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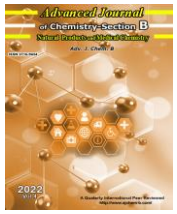

*Original Research Article*

# Relationship between FGFR2 Gene RS2981582 Polymorphism and Breast Cancer Risk Factors in Women Candidates for Surgery

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**ABSTRACT**

**Introduction:** Increased expression of fibroblast growth factor receptor increases the downstream signal. Therefore, the pathways involved in cell proliferation, differentiation, inhibition of apoptosis, and migration are activated. In this study, the relationship between single nucleotide polymorphism rs2981582 of fibroblast growth factor receptor 2 gene and its relationship with breast cancer was studied.

**Procedure:** Five cc of peripheral blood were collected in EDTA tubes. The samples were transferred to -20 °C freezer and kept at this temperature until DNA extraction. Iriazol kit was used for DNA extraction in this study. Extraction was performed according to the protocol of the kit. Determining the quality and also the concentration of extracted DNA was carried out through a spectrophotometer and electrophoresis of the samples on a 1% agarose gel. The samples were genotyped by RFLP-PCR method and AciI restriction enzyme at rs2981582 C/T position.

**Results:** There is a significant relationship between TT genotype and disease. On the other hand, due to the higher frequency of the CC genotype in the control group, this genotype probably has a protective effect on contracting the disease. Likewise, the risk of breast cancer in patients carrying CT+TT genotypes was about three times.

**Conclusion:** Genetic changes in some genes can increase the sensitivity to breast cancer. Concerning the significance of rs2981582 single nucleotide polymorphism in relation to breast cancer, this single nucleotide polymorphism can be used as a biomarker to predict breast cancer.

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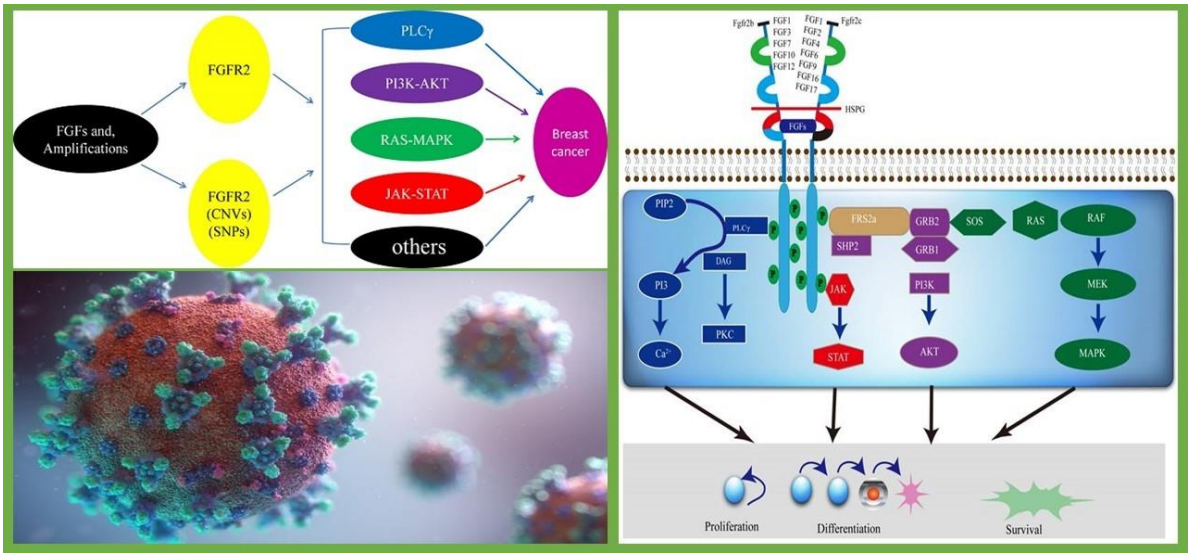
**GRAPHICAL ABSTRACT**




## Introduction

Breast cancer is the most common type of cancer and the leading cause of cancer-related deaths in women worldwide, accounting for 23% of cancers and 400,000 deaths annually [1-3]. The prevalence of breast cancer is about one third of all women's cancers and it is the second most common cancer after lung cancer and the most common cause of cancer death among women [4-6]. According to the statistics of the national cancer center of Iran, during a survey in the period of 2000-2010, 52,167 patients with breast cancer were identified, of which ۷.۹۱% were women [7-9]. According to the research conducted in Central Province between 2015-2015, among the most common cancers in the province, breast cancer was ranked first, followed by skin cancer among the most common cancers [10-12]. Cancer includes a group of diseases whose main feature is unregulated cell growth, invasion, and spread of cells from their original location to the other parts of the body [13-15]. Breast cancer occurs as a result of the accumulation of genetic damage in the epithelial cells of the milk-producing tissue and acquisition of malignant phenotypes by these cells. Age, reproductive factors, personal or family history of breast diseases, genetic background, and environmental factors are associated with increased risk of breast cancer [16-19]. In more than half of breast cancer cases, lifestyle, and the role of environmental factors are important in causing the disease. Different fibroblast growth factors and their related receptors have tissue-specific expression [20-22]. The tissue-specific expression pattern and differentiation in binding indicate specific receptor-ligand interactions [23]. This property is further set by trimming. Receptors are normally expressed in tissues and play a role in cell growth, differentiation, and development of a number of tissues, including breast and kidney (Figure 1). This receptor family has four members. Four genes are identified in different chromosomal positions that encode proteins similar to the fibroblast growth factor receptor family [24]. Fibroblast growth factor receptors play a role in carcinogenesis and have been investigated in recent research for medicinal purposes in breast cancer and cause malignancies and tumor proliferation through several mechanisms. In most cases, gene duplication, increased expression, or mutation of

tyrosine kinase receptors cause cancer. With a change in the level of fibroblast growth factor receptors, expression increases due to point mutation or different splicing changes the fibroblast growth factor receptor signal and has been identified in various human tumors [25]. For example, increased expression of the fibroblast growth factor receptor has been observed in a number of tissues including breast, prostate, melanoma, and thyroid. Fibroblastic growth factor receptor is a tyrosine kinase receptor that plays an important role in cell growth and differentiation. The structure of these receptors has an extracellular ligand-binding domain, a membrane-passing domain, and an intracellular tyrosine kinase domain by binding fibroblast growth factors to the receptor and receptor dimerization; several downstream signaling pathways are activated [26-28]. The most important activated pathways are RAS-MAPK (RAS-mitogen activated protein kinase), PI3K, and (Phosphoinositide 3-kinase), which activate transcription factors by transmitting signals [29-31].

The combination of fibroblast growth factor receptor, fibroblast growth factor, and adapter proteins create a complex signaling network that plays essential roles in development, organogenesis, cell differentiation, angiogenesis, and tumor progression [32-34]. Based on GWA studies, fibroblast growth factor receptor 2 gene has been proposed as a susceptibility gene in breast cancer. Single nucleotide polymorphisms play an important role in medical genetics and are mainly used in association studies in many cancers. Several single nucleotide polymorphisms in the intron 2 region of the fibroblast growth factor receptor gene have been found to be significantly associated with the risk of breast cancer [35-37].

The intron 2 sequence in the fibroblast growth factor receptor gene is a regulatory region. Single nucleotide polymorphisms change the binding sites of transcription factors, and thus regulate the expression level of fibroblast growth factor receptor [38-40]. The difference in binding affinity of transcription factors increases the expression of fibroblast growth factor receptor with high-risk alleles. Increased expression of fibroblast growth factor receptor increases the downstream signal. Therefore, the pathways involved in cell proliferation, differentiation, inhibition of apoptosis, and migration are activated. In this study, the relationship between single nucleotide polymorphism rs2981582 of the fibroblast growth factor receptor gene and its relationship with breast cancer was studied [42-44].

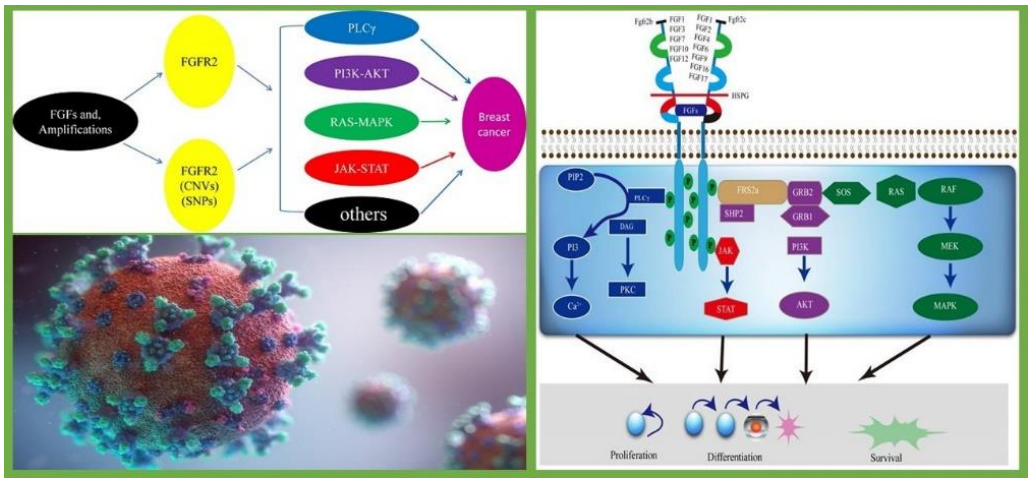



**Figure 1.** Fibroblast growth factor receptor 2 signaling in breast cancer

## Method

Blood samples were taken from 80 patients and 80 healthy people by completing written consent. Five cc of peripheral blood were collected in EDTA tubes. The samples were transferred to -20 °C freezer and kept at this temperature until DNA extraction.

### DNA extraction and genotyping of rs2981582

Iriazol Kit (Rena Biotechnologists) was used for DNA extraction in this study. Extraction was performed according to the kit protocol. Determining the quality and also the concentration of the extracted DNA was done through a spectrophotometer and electrophoresis of the samples on a 1% agarose gel. The samples were genotyped by RFLP-PCR method and AciI restriction enzyme at rs2981582 C/T position. In this technique, both pair of forward and reverse primers were used to amplify the fragment containing the desired polymorphism. Before performing the polymerase chain reaction, the primers were autoclaved in a certain volume of double distilled water, dissolved, and diluted one to ten in double distilled water. In this reaction, depending on the number of samples, a mixture of PCR reaction components including 15.6 microliters of distilled water, 4.0 microliters of F and R primers, 5.0 microliters of Mgcl2, 4.0 microliters of dntp, 5.2 microliters of buffer, and 2.0 A microliter of Taq enzyme was prepared in a 5/1 microtube. After preparing the mother master mix, twenty microliters of it were added to each of tubes containing five microliters of DNA so that the total volume of the reaction mixture in each tube reached 25 microliters. The target fragment is subjected to initial annealing at 94 °C for five minutes, annealing at 94 °C for 30 seconds, binding of primers at 56 °C for 30 seconds, extension or amplification at 72 °C for 30 seconds, and the final extension step was performed at 72 degrees for ten minutes. The intended amplification product was a fragment of 251 bp. After confirming the correctness of the amplification band size by electrophoresis on 2% agarose gel, the PCR products were subjected to enzymatic digestion by AciI enzyme. This reaction was carried out in a final volume of fifteen microliters, including 2.0 microliters of restriction enzyme, 5.1 microliters of buffer with enzyme, 3.8 microliters of distilled water and five microliters of PCR product at 37 °C for eight hours. Then, the resulting products were electrophoresed on a 3% electrophoresis gel. The amplified fragment has two cutting sites for the desired enzyme, only one of which is related to the desired polymorphism. If the C allele (wild) is present, the cutting is done, but if the T allele (mutant) is present, the cutting is not done. In this experimental control study, chi-square test with 95% confidence interval was used by SPSS version 19 software. Furthermore, association between disease and genotypes was calculated using odds ratio. The significance level (P-value) was considered less than 0.05.

## Results

Based on the calculations, there is a significant relationship between TT genotype and disease. On the other hand, due to the higher frequency of the CC genotype in control group, this genotype probably has a protective effect on contracting the disease. Moreover, the risk of breast cancer in patients carrying CT+TT genotypes was about three times. According to the demographic information of subjects of this study, the average age of patients was fifty and the average age of control group was forty years old. The results of examining the age factor of two groups showed that there is a significant relationship between age and breast cancer. Examining the family history of breast cancer between both groups further showed a significant relationship between this factor and getting the disease, but examining factors such as marital status or the use of birth control pills in the two groups did not

indicate any significant relationship with breast cancer.

## Discussion

Breast cancer is the most common type of cancer and the leading cause of cancer-related death in women worldwide. In Iran, this type of cancer has a high prevalence among women. Genetic factors and people's lifestyle play a role in the risk of breast cancer. The role of genetic factors in developing breast cancer is well-established [45-47]. Among these genes, the fibroblast growth factor receptor gene, which belongs to the family of fibroblast growth factor receptors and is involved in the growth and development of mammary gland, is known as a prominent candidate in breast cancer [48-50]. This receptor is involved in several processes including cell proliferation, angiogenesis, and migration. About 5-10% of breast tumors are related to overexpression or amplification of fibroblast growth factor receptor gene. Genetic variants of this gene are further considered as a risk factor for breast cancer. In the present study, the effect of rs2981582 polymorphism in 80 patients and the same number of controls on the risk of breast cancer was investigated, statistical calculations showed a significant relationship between this polymorphism and the disease [51-53]. In this study, it was found that the T allele of this single nucleotide polymorphism is present in sick people with a higher frequency than in healthy people, and the minor heterozygous genotype (TT) was associated with the disease. On the other hand, C allele has a protective effect on contracting the disease. In addition, people with at least one T allele in their genotype (CT+TT) are almost three times more likely to develop breast cancer [54-56]. Based on the results of a study, a significant relationship was observed between the T allele of this polymorphism and cancer risk. A study was conducted to investigate the polymorphism of rs2981582 and after obtaining the results, they realized that there is a relationship between this polymorphism and the risk of breast cancer. Also, in 2013, Liu *et al.* investigated the polymorphism of rs2981582 along with three other polymorphisms of fibroblast growth factor receptor gene and concluded that there is a significant relationship between rs2981582 and the risk of breast cancer. In fact, the rs2981582 polymorphism, which is located upstream of intron2, the fibroblast growth factor receptor gene, demonstrates a strong relationship with breast cancer, and the minor allele of this polymorphism (T) in cancer cells and tumors increases the expression of fibroblast growth factor receptor [57-59]. Also, according to Meier *et al.*'s study in 2008, rs2981582 polymorphism is important in breast cancer. Meier *et al.* showed that the minor allele haplotype rs2981582 causes more transcription of the fibroblast growth factor receptor gene in tumor and cell lines and this increased expression increases the risk of breast cancer. The polymorphic region of rs2981582 is located in the binding site of the estrogen receptor, and it is possible that breast cancer manifests more in $ER^+$ than $ER^-$. All these results are consistent with the results obtained in the study and suggest this single nucleotide polymorphism as a sensitive genetic marker for breast cancer. In fact, studies on the expression of fibroblast growth factor receptor gene showed that in cells with minor haplotypes, the level of expression of the fibroblast growth factor receptor gene increases. Because the transcription factors oct1/runx2 and C/EBPβ (proteinβCCAAT/enhancer binding) bind to the minor homozygous allele in intron region with a higher affinity and cause the expression of fibroblast growth factor receptor gene, increasing the expression of fibroblast growth factor receptor gene increases the risk of developing increases breast cancer. There are other studies that did not find a significant relationship between this single nucleotide polymorphism and the risk of breast cancer in the studied population, such as Ozgoz *et al.*'s study in

2013 that examined the rs2981582 polymorphism. In this study, 61 people with breast cancer and 50 healthy people were genotyped by sequencing technique. Based on the calculations, no significant relationship was observed between rs2981582 polymorphism and the risk of breast cancer [60]. Besides, it was found that the frequency of CT genotype and T allele in the patient group is higher than in the control group, and the authors stated that CT genotype and T allele can be related to breast cancer.

Likewise, in 2016, Pan *et al.* conducted a study to investigate the rs2981582 snip on 340 patients and 400 healthy individuals from Chinese population, and the results revealed no significant relationship between this polymorphism and increased risk of breast cancer. In this study, variables such as age, family history, education, and low age at the onset of menstruation were also associated with breast cancer [61-63].

With increasing age, the probability of getting the disease increases and having a family history of breast cancer is effective in getting the disease [64-66]. On the other hand, the increase in the educational level of people at the community level has made people more aware of their health status, and people with university education have more self-awareness and desire to find breast cancer symptoms, risk factors, breast self-examination and the early diagnostic methods than others [67].

## Conclusion

Breast epithelial malignancies are among the most common causes of cancer in women. Due to the improvement of treatment and diagnosis methods in the earlier stages, the death rate due to breast cancer has decreased to a great extent. In addition to the environmental factors, genetic factors are also very important. Genetic changes in some genes can increase susceptibility to this disease. Concerning the significance of rs2981582 single nucleotide polymorphism in relation to breast cancer, this single nucleotide polymorphism can be used as a biomarker to predict breast cancer.

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