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Evaluation of FGFR2 gene polymorphism in women with breast cancer

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Abstract

Breast cancer (BC) is one of the most frequent cancers among women worldwide. It is a complex polygenic disorder that genetic factors play an important role in disease etiology. The highly significant association of the Fibroblast growth factor receptor 2 (FGFR2) locus with breast cancer risk has been replicated in multiple genome association study; however, it's mechanism of action remains unclear. The aim of this study was to investigate whether the single nucleotide polymorphism (SNP) C-906T within intron 2 of FGFR2 is responsible for susceptibility to breast cancer. This case–control study included 108 breast cancer cases and 108 cancer–free controls. The prevalence of genotype frequencies of the FGFR2 *CC/CT/TT* was 5.5%, 90.7% and 3.7%, respectively, in cancer cases. Among controls, the distribution of *CC*, *CT* and *TT* genotype was 48.14%, 47.66% and 10.18% respectively. Significant differences in allele and genotype distribution among controls and patients were found (OR, 18.87 95% CI, 7.55-47.16; $p = 0.0001$). The results from this study suggest that the FGFR2 C-906T polymorphism may be associated to breast cancer in population studied. Well-designed studies with larger sample sizes are needed to confirm the role of FGFR2 SNP in breast cancer risk.

Key words: Breast Cancer, FGFR2, Single Nucleotide Polymorphism.

Introduction

Breast cancer (BC) is considered the most commonly occurring cancer among women on the globe, comprising 23% of all cancers and 400,000 deaths annually. Several common genetic susceptibility variants have been identified, predominantly by genome-wide association studies (GWAS). Over 40 common low-penetrance variants in 25 loci, such as *FGFR2*, *LSP1*, *MAP3K1*, *TOX3*, *MRPS30*, *COX 11* and *SLC4A7*, have been reported which might be associated with the breast cancer risk (1). Even more telling, a number of these SNPs along with other risk factors have turned out to be associated with estrogen receptor (ER)-positive and ER-negative disease (2). By far the most strongly associated SNPs are located in intron 2 of *FGFR2* gene at 10q26.13 (rs2981582) (Fig. 1) and near the 5' end of the *TOX3* gene at 16q12.1 (rs3803662) (3). Fibroblast growth factor receptor type 2 (FGFR2) is one of five fibroblast growth factor receptors known in humans and involves in numerous signaling pathways that regulate processes such as cell growth, apoptosis and differentiation (4). FGFR2 and its signaling pathway are reported to be activated in many cancers due to gene amplification and point mutation. In addition, FGFR2 is a potential therapeutic molecular target in FGFR2 activation-associated cancers (5). FGFR2 has been identified in terminal end buds during mammary gland development. Having nuclear localization in breast tissue, this receptor is suggested to play a crucial role in breast development (6). Although the FGFR2 being nuclear localized in a number of breast cancers and cancer related contexts is obvious, it is mostly referred to as a cell surface receptor (7). There are two isoforms FGFR2-IIIb and FGFR2-IIIc, which come out of mutually alternative splicing event at the mRNA level. FGFR2 IIIb binds specifically to FGF-1, 3, 7, 10, while IIIc binds to FGF-1, 2, and 9 (8). Shifting from the IIIb to IIIc isoform in tumor cells followed by activation of the receptor by other FGFs has been reported in a few breast cancer cell lines (9). Downregulation of FGFR2 protein has been reported in up to 67% of breast tumors (10). The amplification of FGFR2 and upregulation of FGFR2 mRNA expression have been reported in less than 10% of breast tumors (9), which suggests that progression of breast tumor is more probable due to underexpression of FGFR2. Closely linked to estrogen receptor-positive or progesterone receptor-positive cancer (11), SNPs within intron 2 of *FGFR2* gene have been found to be possibly associated with breast cancer in a hormone-dependent manner. For several years, great effort has been devoted to the study of FGFR2 (C-906T) in breast cancer. However, there are contradictory findings about the association between FGFR2 (C-906T) and high risk of breast cancer. For example, in a study by Samason et al. there was no significant association between the SNP (C-906T) and susceptibility to breast cancer, while having the association has been underpinned in studies by Easton et al. and Hunter et al. (12, 13). In addition, the mechanism of mammary carcinogenesis for FGFR2 (C-906T) remains unclear. This study particularly aims at investigating the possible association between SNP within intron2 of FGFR2 and breast cancer.

Materials and methods

Subjects

The present research considered 108 women with breast cancer and 108 women as controls. Controls and patients were selected from the same population living

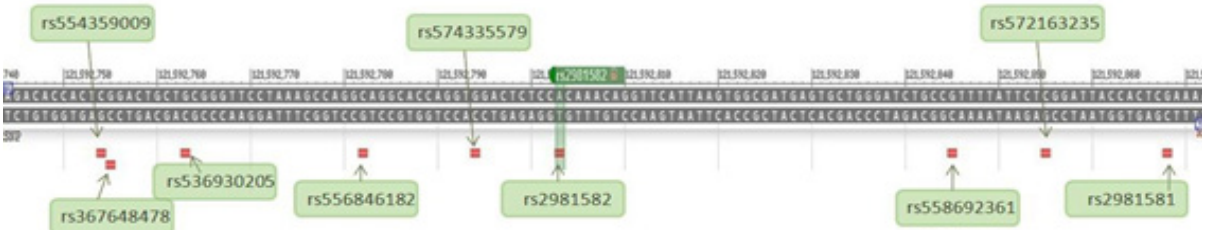

Figure 1. rs2981582 location in the genome. There are several SNPs in *FGFR2*. rs2981582 was located in intron 2.

in Guilan province, north of Iran and including unrelated subjects. Informed consent was obtained from all individual. All breast cancer cases were newly diagnosed and histopathologically confirmed. Data or patient characteristics at the study entry for each subjects was collected from Razi Hospital (Rasht, Iran) between October and December 2013. Clinical and laboratory data including age, age at diagnosis, family history, clinical stage and life style were obtained from medical records at the time of enrolment. This study was performed in accordance with the declaration of Helsinki.

DNA extraction

Blood samples were collected in vacutainer tubes containing EDTA for DNA extraction at 4°C and centrifuged at 2800 rpm for 10 min. Then the genomic DNA was extracted from 200µl of blood using the GPP solution DNA extraction kit (Genpajoohan, Iran) according to the manufacturer's instruction. DNA purity and concentration were determined by spectrophotometric measurement of absorbance at 260 and 280 nm by UV spectrophotometer. The extracted DNA sample was placed into a 1.5ml micro-centrifugal tube and stored at -80°C.

Genotyping

To analyze the C-906T polymorphism, we amplified a region of the *FGFR2* gene by Amplification Refractory Mutation System PCR (ARMS–PCR) with two forward primers 5́-ATCGCCACTTAATGAACCTGTTTGC-3́ and 5́-ATCGCCACTTAATGAACCTGTTTGT-3́ and a common reverse primer 5́-AGTGTGCTGTTCATTCACCCC-3́ (BIONEER, Republic of Korea), which were designed using primer analysis software (Version 7.54, Molecular Biology Insights Inc., Cascade, Co, USA). Reactions were performed using 22 µl volume containing 20 ng of genomic DNA, 12 pmol each of primers, 1X PCR buffer, 1.5 nM $MgCl_2$, 0.2 mM dNTPs, and 1.5U Taq DNA polymerase (Bioflux, Japan). PCR cycle conditions consisted of an initial denaturation step of 95°C for 5 min followed by 34 cycles of 45s at 95C, 1min at 64°C, 45s at 72°C, and a final elongation at 72°C for 5 min. The PCR products were electrophoresed in 2% agarose gel and were visualized under UV illumination. A random of 20% of the samples was regenotyped by another laboratory member to improve the quality of genotyping and its validity and no discrepancy in genotyping was found.

Statistical analysis

The differences in the means of variables between the cases and controls were analysed using the t-test by MedCalc statistical software (version 12.1.4.0). The risk of endometriosis was estimated with odds ratio (OR) and 95% confidence intervals (95%) using unconditional logistic regression models. A p value<0.05 was considered statistically significant.

Results

In this case-control study, a total of 108 patients diagnosed with breast cancer and an equal number of controls enrolled. Healthy controls had no history of breast cancer. The breast cancer patients' ages ranged between 30 and 65 years, and for healthy controls it ranged between 28 and 68 years. We examined the C-906T polymorphism distribution in FGFR2 gene by ARMS-PCR among breast cancer patients and control subjects (Fig. 2). Table1 presents C-906T genotype and allele frequencies for breast cancer cases and control groups. Our results showed distribution of C-906T genotype to be significantly associated with breast cancer. We observed a considerably higher frequency of *CC* genotype (48.14%) in controls compared with that of patients (5.5%). Similarly, the frequency of the *CT* genotype (90.7%) among healthy participants was greater than that of patients (47.66%). The results, however, indicated a significant fall in *TT* genotype frequencies (3.7%) for patients when compared with controls (10.18%). The allele frequencies of C and T alleles were 0.68 and 0.31 in controls and 0.5 and 0.49 in patients, respectively.

Discussion

The incidence and overall mortality rates of breast cancer continue to be lower than that of most high income countries, while fatality rates are very high. For Iranian people, breast cancer is the most typical cancer among women (14). Different pathogenic mechanisms have been suggested to be involved in the development of breast cancer. Further, besides environmental factors, the genetic background of an individual may contribute

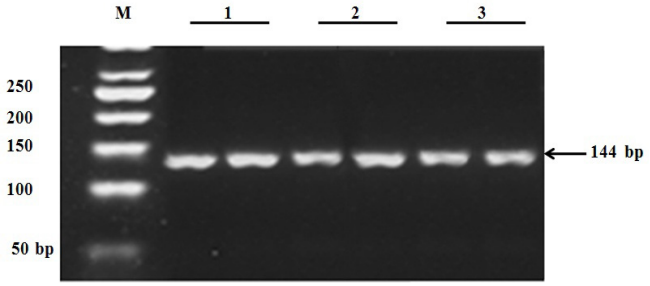

Figure 2. Detection of FGFR2 (C-906T) polymorphism by ARMS-PCR. The ethidium bromide-stained 2% agarose gel used for genotyping is shown. Lane: (M), 50 bp molecular weight marker shown in the left part of gel; (1), fragments presenting the C allele for three heterozygous patients; (2), fragments indicating the T allele for the same three heterozygous patients.

Table 1. Genotype and allele distribution of FGFR2 SNPC-906T polymorphism in patients and controls.

Genotype	Cases n (%)	Controls n (%)	OR	95% CI	*P* value
C/C	6(5.5%)	52(48.14%)	1.00	Ref	-
C/T	98(90.7%)	45(47.66%)	18.87	7.55-47.16	0.0001
T/T	4(3.7%)	11(10.18%)	3.15	0.75-13.07	0.2234
Allele					
C	110(50%)	149(68%)	1.00	Ref	-
T	106(49%)	67(31%)	2.14	1.44-3.17	0.0002

to the development and final outcome of breast cancer. Thus, research into the risk factors of breast cancer is very important to understand and address trends of the disease in Iran and subsequently implementing the proper population specific interventions. In researches carried out by GWAS, SNP haplotypes in intron 2 of FGFR2 were indicated as risk factors for the development of breast cancer (15, 16). The potential effects of these FGFR2 variants were revealed to be due to differential expression of *FGFR2* in relation to intron 2 SNPs (9). These single nucleotide polymorphisms also were postulated to result in differential binding of cis-regulatory elements, such as transcription factors (17). There are several other SNPs in gene regulatory regions that have been associated with variation in enzyme levels and human diseases. The SNP (1323 T > C) in promoter region of the G-substrate gene (GSBS) correlates with hypercholesterolemia. The UGT1A1 gene has a TATA box polymorphism that reduces expression of UGT1A1, leading to Gilbert's syndrome. (18). However, despite the above-mentioned explanations for the association of *FGFR2* SNPs with the risk of breast cancer, the exact mechanism of breast carcinogenesis for these SNPs remains unclear. This study was powered to detect the association of C-906T polymorphism with breast cancer. To the best of our knowledge, this may be the first report of demonstrating the association of *FGFR2* C-906T with breast cancer among women in northern part of Iran. The most obvious finding resulting from this study is the lower frequency of *CC* genotypes in women with breast cancer (5.5%) compared with controls (48.14%). Results from a study by Ozgöz et al. in 766 cases and 665 healthy individuals of Turkish community, however, didn't support our findings mentioned earlier (13). Several studies performed in different populations indicated higher number of individuals carrying *CT* genotype of C-906T in breast cancer groups than that of controls (6, 13, 19). Our results are consistent with Boyarskikh et al. (19) findings of *CT* genotype in Siberia, Russian Federation being at high frequencies among breast cancer patients (90.7%) when compared with controls (47.66%). Supported by the results from Liang et al. in Chinese women population (6), the data obtained shows a higher proportion of patients with T allele (49%) than that of controls (31%). Besides a strong association found between FGFR2 C-906T and breast cancer, the contribution of other polymorphisms within intron 2 region of this gene was confirmed, with different degrees of risk, by data from several studies. Raskin et al. showed that four SNPs (rs11200014, rs2981579, rs1219648 and rs2420946) were associated with increased risk of breast cancer in Ashkenazi and Sephardi Jews (20). Moreover, in a study by Siddiqu et al., the variant genotypes rs2981578A/G and rs7895676T/C of FGFR2 were noted to increase the breast cancer susceptibility in North Indian women (21). These disparate findings may be due partly to insufficient power, phenotypic heterogeneity, population stratification, small effect of the polymorphism on breast cancer risk and publication biases. Thus more studies are required to clarify these variations.

This analysis suggests that *FGFR2* (C-906T) polymorphism may be associated with breast cancer susceptibility among women of northern Iran. This SNP is recommend to be included in future association studies and functional assays. It is known that the pathogenesis of breast cancer is complex and polygenic in the vast majority of patients, with several genes, each with small to moderate effect, acting individually, together or in association with important environmental determinants. Further studies of *FGFR2* are needed to understand the role of *FGFR* gene polymorphisms in the development of breast cancer.

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