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Original Article

FGFR2 gene polymorphisms are associated with breast cancer risk in the Han Chinese population

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Abstract: Aims and background: Breast cancer is one of the most common neoplasms among women in many developing countries including China, and is the leading cause of female cancer-related deaths worldwide. Methods: In the current study, we analyzed the relationship between 14 tag single-nucleotide polymorphisms (tSNPs) and breast cancer risk in the Han Chinese population including 185 breast cancer patients and 199 healthy women controls on the different types of breast cancer and menopausal status. Results: Overall, we found rs2981579 in the *FGFR2* gene, and rs2380205 were associated with breast cancer susceptibility.

Keywords: Single nucleotide polymorphism (SNP), breast cancer, *FGFR2*, case-control studies

Introduction

Breast cancer is one of the most common malignancies in women worldwide. In the past 10 years, the incidence of breast cancer rose by 20-30% among China's urban registries [1]. With an investigation of 32,798,187 breast cancer from 41 registries in 2008 in China [2], breast cancer has become the leading cause of cancer-related deaths in women.

Breast cancer is a complex disease, and may be caused by combination of genetic, environmental, and behavioral factors [3, 4]. Genome-wide association studies (GWAS) have reported some susceptibility variants [5-8]. Among these variants, fourteen sites have been researched in Chinese. However, the results in Chinese were inconsistent with across studies. The aim of this study was to examine the association between the 14 SNPs and breast cancer risk in the Xi'an Han Chinese. To investigate potential relationships between gene single nucleotide polymorphisms (SNPs) and the susceptibility of breast cancer, we performed a comprehensive association analysis in a case-control study and a stratified analysis by menopausal status and analysis of cancer subtype in the Han Chinese population.

Materials and methods

Study participants

Two hundred breast cancer patients recently diagnosed and 200 unrelated healthy women at the First Affiliated Hospital, Xi'an Jiaotong University from December 2011 to October 2012 in Xi'an, China were included in this study. All participants were ≥ 18 years and living in Xi'an city or nearby areas.

Fifteen cases were excluded due to unclear clinical information. Finally, we successfully genotyped 185 breast cancer cases. All controls were healthy without any diseases related to vital organs. We evaluated α-fetoprotein and plasma carcinoembryonic antigen to ensure the quality of the controls. Finally, we selected 199 unrelated healthy subjects to further analysis.

Table 1. Characteristics of breast cancer patients and controls

	Patients (n = 185)	Controls (n = 199)	*p*
Age (years)	46.5 ± 9.4	45.4 ± 6.9	0.209[a]
25-40 years	57 (30.8%)	57 (28.6%)	
41-55 years	95 (51.4%)	130 (65.3%)	
> 55 years	33 (17.8%)	12 (6.1%)	
BMI (kg/m2)	23.1±3.0	22.5 ± 2.5	0.038*[,a]
Sex			
Women	185 (100%)	199 (100%)	
Menopausal state			
Premenopausal	115 (62.2%)	121 (60.8%)	0.785[b]
Postmenopausal	70 (37.8%)	78 (39.2%)	
Tumor size (cm)			
≤ 2.0	41 (22.2%)		
> 2.0	144 (77.8%)		
Histology			
DIC	166 (89.7%)		
LIC	5 (2.7%)		
Others	14 (7.6%)		
Clinical stages			
Grades 1-2	137 (74.1%)		
Grades 3-4	48 (25.9%)		
Lymph node metastasis			
Node-negative	107 (57.8%)		
Node-positive	78 (42.2%)		

[a]*p* values were calculated using Student's t-tests. [b]*p* values were calculated from two-sided chi-square tests. *$p \leq 0.05$ indicates statistical significance.

Clinical data and demographic information

We used a standardized epidemiological questionnaire to collect demographic and personal data. The use of human blood sample and the protocol in this study were strictly conformed to the principles expressed in the Declaration of Helsinki and were approved by the institutional ethical committees of the First Affiliated Hospital, Xi'an Jiaotong University. We also obtained signed informed consent from each participant.

SNP selection and gen otyping

Fourteen tSNPs with minor allele frequencies (MAF) >5% in the Chinese Han Beijing population were successfully genotyped. The GoldMag® nanoparticles method (GoldMag Co. Ltd., Xi'an City, China) was used to extract genomic DNA. We used Sequenom MassARRAY Assay (Sequenom Co. Ltd., San Diego, California, USA) platform to design Multiplexed SNP MassEXTEND assays [9], genotyped SNP, and data management and analyses [10].

Statistical analyses

Fisher's exact test and χ^2 tests were used to evaluate departure from Hardy-Weinberg equilibrium (HWE) in control subjects and calculate the difference in tSNP allele distribution between cases and controls, respectively [11]. $p = 0.05$ was used as the threshold of statistical significance. Associations between the selected SNPs and the risk of breast cancer were assessed using genotypic model analysis (co-dominant, dominant, recessive, over-dominant, and log-additive) by unconditional logistic regression analysis adjusted for age and gender age, menopausal state and body mass index [12].

In stratified analysis by menopausal status, we used ordinal variables coded as the number of variant alleles, 0, 1 or 2, assuming a log-additive genetic model to increase the statistical power. To test for interaction between SNP's and menopausal status, we computed p values from a one degree of freedom likelihood ratio test comparing logistic regression models with and without the interaction term.

In analysis of tumor subtype, we examined associations separately for women with different ER and/or PR status, each compared to all controls. Effect heterogeneity by ER and/or PR status was tested using Cochran-Armitage trend test based on case-case study.

The association of SNPs genotype with breast cancer risk was tested using SNPStats software (http://bioinfo.iconcologia.net/snpstats/start.htm) [13].

Results

The distribution of selected cases and controls characteristics are shown in **Table 1**. The body mass index (BMI) was significantly different between breast cancer patients and healthy controls ($p = 0.038$). We found a correlation between rs2380205 and increased breast cancer susceptibility (OR = 1.79, 95% CI, 1.13-2.83; $p = 0.012$) using χ^2 test. Moreover,

Table 2. Basic information of candidate SNPs

SNP ID	Gene Name	Allele (A/B)	Chromosome position	MAF		HWE *p*	ORs	95% CI		*p*
				Case	Control					
rs11249433	LOC647121	C/T	chr1: 121280613	0.019	0.033	0.892	0.57	0.23	1.46	0.238
rs2981579	FGFR2	C/T	chr10: 123337335	0.431	0.480	0.706	0.82	0.62	1.10	0.180
rs1219648	FGFR2	G/A	chr10: 123346190	0.494	0.452	0.998	1.19	0.89	1.58	0.139
rs10510102	ATE1	G/A	chr10: 123625190	0.157	0.206	0.766	0.72	0.49	1.04	0.081
rs2380205		T/C	chr10: 5886734	0.144	0.086	0.915	1.79	1.13	2.83	0.012*
rs10822013	ZNF365	T/C	chr10: 64251977	0.489	0.447	0.888	1.19	0.89	1.58	0.245
rs10995190	ZNF365	A/G	chr10: 64278682	0.022	0.005	0.997	4.40	0.93	20.88	0.086
rs704010	ZMIZ1	A/G	chr10: 80841148	0.343	0.302	0.010#	1.21	0.89	1.64	0.223
rs3817198	LSP1	C/T	chr11: 1909006	0.119	0.145	0.474	0.80	0.52	1.22	0.294
rs614367		T/C	chr11: 69328764	0.019	0.005	0.997	3.86	0.80	18.73	0.071
rs999737	RAD51L1	T/C	chr14: 69034682	0.003	0.005	0.997	0.54	0.05	5.98	0.610
rs3803662	TOX3	C/T	chr16: 52586341	0.315	0.334	0.795	0.92	0.67	1.24	0.573
rs3112612	LOC643714	C/T	chr16: 52635164	0.255	0.216	0.997	1.25	0.89	1.75	0.197
rs4973768	SLC4A7	T/C	chr3: 27416013	0.261	0.234	0.882	1.16	0.83	1.61	0.380

#site with HWE $p \leq 0.01$ is excluded; *p value ≤ 0.05 indicates statistical significance; Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odd ratio; CI, confidence interval; A/B stands for minor/major alleles on the control sample frequencies.

Table 3. Relationship between rs2380205, rs2981579 and breast cancer risk (age adjusted)

SNP ID	Model	Genotype	Control	Case	Without adjustment		With adjustment	
					OR (95% CI)	*p*-value[a]	OR (95% CI)	*p*-value[b]
rs2380205	Codominant	C/C	164 (83.2%)	132 (73.3%)	1.00	0.039	1.00	0.055
		T/C	32 (16.2%)	44 (24.4%)	1.69 (1.02-2.82)		1.69 (1.02-2.82)	
		T/T	1 (0.5%)	4 (2.2%)	5.19 (0.57-47.34)		5.19 (0.57-47.34)	
	Dominant	C/C	164 (83.2%)	132 (73.3%)	1.00	0.021	1.00	0.034*
		T/C-T/T	33 (16.8%)	48 (26.7%)	1.80 (1.09-2.96)		1.72 (1.04-2.86)	
	Recessive	C/C-T/C	196 (99.5%)	176 (97.8%)	1.00	0.120	1.00	0.120
		T/T	1 (0.5%)	4 (2.2%)	4.68 (0.51-42.49)		4.99 (0.53-47.41)	
	Over-dominant	C/C-T/T	165 (83.8%)	136 (75.6%)	1.00	0.052	1.00	0.082
		T/C	32 (16.2%)	44 (24.4%)	1.65 (0.99-2.75)		1.58 (0.94-2.65)	
	Log-additive	---	---	---	1.79 (1.12-2.84)	0.012*	1.73 (1.08-2.76)	0.020*
rs2981579	Codominant	T/T	56 (28.6%)	55 (30.4%)	1.00	0.120	1	0.120
		C/T	92 (46.9%)	96 (53%)	1.07 (0.67-1.71)		1.09 (0.68-1.76)	
		C/C	48 (24.5%)	30 (16.6%)	0.62 (0.34-1.12)		0.62 (0.34-1.13)	
	Dominant	T/T	56 (28.6%)	55 (30.4%)	1.00	0.690	1	0.740
		C/T-C/C	140 (71.4%)	126 (69.6%)	0.91 (0.59-1.42)		0.93 (0.59-1.45)	
	Recessive	T/T-C/T	148 (75.5%)	151 (83.4%)	1.00	0.043*	1	0.042*
		C/C	48 (24.5%)	30 (16.6%)	0.59 (0.35-0.99)		0.59 (0.35-0.99)	
	Over-dominant	T/T-C/C	104 (53.1%)	85 (47%)	1.00	0.210	1	0.180
		C/T	92 (46.9%)	96 (53%)	1.30 (0.87-1.95)		1.33 (0.88-2.00)	
	Log-additive	---	---	---	0.81 (0.61-1.08)	0.160	0.81 (0.61-1.09)	0.170

*p value ≤ 0.05 indicates statistical significance; Abbreviations: OR, odd ratio; CI, confidence interval; p^a: p values were calculated from two-sided chi-square tests or Fisher's exact tests for either genotype distribution. p^b: p values were calculated by unconditional logistic regression adjusted for age, menopausal state and body mass index.

rs2380205 remained significant after further adjustment (p = 0.020). One tSNP, rs704010, was excluded for further analysis since it derived from HWE at 1% p level (**Table 2**).

Table 4. Haplotype association with response (age-adjusted)

	rs10510102	rs1219648	rs2981579	Freq	OR (95% CI)	*p*-value
1	A	G	T	0.4065	1.00	---
2	A	A	C	0.3519	0.83 (0.58-1.19)	0.31
3	G	A	C	0.1022	0.57 (0.34-0.97)	0.037*
4	G	G	T	0.0655	0.75 (0.34-1.67)	0.48
5	A	A	T	0.0554	0.68 (0.32-1.43)	0.31
6	G	A	T	0.0143	0.99 (0.17-5.70)	0.99
rare	*	*	*	0.0042	0.48 (0.04-5.76)	0.57

*p value ≤ 0.05 indicates statistical significance; Abbreviations: OR, odds ratio; CI, confidence interval.

Table 5. Odds ratios for breast cancer risk by menopausal status

ID	Premenopausal		Postmenopausal		Phet
	OR	*p*-value	OR	*p*-value	
rs11249433	0.33 (0.09-1.27)	0.107	0.92 (0.21-4.12)	0.916	0.265
rs4973768	1.23 (0.82-1.86)	0.312	0.83 (0.45-1.54)	0.560	0.416
rs2380205	2.40 (1.29-4.45)	0.005	1.01 (0.47-2.19)	0.974	0.107
rs10822013	1.22 (0.840-1.77)	0.298	0.92 (0.57-1.50)	0.743	0.544
rs10995190	/	0.999	1.13 (0.15-8.61)	0.906	0.031
rs704010	1.05 (0.70-1.57)	0.827	1.74 (0.97-3.15)	0.065	0.146
rs2981579	0.80 (0.54-1.15)	0.223	0.85 (0.53-1.36)	0.503	0.758
rs1219648	1.35 (0.92-1.99)	0.124	1.22 (0.75-1.97)	0.422	0.627
rs10510102	0.63 (0.40-1.00)	0.045	0.89 (0.46-1.69)	0.713	0.296
rs3817198	0.93 (0.54-1.61)	0.803	0.55 (0.27-1.15)	0.111	0.316
rs614367	2.87 (0.54-15.28)	0.216	/	0.999	0.323
rs999737	0.99 (0.06-16.15)	0.995	/	0.999	0.337
rs3803662	0.87 (0.59-1.28)	0.466	0.96 (0.57-1.60)	0.866	0.729
rs3112612	1.42 (0.91-2.19)	0.121	0.98 (0.57-1.69)	0.949	0.309

p value ≤ 0.05 indicates statistical significance OR, odd ratio; CI, confidence interval.

We further used SNPStats software to analyze the associations between tSNPs and breast cancer risk. In the log-additive model, allele "T" of rs2380205 increased breast cancer risk by 1.79-fold (OR = 1.79, 95% CI, 1.12-2.84; p = 0.012). In the recessive model, we found that genotype "CC" of rs2981579 in *FGFR2* decreased breast cancer risk by 0.59-fold (OR = 0.59, 95% CI, 0.35-0.99; p = 0.043) (**Table 3**).

The relationship between *FGFR2-ATE1* haplotypes and breast cancer risk are listed in **Table 4**. Haplotype "GAC" in the *FGFR2-ATE1* gene was found to decrease the risk of breast cancer (OR = 0.57, 95% CI, 0.34-0.97; p = 0.037).

Results of the study of the association between gene polymorphism and breast cancer risk, evaluated by menopausal status, are shown in **Table 5**. Stratification by menopausal status revealed that the risk of breast cancer was significantly elevated for the minor allele (T) of rs2380205 among premenopausal women (OR = 2.40, 95% CI, 1.29-4.45) in log-additive genetic model. The minor allele (G) of rs10510102 of risk was slight lower among premenopausal women (OR = 0.63, 95% CI, 0.40-1.00) than among postmenopausal women (OR = 0.89, 95% CI 0.46-1.69). However, there was considerable overlap in CIs, which were wide due to small numbers of women in each genotype-exposure category.

As show **Table 6**, when the cases were divided into subgroups by ER/PR status, the effects the minor allele (C) of rs3112612 was more evident for the ER/PR cases in log-additive genetic model. However, the effects of other genotypes were not different by ER/PR status. The minor allele (C) of rs3112612 shows significantly stronger association with risk of ER-negative tumors, PR negative tumors, ER/PR negative tumors respectively (OR = 1.97, 95% CI, 1.22-3.17; OR = 1.80, 95% CI, 1.149-2.81; OR = 2.08, 95% CI, 1.25-3.46) in log-additive genetic model.

Discussion

Fibroblast growth factor receptor 2 (*FGFR2*) is a member of the fibroblast growth receptor family. The extracellular portion of the protein interacts with fibroblast growth factors, initiating a cascade of downstream signals, ultimately influencing mitogenesis and differentiation [14]. Rs2981579 in the *FGFR2* have been

Table 6. Breast cancer risks among subgroups of cases by ER and PR status

ID	ER			PR			ER/PR		
	+	-	Phet	+	-	Phet	+	-	Phet
rs11249433	0.59 (0.20-1.71)	0.48 (0.10-2.25)	0.801	0.67 (0.23-1.96)	0.38 (0.08-1.78)	0.507	2.15 (0.26-2.15)	0.57 (0.12-2.66)	0.756
rs4973768	1.10 (0.76-1.59)	1.12 (0.69-1.81)	0.663	1.13 (0.77-1.66)	1.09 (0.70-1.70)	0.877	1.68 (0.76-1.68)	1.17 (0.71-1.93)	0.820
rs2380205	1.87 (1.11-3.13)	1.52 (0.78-2.94)	0.673	1.82 (1.05-3.13)	1.72 (0.95-3.12)	0.909	2.98 (0.97-2.98)	1.31 (0.64-2.67)	0.607
rs10822013	1.07 (0.77-1.49)	1.22 (0.80-1.85)	0.322	1.04 (0.74-1.48)	1.21 (0.82-1.78)	0.309	1.49 (0.74-1.49)	1.25 (0.80-1.95)	0.264
rs10995190	4.11 (0.77-22.00)	6.71 (0.99-45.44)	0.780	5.76 (1.12-29.55)	3.48 (0.44-27.5)	0.356	27.01 (0.95-27.01)	5.47 (0.68-44.36)	0.756
rs704010	1.25 (0.86-1.81)	1.16 (0.71-1.89)	0.775	1.20 (0.80-1.79)	1.25 (0.81-1.92)	0.623	1.78 (0.79-1.78)	1.14 (0.68-1.90)	1.000
rs2981579	0.83 (0.60-1.15)	0.78 (0.52-1.19)	0.972	0.81 (0.58-1.14)	0.83 (0.57-1.21)	0.960	1.18 (0.59-1.18)	0.83 (0.54-1.29)	0.905
rs1219648	1.36 (0.97-1.90)	1.21 (0.80-1.84)	0.390	1.24 (0.88-1.77)	1.37 (0.93-2.01)	0.624	1.84 (0.89-1.84)	1.26 (0.80-1.97)	0.792
rs10510102	0.65 (0.43-1.00)	0.82 (0.49-1.39)	0.349	0.70 (0.45-1.09)	0.71 (0.43-1.18)	0.818	1.01 (0.40-1.01)	0.72 (0.40-1.29)	0.568
rs3817198	0.64 (0.38-1.08)	0.99 (0.55-1.77)	0.183	0.69 (0.404-1.18)	0.85 (0.49-1.50)	0.441	1.12 (0.36-1.12)	0.95 (0.51-1.79)	0.253
rs614367	3.93 (0.74-20.86)	5.35 (0.66-43.42)	0.793	4.46 (0.836-23.75)	3.75 (0.48-29.52)	0.499	26.10 (0.93-26.10)	5.64 (0.70-45.35)	0.747
rs999737	0.79 (0.07-8.84)	/	0.482	0.90 (0.08-10.10)	/	0.407	10.91 (0.09-10.91)	/	0.471
rs3803662	0.80 (0.56-1.14)	1.14 (0.74-1.75)	0.131	0.76 (0.53-1.10)	1.13 (0.761-1.69)	0.051	1.05 (0.49-1.05)	1.10 (0.70-1.75)	0.075
rs3112612	0.98 (0.66-1.44)	1.97 (1.22-3.17)	0.010	0.95 (0.63-1.41)	1.80 (1.149-2.81)	0.016	1.40 (0.61-1.40)	2.08 (1.25-3.46)	0.006

p value ≤ 0.05 indicates statistical significance.

reported to associate with risk of sporadic postmenopausal breast cancer in European women [15]. In addition, our result showed rs2981579 that are associated with breast cancer in the Han Chinese population. These evidences both indicate that *FGFR2* polymorphisms may have important implications in breast cancer carcinogenesis.

The SNP rs2380205 lies in a 105-kb block on chromosome 10p15, which contains the genes ANKRD16 and FBX018 [16]. In our study, we identified rs2380205 of Han Chinese living in Xi'an (northwest of China) was associated with an increased risk of breast cancer. However, in a large scale case-control study in Nanjing (east of China), no significant association was observed between rs2380205 and breast cancer risk [17]. Taken together, these results indicate a contradiction for chromosome 10p15 in breast cancer risk; therefore, whether this SNP has breast susceptibility warrants further study.

Our study shows that differ according to ER and PR status breast cancer risk are different. A number of studies suggested the different relationship between risk factors such as age, body mass index smoking of breast cancer, and breast cancer by ER and PR status [18-21]. It is known that patients who have ER^- or PR^- receptors tend to have a poor prognosis than patients with these receptors and the hormone receptor status has a profound effect on therapeutic decisions. Colditz et al. [18] have concluded that the incidence rates and risk factors for breast cancer differ according to ER and PR status and that breast cancer risk should be estimated according to the ER and PR status. However, other studies did not find any significant differences in the profile of risk factors by breast cancer subtypes [22, 23]. Although the underlying biological mechanisms still remain to be investigated, examining potentially modifiable breast cancer risk factors by tumor ER and PR status may provide us greater insight into breast cancer etiology and the mechanisms underlying the risk of associations [24].

In our study we sought to determine whether these loci polymorphisms are associated with breast cancer risk may be modified by menopausal status. Although the mechanisms are not elucidated, these data suggest that there may be an interaction between the gene polymorphism and menopausal status in breast cancer risk. This further supports arguments from a number of studies suggesting that breast cancer etiology may differ between premenopausal and postmenopausal women, warranting the careful classification and separation of women by menopausal status in studies of breast cancer risk factors.

Here, we identified for the first time one risk tSNP on 10p15 (rs2380205) and one protective tSNPs in *FGFR2* (rs2981579) that are associated with breast cancer in the Han Chinese population. In stratified analysis we need to further larger sample studies, gene-environment and gene-gene interaction in breast cancer development.

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Conclusions

These findings indicate that *FGFR2* was associated with breast cancer risk in the Han Chinese population, support the hypothesis that the applicability of a common susceptibility locus must be confirmed among genetically different populations.

Disclosure of conflict of interest

None.

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