Association between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and breast cancer susceptibility: a meta-analysis

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Keywords: breast cancer, FGFR2, polymorphism
Received: August 08, 2016  Accepted: November 22, 2016  Published: December 09, 2016

ABSTRACT

The association between fibroblast growth factor receptor 2 (FGFR2) polymorphism and breast cancer (BC) susceptibility remains inconclusive. The purpose of this systematic review was to evaluate the relationship between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk. PubMed, Web of science and the Cochrane Library databases were searched before October 11, 2015 to identify relevant studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of associations. Sensitivity and subgroup analyses were conducted. Thirty-five studies published from 2007 to 2015 were included in this meta-analysis. The pooled results showed that there was significant association between all the 3 variants and BC risk in any genetic model. Subgroup analysis was performed on rs2981582 and rs2420946 by ethnicity and Source of controls, the effects remained in Asians, Caucasians, population-based and hospital-based groups. We did not carry out subgroup analysis on rs2981578 for the variant included only 3 articles. This meta-analysis of case-control studies provides strong evidence that FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphisms were significantly associated with the BC risk. For rs2981582 and rs2420946, the association remained significant in Asians, Caucasians, general populations and hospital populations. However, further large scale multicenter epidemiological studies are warranted to confirm this finding and the molecular mechanism for the association need to be elucidated further.

INTRODUCTION

Breast cancer (BC), one of the most common malignant tumors among women worldwide, has the highest mortality rate in female cancer. Its incidence rate is increasing year by year and the patients are becoming younger and younger in the world [1, 2]. BC is the result of the interaction of environmental and genetic factors. Under the same carcinogenic factors, only a small fraction of people develop BC, which suggests that the genetic background differences lead to individual differences in BC susceptibility [3].

In recent years, genome-wide association study (GWAS) provides a good technical support for the study on the susceptibility loci with high variation frequency and low penetrance [4]. Large numbers of BC related susceptibility genes and single nucleotide polymorphism sites have been found through GWAS, such as LSP1, MAP3K1, FGFR2, TGFB1, TOX3, etc [5]. The discovery of these genes will have an important impact on the prevention and treatment of BC, especially FGFR2 (rs2981582, rs2420946 and rs2981578). FGFR2 gene is located in 10q26, and contains at least 22 exons [6]. FGFR2 is a member of the tyrosine kinase receptor family. It is a transmembrane protein, and is mainly composed of three parts: extracellular region, transmembrane region and intracellular region. The extracellular segment has three immunoglobulin like protein functional areas. Through the combination with
FGFs, the functional areas could activate the tyrosine kinase activity and induce receptor tyrosine phosphorylation. It also starts series of cascade reaction through the RAS-MAPK, JAK-STATs and PLC-Y signal system, and then regulate the transcription of downstream genes involve in the body's physiological and pathological activities, such as cell proliferation, differentiation, migration and apoptosis, angiogenesis, skeletal development. So FGFR2 plays an important role in the processes of human growth and development [7].

Lots of researches have reported the association between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk. However, due to differences in ethnic and regional and other factors, the conclusions of related reports are still inconclusive. Raskin et al [8] found FGFR2 rs2420946 was significantly associated with BC risk in Ashkenazi and Sephardi Jews, with a similar but not significant trend in Arabs. Liang et al’s [9] study indicated that each of the single nucleotide polymorphisms (SNPs) (rs2981582 and rs2420946) was significantly associated with increased BC risk, and the risk was the highest for those carrying the 2 mutation sites at the same time. While, there are also some different reports. Liu et al [10] found that FGFR2 rs2420946 was not significantly correlated with the occurrence of BC in Chinese population. These different conclusions may result from the diversity of genetic background and carcinogenic factors, therefore, further studies in different populations should be implemented to assess the correlation between SNPs and BC risk. Although five meta-analysis [11–15] on the associations between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk had been implemented, yet the results remained inconclusive and some just no subgroup. Therefore, we carried out this meta-analysis on all the included case-control researches to make a more accurate assessment of the relationship.

RESULTS

Characteristics of included papers

The specific search process is shown in Figure 1. A total of 563 references were preliminarily identified at first based on our selection strategy. We also identified 2 papers
through other sources. 454 records left after removing repeated studies. We refer to titles or abstracts of all the included literatures, and then removed obviously irrelevant papers. In the end, the whole of the rest of the papers were checked based on the inclusion and exclusion criteria.

Finally, 35 studies on FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and the occurrence of BC were eventually included in our study. Characteristics of eligible analysis are shown in Table 1. The 35 case-control papers were published between 2007 and 2015, among them, 1 study was performed in African, 17 in Asian, 14 in Caucasians and 3 in both Asian and Caucasians. All studies were case-controlled.

Meta-analysis results

The FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphisms genotype distribution and allele frequencies in case groups and control groups were shown in Table 2. Main results of our study were shown in Table 3. There were 31 studies with 54,677 cases and 80,418 controls for FGFR2 rs2981582 variants. As shown in Table 3, Figure 2 and Figure 3, the pooled results indicated that the correlation between FGFR2 rs2981582 polymorphism and the occurrence of BC was significant in any genetic model: Allele model (OR: 1.23; 95% CI: 1.19-1.26; P< 0.00001), Dominant model (OR: 1.29; 95% CI: 1.24-1.34; P< 0.00001), Recessive model (OR: 1.35; 95% CI: 1.31-1.40; P<0.00001), Homozygous genetic model (OR: 1.50; 95% CI: 1.42-1.58; P< 0.00001), Heterozygote comparison (OR: 1.22; 95% CI: 1.17-1.27; P< 0.00001). In ethnicity specific analysis, FGFR2 rs2981582 were significantly associated with BC risk both in Asians (Allele model: OR=1.19, 95% CI=1.15-1.24, P< 0.00001; Dominant model: OR=1.23, 95% CI=1.17-1.29, P< 0.00001; Recessive model: OR=1.31, 95% CI=1.21-1.42, P< 0.00001; Homozygous genetic model: OR=1.42, 95% CI=1.31-1.54, P< 0.00001; Heterozygote comparison: OR=1.18, 95% CI=1.12-1.25, P< 0.00001) and Caucasians (Allele model: OR=1.25, 95% CI=1.21-1.30, P< 0.00001; Dominant model: OR=1.33, 95% CI=1.26-1.40, P< 0.00001; Recessive model: OR=1.37, 95% CI=1.28-1.46, P< 0.00001; Homozygous genetic model: OR=1.56, 95% CI=1.45-1.68, P< 0.00001; Heterozygote comparison: OR=1.26, 95% CI=1.19-1.33, P< 0.00001). We didn’t discuss the African subgroup for just one study from African. The analysis in different source of controls showed the same association between FGFR2 rs2981582 polymorphism and BC susceptibility in all the five genetic models: Allele model (OR= 1.23; 95% CI: 1.18-1.29; P< 0.00001); Dominant model (OR= 1.28; 95% CI: 1.20-1.37; P< 0.00001); Recessive model (OR= 1.36; 95% CI: 1.26-1.48; P< 0.00001); Homozygous genetic model 1.52 (95% CI: 1.39-1.66; P< 0.00001); Heterozygote comparison 1.21 (95% CI: 1.13-1.29; P< 0.00001). When stratified by Ethnicity and Source of controls, the results showed that FGFR2 rs2420946 was significantly associated with BC risk in Asians, Caucasians, HB and PB.

3 papers with 833 cases and 1012 controls were adopted to evaluate the association between the rs2981578 polymorphism and the BC risk. As shown in Table 3, Figure 4 and Figure 5, the pooled ORs suggested that rs2420946 was significantly associated with BC susceptibility in all the five genetic models: Allele model 1.23 (95% CI: 1.18-1.29; P< 0.00001), Dominant model 1.28 (95% CI: 1.20-1.37; P< 0.00001), Recessive model 1.36 (95% CI: 1.26-1.48; P< 0.00001), Homozygous genetic model 1.52 (95% CI: 1.39-1.66; P< 0.00001), Heterozygote comparison 1.21 (95% CI: 1.13-1.29; P< 0.00001). When stratified by Ethnicity and Source of controls, the results showed that FGFR2 rs2420946 was significantly associated with BC risk in Asians, Caucasians, HB and PB.

Sensitivity analyses

As shown in Table 1, all the studies conformed to the balance of HWE in controls except Chen’s(2012), Gorodnova’s(2012), Ren’s(2012), Zhao’s(2012) studies(P<0.05) in rs2981582 group, however, after performing the sensitivity analyses, the overall outcomes were no statistically significant change when removing any of the articles, indicating that our study has good stability and reliability.

Detection for heterogeneity

Heterogeneity among studies was obtained by Q statistic. Random-effect models were applied if p-value of heterogeneity tests were less than 0.1 (p ≤ 0.1), otherwise, fixed-effect models were selected (Table 3).

Publication bias

As Figure 7 indicated, the symmetrical funnel plot indicated that there is no significant publication bias in the total population. We use Begg's funnel plot and Egger test to evaluate the published bias, no significant publication bias was found in the Begg's test and Egger's test (P>0.05).
| First author | Year  | Country    | Ethnicity  | Source of controls | Genotyping method | Number (case/control) | HWE          |
|-------------|-------|------------|------------|--------------------|-------------------|-----------------------|-------------|
| rs2981582 (C>T) |       |            |            |                    |                   |                       |             |
| Kawase [20]  | 2009  | Japan      | Asian      | HB                 | TaqMan            | 455/912               | 0.773315    |
| Hu [25]      | 2011  | China      | Asian      | PB                 | PCR-RFLP         | 203/200               | 0.758366    |
| Li [26]      | 2011  | China      | Asian      | HB                 | MassArray        | 401/441               | 0.219207    |
| Chen [27]    | 2012  | China      | Asian      | PB                 | PCR-SSCP         | 388/424               | 0.048991    |
| Butt [28]    | 2012  | Swedish    | Caucasian  | PB                 | MassArray        | 713/1399              | 0.816442    |
| Shan [29]    | 2012  | Tunisian   | African    | PB                 | TaqMan            | 600/358               | 0.060883    |
| Fu [30]      | 2012  | China      | Asian      | HB                 | iPLEX            | 118/104               | 0.474243    |
| Campa [31]   | 2011  | Mixed      | Mixed      | PB                 | Taqman            | 8313/11594            | 0.607558    |
| Slattery [32]| 2011  | American   | Caucasian  | PB                 | Taqman            | 1734/2040             | 0.822553    |
| Han [33]     | 2011  | Korean     | Asian      | PB                 | Taqman            | 3232/3489             | 0.361342    |
| Tamimi [34]  | 2010  | Swedish    | Caucasian  | PB                 | Taqman            | 680/734               | 0.535243    |
| Gorodnova [35]| 2010 | Russian    | Caucasian  | NA                 | Taqman            | 140/174               | 0.000621    |
| Ren [36]     | 2010  | China      | Asian      | HB                 | Taqman            | 956/471               | 0.024883    |
| McInerney [37]| 2009 | British    | Caucasian  | PB                 | KASPar            | 941/997               | 0.83057     |
| Boyarskikh [38]| 2009 | Russia     | Caucasian  | PB                 | Taqman            | 744/628               | 0.659988    |
| Garcia-Closas [39]| 2008 | Mixed      | Mixed      | PB, HB             | Taqman            | 16882/26058           | 0.892667    |
| Liang [9]    | 2008  | China      | Asian      | HB                 | Taqman            | 1026/1062             | 0.97418     |
| Antoniou [40]| 2008  | European   | Mixed      | NA                 | Taqman, MALDI-TOF | 4990/4301             | 0.596563    |
| Zhao [41]    | 2010  | China      | Asian      | HB                 | PCR-RFLP         | 956/471               | 0.024883    |
| Xi [42]      | 2014  | China      | Asian      | HB                 | MALDI-TOF        | 815/849               | 0.959015    |
| Campa [19]   | 2015  | Mixed      | Caucasian  | PB                 | TaqMan            | 1234/12231            | 0.779613    |
| Slattery [43]| 2013  | American   | Caucasian  | PB                 | multiplexed      | 3560/4138             | 0.364662    |
| Chan [44]    | 2012  | China      | Asian      | HB                 | Taqman            | 1168/1475             | 0.164674    |
| Dai [45]     | 2012  | China      | Asian      | HB                 | TaqMan            | 1768/1844             | 0.423521    |
| Jara [46]    | 2013  | Chile      | Caucasian  | PB                 | TaqMan            | 351/802               | 0.138274    |
| Liang [18]   | 2015  | China      | Asian      | HB                 | MassARRAY        | 607/856               | 0.298476    |
| Liu [47]     | 2013  | China      | Asian      | HB                 | PCR-RFLP         | 203/200               | 0.758366    |
| Murillo-Zamora [48]| 2013 | Mexico     | Caucasian  | PB                 | Multiplexed      | 687/907               | 0.351295    |
| Ottini [49]  | 2013  | Italy      | Caucasian  | PB                 | TaqMan            | 413/745               | 0.76716     |
| Ozgoz [50]   | 2013  | Turkey     | Caucasian  | PB                 | PCR-RFLP         | 31/30                 | 0.281979    |
| Siddiqui [51]| 2014  | India      | Asian      | HB                 | PCR-RFLP         | 368/484               | 0.526174    |

(Continued)
| First author | Year | Country | Ethnicity | Source of controls | Genotyping method | Number(case/control) | HWE  |
|--------------|------|---------|-----------|--------------------|-------------------|----------------------|------|
| rs2420946 (C>T) |      |         |           |                    |                   |                      |      |
| Raskin [8]    | 2008 | USA     | Caucasian | PB                 | TaqMan            | 1480/1474            | 0.224235 |
| Kawase [20]   | 2009 | Japan   | Asian     | HB                 | TaqMan            | 453/912              | 0.519554 |
| Liu [10]      | 2009 | China   | Asian     | PB                 | PCR-RFLP          | 106/116              | 0.361602 |
| Hu [25]       | 2011 | China   | Asian     | PB                 | PCR-RFLP          | 203/200              | 0.325727 |
| Li [26]       | 2011 | China   | Asian     | HB                 | MassArray         | 391/432              | 0.703117 |
| Fu [30]       | 2012 | China   | Asian     | HB                 | iPLEX             | 118/104              | 0.505449 |
| Liang [9]     | 2008 | China   | Asian     | HB                 | Taqman            | 1020/1050            | 0.413194 |
| Hunter [52]   | 2007 | USA     | Caucasian | PB                 | Taqman            | 2912/3212            | 0.293864 |
| Jara [46]     | 2013 | Chile   | Caucasian | PB                 | TaqMan            | 351/802              | 0.292806 |
| Li [26]       | 2013 | China   | Asian     | HB                 | MassARRAY         | 603/847              | 0.063645 |
| Liu [47]      | 2013 | China   | Asian     | HB                 | PCR-RFLP          | 391/432              | 0.325727 |
| rs2981578 (A>G) |      |         |           |                    |                   |                      |      |
| Chen [27]     | 2012 | China   | Asian     | PB                 | PCR-SSCP          | 378/458              | 0.290218 |
| Lin [53]      | 2012 | Taiwan  | Asian     | PB                 | PCR-RFLP          | 87/70                | 0.724138 |
| Siddiqui [51] | 2013 | India   | Asian     | HB                 | PCR-RFLP          | 368/484              | 0.278456 |

HWE: hardy-weinberg equilibrium; PB: population based; HB: hospital-based.

Table 2: Polymorphisms genotype distribution and allele frequency in cases and controls

| First author | Genotype (N) | Allele frequency (N) |
|--------------|--------------|----------------------|
|              | Case         | Control              |                      |
|              | T            | C                    | T                   | C                   |
| rs2981582 (C>T) |               |                      |                      |
| Kawase [20]   |               |                      |                      |
| Hu [25]       |               |                      |                      |
| Li [26]       |               |                      |                      |
| Chen [27]     |               |                      |                      |
| Butt [28]     |               |                      |                      |
| Shan [29]     |               |                      |                      |
| Fu [30]       |               |                      |                      |
| Campa [31]    |               |                      |                      |
| Slattery [32] |               |                      |                      |
| Han [33]      |               |                      |                      |
| Tamimi [34]   |               |                      |                      |
| Gorodanova [35]|             |                      |                      |
| Ren [36]      |               |                      |                      |
| Mcnnerney [37]|               |                      |                      |
| Boyarskikh [38]|             |                      |                      |

(Continued)
| First author           | Genotype (N) | Allele frequency (N) |
|-----------------------|--------------|---------------------|
|                        | Case         | Control             | Case          | Control     |
| Garcia-Closas [39]    | 16882        | 3243                | 8218          | 5421        | 26058      | 3747        | 12255       | 10056       | 14704       | 19060       | 19749       | 32367       |
| Liang [9]             | 1026         | 119                 | 460           | 447         | 1062       | 91          | 439         | 532         | 698         | 1354        | 621         | 1503        |
| Antoniou [40]         | 4990         | 936                 | 2407          | 1647        | 4301       | 703         | 2051        | 1547        | 4279        | 5701        | 3457        | 5145        |
| Zhao [41]             | 956          | 130                 | 400           | 426         | 471        | 56          | 181         | 234         | 660         | 1252        | 293         | 649         |
| Xi [42]               | 815          | 100                 | 423           | 292         | 849        | 94          | 376         | 379         | 623         | 1007        | 564         | 1134        |
| Campa [19]            | 1234         | 241                 | 608           | 385         | 12231      | 1847        | 5793        | 4591        | 1090        | 1378        | 9487        | 14975       |
| Slattery [43]         | 3560         | 708                 | 1749          | 1103        | 4138       | 638         | 2009        | 1491        | 3165        | 3955        | 3285        | 4991        |
| Chan [44]             | 1168         | 155                 | 527           | 486         | 1475       | 162         | 618         | 695         | 837         | 1499        | 942         | 2008        |
| Dai [45]              | 1768         | 216                 | 820           | 732         | 1844       | 164         | 796         | 884         | 1252        | 2284        | 1124        | 2564        |
| Jara [46]             | 351          | 80                  | 178           | 93          | 802        | 141         | 366         | 295         | 338         | 364         | 648         | 956         |
| Liang [18]            | 607          | 103                 | 266           | 238         | 856        | 111         | 375         | 370         | 472         | 742         | 597         | 1115        |
| Liu [47]              | 203          | 47                  | 78            | 78          | 200        | 26          | 95          | 79          | 172         | 234         | 147         | 253         |
| Murillo-Zamora [48]   | 687          | 145                 | 309           | 233         | 907        | 139         | 415         | 353         | 599         | 775         | 693         | 1121        |
| Ottini [49]           | 413          | 98                  | 205           | 110         | 745        | 139         | 361         | 245         | 401         | 425         | 639         | 851         |
| Ozgoz [50]            | 31           | 9                   | 16            | 6           | 30         | 10          | 12          | 8           | 34          | 28          | 32          | 28          |
| Siddiqui [51]         | 368          | 76                  | 148           | 144         | 484        | 53          | 205         | 226         | 280         | 456         | 311         | 657         |
| rs2420946 (C>T)       | Total TT     | 1480                | 1715          | 409         | 1474       | 285         | 700         | 489         | 1427        | 1533        | 1270        | 1678        |
| Raskin [8]            | 453          | 60                  | 226           | 167         | 912        | 99          | 416         | 397         | 346         | 560         | 614         | 1210        |
| Kawase [20]           | 106          | 16                  | 51            | 39          | 116        | 21          | 51          | 44          | 83          | 129         | 93          | 139         |
| Hu [25]               | 203          | 50                  | 92            | 61          | 200        | 34          | 105         | 61          | 192         | 214         | 173         | 227         |
| Li [26]               | 391          | 74                  | 186           | 131         | 432        | 68          | 202         | 162         | 334         | 448         | 338         | 526         |
| Fu [30]               | 118          | 25                  | 55            | 38          | 104        | 9           | 48          | 47          | 105         | 131         | 66          | 142         |
| Liang [9]             | 1020         | 163                 | 519           | 338         | 1050       | 142         | 505         | 403         | 845         | 1195        | 789         | 1311        |
| Hunter [52]           | 2912         | 603                 | 1409          | 900         | 3212       | 484         | 1562        | 1166        | 2615        | 3209        | 2530        | 3894        |
| Jara [46]             | 351          | 85                  | 175           | 91          | 802        | 143         | 374         | 285         | 345         | 357         | 660         | 944         |
| Liang [18]            | 603          | 116                 | 297           | 190         | 847        | 145         | 379         | 323         | 529         | 677         | 669         | 1025        |
| Liu [47]              | 203          | 50                  | 92            | 61          | 200        | 34          | 105         | 61          | 192         | 214         | 173         | 227         |
| rs2981578 (A>G)       | Total GG     | 378                 | 150           | 188         | 40         | 458        | 160         | 212         | 86          | 488         | 268         | 532         | 384         |
| Chen [27]             | 87           | 35                  | 39            | 13          | 70         | 21          | 36          | 13          | 109         | 65          | 78          | 62          |
| Siddiqui [51]         | 368          | 129                 | 185           | 54          | 484        | 151         | 228         | 105         | 443         | 293         | 530         | 438         |

**DISCUSSION**

FGFR2 has been proved to be associated with many diseases, especially the relationship between FGFR2 and cancer, which has become a hot research topic in recent years [16]. GWAS analysis revealed that FGFR2 gene was one of the BC susceptibility genes. There are 8 SNPs (rs35054928, rs2981578, rs2912778, rs2912781, rs35393331, rsI0736303, rs7895676, rs33971856) in its second intron and the SNPs of FGFR2 have become the hotspot in BC susceptibility gene study [17–19]. But the difference of SNPs allele frequency and LD structure
### Table 3: Meta-analysis results

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate       | P value       | Heterogeneity | I²   | P value |
|---------------------|---------|--------------|--------------------|-----------------------|---------------|---------------|------|---------|
| Allele model        |         |              |                    |                       |               |               |      |         |
| rs2981582 (C>T)     | 31      | 270190       | OR (M-H, Random, 95% CI) | 1.23 [1.19, 1.26] | < 0.00001    | 41%           | 0.01 |         |
| Asian               | 15      | 51892        | OR (M-H, Fixed, 95% CI) | 1.19 [1.15, 1.24] | < 0.00001    | 0%            | 0.54 |         |
| Caucasian           | 12      | 72106        | OR (M-H, Fixed, 95% CI) | 1.25 [1.21, 1.30] | < 0.00001    | 4%            | 0.4  |         |
| HB                  | 12      | 36020        | OR (M-H, Fixed, 95% CI) | 1.22 [1.16, 1.27] | < 0.00001    | 0%            | 0.87 |         |
| PB                  | 16      | 129080       | OR (M-H, Random, 95% CI) | 1.24 [1.19, 1.29] | < 0.00001    | 46%           | 0.02 |         |
| rs2420946 (C>T)     | 11      | 34378        | OR (M-H, Fixed, 95% CI) | 1.23 [1.18, 1.29] | < 0.00001    | 0%            | 0.67 |         |
| Asian               | 8       | 13916        | OR (M-H, Fixed, 95% CI) | 1.19 [1.11, 1.28] | < 0.00001    | 0%            | 0.67 |         |
| Caucasian           | 3       | 20462        | OR (M-H, Fixed, 95% CI) | 1.26 [1.19, 1.33] | < 0.00001    | 0%            | 0.53 |         |
| HB                  | 6       | 12666        | OR (M-H, Fixed, 95% CI) | 1.20 [1.12, 1.29] | < 0.00001    | 0%            | 0.61 |         |
| PB                  | 5       | 21712        | OR (M-H, Fixed, 95% CI) | 1.25 [1.18, 1.32] | < 0.00001    | 0%            | 0.5  |         |
| rs2981578 (A>G)     | 3       | 3690         | OR (M-H, Fixed, 95% CI) | 1.29 [1.13, 1.47] | 0.0002       | 0%            | 0.93 |         |
| Dominant model      |         |              |                    |                       |               |               |      |         |
| rs2981582 (C>T)     | 31      | 135095       | OR (M-H, Random, 95% CI) | 1.29 [1.24, 1.34] | < 0.00001    | 46%           | 0.003|         |
| Asian               | 15      | 25946        | OR (M-H, Fixed, 95% CI) | 1.23 [1.17, 1.29] | < 0.00001    | 0%            | 0.63 |         |
| Caucasian           | 12      | 36053        | OR (M-H, Fixed, 95% CI) | 1.33 [1.26, 1.40] | < 0.00001    | 16%           | 0.28 |         |
| HB                  | 12      | 18010        | OR (M-H, Fixed, 95% CI) | 1.27 [1.20, 1.35] | < 0.00001    | 0%            | 0.89 |         |
| PB                  | 16      | 64540        | OR (M-H, Random, 95% CI) | 1.31 [1.23, 1.40] | < 0.00001    | 55%           | 0.004|         |
| rs2420946 (C>T)     | 11      | 17189        | OR (M-H, Fixed, 95% CI) | 1.28 [1.20, 1.37] | < 0.00001    | 0%            | 0.77 |         |
| Asian               | 8       | 6958         | OR (M-H, Fixed, 95% CI) | 1.25 [1.13, 1.39] | < 0.00001    | 0%            | 0.75 |         |
| Caucasian           | 3       | 10231        | OR (M-H, Fixed, 95% CI) | 1.31 [1.20, 1.42] | < 0.00001    | 0%            | 0.38 |         |
| HB                  | 6       | 6333         | OR (M-H, Fixed, 95% CI) | 1.28 [1.15, 1.42] | < 0.00001    | 0%            | 0.73 |         |
| PB                  | 5       | 10856        | OR (M-H, Fixed, 95% CI) | 1.29 [1.19, 1.40] | < 0.00001    | 0%            | 0.44 |         |
| rs2981578 (A>G)     | 3       | 1845         | OR (M-H, Fixed, 95% CI) | 1.71 [1.32, 2.21] | < 0.0001     | 0%            | 0.63 |         |
| Recessive model     |         |              |                    |                       |               |               |      |         |
| rs2981582 (C>T)     | 31      | 135095       | OR (M-H, Fixed, 95% CI) | 1.35 [1.31, 1.40] | < 0.00001    | 15%           | 0.24 |         |
| Asian               | 15      | 25946        | OR (M-H, Fixed, 95% CI) | 1.31 [1.21, 1.42] | < 0.00001    | 19%           | 0.24 |         |
| Caucasian           | 12      | 36053        | OR (M-H, Fixed, 95% CI) | 1.37 [1.28, 1.46] | < 0.00001    | 0%            | 0.74 |         |
| HB                  | 12      | 18010        | OR (M-H, Fixed, 95% CI) | 1.31 [1.20, 1.44] | < 0.00001    | 0%            | 0.5  |         |

(Continued)
| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate | P value | Heterogeneity |
|---------------------|---------|--------------|--------------------|----------------|---------|---------------|
| PB                  | 16      | 64540        | OR (M-H, Fixed, 95% CI) | 1.35 [1.29, 1.42] | < 0.00001 | 0%            |
| rs2420946 (C>T)     | 11      | 17189        | OR (M-H, Fixed, 95% CI) | 1.36 [1.26, 1.48] | < 0.00001 | 4%            |
| Asian               | 8       | 6958         | OR (M-H, Fixed, 95% CI) | 1.27 [1.12, 1.45] | 0.0003   | 8%            |
| Caucasian           | 3       | 10231        | OR (M-H, Fixed, 95% CI) | 1.42 [1.29, 1.57] | < 0.00001 | 0%            |
| HB                  | 6       | 6333         | OR (M-H, Fixed, 95% CI) | 1.27 [1.11, 1.46] | 0.0006   | 4%            |
| PB                  | 5       | 10856        | OR (M-H, Fixed, 95% CI) | 1.41 [1.28, 1.56] | < 0.00001 | 0%            |
| rs2981578 (A>G)     | 3       | 1845         | OR (M-H, Fixed, 95% CI) | 1.24 [1.02, 1.50] | 0.03     | 0%            |
| Homozygous genetic model |      |              |                     |                |         |               |
| rs2981582 (C>T)     | 31      | 71786        | OR (M-H, Random, 95% CI) | 1.50 [1.42, 1.58] | < 0.00001 | 33%           |
| Asian               | 15      | 14673        | OR (M-H, Fixed, 95% CI) | 1.42 [1.31, 1.54] | < 0.00001 | 2%            |
| Caucasian           | 12      | 18824        | OR (M-H, Fixed, 95% CI) | 1.56 [1.45, 1.68] | < 0.00001 | 0%            |
| HB                  | 12      | 10192        | OR (M-H, Fixed, 95% CI) | 1.45 [1.31, 1.60] | < 0.00001 | 0%            |
| PB                  | 16      | 34101        | OR (M-H, Fixed, 95% CI) | 1.50 [1.43, 1.58] | < 0.00001 | 32%           |
| rs2420946 (C>T)     | 11      | 8925         | OR (M-H, Fixed, 95% CI) | 1.52 [1.39, 1.66] | < 0.00001 | 0%            |
| Asian               | 8       | 3629         | OR (M-H, Fixed, 95% CI) | 1.40 [1.21, 1.62] | < 0.00001 | 0%            |
| Caucasian           | 3       | 5296         | OR (M-H, Fixed, 95% CI) | 1.60 [1.43, 1.79] | < 0.00001 | 0%            |
| HB                  | 6       | 3303         | OR (M-H, Fixed, 95% CI) | 1.43 [1.22, 1.66] | < 0.00001 | 0%            |
| PB                  | 5       | 5622         | OR (M-H, Fixed, 95% CI) | 1.57 [1.41, 1.76] | < 0.00001 | 0%            |
| rs2981578 (A>G)     | 3       | 957          | OR (M-H, Fixed, 95% CI) | 1.80 [1.36, 2.39] | < 0.0001  | 0%            |
| Heterozygote genetic model |      |              |                     |                |         |               |
| rs2981582 (C>T)     | 31      | 114046       | OR (M-H, Random, 95% CI) | 1.22 [1.17, 1.27] | < 0.00001 | 42%           |
| Asian               | 15      | 23025        | OR (M-H, Fixed, 95% CI) | 1.18 [1.12, 1.25] | < 0.00001 | 1%            |
| Caucasian           | 12      | 30051        | OR (M-H, Fixed, 95% CI) | 1.26 [1.19, 1.33] | < 0.00001 | 26%           |
| HB                  | 12      | 15893        | OR (M-H, Fixed, 95% CI) | 1.23 [1.15, 1.31] | < 0.00001 | 0%            |
| PB                  | 16      | 54285        | OR (M-H, Random, 95% CI) | 1.23 [1.15, 1.31] | < 0.00001 | 52%           |
| rs2420946 (C>T)     | 11      | 14127        | OR (M-H, Fixed, 95% CI) | 1.21 [1.13, 1.29] | < 0.00001 | 0%            |
| Asian               | 8       | 5852         | OR (M-H, Fixed, 95% CI) | 1.21 [1.08, 1.34] | 0.0005   | 0%            |
| Caucasian           | 3       | 8275         | OR (M-H, Fixed, 95% CI) | 1.21 [1.11, 1.32] | < 0.0001  | 0%            |
| HB                  | 6       | 5348         | OR (M-H, Fixed, 95% CI) | 1.23 [1.10, 1.38] | 0.0002   | 0%            |
| PB                  | 5       | 8779         | OR (M-H, Fixed, 95% CI) | 1.19 [1.09, 1.30] | < 0.0001  | 0%            |
| rs2981578 (A>G)     | 3       | 1199         | OR (M-H, Fixed, 95% CI) | 1.65 [1.26, 2.16] | 0.0003   | 0%            |

CI: Confidence interval.
Figure 2: Forest plots of rs2981582 (C>T) polymorphism and breast cancer risk stratified by ethnicity (Recessive model TT vs. CC + TC).
reflects the difference of the genetic variation in the race, so the occurrence and characteristics of BC were different. Therefore, a variation in one study does not have the same risk impact on other crowds. This requires repeated studies on previously related loci in multiple populations worldwide.

Lots of researches have reported the association between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk. However, due to differences in ethnic and regional and other factors, the conclusions of related reports are still inconclusive. Thus, we conducted the meta-analysis to evaluate the relationship

| Study or Subgroup | Case | Control | Odds Ratio | Odd Ratio |
|-------------------|------|---------|------------|-----------|
|                  | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 2,3.1 HB          | Chan 2012 | 155 | 1168 | 162 | 1475 | 1.8% | 1.24 [0.98, 1.57] |
|                   | Dai 2012  | 216 | 1768 | 164 | 1844 | 2.0% | 1.43 [1.15, 1.77] |
|                   | Fu 2012   | 21 | 118 | 8 | 104 | 0.1% | 2.60 [1.10, 6.15] |
|                   | Kawase 2009 | 42 | 455 | 63 | 912 | 0.5% | 1.37 [0.91, 2.06] |
|                   | Li 2011   | 54 | 401 | 60 | 441 | 0.7% | 0.99 [0.67, 1.47] |
|                   | Liang 2008 | 119 | 1026 | 91 | 1062 | 1.1% | 1.40 [1.05, 1.87] |
|                   | Liang 2015 | 103 | 607 | 111 | 856 | 1.1% | 1.37 [1.03, 1.83] |
|                   | Liu 2013  | 47 | 203 | 26 | 200 | 0.3% | 2.02 [1.19, 3.41] |
|                   | Ren 2010  | 120 | 956 | 56 | 471 | 0.9% | 1.17 [0.83, 1.63] |
|                   | Siddiqui 2014 | 56 | 368 | 53 | 484 | 0.8% | 1.46 [0.96, 2.19] |
|                   | Xi 2014   | 100 | 815 | 94 | 849 | 1.2% | 1.12 [0.83, 1.52] |
|                   | Zhao 2010 | 130 | 956 | 56 | 471 | 0.9% | 1.17 [0.83, 1.63] |
| Subtotal (95% CI)  | 8841 | 9169 | 11.3% | 1.31 [1.20, 1.44] |
| Total events       | 1173 | 944 |
| Heterogeneity: Chi² = 10.33, df = 11 (P = 0.50); I² = 0% |
| Test for overall effect: Z = 5.74 (P < 0.00001) |

2,3.2 PB

| Study or Subgroup | Case | Control | Odds Ratio | Odd Ratio |
|-------------------|------|---------|------------|-----------|
|                  | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Boyarskikh 2009   | 126 | 744 | 71 | 628 | 0.9% | 1.60 [1.17, 2.19] |
| Butt 2011        | 124 | 713 | 185 | 1989 | 1.5% | 1.36 [1.08, 1.77] |
| Campa 2011       | 1568 | 8313 | 1710 | 11594 | 16.8% | 1.34 [1.24, 1.44] |
| Campa 2015       | 241 | 1234 | 1847 | 12231 | 3.9% | 1.36 [1.18, 1.56] |
| Chen 2012        | 48 | 388 | 60 | 424 | 0.7% | 0.96 [0.57, 1.62] |
| Han 2011         | 342 | 3232 | 281 | 3489 | 3.5% | 1.35 [1.14, 1.59] |
| Hu 2011          | 47 | 203 | 26 | 200 | 0.3% | 2.02 [1.19, 3.41] |
| Jara 2013        | 80 | 351 | 141 | 802 | 1.0% | 1.38 [1.02, 1.88] |
| McNenney 2009    | 214 | 941 | 179 | 997 | 1.9% | 1.35 [1.08, 1.68] |
| Murillo-Zamora 2013 | 145 | 687 | 139 | 907 | 1.4% | 1.48 [1.14, 1.91] |
| Ottini 2013      | 98 | 413 | 139 | 745 | 1.1% | 1.36 [1.01, 1.82] |
| Ozgoz 2013       | 9 | 31 | 10 | 30 | 0.1% | 0.82 [0.28, 2.42] |
| Shan 2012        | 147 | 600 | 64 | 358 | 0.9% | 1.49 [1.07, 2.07] |
| Slattery 2011    | 315 | 1734 | 319 | 2040 | 3.4% | 1.20 [1.01, 1.43] |
| Stalder 2013     | 708 | 3560 | 638 | 4138 | 6.8% | 1.36 [1.21, 1.53] |
| Tamimi 2010      | 136 | 880 | 91 | 734 | 1.0% | 1.77 [1.32, 2.36] |
| Subtotal (95% CI) | 23924 | 40716 | 45.2% | 1.35 [1.29, 1.42] |
| Total events     | 4348 | 5907 |
| Heterogeneity: Chi² = 15.06, df = 15 (P = 0.45); I² = 0% |
| Test for overall effect: Z = 13.05 (P < 0.00001) |

2,3.3 NA

| Study or Subgroup | Case | Control | Odds Ratio | Odd Ratio |
|-------------------|------|---------|------------|-----------|
|                  | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Antoniou 2008     | 936 | 4990 | 703 | 4301 | 8.8% | 1.18 [1.06, 1.32] |
| Garcia-Closas 2008 | 3243 | 16882 | 3747 | 26058 | 34.3% | 1.42 [1.34, 1.49] |
| Gorodnova 2010    | 23 | 140 | 25 | 174 | 0.3% | 1.17 [0.83, 2.17] |
| Subtotal (95% CI) | 22912 | 36533 | 43.4% | 1.37 [1.30, 1.43] |
| Total events      | 4202 | 4475 |
| Heterogeneity: Chi² = 9.05, df = 2 (P = 0.01); I² = 78% |
| Test for overall effect: Z = 13.18 (P < 0.00001) |

Total (95% CI) 54677 80418 100.0% 1.35 [1.31, 1.40] |

Figure 3: Forest plots of rs2981582 (C>T) polymorphism and breast cancer risk stratified by Source of controls (Recessive model TT vs. CC + TC).
Figure 4: Forest plots of rs2420946 (C>T) polymorphism and breast cancer risk stratified by ethnicity (Dominant model TC + TT vs. CC).

| Study or Subgroup | Case Events | Control Events | total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|-------|--------|-------------------------------|
| 3.2.1 Asian       |             |                |       |        |                               |
| Fu 2012           | 80          | 118            | 57    | 104    | 1.2% 1.74 [1.01, 3.00]         |
| Hu 2011           | 142         | 203            | 139   | 200    | 2.6% 1.02 [0.67, 1.56]         |
| Kawase 2009       | 286         | 453            | 515   | 912    | 7.7% 1.32 [1.05, 1.66]         |
| Li 2011           | 260         | 391            | 270   | 432    | 5.2% 1.19 [0.89, 1.59]         |
| Liang 2008        | 682         | 1020           | 647   | 1050   | 12.8% 1.26 [1.05, 1.50]        |
| Liang 2015        | 413         | 603            | 524   | 847    | 8.3% 1.34 [1.07, 1.67]         |
| Liu 2009          | 87          | 106            | 72    | 116    | 1.5% 1.05 [0.61, 1.91]         |
| Liu 2011          | 142         | 203            | 139   | 200    | 2.6% 1.02 [0.67, 1.56]         |
| Subtotal (95% CI) | 3097        | 3861           | 41.9% |        | 1.25 [1.13, 1.39]              |
| Total events      | 2072        | 2363           |       |        |                               |
| Heterogeneity: $\chi^2 = 4.22, df = 7 (P = 0.75)$; $I^2 = 0\%$ |
| Test for overall effect: $Z = 4.44 (P < 0.00001)$ |

3.2.2 Caucasian

| Study or Subgroup | Case Events | Control Events | total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|-------|--------|-------------------------------|
| Hunter 2007       | 2012        | 2912           | 2046  | 3212   | 36.6% 1.27 [1.15, 1.42]       |
| Jara 2013         | 280         | 351            | 517   | 802    | 5.0% 1.59 [1.19, 2.08]        |
| Raskin 2008       | 1071        | 1480           | 965   | 1474   | 16.6% 1.30 [1.11, 1.52]       |
| Subtotal (95% CI) | 4743        | 5488           | 58.1% |        | 1.31 [1.20, 1.42]             |
| Total events      | 3343        | 3548           |       |        |                               |
| Heterogeneity: $\chi^2 = 1.94, df = 2 (P = 0.38)$; $I^2 = 0\%$ |
| Test for overall effect: $Z = 6.25 (P < 0.00001)$ |

Total (95% CI) 7840 9349 100.0% 1.28 [1.20, 1.37]

Figure 5: Forest plots of rs2420946 (C>T) polymorphism and breast cancer risk stratified by Source of controls (Dominant model TC + TT vs. CC).

| Study or Subgroup | Case Events | Control Events | total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|-------|--------|-------------------------------|
| 4.2.1 HB          |             |                |       |        |                               |
| Fu 2012           | 80          | 118            | 57    | 104    | 1.2% 1.74 [1.01, 3.00]        |
| Kawase 2009       | 286         | 453            | 515   | 912    | 7.7% 1.32 [1.05, 1.66]        |
| Li 2011           | 260         | 391            | 270   | 432    | 5.2% 1.19 [0.89, 1.59]        |
| Liang 2008        | 682         | 1020           | 647   | 1050   | 12.8% 1.26 [1.05, 1.50]       |
| Liang 2015        | 413         | 603            | 524   | 847    | 8.3% 1.34 [1.07, 1.67]        |
| Liu 2013          | 142         | 203            | 139   | 200    | 2.6% 1.02 [0.67, 1.56]        |
| Subtotal (95% CI) | 2788        | 3545           | 37.8% |        | 1.28 [1.15, 1.42]             |
| Total events      | 1863        | 2152           |       |        |                               |
| Heterogeneity: $\chi^2 = 2.78, df = 5 (P = 0.73)$; $I^2 = 0\%$ |
| Test for overall effect: $Z = 4.59 (P < 0.00001)$ |

4.2.2 PB

| Study or Subgroup | Case Events | Control Events | total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|-------|--------|-------------------------------|
| Hu 2011           | 142         | 203            | 139   | 200    | 2.6% 1.02 [0.67, 1.56]        |
| Hunter 2007       | 2012        | 2912           | 2046  | 3212   | 36.6% 1.27 [1.15, 1.42]       |
| Jara 2013         | 280         | 351            | 517   | 802    | 5.0% 1.59 [1.19, 2.08]        |
| Liu 2009          | 87          | 106            | 72    | 116    | 1.5% 1.05 [0.61, 1.91]        |
| Raskin 2008       | 1071        | 1480           | 965   | 1474   | 16.6% 1.30 [1.11, 1.52]       |
| Subtotal (95% CI) | 5052        | 5804           | 62.2% |        | 1.29 [1.19, 1.40]             |
| Total events      | 3552        | 3759           |       |        |                               |
| Heterogeneity: $\chi^2 = 3.72, df = 4 (P = 0.44)$; $I^2 = 0\%$ |
| Test for overall effect: $Z = 8.11 (P < 0.00001)$ |

Total (95% CI) 7840 9349 100.0% 1.28 [1.20, 1.37]

Total events 5415 5911

Heterogeneity: $\chi^2 = 6.54, df = 10 (P = 0.77)$; $I^2 = 0\%$

Test for overall effect: $Z = 7.84 (P < 0.00001)$

Test for subvarious differences: $\chi^2 = 0.39, df = 1 (P = 0.53)$; $I^2 = 0\%$
between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk.

In our study, there were 31 studies with 54,677 cases and 80,418 controls for FGFR2 rs2981582 variants. In the total population, the pooled results indicated that the correlation between FGFR2 rs2981582 polymorphism and the occurrence of BC was significant in any genetic model. Furthermore, in ethnicity-specific analysis, FGFR2 rs2981582 were also significantly associated with BC risk both in Asians and Caucasians. We didn’t discuss the African subgroup for just one study was from African. The analysis in different source of controls showed the same association between FGFR2 rs2981582 polymorphism and BC susceptibility both in HB and PB, indicating that both hospital populations and general populations followed the same relationship. For rs2420946, 11 studies with 7,840 cases and 9,349 controls were included to assess the association. In the total population, the pooled ORs suggested that rs2420946 was significantly associated with BC susceptibility in all the five genetic models. When stratified by ethnicity and source of controls, the results showed the same association in Asians, Caucasians, hospital populations and general populations, indicating that different genetic backgrounds and living environment were not strong enough to change these associations. All the results for the two variants (rs2981582, rs2420946) were partially consistent with the consequences of Wang’s [13], Peng’s [14], Zhang’s [12] and Jia’s [15] meta-analysis, while they didn’t conduct analysis in different source of controls, making our results more valuable. Furthermore, they didn’t use all the five genetic models (allele model, dominant model, recessive model, homozygous model and heterozygous model) to assess the strength of association. Wang’s [13] study also reported that the association appeared to be much stronger for estrogen receptor-positive and progesterone receptor-positive BC, which was not analyzed in our study. Peng’s [14] study was conducted on the base of present meta-analyses, which may missed some individual studies with larger sample sizes, and this type meta-analysis may not appropriate. In Zhang’s [12] study, the increased risk was found in the subgroup of postmenopausal women for rs2420946. However, only one study [20] reported that risk in premenopausal women. For Jia’s [15] study, in the ethnicity subgroup, using Non-Caucasians represent different ethnicities may cause some heterogeneity.

Three articles with 833 cases and 1012 controls were adopted to evaluate the association between the rs2981578 polymorphism and the BC risk. As the preceding two variants, the association between rs2981578 variant and BC susceptibility was also significant in any genetic model. For just only 3 studies, no stratified study was conducted for rs2981578 polymorphism. However, in Zhou’s [11] meta-analysis, they found that rs2981578 polymorphism might decrease BC risk. This may result from the literature selection bias. While the sample size of our study for rs2981578 was so small, data from a large sample of multiple centers is still needed to assess the association.

Our meta-analysis has several limitations. First, our study is a summary of the data. For lack of all individual raw data, we could not assess the cancer risk stratified by other covariates including age, sex, environment, hormone level, menopause age and other risk factors. We also cannot analyze the potential interaction of gene-environment and gene-gene. Second, only published papers were included in our meta-analysis, there still may be some unpublished studies which are in line with the conditions. Therefore, publication bias may exist even no statistical evidence was found in the meta-analysis. Third, for just only 3 papers, no stratified study was conducted for rs2981578 polymorphism. Moreover, our study is a summary of the data. We did not verify it from the level of molecular mechanism. Data from large scale multicenter epidemiological studies is still needed to confirm the relationship between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphisms and BC risk, and the molecular mechanism for the associations need to be elucidated further.

In conclusion, our meta-analysis based on case-control studies provides strong evidence that FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphisms

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**Figure 6:** Forest plots of rs2981578 (A>G) polymorphism and breast cancer risk (Allele model G vs. A).
Figure 7: Funnel plot assessing evidence of publication bias. A. rs2981582 (C>T) (Recessive model TT vs. CC + TC). B. rs2420946 (C>T) (Dominant model TC + TT vs. CC). C. rs2981578 (A>G) (Allele model G vs. A). SE: standard error; OR: odds ratio.
are significantly associated with the BC risk. For rs2981582 and rs2420946, the association remained significant in Asians, Caucasians, general populations and hospital populations. However, further large scale multicenter epidemiological studies are warranted to confirm this finding and the molecular mechanism for the associations need to be elucidated further.

MATERIALS AND METHODS

Literature search

We searched PubMed, Web of science and the Cochrane Library for relevant studies published before October 11, 2015. The following keywords were used: (Fibroblast Growth Factor Receptor 2 or FGFR2) and (variant* or genotype or polymorphism or SNP) and (breast) and (cancer or carcinom* or neoplasm* or tumor), and the combined phrases for all genetic studies on the association between the FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk. The reference lists of all articles were also manually screened for potential studies. Abstracts and citations were screened by two researchers independently. All the eligible articles need a second screening for the full-text. The searching was done without language limitations.

Selection and exclusion criteria

Inclusion criteria: A study was included in this meta-analysis if it met the following criteria: i) independent case-control studies for humans; ii) the study evaluating the association between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk; iii) the study presenting available genotype frequencies in cancer cases and control subjects for risk estimated; iii) cases should have been diagnosed by a pathological examination. We excluded comments, editorials, systematic reviews and studies lacking sufficient data or studies with male cases. If the researches were duplicated or shared in more than one study, the most recent publications were included.

Data extraction and synthesis

We used endnote bibliographic software to construct an electronic library of citations identified in the literature search. All the PubMed, Web of science and the Cochrane Library searches were performed using Endnote. Duplicates were found automatically by endnote and deleted manually. All data extraction were checked and calculated twice according to the inclusion criteria listed above by two independent investigators. Data extracted from the included studies were as follows: First author, year of publication, country, Ethnicity, Source of controls, Genotyping method, number of cases and controls and evidence of Hardy-Weinberg equilibrium (HWE) in controls. A third reviewer would participate if some disagreements were emerged, and a final decision was made by the majority of the votes.

Statistical analysis

All statistical analyses were performed using STATA version 11.0 software (StataCorp LP, College Station, TX) and Review Manage version 5.2.0 (The Cochrane Collaboration, 2012). Hardy-Weinberg equilibrium (HWE) was assessed by \( \chi^2 \) test in the control group of each study [21]. The strength of associations between the FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and BC risk were measured by odds ratio (ORs) with 95% confidence interval (CIs). Z test was used to assess the significance of the ORs, \( F \) and \( Q \) statistics was used to determine the statistical heterogeneity among studies. A random-effect model was used if \( p \) value of heterogeneity tests was no more than 0.1 (\( p \leq 0.1 \)), and otherwise, a fixed-effect model was selected [21, 22]. Sensitivity analyses were performed to assess the stability of the results. We used Begg’s funnel plot and Egger’s test to evaluate the publication bias [23, 24]. The strength of the association was estimated in the allele model, the dominant model, the recessive model, the homozygous genetic model and the heterozygous genetic model, respectively. \( p < 0.05 \) was considered statistically significant. We performed subgroup according to Ethnicity and Source of controls.

CONFLICTS OF INTEREST

The authors have declared that no conflicts of interest exists.

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