Association between 8q24 (rs13281615 and rs6983267) polymorphism and breast cancer susceptibility: a meta-analysis involving 117,355 subjects

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ABSTRACT

Published data on the association between 8q24 polymorphism and breast cancer (BC) risk are inconclusive. Thus, we conducted a meta-analysis to evaluate the relationship between 8q24 (rs13281615 and rs6983267) polymorphism and BC risk. We searched PubMed, EMBASE, Web of Science and the Cochrane Library up to August 13, 2015 for relevant studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of associations. Twenty-six studies published from 2008 to 2014, with a total of 52,683 cases and 64,672 controls, were included in this meta-analysis. The pooled results showed that there was significant association between 8q24 rs13281615 polymorphism and BC risk in any genetic model. In the subgroup analysis by ethnicity, the effects remained in Asians and Caucasians. However, no genetic models reached statistical association in Africans. There was no association in any genetic model in rs6983267. This meta-analysis suggests that 8q24 rs13281615 polymorphism is a risk factor for susceptibility to BC in Asians, Caucasians and in overall population, While, there was no association in Africans. The rs6983267 polymorphism has no association with BC risk in any genetic model. Further large scale multicenter epidemiological studies are warranted to confirm this finding.

INTRODUCTION

Breast cancer (BC), one of the most frequently encountered malignant tumors in women, has become the main reason of tumor-associated death in our word [1], whose incidence rate is increasing year by year and accompanied by younger trend in the world [2, 3]. The etiology of BC is very complex, many factors cause it’s occurrence and development, the specific mechanism has not been clarified. Epidemiology and basic etiology studies have shown that BC’s occurrence and progression is closely related to multiple factors interaction between genetic, endocrine and external environment [4-6].

The genetic markers of BC are mainly expressed in two forms, that is, the higher external rate mutation gene and the lower external rate polymorphism gene. Compared with familial BC, most sporadic BC is associated with lower external rate polymorphism genes [7, 8]. The distribution of these genes in the population is more than 1%, and the genetic variation of these genes (Single nucleotide polymorphism, SNP) is mainly by changing the expression level and function of the protein and the modified factor inside and outside the cell, thus affecting the genetic susceptibility of BC [8]. In recent years, many BC-associated gene loci have been demonstrated by GWAS, 8q24 (rs13281615 and rs6983267) is the gene mutation site selected by this technique [7].

Previous functional studies have reported the association between 8q24 (rs13281615 and rs6983267) polymorphism and BC risk [9-29]. Because of differences in race and region, studies of this site are not entirely consistent with the conclusion that whether the site is associated with the risk of BC. To clarify the role of 8q24 (rs13281615 and rs6983267) polymorphism in BC risk, five meta-analysis [30-34] on the associations between
8q24 (rs13281615 and rs6983267) polymorphism and BC had been carried out. However, the results remain inconclusive and number of their studies included in their meta-analysis about BC is small. In the subgroup of their analyses the sample size is extremely small, and some just no subgroup. Therefore, we decided to carry out this meta-analysis on all the included case-control researches to make a more accurate assessment of the relationship. Moreover, we performed a subgroup analysis stratified by ethnicity.

**RESULTS**

**Characteristics of included papers**

The specific search process is shown in Figure 1. A total of 447 references were preliminarily identified at first based on our selection strategy. We also identified 2 papers [11, 29] through other source. 347 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, 21 studies [9-29] on 8q24 (rs13281615 and rs6983267) polymorphism and the occurrence of BC were eventually included in our study, including 52,683 cases and 64,672 controls. Characteristics of eligible analysis are shown in Table 1. The 21 case-control papers were published between 2008 and 2014, among them, 1 study was performed in African, 7 in Asian, 12 in Caucasians and 1 in both African and Caucasians. All studies were case-controlled.

**Meta-analysis results**

Table 2 and Table 3 shows the 8q24 (rs13281615 and rs6983267) polymorphisms genotype distribution and allele frequencies in in case group and control group. Main results of our study were shown in Table 4. A total
of 21 studies with 52,683 cases and 64,672 controls were included. As shown in Table 4, The pooled results indicated that the correlation between 8q24 rs13281615 polymorphism and the occurrence of BC was significant in any genetic model: Allele model (OR = 1.10, 95% CI = 1.07-1.13, \(P < 0.00001\)), dominant model (OR = 1.13, 95% CI = 1.08-1.18, \(P < 0.00001\)) recessive model (OR = 1.13, 95% CI = 1.08-1.18, \(P < 0.00001\)) homozygous genetic model (OR = 1.20, 95% CI = 1.13-1.27, \(P < 0.00001\)) heterozygote comparison (OR = 1.09, 95% CI = 1.00-1.18, \(P = 0.06\)).

The subgroup study stratified by ethnicity showed an increased BC risk in Asians (Allele model: OR = 1.08, 95% CI = 1.03-1.14, \(P = 0.001\); dominant model: OR = 1.11, 95% CI = 1.03-1.21, \(P = 0.009\); recessive model: OR = 1.11, 95% CI = 1.03-1.20, \(P = 0.008\); homozygous genetic model: OR = 1.17, 95% CI = 1.07-1.29, \(P = 0.001\); heterozygote comparison: OR = 1.08, 95% CI = 1.00-1.18, \(P = 0.06\)) and Caucasians (Allele model: OR = 1.11, 95% CI = 1.06-1.16, \(P < 0.00001\); dominant model: OR = 1.14, 95% CI = 1.07-1.21, \(P < 0.001\); recessive model: OR = 1.15, 95% CI = 1.08-1.22, \(P < 0.00001\); homozygous genetic model: OR = 1.22, 95% CI = 1.12-1.32, \(P < 0.00001\); heterozygote comparison: OR = 1.11, 95% CI = 1.05-1.17, \(P = 0.005\)). While, there was not any genetic model attained statistical correlation in Africans. There was no association in any genetic model in rs6983267 (Table 4).

### Sensitivity analyses

As shown in Table 1, all the studies conformed to be balance of Hardy-Weinberg equilibrium (HWE) in controls except 5 studies (\(P < 0.05\)), 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 (\(p \leq 0.1\)), otherwise, fixed-effect models were selected (Table 4).

| First author | Genotype (N) | Allele frequency (N) |
|--------------|--------------|----------------------|
| Total | GG AG AA | G A | Total | GG AG AA | G A |
| Case | Control | Case | Control | Case | Control | Case | Control |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Antoniou | 7787 | 1396 | 3872 | 2519 | 6662 | 1158 | 62 | 158 | 67 | 278 | 282 | 282 | 292 |
| Bai | 280 | 63 | 152 | 65 | 287 | 62 | 158 | 67 | 278 | 282 | 282 | 292 |
| Barnholtz-Sloan | 1223 | 230 | 604 | 389 | 1117 | 194 | 519 | 404 | 1064 | 1382 | 907 | 1327 |
| Barnholtz-Sloan | 736 | 130 | 387 | 219 | 658 | 123 | 331 | 204 | 647 | 825 | 577 | 739 |
| Campa | 8302 | 1764 | 4044 | 2494 | 11615 | 2193 | 5609 | 3813 | 7572 | 9032 | 9955 | 13235 |
| Chan | 1174 | 317 | 554 | 303 | 1463 | 364 | 693 | 406 | 1188 | 1160 | 1421 | 1505 |
| Elematore | 347 | 131 | 148 | 68 | 801 | 255 | 394 | 152 | 410 | 284 | 904 | 698 |
| Fletcher | 1470 | 305 | 730 | 435 | 1341 | 225 | 629 | 487 | 1340 | 1600 | 1079 | 1603 |
| Garcia-Closas | 15084 | 2921 | 7284 | 4879 | 22105 | 3773 | 10682 | 7650 | 13126 | 17042 | 18228 | 25982 |
| Gorodnova | 140 | 42 | 63 | 35 | 174 | 38 | 84 | 52 | 147 | 133 | 160 | 188 |
| Harlid | 3545 | 719 | 1723 | 1103 | 5007 | 884 | 2357 | 1766 | 3161 | 3929 | 4125 | 5889 |
| Jiang | 493 | 125 | 247 | 121 | 510 | 127 | 255 | 128 | 497 | 489 | 509 | 511 |
| Latif | 919 | 185 | 464 | 270 | 343 | 56 | 160 | 127 | 834 | 1004 | 272 | 414 |
| Li | 558 | 162 | 285 | 111 | 635 | 173 | 313 | 149 | 609 | 507 | 659 | 611 |
| Long | 2945 | 796 | 1470 | 679 | 2981 | 745 | 1491 | 745 | 3062 | 2828 | 2981 | 2981 |
| McInerney | 917 | 178 | 467 | 272 | 993 | 182 | 456 | 355 | 823 | 1011 | 820 | 1166 |
| Mizoo | 466 | 180 | 211 | 75 | 458 | 177 | 206 | 75 | 571 | 361 | 560 | 356 |
| Shan | 639 | 201 | 303 | 135 | 365 | 96 | 176 | 93 | 705 | 573 | 368 | 362 |
| Tamimi | 661 | 223 | 263 | 175 | 711 | 273 | 277 | 161 | 709 | 613 | 823 | 599 |
| Teraoka | 606 | 140 | 292 | 174 | 1194 | 213 | 623 | 358 | 572 | 640 | 1049 | 1339 |
| Zhang | 482 | 143 | 248 | 91 | 527 | 124 | 283 | 120 | 534 | 430 | 531 | 523 |

Table 2: rs13281615 polymorphisms genotype distribution and allele frequency in cases and controls
Figure 2: Funnel plot on the association of rs13281615 variant and breast cancer in a fixed-effect model (heterozygote comparison). Abbreviations: SE, standard error; OR, odds ratio; A vs. G, Allele model.

Figure 3: Funnel plot on the association of rs6983267 variant and breast cancer in a fixed-effect model (recessive model). Abbreviations: SE, standard error; OR, odds ratio; A vs. G, Allele model.
| First author | Genotype (N) | Allele frequency (N) |
|--------------|-------------|---------------------|
|              | Case Total | Control Total | Case G | Case A | Control G | Control A |
|              | Case GG | Case AG | Case AA | Control GG | Control AG | Control AA |
| Fletcher     | 1480 | 338 | 734 | 408 | 1336 | 312 | 653 | 371 |
| McInerney    | 945 | 230 | 464 | 251 | 957 | 245 | 464 | 248 |
| Wokolorczyk | 1006 | 254 | 507 | 245 | 1910 | 513 | 977 | 420 |
| Zhang        | 478 | 151 | 218 | 109 | 522 | 183 | 233 | 106 |

**Publication bias**

We use Begg’s funnel plot and Egger test to evaluate the published bias. As Figure 2 (rs13281615) and Figure 3 (rs6983267) indicated, the funnel plot is symmetrical, indicating that there is no significant publication bias in the total population. In our study, no significant publication bias was found in the Begg’s test and Egger’s test ($P > 0.05$).

**DISCUSSION**

A large amount of evidence suggests that genetics is important in determining the risk of cancer [35]. Related research is to search for the susceptibility genes associated with cancer. It is believed that SNP is the main cause of human genetic variation, which may increase individual risk to suffer cancer [14, 18, 22, 23]. With the development of medical science, hereditary susceptibility to cancer has caused people’s great interest, and the study on the genetic polymorphism of the tumor is increasing.

At present, BRCA1 and BRCA2 gene polymorphisms are generally considered to be associated with BC, but because of the low mutation rate, it can only be detected in the small part of BC patients [36]. In 2007, the whole genome association analysis identified many genetic polymorphisms that may be associated with the development of BC, which included rs6983267 and rs13281615 [37].

The 8q24 rs6983267 and rs13281615 bit is located in the non-base region of the dye-color 8q24, and its function is not very clear. 8q24.12-24.13 location myelocytomatosis oncogene (MYC), MYC is a group of cancer genes, which are not expressed in normal cells, and expressed in some cancer cells. MYC can promote cell proliferation, immortalized, differentiation and transformation. It is an important factor in the formation of BC, colon cancer and prostate cancer [38, 39]. Studies shown that the chromosome 8q24 region is related to the occurrence of prostate cancer and colon cancer, which can play a role in carcinogenesis through interacting with MYC gene amplification and over expression [40]. The change of some loci of a single gene may have limited impact on the ultimate effect of cancer, and it is needed to carry out large-scale studies in populations.

Recently, a growing number of epidemiological studies have been carried out to explore the relationship between 8q24 (rs13281615 and rs6983267) polymorphisms and the occurrence of BC. Nevertheless, the conclusions are still inconclusive. Therefore, we carried out the meta-analysis on the whole included case-control researches to make a more accurate assessment of the relationship.

In our study, 21 studies were eventually included, including 52,683 cases and 64,672 controls. And we assessed the relationship between 8q24 (rs13281615 and rs6983267) polymorphisms and the occurrence of BC. In the total population, the pooled results indicated that the correlation between 8q24 rs13281615 polymorphism and the occurrence of BC was significant in any genetic model (Table 4). It was partially consistent with the consequences of previous five meta-analysis [30-34], while the sample size was several times than theirs, make the results more convincing.

BC is a disease with a difference in the incidence and mortality among different ethnic groups. Each increase of 25% European descent, the risk of developing BC will increase by 1.79 times [41]. Easton [42] et al believes that the incidence of the European population is higher than that of other ethnic groups, which are consistent with the results of this study. The subgroup study stratified by ethnicity showed an increased BC risk in Asians and Caucasians (Table 4). While, there was not any genetic model attained statistical correlation in Africans. There was no association in any genetic model in rs6983267 (Table 4). It was partially consistent with the Dai(2013)’s study [30] (with 11 papers containing 40,762 cases and 50,380 controls) and Pei(2013)’s [32] (with 12 eligible studies including 42,508 cases and 53,928 controls) findings. Another meta-analysis by Song(2012) [33] et al, including seven papers with 22,128 cases and 29,276 controls, they found no relationship between rs13281615 polymorphism and BC susceptibility in Asians. This contradiction may be caused by sample sizes and racial differences.

Our meta-analysis has some limitations in the following aspects. First, our study is a summary of the data. Due to the lack of the original data needed, we could not evaluate the cancer susceptibility stratified by age, Sex, environment, hormone level, menopause age and...
other risk factors. We also cannot analyze these studies to analyze the potential interaction of gene - environment and gene - gene. Secondly, we just included the published papers in our study, there may still be some published studies in line with the conditions. Moreover, our study is a summary of the data. We did not verify it from the level of basic experiments. Data from a large sample of multiple centers is still needed to confirm the relationship between 8q24 (rs13281615 and rs6983267) polymorphisms and BC risk.

In summary, our study suggests that 8q24 rs13281615 polymorphism could increase the risk of BC in Asians, Caucasians and in overall population, While, there was no association in Africans. The rs6983267
polymorphism has no relationship with the occurrence of BC in any genetic model. Data from a large sample of multiple centers is still needed to confirm our findings.

MATERIALS AND METHODS

Literature searching strategy

We searched PubMed, EMBASE, Web of science, the Cochrane Library for relevant studies published before August 13, 2015. The following keywords were used: rs6983267/rs13281615/8q24, variant*/genotype/polymorphism/SNP, breast AND (cancer or carcinom* or neoplasm* or tumor) and the combined phrases for all genetic studies on the association between the 8q24 (rs13281615 and rs6983267) polymorphism and BC risk. The reference lists of all articles were also manually screened for potential studies. Abstracts and citations were screened independently by two authors, all the agreed articles need a second screen for full-text reports. The searching was done without restriction on language.

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 evaluated the association between 8q24 (rs13281615 and rs6983267) polymorphism and BC risk; iii) has available genotype frequencies in cancer cases and control subjects for risk estimate. We excluded comments, editorials, systematic reviews or studies lacking sufficient data. If the publications were duplicated or shared in more than one study, the most recent publications were included. All identified studies were screened by two investigators independently. What’s more, there was no limitation for publication language.

Data extraction and synthesis

We used endnote bibliographic software to construct an electronic library of citations identified in the literature search. All the PubMed, EMBASE, 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 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 y² test in the control group of each study [43]. The strength of associations between the 8q24 (rs13281615 and rs6983267) 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 ≤ 0.1), otherwise, a fixed-effect model was selected [43, 44]. 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 [45, 46]. 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.

CONFLICTS OF INTEREST

The authors have declared that no conflict of interest exists.

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