. *P* values<0.05 were considered to be statistically significant. Unconditional logistic regression was used to calculate odds ratio (OR) and a 95% confidence interval (CI) as an estimate of the relative risk for the alleles and genotypes.

## Result

The *FGFR2* rs1219648 polymorphism has been successfully determined by real-time PCR in all patients and controls. The sociodemographic and tumor characteristics of the patients are summarised in **Table 1**. The genotype frequencies of the rs1219648 polymorphism in controls and patients were coherent with the expectation under Hardy-Weinberg equilibrium (*P*=0.1275 and *P*=0.2608 respectively). We detected all 3 genotypes in our groups. The frequencies of AA, AG, and GG genotypes were 35.4% (34), 54.2% (52) and 10.4% (10), respectively, in the healthy controls, and 17.3% (13), 56% (42) and 26.7% (20) respectively, in the patients (**Table 2**). Our result indicated that the rs1219648 polymorphism in the *FGFR2* gene was statistically associated with the risk of early-onset breast cancer in eastern Turkey (P<0.05) and according to the **Table 2**, G allele of the rs1219648 was strongly prominent in the breast cancer patients (OR: 2.0098, 95% CI 1.3016-3.1032, P=0.002). The rs1219648 was examined as a categorical variable related to the wild-type genotype (AA). The calculated OR was 2.1124 (95% CI 0.9904-4.5058), *P*=0.053, and 5.2308 (95% CI 1.9391-14.1102), *P*=0.001, for genotypes AG and GG, respectively (**Table 2**). Notably, GG genotype was more pronounced in the patients group than in the control group and it was statistically significant when compared with AA + AG genotype (*P*=0.006).

We have also examined the pathological characteristics of GG and AG + AA genotype groups in the premenopausal cancer patients to figure out whether early-onset breast cancer genetic risk factors are linked to the tumors with specific intrinsic subtypes (estrogen receptor status, progesterone receptor status, and HER-2 status), which may enable a way for developing individual prevention and improving early detection methods. However, there was no meaningful correlation between estrogen receptor status, progesterone receptor status and HER-2 status determined among breast cancer patients utilized in this study (**Table 3**).

## Discussion

The role of genetic factors in the development of breast cancer is well-documented. Among these genes, *FGFR2*, belonging to the family of

**Table 2.** Genotypes, allele frequencies, OR, 95% CI (in parentheses) and *p* values of *FGFR2* (rs1219648) in early-onset breast cancer and controls

| Genotype | Patients (n)=75 | % | Controls (n)=96 | % | #OR (95% CI) | *p value |
|---|---|---|---|---|---|---|
| GG | 20 | 26.7 | 10 | 10.4 | 5.2308 (1.9391-14.1102) | 0.001 |
| AG | 42 | 56 | 52 | 54.2 | 2.1124 (0.9904-4.5058) | 0.053 |
| AA | 13 | 17.3 | 34 | 35.4 | Reference | - |
| Alleles | | | | | | |
| G | 82 | 54.7 | 72 | 37.5 | 2.0098 (1.3016-3.1032) | 0.002 |
| A | 68 | 45.3 | 120 | 62.5 | Reference | - |

**p*-value was obtained by chi-square test. #Odds ratio for genotype was calculated as selected genotype vs. Other genotypes. OR indicates crude odds ratio.

**Table 3.** The pathological characteristics of GG and AG + AA genotype groups in early-onset breast cancer patients

| | GG | AG + AA | *p value |
|---|---|---|---|
| Estrogen receptor (ER) status | | | |
| ER (+) | 13 (19.7%) | 24 (36.3%) | 0.11 |
| ER (-) | 5 (7.6%) | 24 (36.3%) | |
| Progesterone receptor (PgR) status | | | |
| PgR (+) | 12 (18.2%) | 21 (31.8%) | 0.10 |
| PgR (-) | 6 (9%) | 27 (41%) | |
| HER-2 status | | | |
| HER-2 (+) | 13 (19.7%) | 23 (34.8%) | 0.08 |
| HER-2 (-) | 5 (7.6%) | 25 (37.9%) | |

Due to missing values, percentages may not be totally 100%. **p*-value was obtained by chi-square test.

fibroblast growth factor receptors and involved in mammary gland development, has been identified as a prominent candidate in breast cancer [20]. As transmembrane catalytic receptors, FGFRs display intracellular tyrosine kinase activity. A cascade of downstream signals is activated when these receptors interact with the mitogenic ligand FGFs, with significant implications for various processes including angiogenesis, wound healing, cell migration, neural outgrowth, and embryonic development [21]. There is ample support for both the pro- and anti-oncogenic effects exerted by *FGFR2* according to context [18, 22, 23]. A proportion of 5-10% of cases of human breast tumors is associated with over-expression or amplification of the *FGFR2* gene [24, 25]. The genetic variations of this gene constitute a risk factor for breast cancer, aside from being involved in regulating the amplification and expression of the gene. The findings of a genome-wide association study suggested a close correlation between fourSNPs,especiallyrs1219648 SNP ($p=1.1 \times 10^{-10}$), in intron 2 of *FGFR2* and breast cancer [16]. Similarly, the risk of breast cancer was notably correlated with every one of the four SNPs examined by Raskin et al. in *FGFR2* ($P<0.0001$). It is believed that a considerable proportion of breast cancer in Arab (12%), Ashkenazi (15%) and Sephardi Jewish (22%) populations are caused by genetic variation in *FGFR2* rs1219648 [26]. In particular, this SNP has been related to breast cancer development in women who have gone through menopause. On the other hand, the influence of rs1219648 on early-onset breast cancer has not been extensively investigated. Whereas the association between rs1219648 and breast cancer in women who have not gone through menopause has not been confirmed by Chuan-Lian Liu et al. [27], rs1219648 was found to be related to premenopausal breast cancer by different studies conducted on Chinese Han women by Fangmeng Fu et al., [28] and on *Iranian Azeri population* by Zahra Saadatian et al. [29]. The present study is the first to distinguish the correlation between *FGFR2* rs1219648 variant and early-onset breast cancer in women living in Turkey. According to the findings obtained, there is a significant relationship between the *FGFR2* rs1219648 polymorphism and the heightened risk of women younger than 40 years of age developing breast cancer. However, the clinical pathology data suggest that there is no significant correlation between *FGFR2* rs1219648 polymorphism and the estrogen receptor, progesterone receptor, HER-2 receptor status. The clinical characteristics of some patients were inaccessible. A larger-scale study should be propelled to affirm these discoveries and to investigate the relationship between the

estrogen receptor status, progesterone receptor status, and HER-2 receptor status with the polymorphism of *FGFR2* rs1219648 on early-onset breast cancer.

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## Disclosure of conflict of interest

None.

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