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Original article

Fibroblast growth factor receptor 2 gene (*FGFR2*) rs2981582T/C polymorphism and susceptibility to breast cancer in Saudi women

Rawya Ibrahim Rabeh AlRaddadi [a], Razan Jamaan Nafaa Alamri [a], Weam Talal Yehya Shebli [a], Emad Ibrahim Yagoub Fallatah [b], Ahmed Safar Alhujaily [c], Hiba Salaheldin Mohamed [a,d], Mohammad Kdaimes H. Alotibi [a,*]

[a] Department of Biology, College of Science, Taibah University, Madinah, Saudi Arabia
[b] Department of Oncology, King Fahad Hospital, Madinah, Saudi Arabia
[c] Department of Pathology, King Fahad Hospital, Madinah, Saudi Arabia
[d] Institute of Endemic Diseases. University of Khartoum, Sudan

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ABSTRACT

Fibroblast growth factor receptor 2 is a protein encoded by *FGFR2* gene and plays an important role in cellular growth. This study was conducted to investigate a potential association of *FGFR2* rs2981582 with breast cancer. DNA was obtained from 137 Formalin-fixed, paraffin-embedded tumors and 98 normal breast tissue samples. Genotypes were carried out with PCR-RFLP. The odds ratio and 95% confidence interval (CI) were used to evaluate the power of the associations. A significant association between FGFR2 rs2981582 C allele and susceptibility to breast cancer was found (p-value < 0.0001, Odds Ratio = 2.3, %95 CI (1.5–3.0). No significant differences in FGFR2 rs2981582 genotypes and alleles distribution among breast patients with different hormonal receptor status ($p > 0.05$) were detected. However, a significant difference was found in genotypes and alleles distribution in ER+, PR- and HER2 between breast cancer cases and controls. This study showed an association of FGFR2 rs2981582T/C with breast cancer in Saudi women, further large study is required to validate the results.

1. Introduction

Breast cancer (BC) is the predominant type of cancer among women in the world. Globally, most incidence of breast cancer in 2018 has been reported in Belgium (Sharma, 2021). It is the second cause of mortality following lung cancer (Bray et al., 2018). However; diets are most likely to positively affect quality of life for BC patients (Porciello et al., 2020). It has been documented that physical activity appears to reduce the risk of recurrence and mortality among BC patients (Cannioto et al., 2021). Fibroblast growth factor receptor 2 (FGFR2) is a tyrosine kinases receptor that controls cell differentiation, proliferation, and apoptosis (Powers et al., 2000). FGFR2 plays a significant role in different cancers (Shoji et al., 2015). Breast cancer tumor and cell line revealed in *FGFR2* overexpression (Penault-Llorca et al., 1995; Adnane et al., 1991).

The gene *FGFR2* is located on 10q26 chromosome and comprises 20 exons (Katoh, 2008). Several studies have confirmed that *the FGFR2* gene has an important role in susceptibility to breast cancer. The association was confirmed with polymorphisms within *FGFR2* intron 2 and susceptibility to BC was increased by 5–10% (Liang et al., 2015; Easton et al., 2007). Several multiple genetic aberrations have been identified in *FGFR2* that cause activation of *FGFR2* signaling pathways up and/or downstream in breast cancer (Lei and Deng, 2017). Five single nucleotide polymorphisms (SNPs), rs2981579, rs11200014, rs1219648, rs2981582, and rs2420946, within *FGFR2*, was discovered by two genome association studies and showed association with BC (Easton et al., 2007; Hunter et al., 2007). The polymorphisms remained within the linkage disequilibrium block in intron 2 (Liu et al., 2013). Genetic association of *FGFR2* gene and different types of cancer was found in gastric cancer (Shoji et al., 2015), endometriosis (Zhao et al., 2008), pancreatic cancer (Nomura et al., 2008), squamous cell carcinoma in

* Corresponding author at: Department of Biology, College of Science, Taibah University, P.O. BOX 344, Madinah, Saudi Arabia.
E-mail address: mkotaibi@taibahu.edu.sa (Mohammad Kdaimes H. Alotibi).
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the lung (Liao et al., 2014), and ovarian cancer (Meng et al., 2014). Several studies have been performed to confirm the role of *the FGFR2* gene in susceptibility in different populations including Chinese (Liu et al., 2013), North India (Siddiqui et al., 2014), European Americans, and African Americans (Rebbeck et al., 2009). It was proven that *FGFR2* gene intron 2 polymorphisms were associated with BC in several populations. One of the most important SNP in intron 2 which showed a strong association with the risk of breast cancer is rs2981582 (Wang et al., 2016). Several studies have found the association between *FGFR2* gene polymorphisms rs2981582 and BC risk (Liang et al., 2015; Liu et al., 2013; Xia et al., 2015; Wang et al., 2016; Chen et al., 2016). However, no study investigated the role of rs2981582 gene polymorphism and susceptibility to BC in Saudi women.

This work was conducted to detect the association of rs2981582 variant and susceptibility to BC in Saudi women, to assess the association of this polymorphism with estrogen receptor (ER), progesterone receptor (PR), and human epidermal receptor 2 (HER2) status in Saudi women.

2. Materials and Methods

2.1. Ethical considerations

Ethical approval was obtained from Taibah University (TUC-DREC/20170607) and King Fahad Hospital Ethical Committees.

2.2. Samples

Data of archive samples were retrieved from the King Fahad Hospital database in Madinah. Different BC subtypes were included. DNA was extracted from 137 cases (Tumor) and 98 healthy controls. The distribution of cases according to age is as following: Premenopausal < 50 is 62 (45%), Postmenopausal ≥ 50 is 67 (49%) Samples were formalin-fixed paraffin-embedded breast tissue (FFPE). Samples were anonymous, and codes were used to identify samples. The FFPE samples were either mastectomy or biopsy from breast tissue.

2.3. Genotyping

The heating out method which was modified from phenol-chloroform protocol was used for DNA extraction. PCR was conducted in a 25-μL mix. The i-Taq- PCR dried master mix from iNtRON Biotechnology. To the mix, 1 μL of 10 mM forward primer and reverse primer as described previously (Liu et al., 2013) was added. 1 μL of 100 ng/ μL DNA and the volume was completed to 25 μL with ddH2O. PCR carried out using forward primer: 5′CCCTTTGGAGACAACGTGAGCC3′ and reverse primer: 5′ CAGG-CACCAGGTGGACTC TGC3′. PCR conditions consisted of 35 cycles following a hot start at 95 °C for 3 min. Each cycle included the following three steps: DNA denaturation (20 s at 95 °C), primer annealing (1 min at 56 °C), and primer extension (1 min at 72 °C). There was a final extension cycle for 5 min at 72 °C. Genotyping was carried out with PCR-RFLP using the Hin6I enzyme and confirmed by sequencing of few samples with different genotypes.

2.4. Statistical analysis

The deviation from Hardy-Weinberg equilibrium for *FGFR2* rs2981582 has been tested, then odds ratios (ORs) and 95% confidence intervals (CIs) were used to calculate the strength of genetic associations using AssociatORRR software at (https://www.genecalculators.net/associatorrr-cc.html). Statistically significant results were considered if the *p*-value was <0.05.

3. Results

137 BCE cases and 98 control records were retrieved from the Department of Histopathology at King Fahad Hospital. The result of Histopathological types of breast cancer showed that invasive/infiltrating ductal carcinoma was the most common among women 82.5% (n = 113). Grade II and III, showed the highest rate 43.1% (n = 56), and 42.3% (n = 55) respectively. The frequency of cases with negative ER, PR and HER2 were 37.8% (n = 45), 37.8% (n = 45) and HER2 were 67.8% (n = 38) respectively. Triple-negative hormone showed the lowest rate 13.9% (n = 19).

FGFR2 rs2981582 allele and genotype frequencies were in Hardy-Weinberg equilibrium (*p*-value > 0.05). Table 1 shows the allele and genotype distributions of rs2981582 in cases and controls. Recessive allele (C) showed significantly higher frequency in cases than in control (P = $\mathbf{9.69 \times 10^{-5}}$) with Odds Ratio = 2.3, %95 CI = 1.5 ~ 3.4. Genotype distribution was different in cases and controls (p = 0.019). CC and T/C genotype were predominant in cases.

Frequencies of the rs2981582 alleles and genotypes in BC cases, association with ER, PR, and HER2 status were demonstrated in Table 2. When rs2981582 genotype and allele rates in BC cases were compared between ER, PR, HER2 positive and ER, PR, HER2 negative. The findings revealed no significant differences (p-value > 0.05). However, when the hormonal receptor status is compared with the controls. There was a significant deviation in allele and genotype distribution in ER+, PR+, PR- and HER2- tumors. However, highly significant differences in alleles distribution were found among ER+ (p = 6.8×10^{-6}), PR- (p = 4.6×10^{-5}), and HER2- (p = 5.9×10^{-5}).

4. Discussion

The current research was carried out to detect an association between rs2981582T/C polymorphism within the *FGFR2* gene and susceptibility to BC in Saudi women and to assess the association of this polymorphism with ER, PR, and HER2 status in Saudi women. *FGFR2* gene was investigated widely for its crucial effect on BC tissue growth. There was no single study on the *FGFR2* gene and susceptibility to BC in Saudi Arabia. SNPs within the intron 2 of FGFR2 have been linked to a 5–10% elevated chance of BC (Liang et al., 2015; Wang and Ding, 2017). The most important SNPs within intron 2 of *FGFR2* gene are: rs2981582, rs1219648, rs2981579, rs2912778 and rs2420946 (Liu et al., 2013; Wang et al., 2016). *FGFR2* rs2981582T/C polymorphism associated with BC in different populations. Due to a lack of research on *the FGFR2* gene in Saudi Arabia, *FGFR2* rs2981582T/C has been chosen. The results obtained from this study showed a genetic association between rs2981582T/C and susceptibility to BC in Saudi women. The role of rs2981582T/C polymorphism in *FGFR2* gene expression regulation was not fully explained. Intron 2 variants act as an enhancer and induce upregulation of *FGFR2* expression in breast cancer tissues, which may lead to the formation of a tumor. Additionally, it was shown that there is numerous known binding site

Table 1
Distribution of *FGFR2* rs2981582T/C polymorphism; genotype and allele frequencies in breast cancer cases and controls.

Genotype/allele	Cases (*n* = 137)	Controls (*n* = 98)	*P value Odd ratio (95 %CI)
TT	50 (0.365)	57 (0.58)	**0.019**
TC	66 (0.482)	38 (0.39)	1.98 (1.14–3.44)
CC	21 (0.153)	3 (0.03)	
T	166 (0.606)	152 (0.78)	$\mathbf{9.69 \times 10^{-5}}$
C	108 (0.394)	44 (0.22)	2.3 (1.5 ~ 3.4)

Table 2
Stratified analyses of combined outcomes of *FGFR2* rs2981582T/C polymorphism and breast cancer risk by age, hormonal receptors status.

Genotype/allele	Controls	ER+ cases	ER− cases	ER+ *vs.* ER− OR (95%CI) *P-value	Controls *vs.* ER+ OR (95%CI) *P-value	Controls *vs.* ER− OR (95%CI) *P-value
TT	57	23	19	1.3 (0.6–2.9)	2.2(1.1–4.3)	1.7(0.8–3.8)
TC	38	34	22	0.68	**0.03**	0.19
CC	3	17	4			
T	152	80	60	1.7 (0.9–2.9)	2.94 (1.84–4.08)	1.7(0.99–3)
C	44	68	30	0.06	**6.8×10^{-6}**	0.06
Genotype/allele	**Controls**	**PR+ cases**	**PR− cases**	**PR+ *vs.* PR− OR (95%CI) *P-value**	**Controls *vs.* PR+ OR (95%CI) *P-value**	**Controls *vs.* PR− OR (95%CI) *P-value**
TT	57	24	17	0.6 (0.3–1.4)	1.7 (0.9–3.4)	2.65(1.3–5.5)
TC	38	27	30	0.31	0.16	**0.01**
CC	3	10	11			
T	152	75	64	0.77 (0.5–1.3)	2.2(1.3–3.6)	2.8(1.7–4.6)
C	44	47	52	0.36	**0.003**	**4.6×10^{-5}**
Genotype/allele	**Controls**	**HER2+ cases**	**HER2− cases**	**HER2+ *vs.* HER2− OR (95%CI) *P-value**	**Controls *vs.* HER2+ OR (95%CI) *P-value**	**Controls *vs.* HER2− OR (95%CI) *P-value**
TT	57	13	27	0.94 (0.4–2.2)	2.31(1.03–5.1)	2.2(1.1–4.1)
TC	38	20	39	1	0.05	**0.02**
CC	3	6	15			
T	152	46	93	1.1(0.6–1.9)	2.4 (1.4–4.2)	2.6 (1.6–4.1)
C	44	32	69	0.9	**0.003**	**5.9×10^{-5}**

FGFR2 = fibroblast growth factor receptor 2; ER = Estrogen receptor, PR = Progesterone receptor, HER2 = Human epidermal receptor 2 (HER2). OR = odd ratio, CI = confidence interval, *P value = 2 tailed P value- Fisher's Exact Test. Cut off $\leq$ 0.05

of transcription-factor within *FGFR2* near rs2981582T/C (Huijts et al., 2011; Meyer et al., 2008). The two genome studies conducted in European women identified 10q26 (*FGFR2*) locus (Easton et al., 2007) and the rs2981582T/C have been replicated in Chinese populations (Liangy et al., 2008), Tunisians (Shan et al., 2012), African and European American (Rebbeck et al., 2009), along with Hispanic and non-Hispanic (Slattery et al., 2011). This result showed that CC or TC was significantly predominant in cases than controls. Consistently with our results T allele of *FGFR2* rs2981582T/C was associated with a low likelihood of BC and has also revealed and TT protects Han Chinese (Chen et al., 2016). Many studies have shown a positive association of *FGFR2* rs2981582 T allele with a high risk of BC. A significant association between BC risk and T/C genotype of *FGFR2* rs2981582T/C was found among Pakistani women. However, homozygote TT genotype was not associated (Mazhar et al., 2016). The definitive association between rs2981582T/C and BC is still inconclusive, this may be due to various factors such as regional and ethnic differences. Interracial differences may cause variations in the prevalence and types of BC. Therefore, a variant discovered in one population may not have a similar impact on other populations. Several validated studies have shown inconsistent results in terms of ethnic and pathological characteristics. Therefore, verification by the intrinsic subtypes (ER−, PR− and HER2+) is crucial. The current study demonstrated that luminal A (48.8%), which is ER and PR positive, and HER2 negative was the most frequent subtype among cases. Luminal A shows a good prognosis, where the chances of treatment are better, and the response is good. A previous study in Saudi Arabia was estimated luminal A to be 58.5%,(Alnegheimish et al., 2016). No allelic or genotype association between *FGFR2* rs2981582T/C and susceptibility to breast cancer were found when cases stratified by hormonal status, ER+ compared to ER-, PR+ to PR-, HER2+ to HER2- in cases, however, allele and genotype frequencies in ER+, PR- and HER2- tumors were significantly different between cases and controls. Many studies identified a strong association of *FGFR2* gene rs2981582 polymorphism in ER+ rather than ER- patients. In a previous study, a strong relationship was found between *FGFR2* and positive estrogen hormone (ER+). The results suggested reduction of *FGFR2* expression was found in breast cancer ER+ patients (Campbell et al., 2016). Therefore, looking at different tumor subtypes and their relation to BC is an important etiologic issue. FGFR2 polymorphisms showed significant association for (ER+) than (ER−) (Liang et al., 2015; Siddiqui et al., 2014; Wang and Ding, 2017; Shan et al., 2012; Cen et al., 2013; Fu et al., 2012). *FGFR2* SNPs and BC subtypes and hormone exposure were studied in a woman of European and an African- American origin. The results confirmed *FGFR2* had a role in BC predisposition and the impact was mainly on ER+ and PR+ tumors (Rebbeck et al., 2009). *FGFR2* polymorphisms were showed an association with ER-/PR- and ER+/PR+ in Hispanic and non-Hispanic respectively (Slattery et al., 2011). Strong evidence was provided for an association between the *FGFR2* gene and HER2-negative disease (Cox et al., 2016).

5. Conclusion

Breast cancer susceptibility genes may help in early diagnosis, comprehensive screening, and gene therapy, which has become a hot spot in BC research. The current study showed that *FGFR2* rs2981582T/C was associated with susceptibility to BC in Saudi women. Nevertheless, to replicate this study, a larger sample size is needed. Additionally, to understand the effect of rs2981582 polymorphism in pathogenesis, a further functional study is required to highlight the *FGFR* signaling pathway in tumor development and propose that *FGFR2* could be considered as a predictive marker that may facilitate the process of diagnosis and treatment of Saudi women.

CRediT authorship contribution statement

Rawya Ibrahim Rabeh AlRaddadi: Methodology, Formal analysis, Writing - original draft. **Razan Jamaan Nafaa Alamri:** Methodology. **Weam Talal Yehya Shebli:** Methodology. **Emad Ibrahim Yagoub Fallatah:** Resources, Methodology. **Ahmed Safar Alhujaily:** Resources, Methodology. **Hiba Salaheldin Mohamed:** Conceptualization, Supervision. **Mohammad Kdaimes H. Alotibi:** Conceptualization, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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