Association between CYP17 T-34C rs743572 and breast cancer risk

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ABSTRACT

Association between CYP17 T-34C (rs743572) polymorphism and breast cancer (BC) risk was controversial. In order to derive a more definitive conclusion, we performed this meta-analysis. We searched in the databases of PubMed, EMBASE and Cochrane for eligible publications. Pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) were used to assess the strength of association between CYP17 T-34C polymorphism and breast cancer risk. Forty-nine studies involving 2,7104 cases and 3,4218 control subjects were included in this meta-analysis. In overall, no significant association between CYP17 T-34C polymorphism and breast cancer susceptibility was found among general populations. In the stratified analysis by ethnicity and source, significant associations were still not detected in all genetic models; besides, limiting the analysis to studies with controls in agreement with HWE, we also observed no association between CYP17 T-34C polymorphism and breast cancer risk. For premenopausal women, we didn’t detect an association between rs743572 and breast cancer risk; however, among postmenopausal women, we observed that the association was statistically significant under the allele contrast genetic model (OR = 1.10, 95% CI = 1.03–1.17, P = 0.003), but not in other four models. In conclusion, rs743572 may increase breast cancer risk in postmenopausal individuals, but not in premenopausal folks and general populations.

INTRODUCTION

Breast cancer (BC), the most frequent malignant neoplasm among female worldwide, accounts for approximate 25% of women malignant tumor. It is reported that 1.67 million people were diagnosed as BC ever year, therefore it has become a serious health issue, especially in the developing countries [1]. It is well known that the lifetime presence of the estrogen in the blood is an important pathogenic factor of BC, and this is in consistence with the low incidence of the breast cancer in males that is due to the lower estrogen levels and lower breast tissue volume. By now, researches on the status of hormone receptors and/or menopause associated with
genetic alterations in BC risk have attracted an increasing number of attention, and lots of genes, including BRIP1, CHEK2, MDM, TGFB, TP53, BRCA1, BRCA2, and PTEN, and also several gene polymorphisms. Among genes of this family, CYP17, CYP19 and CYP1A1 have important functions in synthesis, metabolism and maintaining the levels of the androgen and estrogen hormones [2]. Previous published reasearches have demonstrated that estrogen act as a crucial role in the formation of BC; in addition, evidences have also been found about the positive role of cell surface receptors of estrogen in tumorigenesis [3]. Nevertheless, the precise mechanism behind estrogen in the formation of BC remains unknown. Previous studies have indicated that cytochrome P450c17a, which is a key enzyme in the synthesis of estrogen, and could increase the breast neoplasm risk [4]. The cytochrome P450c17a enzyme, predominantly catalyzes the formation of the precursor dehydroepiandrosterone (DHEA). Meanwhile, precursor DHEA could further be converted into estrogen through a succession of tissue-specific pathways [5, 6]. Estrogen, plays a vital part in the etiology of BC and identified the risk between estrogen and BC could well elucidate the biosynthesis and metabolism mechanisms. So far, more and more researches have demonstrated the correlation of estrogen-related genes genetic variations with BC risk. The CYP17T-34C (rs743572) polymorphism which is located on the human chromosome 10, in the 50-untranslated region has been most commonly reported [7].

Many studies about the genetic mutations or SNP occurring in CYP17 gene could enhance CYP17’s transcription rate and increase the enzyme cytochrome P450c17 level, resulting in an increasing number of bioavailable estrogen, which is likely to affect the risk and aggressiveness of BC [8]. But many previous article results between rs743572 mutations and BC risk remain conflicting: Han’s research [9] revealed that no statistically meaningful correlation of rs743572 with risk of BC. However, significant correlation was found between rs743572 and BC risk in another research on the same theme [10]. Since few new high-quality investigations were published, we performed this study to take a more precise evaluation of rs743572 with the risk of BC.

RESULTS

The main feature of included studies

As showed in Figure 1, 331 references were retrieved at first based on our selection strategy. 186 papers were remained after removing the duplicate reports. After reading titles and abstracts, we excluded 104 studies which were clearly unrelated. In the end, the whole of the rest of the papers were checked based on the inclusion and exclusion criteria. Finally, forty-nine studies on rs743572 and the risk of BC were eventually included in our study.

Thirteen articles showed the number of three genotypes (TT, TC, and CC) among premenopausal women, and thirteen studies report TT, TC, and CC number in postmenopausal women. Main information of included studies were shown in Table 1. Among these qualified researches, seventeen were performed in Asians, twenty-five in Caucasians, one in Africans, one in both Asians and Caucasians, one in both Africans and Caucasians, and four in mixed ethnicity. Moreover, twenty-two studies were considered as moderate-quality studies (NOS scores of these researches were 4–6), and other twenty-seven studies were considered as high-quality studies (NOS scores of these studies were seven or above). Except for four included researches were not in agreement with Hardy–Weinberg equilibrium (HWE), genotype distributions in the control groups of other 45 researches were all satisfied with HWE.

Meta-analysis results

Meta-analysis results among overall populations, distribution of this polymorphism in case groups and control groups are presented in Table 2. For premenopausal women and postmenopausal women, distribution of this polymorphism in case groups and control groups are presented in Table 3, and the main outcome of our study are shown in Tables 4 and 5.

In overall populations, the association of CYP17 T-34C polymorphism with BC susceptibility was studied in forty-nine researches including 27,104 cases and 34,218 controls. No significant correlation was found between this polymorphism and BC susceptibility among any of the five genetic models: T/C (OR = 0.99, 95% CI = 0.96–1.01, P = 0.281), TT/CC (OR = 0.99, 95% CI = 0.98–1.01, P = 0.309), TC/CC (OR = 0.98, 95% CI = 0.93–1.03, P = 0.365), TT+TC/CC (OR = 0.98, 95% CI = 0.93–1.02, P = 0.287) and TT/TC+CC (OR = 0.99, 95% CI = 0.95–1.02, P = 0.463). Analogously, further subgroup analysis by ethnicity and source found similar results that in all the ethnic groups, HB group and PB group there is no significant correlation between rs743572 and BC susceptibility. Moreover, if we only analyze the studies with controls in agreement with HWE, no correlation between rs743572 and BC risk were observed (Table 4) (Figure 2).

In premenopausal individuals, thirteen included researches with 2,029 breast cancer case groups and 2,920 control groups were eventually included. There is no statistical correlation of rs743572 with breast cancer susceptibility in T/C model, the TT/CC, the TC/CC, the TT+TC/CC, and the TT/TC+CC (OR = 1.02 with 95% CI 0.93–1.10, OR = 1.01 with 95% CI 0.85–1.20, OR = 0.97 with 95% CI 0.83–1.14, OR = 0.95 with 95% CI 0.81–1.10, and OR = 1.04 with 95% CI 0.92–1.18, respectively). In postmenopausal women, significant correlation was found in T/C model (OR = 1.10, 95% CI = 1.03–1.17, P = 0.003)
(Table 5) (Figure 3). However, there were no significant associations between the rs743572 polymorphism and breast cancer risk in other genotype distributions: TT/CC (OR = 0.96, 95% CI = 0.84–1.10, \( P = 0.539 \)), TC/CC (OR = 0.96, 95% CI = 0.85–1.08, \( P = 0.478 \)), TT+TC/CC (OR = 0.96, 95% CI = 0.85–1.08, \( P = 0.930 \)) and TT/TC+CC (OR = 0.99, 95% CI = 0.90–1.08, \( P = 0.357 \)) (Table 5).

**Sensitivity analysis**

Even though four researches included in our studies were not conformed to the HWE balance (\( P < 0.05 \)), final consequences were not changed when we excluded the abovementioned four studies. Besides, after performing the sensitivity analysis, the pooled OR values were not statistically significant changed when we delete each of the researches, indicating that this study has good stability and reliability.

**Heterogeneity analysis**

Heterogeneity was obtained by Q statistic. When the \( P \) value more than 0.1 in the \( Q \) test, then the fixed-effect models were selected to conduct relevant statistical analysis; otherwise, random-effect models were selected.

**Publication bias**

No statistical evidence of publication bias was found in the Begg’s test and Egger’s test. What’s more, funnel plot also did not show any evidence of obvious asymmetry (Table 4) (Figure 4).

**DISCUSSION**

With the popularization and the rapid development of technology in the field of medicine, people have a deeper recognition of breast cancer. However, the specific mechanisms of the occurrence and the development of this cancer remain unclear. It is well established that estrogen involves in the development of mammary gland and plays crucial role in initiating of BC [2]. Extensive evidences have also been demonstrated that lifetime exposure to endogenous and/or exogenous estrogen, increased the risk of the morbidity of breast cancer [11]. Besides, estrogen plays a positive role of cell surface receptors of in tumorigenesis [2, 3]. Significance of genes functioning in steroid hormone synthesis is well established in breast cancer susceptibility. CYP17, a commonly known gene could code for the cytochrome P450c17α enzyme that is one of the key enzymes participated in estrogen biosynthesis [4]. CYP17 T-34C polymorphism, in the region (5′-UTR) of CYP17, has been reported up-regulate CYP17 transcription in some studies but not in others [7]. The functional impact of the T/C change is still an unresolved mystery. Moreover several studies have reported conflicting results with respect to menopausal status and CYP17 polymorphism. Hence, for the purpose of acquire a more accurate assessment of the association...
| First author   | Year | Country | Ethnicity | Source of control | Number (case/control) | HWE ($P$ value) | NOS |
|---------------|------|---------|-----------|-------------------|-----------------------|-----------------|-----|
| Dunning [17]  | 1998 | UK      | Caucasian | PB                | 835/591               | 0.261           | 7   |
| Weston [21]   | 1998 | USA     | Caucasian | HB                | 103/205               | 0.449           | 6   |
| Weston [21]   | 1998 | USA     | African   | HB                | 20/35                 | 0.253           | 6   |
| Helzlsouer [22]| 1998 | USA     | Caucasian | PB                | 109/113               | 0.549           | 6   |
| Bergman [23]  | 1999 | Sweden  | Caucasian | PB                | 109/117               | 0.304           | 6   |
| Haiman [24]   | 1999 | USA     | Caucasian | PB                | 436/618               | 0.391           | 7   |
| Huang [25]    | 1999 | China   | Asian     | PB                | 123/126               | 0.972           | 6   |
| Young [26]    | 1999 | UK      | Caucasian | PB                | 39/58                 | 0.732           | 5   |
| Kristensen [27]| 1999 | Norway  | Caucasian | PB                | 510/201               | 0.351           | 7   |
| Hamajima [28] | 2000 | Japan   | Asian     | HB                | 144/166               | 0.044           | 6   |
| Kuligina [29] | 2000 | Russia  | Caucasian | HB                | 240/182               | 0.017           | 6   |
| Mitrunen [30] | 2000 | Finland | Caucasian | PB                | 479/480               | 0.967           | 7   |
| Feigelson [18]| 2001 | USA     | Mixed     | PB                | 850/1508              | 0.335           | 7   |
| Gudmundsdottir [31]| 2003 | Iceland | Caucasian | PB                | 500/395               | 0.131           | 7   |
| Wu [32]       | 2003 | Singapore | Asian    | PB                | 188/671               | 0.512           | 6   |
| Ambrosone [33]| 2003 | USA     | Caucasian | PB                | 207/188               | 0.130           | 7   |
| Tan [34]      | 2003 | China   | Asian     | PB                | 250/250               | 0.117           | 7   |
| Hefer [35]    | 2004 | Austria | Asian     | PB                | 388/1698              | 0.455           | 7   |
| Ahsan [36]    | 2004 | USA     | Mixed     | HB                | 313/271               | 0.457           | 6   |
| Chacko [37]   | 2005 | India   | Asian     | HB                | 140/140               | 0.133           | 6   |
| Einarsson[38] | 2005 | Sweden  | Caucasian | PB                | 1499/1338             | 0.885           | 7   |
| Shin [39]     | 2005 | Korea   | Asian     | HB                | 462/337               | 0.134           | 7   |
| Verla-Tebit [40]| 2005 | Germany | Caucasian | PB                | 527/904               | 0.380           | 7   |
| Hopper [41]   | 2005 | Australia | Caucasian | PB                | 1404/788              | 0.697           | 7   |
| Onland-More [42]| 2005 | Netherlands | Caucasian | PB                | 335/373               | 0.189           | 7   |
| Han [9]       | 2005 | China   | Asian     | PB                | 210/427               | 0.037           | 6   |
| Piller [43]   | 2006 | Germany | Caucasian | PB                | 608/1298              | 0.062           | 7   |
| Chakraborty [44]| 2007 | India   | Asian     | PB                | 186/212               | 0.550           | 6   |
| Setiawan [45] | 2007 | USA     | Mixed     | PB                | 5147/6882             | 0.312           | 7   |
| Chen [46]     | 2008 | USA     | Caucasian | PB                | 1037/1096             | 0.884           | 7   |
| Sakoda [47]   | 2008 | China   | Asian     | PB                | 615/877               | 0.232           | 7   |
| Zhang [48]    | 2008 | China   | Asian     | PB                | 299/342               | 0.454           | 7   |
| Samson [49]   | 2009 | India   | Asian     | PB                | 250/500               | 0.720           | 7   |
| Sangrakrai [50]| 2009 | Thailand | Asian     | HB                | 564/489               | 0.418           | 7   |
| Sobczuk [51]  | 2009 | Poland  | Caucasian | PB                | 100/106               | 0.503           | 6   |
| Antognelli [52]| 2009 | Italy   | Caucasian | PB                | 547/544               | 0.982           | 7   |
| Hosseini [53] | 2009 | Iran    | Caucasian | HB                | 53/53                 | 0.057           | 5   |
| Jakubowska [54]| 2009 | Poland  | Caucasian | HB                | 319/290               | 0.519           | 6   |
| MARIE-GENICA [55]| 2009 | Germany | Caucasian | PB                | 3145/5487             | 0.254           | 7   |
| Kato [56]     | 2009 | USA     | African   | PB                | 184/189               | 0.152           | 6   |
| Tuzuner [57]  | 2010 | Turkey  | Caucasian | PB                | 55/91                 | 0.466           | 5   |
| Syamala [58]  | 2010 | India   | Asian     | HB                | 359/367               | 0.464           | 7   |
Surekha [59] 2010 India Asian PB 249/249 0.949 7
Iwasaki [60] 2010 Japan Asian HB 388/388 0.299 6
Iwasaki [60] 2010 Brazil Asian HB 78/79 0.144 6
Iwasaki [60] 2010 Brazil Caucasian HB 379/379 0.039 6
Kaufman [61] 2011 Mixed Mixed HB 1175/829 0.944 7
Cribb [10] 2011 Canada Caucasian HB 207/621 0.033 6
Ghisari [62] 2014 Inuit Asian PB 30/113 0.882 5
Chattopadhyay [63] 2014 India Asian PB 360/360 0.692 7
Karakus [64] 2015 Turkey Caucasian PB 199/197 0.934 6
Farzaneh [65] 2016 Iranian Caucasian PB 124/100 0.189 6

HWE: Hardy-Weinberg equilibrium for controls. PB: population-based study. HB: hospital-based study.

Table 2: Genotype distribution of the CYP17 (rs743572) polymorphism in cases and controls among overall populations

| First author    | Genotype (N) | Case | Control |
|-----------------|--------------|------|---------|
|                 | Total CC CT TT | Total CC CT TT |          |
| Dunning         | 835 130 402 303 591 | 85 277 229 |
| Weston          | 103 18 47 38 205 | 35 93 77 |
| Weston          | 20 3 10 7 35 | 2 18 15 |
| Helzlsouer      | 109 21 47 41 113 | 18 58 37 |
| Bergman         | 109 15 62 32 117 | 9 55 53 |
| Haiman          | 463 73 212 178 618 | 94 307 217 |
| Huang           | 123 44 54 25 126 | 35 63 28 |
| Young           | 39 5 13 21 58 | 7 28 23 |
| Kristensen      | 510 67 241 202 201 | 26 101 74 |
| Hamajima        | 144 20 83 41 166 | 27 95 44 |
| Kuligina        | 240 47 111 82 182 | 44 77 61 |
| Mitrunen        | 479 53 227 199 480 | 60 220 200 |
| Feigelson       | 850 149 409 292 1508 | 227 739 542 |
| Gudmundsdottir  | 500 60 247 193 395 | 66 173 156 |
| Wu              | 188 69 82 37 671 | 229 333 109 |
| Ambrosone       | 207 15 83 109 188 | 22 71 95 |
| Tan             | 250 89 115 46 250 | 89 110 51 |
| Heffer          | 388 75 186 127 1698 | 287 804 607 |
| Ahsan           | 313 49 155 109 271 | 51 140 80 |
| Chacko          | 140 6 40 94 140 | 3 22 115 |
| Einarsdóttr     | 1499 238 711 550 1338 | 212 638 488 |
| Shin            | 462 127 223 112 337 | 115 152 70 |
| Verla-Tebit     | 527 103 244 180 904 | 157 424 323 |
| Hopper          | 1404 230 621 553 788 | 113 364 311 |
| Onland-More     | 335 44 140 151 373 | 50 157 166 |
| Han             | 210 52 105 53 427 | 92 235 100 |
| Piller          | 608 119 289 200 1298 | 236 596 466 |
| Chakraborty     | 186 59 98 29 212 | 45 110 57 |
| Setiawan        | 5147 833 2445 1869 6882 | 1070 3338 2474 |

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Table 3: Genotype distribution of the CYP17 (rs743572) polymorphism in cases and controls among premenopausal women and postmenopausal women

| First author | Genotype (N) |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
|--------------|--------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|              | Total | CC | CT | TT | Total | CC | CT | TT | Total | CC | CT | TT | Total | CC | CT | TT | Total | CC | CT | TT | Total | CC | CT | TT |
| Helzlsouer   | 24    | 4  | 9  | 11 | 25    | 4  | 13 | 8  | 29    | 4  | 13 | 8  | 30    | 4  | 13 | 8  | 30    | 4  | 13 | 8  | 30    | 4  | 13 | 8  |
| Bergman      | 109   | 15 | 62 | 32 | 117   | 9  | 55 | 53 | 122   | 9  | 55 | 53 | 122   | 9  | 55 | 53 | 122   | 9  | 55 | 53 | 122   | 9  | 55 | 53 |
| Mitrunen     | 163   | 15 | 71 | 77 | 203   | 27 | 88 | 88 | 230   | 27 | 88 | 88 | 230   | 27 | 88 | 88 | 230   | 27 | 88 | 88 | 230   | 27 | 88 | 88 |
| Wu           | 57    | 24 | 20 | 13 | 203   | 66 | 100| 37 | 124   | 66 | 100| 37 | 124   | 66 | 100| 37 | 124   | 66 | 100| 37 | 124   | 66 | 100| 37 |
| Ambrosone    | 96    | 7  | 31 | 58 | 86    | 10 | 28 | 48 | 97    | 10 | 28 | 48 | 97    | 10 | 28 | 48 | 97    | 10 | 28 | 48 | 97    | 10 | 28 | 48 |
| Verla-Tebit  | 527   | 103| 244|180 |904   |157 |424|323 |904   |157 |424|323 |904   |157 |424|323 |904   |157 |424|323 |904   |157 |424|323 |
| Chen         | 334   | 55 | 153|126|373   |69 | 174|130 |373   |69 | 174|130 |373   |69 | 174|130 |373   |69 | 174|130 |373   |69 | 174|130 |
| Samson       | 115   | 16 | 40 | 59 |303   |31 | 145|127 |303   |31 | 145|127 |303   |31 | 145|127 |303   |31 | 145|127 |303   |31 | 145|127 |
| Antognelli   | 187   | 18 | 81 | 88 |230   |31 | 99 |100 |230   |31 | 99 |100 |230   |31 | 99 |100 |230   |31 | 99 |100 |230   |31 | 99 |100 |
| Kato         | 75    | 12 | 27 | 36 |74    |13 | 30 |31 |74    |13 | 30 |31 |74    |13 | 30 |31 |74    |13 | 30 |31 |74    |13 | 30 |31 |
| Zhang        | 150   | 38 | 87 | 25 |124   |37 | 67 |20 |124   |37 | 67 |20 |124   |37 | 67 |20 |124   |37 | 67 |20 |124   |37 | 67 |20 |
| Tan          | 95    | 32 | 45 | 18 |97    |30 | 40 |27 |97    |30 | 40 |27 |97    |30 | 40 |27 |97    |30 | 40 |27 |97    |30 | 40 |27 |
| Han          | 117   | 25 | 61 | 31 |163   |36 | 85 |42 |163   |36 | 85 |42 |163   |36 | 85 |42 |163   |36 | 85 |42 |163   |36 | 85 |42 |
| Helzlsouer   | 85    | 17 | 38 | 30 |88    |14 | 45 |29 |88    |14 | 45 |29 |88    |14 | 45 |29 |88    |14 | 45 |29 |88    |14 | 45 |29 |
| Mitrunen     | 316   | 38 | 156|122|277   |33 | 132|112|277   |33 | 132|112 |277   |33 | 132|112 |277   |33 | 132|112 |277   |33 | 132|112 |
| Comparisons                  | OR   | 95% CI     | P (OR) | Heterogeneity   | Effects model | P (Begg) | P (Egger) |
|------------------------------|------|------------|--------|-----------------|---------------|----------|-----------|
| **Total**                    |      |            |        |                 |               |          |           |
| T VS C                       | 0.99 | 0.96–1.01  | 0.281  | 37.1%           | 0.005         | R        | 0.856     | 0.766     |
| TT VS CC                     | 0.99 | 0.98–1.01  | 0.309  | 18.6%           | 0.127         | F        | 0.987     | 0.408     |
| TC VS CC                     | 0.98 | 0.93–1.03  | 0.365  | 0.80%           | 0.457         | F        | 0.825     | 0.563     |
| TT+TC VS CC                 | 0.98 | 0.93–1.02  | 0.287  | 15.0%           | 0.182         | F        | 0.975     | 0.574     |
| TT VS TC+CC                 | 0.99 | 0.95–1.02  | 0.463  | 30.5%           | 0.022         | R        | 1.000     | 0.902     |
| **Stratification by ethnicity** |    |            |        |                 |               |          |           |
| **Caucasian**                |      |            |        |                 |               |          |           |
| T VS C                       | 0.99 | 0.96–1.03  | 0.673  | 11.5%           | 0.294         | F        | -         | -         |
| TT VS CC                     | 0.99 | 0.93–1.06  | 0.804  | 10.4%           | 0.233         | F        | -         | -         |
| TC VS CC                     | 1.00 | 0.94–1.07  | 0.936  | 0.00%           | 0.467         | F        | -         | -         |
| TT+TC VS CC                 | 1.00 | 0.94–1.06  | 0.604  | 11.1%           | 0.301         | F        | -         | -         |
| TT VS TC+CC                 | 0.99 | 0.94–1.04  | 0.907  | 0.00%           | 0.596         | F        | -         | -         |
| **Asian**                    |      |            |        |                 |               |          |           |
| T VS C                       | 0.97 | 0.89–1.06  | 0.574  | 60.8%           | 0.023         | R        | -         | -         |
| TT VS CC                     | 0.99 | 0.95–1.02  | 0.483  | 33.9%           | 0.075         | R        | -         | -         |
| TC VS CC                     | 0.97 | 0.88–1.07  | 0.525  | 11.4%           | 0.282         | F        | -         | -         |
| TT+TC VS CC                 | 0.97 | 0.88–1.06  | 0.479  | 29.1%           | 0.114         | F        | -         | -         |
| TT VS TC+CC                 | 0.97 | 0.84–1.11  | 0.652  | 60.0%           | 0.000         | R        | -         | -         |
| **African**                  |      |            |        |                 |               |          |           |
| T VS C                       | 0.83 | 0.63–1.10  | 0.198  | 0.0%            | 0.621         | F        | -         | -         |
| TT VS CC                     | 0.72 | 0.41–1.27  | 0.255  | 0.0%            | 0.393         | F        | -         | -         |
| TC VS CC                     | 0.88 | 0.50–1.54  | 0.654  | 0.0%            | 0.363         | F        | -         | -         |
| TT+TC VS CC                 | 0.80 | 0.47–1.36  | 0.408  | 0.0%            | 0.358         | F        | -         | -         |
| TT VS TC+CC                 | 0.79 | 0.54–1.17  | 0.237  | 0.0%            | 0.859         | F        | -         | -         |
| **Stratification by Source** |      |            |        |                 |               |          |           |
| **PB**                       |      |            |        |                 |               |          |           |
| T VS C                       | 0.98 | 0.95–1.00  | 0.102  | 35.2%           | 0.021         | R        | -         | -         |
| TT VS CC                     | 0.95 | 0.90–1.01  | 0.073  | 18.7%           | 0.165         | F        | -         | -         |
between rs743572 and BC risk we performed this meta-
alysis whose included research studies identified in the
PubMed, EMBASE and the Cochrane.
In overall populations, our results indicate no
significant correlation between rs743572 and the risk of
BC. Similar results could be obtained when stratified by
ethnicity in all ethnic groups. In addition, confining the
analysis to the researches with control groups in consistent
with HWE, we also observed no correlation between
rs743572 and risk of BC. Nevertheless, meaningful
correlation was showed between rs743572 and breast
neoplasm risk in Russian individuals [10]. There were
three meta-analyses, all published in 2010, including
24–43 papers from different populations and demonstrated
no association between the rs743572 and BC, which further
demonstrate that our results are credible [12, 13, 14].

Estrogen is mainly produced in the ovaries and
mammary glands among premenopausal women.
However, in postmenopausal individuals, adipose tissue
mainly acts as an important part in estrogen biosynthesis
[15, 16]. Several studies have reported conflicting results
of menopausal and CYP17 polymorphism: the study

| Comparisons                  | OR  | 95% CI      | P (OR) | Heterogeneity | Effects model | P (Begg) | P (Egger) |
|------------------------------|-----|-------------|--------|---------------|---------------|----------|-----------|
| **Premenopausal**            |     |             |        |               |               |          |           |
| T VS C                       | 1.02| 0.93–1.10   | 0.717  | 17.6%         | 0.267         | F        | -         |
| TT VS CC                     | 1.01| 0.85–1.20   | 0.885  | 6.4%          | 0.383         | F        | -         |
| TC VS CC                     | 0.97| 0.83–1.14   | 0.709  | 0.0%          | 0.492         | F        | -         |
| TT+TC VS CC                  | 1.04| 0.92–1.18   | 0.513  | 21.4%         | 0.227         | F        | -         |
| TT VS TC+CC                  | 0.95| 0.81–1.10   | 0.467  | 29.3%         | 0.151         | F        | -         |
| **Postmenopausal**           |     |             |        |               |               |          |           |
| T VS C                       | 1.10| 1.03–1.17   | 0.003  | 10.6%         | 0.339         | F        | -         |
| TT VS CC                     | 0.96| 0.84–1.10   | 0.539  | 0.0%          | 0.835         | F        | -         |
| TC VS CC                     | 0.96| 0.85–1.08   | 0.478  | 0.0%          | 0.902         | F        | -         |
| TT+TC VS CC                  | 0.96| 0.85–1.08   | 0.467  | 0.0%          | 0.930         | F        | -         |
| TT VS TC+CC                  | 0.99| 0.90–1.08   | 0.796  | 8.9%          | 0.357         | F        | -         |

F: fixed effects model; R: random effects model.

Between rs743572 and BC risk we performed this meta-
analysis whose included research studies identified in the
PubMed, EMBASE and the Cochrane.

In overall populations, our results indicate no
significant correlation between rs743572 and the risk of
BC. Similar results could be obtained when stratified by
ethnicity in all ethnic groups. In addition, confining the
analysis to the researches with control groups in consistent
with HWE, we also observed no correlation between
rs743572 and risk of BC. Nevertheless, meaningful
correlation was showed between rs743572 and breast
neoplasm risk in Russian individuals [10]. There were
three meta-analyses, all published in 2010, including
24–43 papers from different populations and demonstrated
no association between the rs743572 and BC, which further
demonstrate that our results are credible [12, 13, 14].

Estrogen is mainly produced in the ovaries and
mammary glands among premenopausal women.
However, in postmenopausal individuals, adipose tissue
mainly acts as an important part in estrogen biosynthesis
[15, 16]. Several studies have reported conflicting results
of menopausal and CYP17 polymorphism: the study
Figure 2: Forest plots of associations between rs743572 and breast cancer risk. (A) the overall populations in the allele contrast genetic model; (B) limiting the analysis to studies with controls in agreement with HWE under the allele contrast genetic model.

Figure 3: Forest plots of associations between rs743572 and breast cancer risk among postmenopausal women in the allele contrast genetic model.
by Dunning et al. [17] showed the association between increased A2 genotype and premenopausal breast cancer; while Feigelson et al. [18] reported increasing frequency of A2 genotype associated with postmenopausal BC patients. We observed that rs743572 was correlated with an increasing BC risk among postmenopausal women under the allele contrast genetic model, but not in other models; however, no association was found in premenopausal women. Previous published meta-analysis reported that no association existed both in postmenopausal women and among premenopausal women [12, 13, 14]. Compared with them, our study used five genetic models to reduce the probability of class I errors, so our result was more reliable.

Unavoidable, there are some limitations in meta-analysis. First, breast cancer is a multifactorial disease involving genetic and environmental interactions; however, it was still not addressed the impact of gene–environmental interactions in this meta-analysis [19]. Second, the detailed individual information in some studies was unknown; thus, we could not assess the susceptibility of breast cancer according to other risk factors including obesity, family history, radiation therapy in young age, history of pregnancy, breast-feeding, hormone therapy and so on [20]. Last, there are only two studies about Africans, more well designed studies with different population should be performed to make more persuasive conclusions. In summary, our results indicate that rs743572 polymorphism could increase risk of BC in postmenopausal individuals, but not in premenopausal women and the general population. Further multicenter research with complete risk factors are required to validate the potential role of rs743572 polymorphism in BC. More multicenter studies and complete risk factors are needed to further confirm the possible role of rs743572 polymorphism in the occurrence and development of breast cancer.

MATERIALS AND METHODS

Literature and search strategy

We searched the PubMed, EMBASE and Cochrane databases for studies performed prior to March 7, 2017 that reported an association between rs743572 SNP and breast cancer risk. There were no language restrictions in our searching process. The searching strategy was as follow: (breast cancer OR breast carcinoma) AND (polymorphism OR variant OR genotype OR SNP) AND (CYP17 OR CYP17A1 OR P450c17). Besides, the references of the retrieved studies were also reviewed to identify additional eligible studies.

Inclusion criteria

The included studies must meet the following criteria: (1) case-control design; (2) investigating the association between CYP17 T-34C polymorphism and breast cancer risk; (3) sufficient genotyping data that could be used to calculate odds ratios (ORs) and 95% confidence intervals (CIs); (4) all the breast cancer subjects in case groups must be pathologically confirmed. The exclusion criteria were: (1) not case-control studies; (2) review article or commentary; (3) duplicate studies; (4) studies lacking relevant data.

Figure 4: Funnel plots of rs743572 and breast cancer risk in the heterozygote genetic model.
Data extraction

Two reviewers independently extracted the relevant data from the included studies, and discrepancies were resolved during a discussion with a third author. The following information was extracted: the first author, year of publication, country, ethnicity, source of controls, number of cases and controls, and P value for Hardy-Weinberg equilibrium (HWE). In addition, we also evaluated the methodological quality of included studies based on Newcastle-Ottawa Scale (NOS), which scored studies according to three aspects: selection, comparability, and exposure. Therefore, all studies could be divided into three categories: “low quality” studies (score 0–3); “moderate quality” studies (score 4–6); “high quality” studies (score 7–9).

Statistical analysis

The association between CYP17 T-34C polymorphism and BC susceptibility was measured by pooled odds ratios (ORs) and 95% confidence intervals (CIs) in five genetic models, including an allele contrast genetic model, a homozygote genetic model, a heterozygote genetic model, a dominant genetic model, and a recessive genetic model. Pooled ORs were performed for homozygote comparison (TT vs. CC for rs743572), heterozygote comparison (TC vs. CC for rs743572), dominant model (TT/TC vs. CC for rs743572), recessive model (TT vs. TC/CC for rs743572) and allelic model (T vs. C for rs743572) respectively. Statistical heterogeneity was evaluated by $I^2$ test and $Q$ test. $P < 0.05$ was considered statistically significant. For $I^2$ test, the criteria for heterogeneity were as follows: $I^2 < 25\%$, no heterogeneity; $25\%–75\%$, moderate heterogeneity; $I^2 > 75\%$, high heterogeneity. If the $P$ value of $Q$ test was $< 0.1$, the random-effects model was used; otherwise, the fixed-effects model was applied. Sensitivity analysis was performed by excluding one study at a time to assess the influence of each study on the pooled ORs. Begg’s funnel plot and Egger’s tests were used to examine publication bias and to evaluate the stability of the results by sensitivity analysis. The random-effects model was used; otherwise, the fixed-effects model was applied. The authors declare that no conflicts of interest exist.

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