

Association of Fibroblast Growth Factor Receptor Gene (FGFR2) Polymorphism (rs2981582) and its Expression with Breast Cancer

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ABSTRACT

The association between Fibroblast Growth Factor Receptor 2 (FGFR2) gene polymorphism and expression with breast cancer varies with ethnicity and geographical distribution. Several studies have been conducted with different genotypes of this particular gene polymorphism among various ethnicities throughout the world. The main purpose of this study was to evaluate the relationship between FGFR2 (rs2981582) gene polymorphism and FGFR2 gene expression with breast cancer in Indian women and also to establish the relative gene expression with different genotypes of the polymorphism, if there is any. Method: A total of 75 cases were selected, out of which 25 were malignant cases, 25 healthy controls and 25 benign cases. Restriction Fragment Length Polymorphism Polymerase Chain Reaction (RFLP PCR) was used to determine FGFR2 Single Nucleotide Polymorphism and Real Time Quantitative Polymerase Chain Reaction (RT qPCR) for FGFR2 gene expression. The strength of association was estimated using Odds Ratios (ORs) and 95% Confidence Intervals (CIs). RESULTS: Our results showed that FGFR2 (rs2981582) polymorphism is not significantly associated with breast cancer in Indian women. However, FGFR2 gene expression is significantly increased in breast cancer but the differential gene expression associated with different genotypes (TT / TC / CC) is not significant in both malignant and benign cases. Therefore, we conclude from this study that FGFR2 rs2981582 SNP does not influence the expression of FGFR2 in this population.

Introduction

Breast Cancer (BC) is one of the most common malignant tumors among women all over the world and has the highest mortality rate amongst the cancers afflicting women [1]. In recent years, its incidence has increased among young women with increasing

tendency of chemo-resistance and recurrence [2,3]. Genetic factors such as BRCA1, BRCA2, HER2, CyclinD1, MAP3K1, FGFR2, TOX3, etc play a major role in etiopathogenesis of breast cancer [4]. Lots of researchers have reported the association between

FGFR2 polymorphism and BC risk [5-7]. FGFRs mediate signaling of fibroblast growth factors (FGFs) and have numerous important functions [8]. FGFR2 gene is located at chromosome 10q26 and acts through multiple downstream signaling pathways that play vital roles in cell proliferation, survival and differentiation [9]. The role of FGFR pathway as a predictive/prognostic marker has been investigated through various studies. According to these studies, aberrant FGFR2 expression is associated with an increased risk of BC and correlates with poor prognosis [10,11]. According to Gene Wide Association Study (GWAS), five single nucleotide polymorphisms (SNPs) (rs7895676, rs2912781, rs10736303, rs2912778 and rs2981582) in the non-coding region of FGFR2 were found to have a significant association with breast cancer. FGFR2 (rs2981582) in intron 2 has been identified as the most significant breast cancer risk locus by the Breast Cancer Association Consortium genome wide association study [12]. Hunter et.al (2007) also identified four other SNPs, rs11200014, rs2420946, rs1219648 and rs2981579 in intron 2 of FGFR2 that are also associated with breast cancer [13]. Therefore, it becomes very important to understand the FGFR pathway on how it leads to BC and how it can be targeted. Several trials are being done with multiple agents that target FGFR pathway components [14-16]. According to these trials, identification of patients with FGFR pathway amplified tumors who may respond to this treatment may be possible. Large number of studies are available on relevance between FGFR2 single nucleotide gene polymorphisms (rs2981582 and rs2981579) and breast cancer, but the results vary with geographical differences [17]. There is hardly any study exploring the association of rs2981582 FGFR2 polymorphism in patients of breast cancer with Indian ethnicity. Therefore, we developed an interest to elucidate the frequency of this polymorphism and its influence on FGFR2 expression in Indian patients with breast cancer.

Materials and Methods

Study Site and Patient Recruitment

The present study was conducted at the Department of Biochemistry in collaboration with the Department of Surgery and Department of Pathology, Maulana Azad Medical College and Associated Hospitals, New Delhi, India. The Institutional Ethics Committee (IEC) of Maulana Azad Medical College approved the study and written informed consent was provided by all participants for blood sampling and genetic testing. All the research has been conducted in accordance with the Helsinki declaration. Patients were consecutively recruited from July, 2018 to December, 2020 in Lok Nayak Hospital, New Delhi, India. Twenty-five female patients who were histopathologically diagnosed with breast cancer were included in the study. Another 25 patients with benign fibroadenoma were also recruited. The control subjects comprised of twenty-five unrelated healthy women. Patients with history of

other malignancies or other systemic diseases were excluded from the study.

Genotyping

Peripheral blood samples from cases and healthy control subjects were collected in EDTA anticoagulant vials and stored at -80°C until used for further process. Whole genomic DNA was isolated from the peripheral blood mononuclear cells (PBMNCs) using HiPurATM Blood Genomic DNA Miniprep Purification Kit (Ref: MB504-50PR, Country of origin: India) according to the manufacturer's instructions. The quality of DNA was checked by Ethidium Bromide (EtBr) stained 1% agarose gel electrophoresis. The DNA quantity and integrity were determined by A260/280 ratio using NanoDrop spectrophotometer (Washington, DC, USA). Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP) technique was used to study rs2981582 single nucleotide polymorphism in FGFR2 gene. The detailed information of the FGFR2 SNPs, primer sequences used for amplification, PCR amplicon sizes, restriction endonucleases used and size of products obtained after restriction digestion are given in Table 1. The restriction digestion fragments were resolved and analyzed by 3% to 3.5% agarose gel electrophoresis using EtBr as staining dye.

RNA Isolation and cDNA Synthesis

Total RNA was extracted from all the subjects using Geneaid Total RNA Mini Kit (Cat. No. RB100, Country of origin: Taiwan) according to the manufacturer's instructions. Briefly, 300 μL of peripheral blood in an eppendorf was mixed with 900 μL of RBC lysis buffer; incubated at room temperature for half an hour and centrifuged for 10minutes at 3500 RPM. The supernatant was discarded, and this step was repeated till a whitish cell pellet appeared at the bottom of the eppendorf tube. This cell pellet was mixed with 200 μL cell lysis buffer and incubated for 10minutes. The ingredients of the eppendorf tube were then transferred to columns, provided with the kit, and centrifuged at high speed (14000 RPM) for 2minutes. The temperature of the centrifuge machine was set at 4°C . The columns were then washed with 75% alcohol and RNA was eluted down in RNase free water (100 μL). RNA integrity was determined by agarose gel electrophoresis (2%) and concentration was determined by measuring absorbance at 260 nm as discussed above.

The RNA was converted to complementary DNA (cDNA) using cDNA synthesis kit (Thermo Fisher Scientific, USA) by following manufacturer's instructions as provided with minor modifications. I brief, total RNA (100 ng), 2 μL oligo (dT) primer, and 9 μL water were mixed and incubated at 70°C for 5 minutes in a thermal cycler. This reaction mixture was then mixed with 5X RT buffer (4 μL), 5mM dNTPs (2 μL), 1 μL each of RNase inhibitor, and

reverse transcriptase enzyme in a total volume of 20 μ L. This mix was incubated at 42°C for 1 h and then heated to 95°C to stop the reaction. The cDNA was stored at -80°C until used for expression studies.

Quantitative Real Time Polymerase Chain Reaction (qRT-PCR)

Quantitative RT-PCR was used to carry out relative expression of FGFR2 gene on a Rotor-Gene Instrument (QIAGEN; Skelton House, Lloyd, Manchester, UK). β -actin gene was used as reference gene for normalizing. The primers used were as follows:

FGFR2 forward primer 5'-TCCACATGGAGATATGGAACAGGA-3'

FGFR2 Reverse primer 5'-GGAGCTATTTATCCCGAGTG-3'

β -actin Forward primer 5'-CGACAACGGCTCCGGCATGTGC-3'

β -actin Reverse primer 5'-CGTCACCGGAGTCCATCAGATGC-3'

A 20 μ L reaction mixture consisting of 10 μ L SYBR Green Master Mix, 1 μ L cDNA (equivalent to 100 ng RNA), 0.3 μ L forward primer (25 pm/ μ L), 0.3 μ L reverse primer (25 pm/ μ L), and 8.4 μ L water. The thermal cycling conditions were standardized to match both FGFR2 and β -actin specific primers. The final standardized temperature profile consisted of a denaturation program of 95°C for 5 min followed by 40 cycles of denaturation at 95°C for 15 seconds, annealing at 60°C for 45 seconds, and extension at 72°C for 50 seconds with a final extension at 72°C for 10 minutes. The quantification was expressed as $2^{-\Delta\Delta CT}$ or fold change using Livak method adopted from (<https://doi.org/10.1177/1010428317713857> and <https://doi.org/10.1007/s13577-020-00370-6>).

Statistical Analysis

Chi-square test was performed for comparison of genotypic frequency distribution between:

- I) All patients and healthy controls,
- II) Benign patient's vs healthy controls and
- III) Malignant patient's vs healthy controls and IV) benign vs malignant patients. Odds ratio along with corresponding 95% confidence intervals (CIs) were used for estimation of individual genotypic risk for breast cancer by employing codominant model of inheritance. Continuous data was analysed by student t-test and One-way ANOVA (Analysis of variance). Moreover, all the p-values were corrected, in case of multiple comparisons, by employing Tukey's post hoc test. These statistical analyses were performed by GraphPad Prism 5.0 software package and a p value of <0.05 was considered statistically significant.

Results

The clinicopathological and demographic characteristics of patients and healthy controls are represented in Tables 1 & 2. In contrast to healthy controls (mean \pm SD=34.28 \pm 9.3), the breast cancer patients tended to be younger (mean \pm SD=32.52 \pm 11.13) taken together was more. Further, when the breast cancer patients were subdivided, benign patients were comparatively found to be younger (mean \pm SD=30.76 \pm 12.65) followed by healthy subjects (mean \pm SD=34.28 \pm 9.3) and then by malignant patients (mean \pm SD=46.2 \pm 15.54). Principally, we did not find any significant differences in basic demographic characteristics among the healthy subjects and breast cancer patients when taken together except that breast cancer patients significantly tend to be multiparous and married. However, significant differences were seen in basic characteristics including age at menarche, parous status, menopausal status, breast feeding and marital status, but feeding habits, between subtypes. All the basic characteristics of healthy and breast cancer subjects, along with statistical analysis, have been presented in Tables 2 & 3.

Table 1: Score of overall students' barrier perception to exclusive e- learning (n=1137).

Subjects	Age (Mean \pm SD)	p-value	Weight (Kgs)	p-value	Age at Menarche	p-value
Healthy controls	34.28 \pm 9.3	>0.01	59.92 \pm 7.73	>0.05	13.04 \pm 0.93	ns
Benign patients	30.76 \pm 12.65		51.04 \pm 12.15		12.64 \pm .86	
Healthy controls	34.28 \pm 9.3	ns	59.92 \pm 7.73	ns	13.04 \pm 0.93	ns
Malignant patients	46.2 \pm 15.54		65.36 \pm 15.60		13.12 \pm 0.88	
Benign patients	30.76 \pm 12.65	>0.001	51.04 \pm 12.15	>0.001	12.64 \pm .86	ns
Malignant patients	46.2 \pm 15.54		65.36 \pm 15.60		13.12 \pm 0.88	

Table 2: Basic demographic characteristics of healthy controls and breast cancer patients.

Variable	Total Cases and Healthy Controls				Breast cancer subtype			
	Controls (N=25)	Cases (N=50)	Chi-Square	p-value	Benign (N=25)	Malignant (N=25)	Chi-Square	p-value
AGE AT MENARCHE								
> 12.5 N(%)	6 (24)	18 (36)	3.43	0.06	7 (28)	11 (44)	6.11	0.01
<12.5 N(%)	19 (76)	32 (64)			18 (72)	14 (56)		
PAROUS STATUS								
Multiparous N(%)	6 (24)	33 (66)	35.69	<0.0001	12 (48)	21 (84)	29.44	<0.0001
Single N(%)	3 (12)	3 (6)			2 (8)	1 (4)		
Nulliparous N(%)	16 (64)	14 (28)			11 (44)	3 (12)		
MENOPAUSAL STATUS								
Menopausal N(%)	3 (12)	18 (36)	0.57	0.45	6 (24)	12 (48)	12.5	0.0004
Non-menopausal N(%)	22 (88)	32 (64)			19 (76)	13 (52)		
BREAST FEEDING								
Yes N(%)	16 (64)	36 (72)	1.47	0.22	14 (56)	22 (88)	25.4	<0.0001
No N(%)	9 (36)	14 (28)			11 (44)	3 (12)		
MARITAL STATUS								
Married	11 (44)	39 (78)	22.89	<0.0001	16 (64)	23 (92)	21.24	<0.0001
Unmarried	14 (56)	11 (22)			9 (36)	2 (8)		
FOOD HABIT								
Vegetarian	8 (32)	25 (50)	5.97	0.01	14 (56)	11 (44)	2.42	0.11
Non-vegetarian	17 (68)	25 (50)			11 (44)	14 (56)		

Table 3: Association of breast cancer risk with FGFR2 (rs2981582) polymorphism.

Genotype or allele	Controls n (%)	All breast cancer cases (n=50)			Malignant cases (n= 25)			Benign cases (n=25)		
		n (%)	OR (95% CI)	p-value	n (%)	OR (95% CI)	p-value	n (%)	OR (95% CI)	p-value
rs.2981582. Codominant model										
TT	17 (68)	24 (48)	---	---	14 (56)	---	---	10(40)	--	--
TC	01 (4)	05 (10)	3.54(0.378 to 33.107)	0.26	02 (8)	2.42(0.1988 to 29.6617)	0.48	03(12)	5.1(0.4653 to 55.8940)	0.18
CC	07 (28)	21 (42)	2.12(0.7382 to 6.1167)	0.16	09 (36)	0.64(0.2197 to 1.8814)	0.42	12(48)	2.91(0.8637 to 9.8335)	0.08
Dominant model										
TC+CC	08 (32)	26 (52)	2.3(0.8410 to 6.3015)	0.1	11 (44)	1.66(0.5270 to 5.2898)	0.38	15(60)	3.18(0.9989 to 10.1716)	0.05
Allele Specific model										
T	0.7 (70)	0.53 (53)	---	--	0.6 (60)	---	---	0.3 (30)		
C	0.3 (30)	0.47 (47)	2.06(1.1578 to 3.6980)	0.01	0.4 (40)	1.55(0.8660 to 2.7941)	0.13	0.7 (70)	5.44(2.9735 to 9.9688)	< 0.0001

Risk Analysis of FGFR2 Polymorphisms in Concert with Breast Cancer

The genotypic and allele distribution of FGFR2 polymorphisms (rs nos. of FGFR2 pols) are shown in Table 3. The risk analysis based on calculation of odds ratio showed association of FGFR2 polymorphism with overall breast cancer risk. It was observed that

FGFR2 polymorphism exhibited a heightened overall breast risk in both codominant and dominant models though it was not significant. In codominant model the heterozygous genotype (TC) depicted the highest risk (OR=3.54; 95% CI= 0.378 to 33.107; p=0.26) followed by recessive homozygous (CC) (OR=2.12; 95% CI= 0.7382 to 6.1167; p=0.16); dominant model; TC+CC; (OR=2.30; 95% CI= 0.8410 to 6.3015; p=0.10). The allele specific model depicted a statistically

increased risk of overall breast cancer associated with the minor allele of the polymorphism (C allele; OR=2.06 95% CI=1.1578 to 3.6980; p=0.01). When patients were sub-grouped based on the type of tumor; benign and malignant, TC genotype in dominant model, TC+CC additive genotype in dominant model and C allele in allele specific model showed a non-statistical heightened risk for malignant breast cancer (OR=2.42; 95% CI= 0.1988 to 29.6617; p=0.48; OR=1.66; 95% CI= 0.5270 to 5.2898; p=0.38 and OR=1.55; 95% CI= 0.8660 to 2.794; p=0.13 respectively). Further, the recessive CC genotype was found to be associated with decreased risk of malignant breast cancer in codominant model, though the results were not significant (Table 3). Increased associations were observed between benign breast cancer and heterozygous (TC) and recessive homozygous genotypes (CC) (OR=5.10; 95% CI= 0.4653 to 55.8940; p=0.18 and OR=2.91; 95% CI= 0.8637 to 9.8335; p=0.08 respectively) in codominant model. Also, in dominant model of inheritance, the FGFR2 was found to be nonsignificantly associated with increased risk for benign breast tumor (TC+CC: OR=3.18; 95% CI= 0.9989 to 10.1716; p=0.05). Moreover, a statistically increased risk for benign breast tumor was associated with recessive allele (C) of FGFR2 polymorphism in allele specific model of inheritance (OR=5.44; 95% CI= 2.9735 to 9.9688; p<0.0001).

FGFR2 mRNA Expression and Polymorphism (rs2981582) in Concert with Breast Cancer

We analysed the mRNA expression of FGFR2 gene and compared it among healthy controls and breast cancer patients. It was observed that FGFR2 mRNA expression varied significantly among healthy controls and breast cancer patients. Breast cancer patients exhibited an increased FGFR2 mRNA expression compared to healthy control subjects (mean fold \pm SD=4.33+4.20, Table 3). We further compared FGFR2 mRNA expression among benign and malignant breast cancer patients and observed that FGFR2 mRNA expression was significantly raised by 2.95-fold in malignant subjects compared to benign tumor ones (mean fold \pm SD=2.49+1.21 vs 7.35+5.88; p=0.0002 respectively, Table 4 and Figure 1). Next, we categorized patients based on genotypic distribution of FGFR2 (rs2981582) polymorphism and analyzed the FGFR2 mRNA expression in breast cancer patients with reference to their genotype. We observed an increased FGFR2 mRNA expression in patients with mutant homozygous (CC) genotype (mean fold \pm SD=5.51 \pm 5.59) compared to patients with wild type (TT) (mean fold \pm SD=4.46 \pm 3.94) and heterozygous (TC) genotypes (mean fold \pm SD=3.79 \pm 2.10), but this difference did not reach statistical significance (Table 4 & Figure 2). Similarly, FGFR2 mRNA expression in concert with FGFR2 (rs2981582) polymorphism genotype was analysed in patients of benign and malignant tumour separately (Table 5). However, we could not reach any meaningful inference as the FGFR2 mRNA expression did not follow a meaningful pattern. The results of the analysis are depicted in Table 4 below.

Table 4: FGFR2 mRNA expression in healthy controls and breast cancer patients.

FGFR2 expression	Fold change+ SD	p-value
Breast Cancer Patients	4.33+4.20	--
Benign patients	2.49+1.21	0.0002
Malignant patients	7.35+5.88	

Table 5: FGFR2 mRNA expression in concert with FGFR2 (rs2981582) polymorphism.

Genotype	Fold change + SD	p-value
In all breast cancer patients		
TT	4.46+3.94	---
TC	3.79+2.10	>0.05
CC	5.51+5.59	>0.05
Benign subjects		
TT	2.91+1.29	--
TC	2.39+1.21	>0.05
CC	1.93+0.97	>0.05
Malignant subjects		
TT	7.20+6.09	--
TC	5.89+0.05	>0.05
CC	7.83+5.66	>0.05

Discussion

In addition to several known risk factors, studies have shown strong relations with FGFR2 gene in respect to breast cancer. Multiple genetic aberrations in FGFR2 which triggers the activation of up and/ or downstream FGFR2 signaling pathways have been identified in breast cancer [7]. In this study, SNP of FGFR2 rs2981582 of genotype T>C have been chosen for assessing the association with risk of breast cancer. The protocol resulted in fragment lengths of 176 base pairs, with genotype patterns wild type TT [176 base pairs(bp)], heterozygous TC (176+154+22 bp) and homozygous CC (154+22bp). On assessment of specific genotype association with breast cancer, our results show that on comparing malignant with healthy controls, a slightly higher risk is associated with heterozygous genotype TC with OR of 2.4 (95% CI=0.199-29.66) but is not statistically significant (p value=0.481) TT genotype being the wild type (Table 3). Also, while comparing malignant with benign cases, no significant risk in both heterozygous genotype TC (OR=0.47 95% CI=0.067-3.396 P-value=0.46) and homozygous genotype CC (OR=0.53 95%CI = 0.164-1.75 P-value=0.30) (Table 3) was observed. So, rs2981582 SNP did not alter the risk of benign or malignant breast tumour in this population. A study of 203 histopathologically confirmed cases of breast cancer and 200 cancer free controls by Liu et.al showed that the rs2981582 TT genotype is significantly associated with breast cancer in Chinese women (OR=1.831, p-value=0.037) [18] but no evidence of significant association was found in this study

of 25 breast cancer cases and 25 benign cases with 25 healthy controls. The small sample size may be attributed to the above finding in our study.

Our results have shown that FGFR2 expression was significantly increased in malignant cases (mean fold change = 7.35 ± 5.88) as compared to benign cases (mean fold change = 2.49 ± 1.219) with p-value of 0.0002 (Fig.1). This finding is correlating with the previous studies on overexpression of FGFR2 in breast cancer [19]. So we infer that altered expression of FGFR2 might have a

role in pathogenesis/malignant transformation of breast tumor / cancer. However, on comparison of FGFR2 expression among benign patients with different genotypes (rs2981582 T>C) the differential gene expression associated with different genotypes of the polymorphism (TT/TC/CC) was not found to be statistically significant (Figure 2). On comparing the same among malignant patients, FGFR2 gene expression among different genotypes in malignant cases was also statistically insignificant (Figure 3). So, we hypothesize from this study that rs2981582 SNP does not influence the expression of FGFR2 in this population.

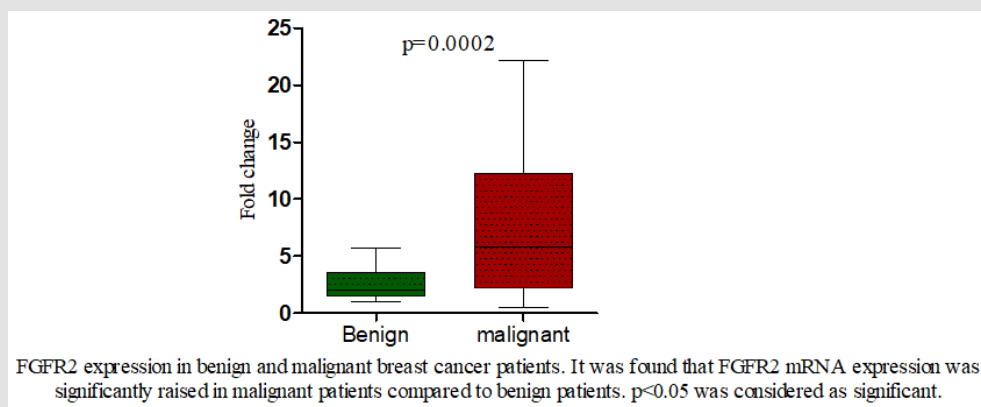


Figure 1: FGFR2 expression among breast cancer and benign breast disease.

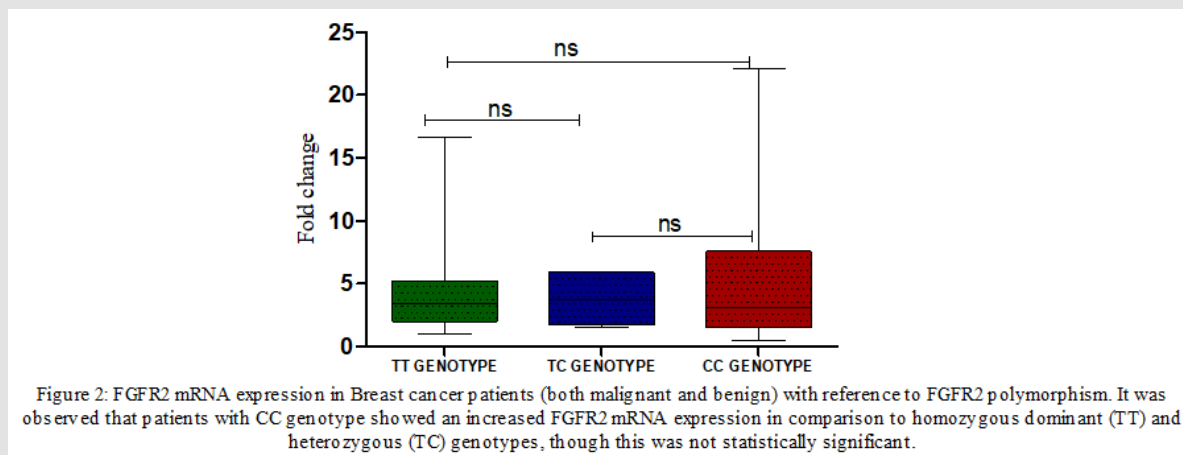


Figure 2: FGFR2 expression with reference to FGFR2 polymorphism.

To the best of our knowledge, previous studies have not clearly documented possible relationship between FGFR2 expression with different genotypes of the polymorphism rs2981582. It is worth exploring which SNPs of FGFR2 gene influence its expression or if there is some gene-gene or gene-environment interaction influencing its expression in breast cancer.

Declarations

a) The authors declare that there are no competing conflicts of interest

- b) No funding was received from any agency for conducting this study
- c) All the details are mentioned in the manuscript and no supplementary files are available. All the data is available.
- d) Ethics approval was obtained from the institutional ethics committee
- e) All the participants were recruited after their written consent
- f) All the authors have provided their consent for publication of the study findings.

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