

Correlation of FGFR2 rs2981582 polymorphisms with susceptibility to breast cancer: a case-control study in a Chinese population

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Abstract

Objective: Breast cancer (BC) is a common malignancy among women worldwide. Fibroblast growth factor receptor 2 (FGFR2) rs2981582 is reported to play a vital role in BC development. However, the relationship between them remains unclear.

Methods: Ninety-five patients and 140 healthy controls were enrolled in the study. Plasma DNA was genotyped by the MassARRAY method. A meta-analysis was conducted to clarify the effect of FGFR2 polymorphism on BC risk.

Results: Our case-control study results revealed a significant difference in CC, TC, and TT genotypes between patients and controls. Logistic regression analysis showed that TT and TC genotype and the dominant mode were significantly correlated with BC development [odds ratio (OR) = 1.21, 95% confidence interval (CI): 1.050–2.27; OR = 1.81, 95% CI: 1.24–2.73; OR = 2.15, 95% CI: 1.25–5.31, respectively], even after adjusting for age, body weight, drinking, smoking, and estrogen receptor status. A meta-analysis of 15 studies showed significant differences among the dominant, recessive, heterozygote, and homozygote models between patients and controls.

Conclusions: Our results showed an association of FGFR2 rs2981582 polymorphism with BC in an Asian population. However, a more comprehensive study of the relationship between the polymorphism and BC is still needed.

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Keywords

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Introduction

Breast cancer (BC) is one of the most common malignancies and a major cause of death among women. In China, BC accounts for 15% of new cases of cancer in women, with morbidity and mortality increasing year by year.^{1,2} Although the exact mechanism of BC is still not completely elucidated, a number of comprehensive analyses have shown that genomic and gene expression patterns contribute to the morbidity.^{3,4}

Fibroblast growth factor receptor 2 (FGFR2, also known as CEK3), located at chromosome 10q26 and containing 22 exons, is a member of the FGFR family of tyrosine kinase receptors.^{5,6} It participates in the process of tumorigenesis by inducing mitogenic and survival signals and promoting invasiveness and angiogenesis.^{7,8} FGFR2 overexpression was observed in breast cancer cell lines and breast tumor tissues in estrogen receptor (ER)-positive BC as early as 1992.⁹ Since then, a large number of studies on the relationship between polymorphisms in the FGFR2 gene and BC have been implemented in different regions of the world.

Large genome-wide association studies (GWAS) have demonstrated that an intronic FGFR2 polymorphism, rs2981582, is significantly associated with BC.^{10–12} Meyer et al.¹³ reported that the T allele of rs2981582 has been linked to a higher level of FGFR2 transcription in both breast cancer cell lines and tumors. This link between rs2981582 and FGFR2

transcription is variable in patients of different ethnic origins and therefore sometimes contradictory. Murillo-Zamora et al.¹⁴ reported that the T allele of rs2981582 was significantly associated with an increased risk of BC in Mexican women [odds ratio (OR)=1.24, 95% confidence interval (CI): 1.06–1.46]. Ledwoń et al.¹⁵ reported a similar result in Polish women (OR=1.31, 95% CI: 1.17–1.45). In contrast, Bayraktar et al. found no relationship of rs2981582 with BC in an American population.¹⁶ Chen et al.¹⁷ demonstrated that the CT and TT genotypes of rs2981582 reduced BC risk in a Han Chinese population ($p=0.006$). Therefore, to clarify the association of FGFR2 rs2981582 polymorphism and sporadic BC, we performed a comprehensive association analysis in a case-control study in a Chinese Han population; we then conducted a meta-analysis on all case-control studies to make a more accurate assessment of the relationship.

Materials and methods

Patient recruitment

Patients were consecutively recruited from June to October 2016 among inpatients in Xi'an Hospital of Traditional Chinese Medicine. Ninety-five female patients who were histopathologically diagnosed with BC and did not have a family history of BC were included in the study. The control group comprised 140 unrelated healthy women. Patients with a history of other

types of cancer, hormone replacement therapy, or other serious diseases were excluded from this study. This study was approved by the Ethical Committee of Xi'an Hospital of Traditional Chinese Medicine, and all patients and controls gave written informed consent for participation in this research. All of the studies were performed in accordance with the Declaration of Helsinki.

Genotyping

Venous blood samples were collected in tubes with EDTA anticoagulant and stored at -80°C until use. Genomic DNA was isolated from whole blood using the Wizard kit (Promega, Madison, WI, USA) according to the manufacturer's protocol. Genotyping of rs2981582 was carried out following time-of-flight mass spectrometry on a MassARRAY iPLEX platform (Sequenom, San Diego, CA, USA). The average genotype call rate for the single nucleotide polymorphism (SNP) was $>99\%$.

Meta-analysis

Studies published through 20 May 2019 were identified by a systematic literature search in PubMed, Embase, Web of Knowledge, China National Knowledge Infrastructure (CNKI), and WanFang Data. The medical subject headings (MeSH) and title/abstract were used to identify all eligible studies that mainly focused on the genotype of rs2981582 polymorphism. Eligible studies had to meet the following criteria: (1) the study evaluated the association between risk of BC and FGFR2 rs2981582 polymorphism in Asian populations; (2) the report focused on detailed genotype frequencies among patients with sporadic BC; and (3) the investigation was a case-control study. The exclusion criteria were as follows: (1) comment, review, or editorial articles; and (2) studies without detailed genotype data

or with overlapping data. Publication bias was evaluated by using the Begg's test.

Statistical analysis

All statistical analyses were performed using SPSS (version 17.0, SPSS Inc., Chicago, IL, USA). Pearson's chi-squared test or the Mann-Whitney U test was performed to test the association between rs2981582 polymorphism in cases and controls. Logistic regression analysis was used to evaluate the contribution of genetic and nongenetic factors under the dominant, recessive, and additive models.

Stata software (version 12.0; Stata Corporation, College Station, TX, USA) was used for meta-analysis. The OR and 95% CI were calculated to assess the relationship between the polymorphism and BC. Pooled ORs were obtained from combinations of single study under the dominant model (TT+TC vs. CC), the recessive model (TT vs. TC+CC), the homozygous model, and the heterozygote model. Heterogeneity was tested by the Q test (Chi squared test; $p < 0.10$ was considered indicative of statistically significant heterogeneity) and the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively). If $I^2 > 50\%$, the random-effect model (DerSimonian-Laird method) was used to calculate the pooled ORs; otherwise, the fixed effect model (Mantel-Haenszel method) was used. Begg's linear regression tests were applied to assess the potential publication bias.

Results

Characteristics of the study participants

Ninety-five patients and 140 healthy controls were recruited in our study. Seventy patients were at clinical stage I to II and 25 patients were at stage III. In the patient

group, 24.3% had a drinking habit and 25.1% had a history of smoking. In the healthy control group, 18.5% had a drinking habit and 19.4% had a history of smoking. The demographic characteristics of the subjects in the patient and control groups are summarized in Table 1.

Genetics analysis

The minor allele frequency (MAF) was 0.419. A significant difference was observed between the patient group and the control group in the three genotypes, TT, TC, and CC ($p=0.021$) (Table 2). A logistic regression analysis of rs2981582 SNP genotype between patients and controls was also performed. The results showed that the TT and TC alleles were significantly correlated with BC development (OR = 1.21, 95% CI: 1.050–2.27, $p=0.019$; OR = 1.81, 95% CI: 1.24–2.73, $p=0.035$), even after adjusting for age, drinking, smoking, and ER status (Table 3).

In addition, we assessed the influence of genetic models (dominant, recessive, and additive models) on BC risk; however, no significant associations in the recessive model were observed (OR = 1.14, 95% CI:

0.37–1.9). In contrast, there was a significant difference in the dominant model (OR = 2.15, 95% CI: 1.25–5.31, $p=0.043$). These differences remained even after adjusting for age, drinking, smoking, and ER status (Table 3).

Meta-analysis

Fifteen relevant studies were identified from the literature search. The flow diagram of the search process is illustrated in Figure 1, and the characteristics of the enrolled studies are summarized in Table 4. Heterogeneity was identified by the Q test and I^2 statistic, and no significant publication bias was found by the Begg's test ($p > 0.05$) (Figure 2). We performed a

Table 2. Genotypes of FGFR2 rs2981582 polymorphism between patient (case) and control group.

rs2981582	Control	Case	p-value
CC	16	24	0.021
TC	59	33	
TT	65	38	
C	91	81	0.025
T	189	109	

Table 1. Demographic data of enrolled participants.

Variable	Case (n = 95)	Controls (n = 140)	p-value
Age (years)	47.22 ± 12.43	48.15 ± 10.61	0.192
Body weight (kg)	48.31 ± 11.64	45.20 ± 10.57	0.086
Tobacco consumption			
Yes	25.1%	19.4%	0.091
No	74.9%	80.6%	
Drinking			
Yes	24.3%	18.5%	0.065
No	75.7%	76.5%	
Clinical stage			
I-II	70		
III	25		
ER			
Positives	31 (32.6%)		
Negative	64 (67.4%)		

Table 3. Logistic regression analysis of rs2981582 SNP genotype with breast cancer.

rs2981582	OR	95% CI	p-value	OR*	95% CI*	p-value*
CC	Reference			Reference		
TT	1.21	1.050–2.27	0.019	1.19	1.172–2.957	0.017
TC	1.81	1.24–2.73	0.035	1.80	1.169–2.71	0.031
Dominant model	2.15	1.25–5.31	0.043	2.1	1.21–5.28	0.041
Recessive model	1.14	0.37–1.9	0.165	1.12	0.31–1.85	0.152

*Adjusting for age, body weight, smoking, drinking, and estrogen receptor status. Significant associations are marked in bold.

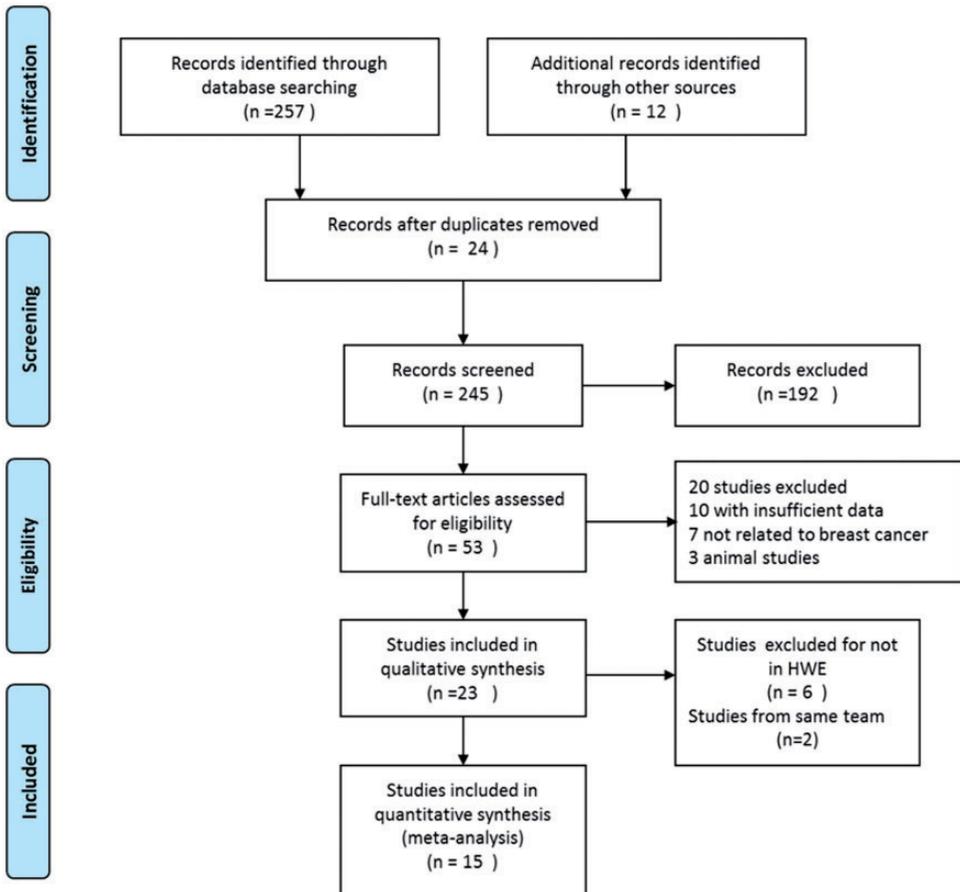


Figure 1. Flow sheet summarizing identification and selection of studies.

sensitivity analysis to assess the influence of each individual study on the pooled OR by sequentially removing each eligible study. The results indicated that no single study

influenced the quality of the pooled ORs in the sensitivity analysis (Figure 3).

We used a pooled meta-analysis to determine BC risk and rs2981582 polymorphism

Table 4. The basic characteristics of the 15 studies in the meta-analysis, showing FGFR2 rs2981582 single nucleotide polymorphism genotype and allele distribution in breast cancer patients (cases) and controls.

Studies	Year	Total Number						Case						Control						Method	HWE
		Case	Control	TT	TC	CC	T	C	TT	TC	CC	T	C	TT	TC	CC	T	C			
Liang J et al. ²²	2008	1049	1073	119	460	447	698	1354	91	439	532	621	1503	Taqman	0.974						
Kawase T et al. ²³	2009	456	912	42	192	221	276	634	63	347	502	473	1351	TaqMan	0.773						
Hu X et al. ²⁴	2011	203	200	47	78	78	172	234	26	95	79	147	253	PCR-RFLP	0.758						
Li X et al. ²⁵	2011	869	464	54	180	167	288	514	60	189	192	309	573	MassArray	0.219						
Ren L et al. ²⁶	2011	936	471	130	400	426	660	1252	56	181	234	293	649	Taqman	0.361						
Fu F et al. ²⁷	2012	118	104	21	55	42	97	139	8	47	49	63	145	MassARRAY	0.474						
Chan M et al. ²⁸	2012	1191	1534	155	527	486	837	1499	162	618	695	942	2008	Taqman	0.165						
Dai J et al. ²⁹	2012	914	967	216	820	732	1252	2284	164	796	884	1124	2564	TaqMan	0.424						
Xi J et al. ³⁰	2014	839	863	100	423	292	623	1007	94	376	379	564	1134	MALDI-TOF	0.959						
Siddiqui S et al. ³¹	2014	368	484	56	168	144	280	456	53	205	226	311	657	PCR-RFLP	0.526						
Liang H et al. ³²	2015	609	882	103	266	238	472	742	111	375	370	597	1115	MassARRAY	0.298						
He YN et al. ³³	2015	253	343	41	103	109	185	321	49	157	137	255	431	iMLDR	0.710						
Jiang Q et al. ³⁴	2014	35	35	16	10	9	42	28	4	18	13	26	44	DHPLC	0.549						
Xu WH et al. ³⁵	2012	280	280	20	174	86	214	346	29	131	120	189	371	PCR-RFLP	0.439						
Lao HM et al. ³⁶	2012	623	620	46	150	155	242	460	48	151	151	247	453	MassARRAY	0.301						

HWE, Hardy-Weinberg equilibrium; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphisms, MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight, iMLDR, improved multiplex ligase detection reaction; DHPLC, denaturing high performance liquid chromatography.

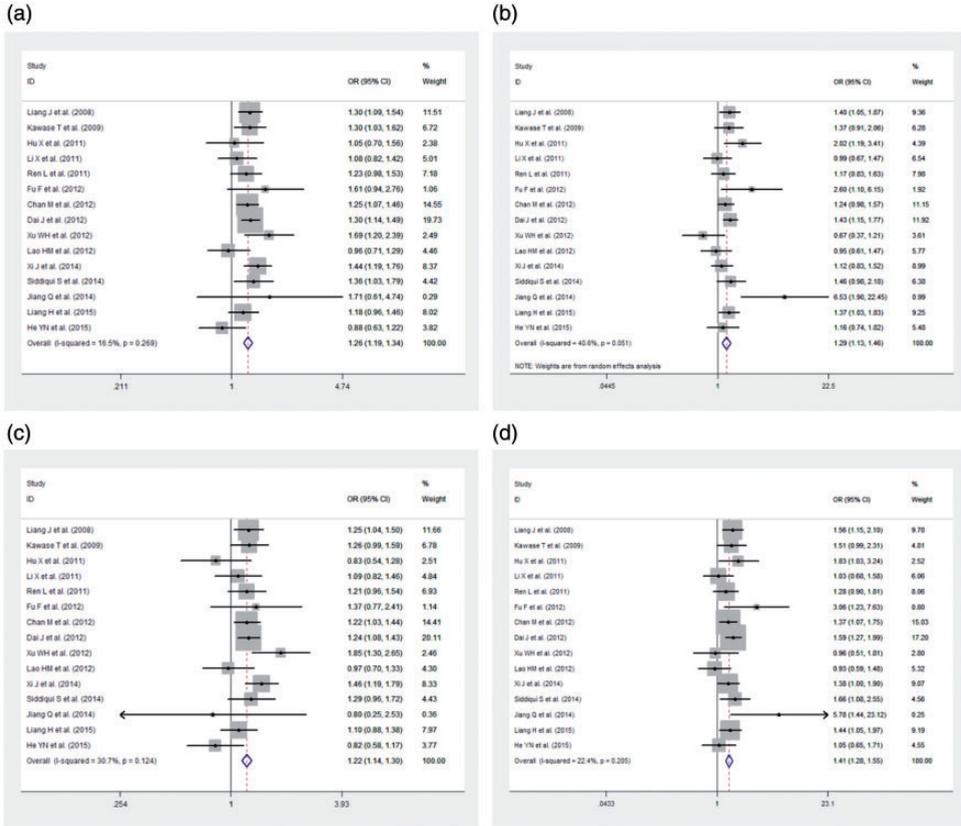


Figure 2. The publication bias examined by Begg’s test in the dominant model (TC + TT vs. CC).

in the Asian population under the recessive, dominant, homozygous, and heterozygote models (Figure 4). Our results showed that all four models could significantly increase the BC risk (dominant model: OR = 1.259, 95% CI: 1.187–1.336; recessive model: OR = 1.29, 95% CI: 1.13–1.46; heterozygote model: OR = 1.22, 95% CI: 1.14–1.30; homozygote model: OR = 1.41, 95% CI: 1.28–1.55).

Discussion

Breast cancer is a disease that results from the interaction of environmental and genetic factors, and it is now a leading cause of

cancer-related deaths in women worldwide.^{18,19} The incidence rate is increasing annually and patients are being diagnosed at an earlier age. However, the etiology, in terms of genetic risk factors associated with prognosis, is still not fully understood. FGFR2 has been reported to be associated with many diseases, especially with carcinogenesis. As a transmembrane protein, FGFR2 has an extracellular region, a transmembrane region, and an intracellular region. Once activated, it begins a cascade reaction through the RAS-MAPK and JAK-STAT signal pathways and then regulates the transcription of downstream genes involved in physiological and pathological

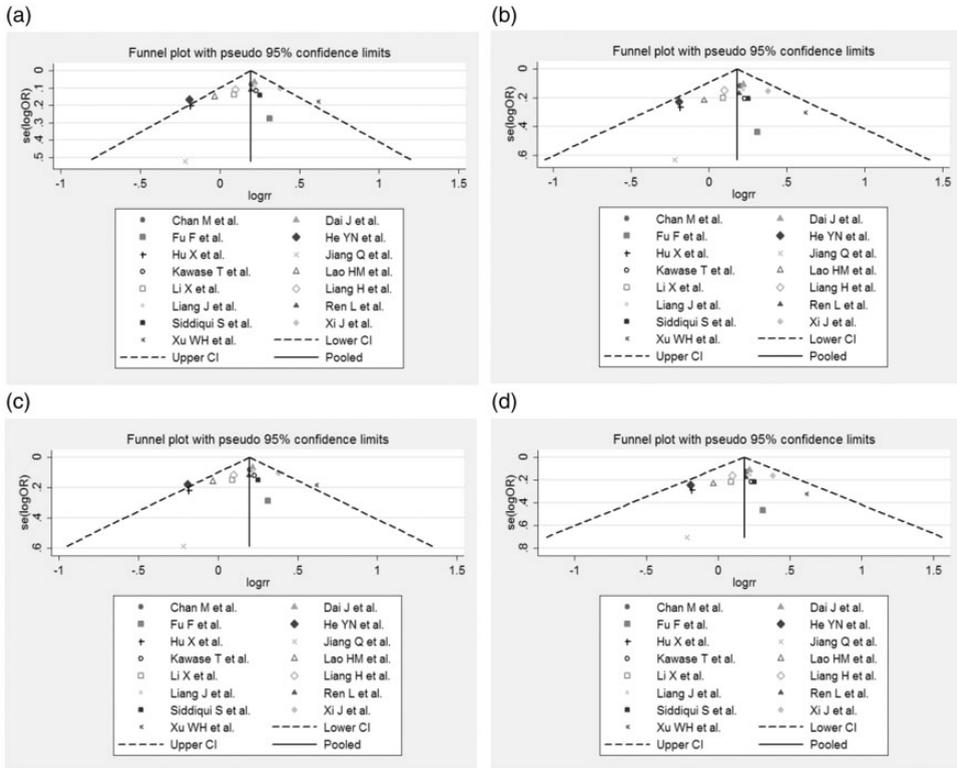


Figure 3. Sensitivity analysis of the association between FGFR2 rs2981582 polymorphism and breast cancer susceptibility in the dominant model (TC + TT vs. CC).

activities, such as cell proliferation, differentiation, migration, and apoptosis.

In our study, the FGFR2 rs2981582 polymorphisms in the TT and TC genotypes were significantly correlated with BC development. These results were partly in accordance with reports by Liu et al.²⁰ and Mazhar et al.²¹ However, those authors reported a significant association of genotype TT with the development of BC, whereas in our study both the TT and TC genotypes were significantly associated with BC. In addition, we found that either the dominant or additive model carried an increased risk of BC. To further elucidate the possible relationship of the polymorphism and BC, we performed a meta-analysis that included 15 studies in the

Asian population. The meta-analysis results showed that the recessive model was also significantly associated with BC, which was different from our result in the case-control study.

Meyer et al.¹³ supplied the first experimental evidence of mechanisms between particular FGFR2 intronic SNPs and breast cancer risk. Those authors showed that 2 FGFR2 intronic SNPs (rs7895676 and rs2981578) altered the binding affinity of FGFR2 for transcription factors and increased FGFR2 expression.¹³ However, based on published studies, the associations of rs2981582 polymorphism with BC are still inconsistent. These different conclusions may result from the diversity of genetic backgrounds and carcinogenic factors.

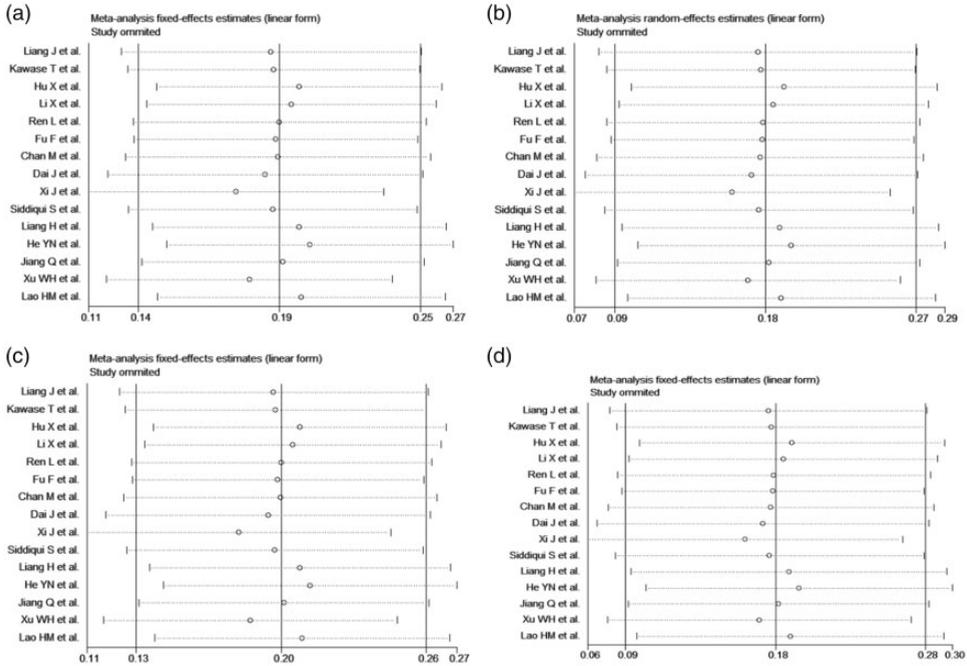


Figure 4. Forest plot of FGFR2 rs2981582 polymorphism and breast cancer susceptibility. (a) Dominant model (TC + TT vs. CC); (b) recessive model (TT vs. TC + CC); (c) heterogeneity model (TC vs. CC); and (d) homozygote model (TT vs. CC).

As a member of the FGFR family, FGFR2 has been found to be overexpressed in breast cancer cell lines. Aberrant expression of alternatively spliced isoforms of FGFR2 has been shown to activate cell mitogenesis and differentiation and lead to transformation in breast cancer cells. Nevertheless, this could be influenced by age, family history, reproductive and gynecologic factors, as well as lifestyle factors, such as alcohol consumption and lack of physical activity. Thus, the association of FGFR2 rs2981582 polymorphism with BC is still worth exploring.

Although our results might be useful in helping to identify patients with BC risk, the results should be considered preliminary and further research is necessary. However, we cannot ignore some of the limitations. First, the mechanism of BC is complex and we observed only one SNP; therefore,

our results cannot completely explain the association of genetic polymorphism and BC. Second, our sample size for BC cases was relatively small and all patients were from ShaanXi Province in northwest China, which may bias the final results. Third, the meta-analysis results were not representative because all enrolled studies were from an Asian population. Furthermore, the existence of confounding factors, such as family history, hormone metabolism, and menopausal status, might have distorted the meta-analysis, explaining the inconsistent results between the case-control study and the meta-analysis.

In summary, our results showed an association of the FGFR2 rs2981582 polymorphism with BC in an Asian population. However, these data need to be replicated in a larger cohort of patients, and functional studies are necessary to investigate

whether and how the polymorphism might influence key pathways involved in the pathogenesis of BC.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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