Original Article
TOX3 rs3803662 C > T polymorphism contributes to breast cancer susceptibility in the Chinese population: evidence from 12,800 cases and 11,550 controls

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Abstract: The association between the TOC high mobility group box family member 3 (*TOX3*) gene rs3803662 C > T polymorphism and breast cancer risk have been investigated in multiple ethnic groups. However, studies conducted in the Chinese population have yielded contradictory results. Therefore, we performed the current meta-analysis to drive a more precise evaluation of the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population. A total of seven eligible studies with 12,800 cases and 11,550 controls were involved in this meta-analysis. Overall, the SNP was shown to significantly increase the risk of developing breast cancer in the Chinese population under all genetic models (homozygous model: OR = 1.28, 95% CI = 1.17-1.39, *P* < 0.001; heterozygous model: OR = 1.12, 95% CI = 1.03-1.22, *P* = 0.009; recessive model: OR = 1.17, 95% CI = 1.11-1.23, *P* < 0.001; dominant model: OR = 1.20, 95% CI = 1.10-1.30, *P* < 0.001; as well as allele comparison: OR = 1.13, 95% CI = 1.09-1.18, *P* < 0.001). Meanwhile, no between-study heterogeneity and publication bias was observed, indicating the reliability of the findings. In conclusion, our meta-analysis results suggested that *TOX3* rs3803662 C > T polymorphism might confer increased susceptibility to breast cancer in the Chinese population.

Keywords: TOX3, polymorphism, breast cancer, risk, meta-analysis

Introduction

Cancer remains an enormous burden on public health with about 14.1 million new cancer cases and 8.2 million deaths having occurred all over the world in 2012 [1]. In women, breast cancer is the most common invasive cancer and the leading cause of cancer deaths worldwide, accounting for 25% of all female cancer cases and 15% of female cancer deaths in 2012 [1]. In China, the incidence rate of breast cancer has sharply increased since 2000 [2], which constituted approximately 16.2% of all cancer cases and 7.9% of cancer deaths in women in 2010 [3]. It is well known that breast cancer is a multifactorial disease caused by interactions between genetic and environmental factors [4-6]. Several high-penetrance mutations in genes (e.g., *BRCA1, BRCA2*) were con-

sidered to be associated with the increase in breast cancer risk [7]. However, such mutations can be contributable to only a small part of breast cancer, approximately 25% of the familial risk and 5% of the total breast cancer incidence [8, 9]. Numerous studies have suggested that some low-penetrance genes may also play a role in the etiology of breast cancer.

TOC high mobility group box family member 3 (TOX3), also known as trinucleotide repeat containing 9 (*TNRC9*), is located on chromosome 16q12 [10]. TOX3 protein contains a putative high-mobility-group box motif, suggesting that it may act as a transcription factor. Abnormal activity of TOX3 protein was related involved in bone metastasis of breast cancer [11]. Many polymorphisms have been identified in the *TOX3* gene [10, 12, 13]. Interestingly, genome-

wide association studies (GWASs) in 2007 indicated that genetic variants in the *TOX3* gene was showed to be significantly associated with breast cancer risk [10, 13]. Moreover, *TOX3* rs3803662 C > T, a common single nucleotide polymorphism (SNP), has been investigated for its association with breast cancer susceptibility [14-16]. Recently, a meta-analysis conducted by Zhang et al. suggested that *TOX3* rs3803662 C > T polymorphism was associated with increased risk of breast cancer, especially in Asians [17]. However, several studies have reported opposite findings that *TOX3* rs3803662 C > T polymorphism did not contribute to the risk of breast cancer in the Chinese population [18-21]. As a result, the genetic effect of this polymorphism on breast cancer susceptibility remains contradictory in the Chinese populations. Therefore, we conducted this meta-analysis to achieve high-quality estimation of the association of *TOX3* rs3803662 C > T polymorphism with breast cancer risk in the Chinese population.

Materials and methods

Identification of eligible relevant studies

We systematically searched the PubMed and Embase databases for studies that assessed the association between *TOX3* rs3803662 C > T polymorphism and the risk of breast cancer in the Chinese population. The following search terms were used: "TOX3 or TNRC9", "polymorphism or variant or variation or rs3803662", and "cancer or tumor or carcinoma". Furthermore, reference lists of important studies and reviews were screened and reviewed manually for additional eligible publications. We performed latest literature search on December 31, 2015. There was no language limitation.

Inclusion and exclusion criteria

Eligible studies included into our meta-analysis were required to meet all of the following inclusion criteria: (1) human studies, (2) case-control studies, (3) investigation of the association between *TOX3* rs3803662 C > T polymorphism and the risk of breast cancer, (4) focusing on the Chinese population, (5) sufficient data for estimating odds ratio (OR) and their 95% confidence interval (CI), (6) genotype frequency distributions in the control group being in Hardy-Weinberg equilibrium (HWE). If the studies involved partly overlapped subjects, only the one with largest sample size or the latest study was chosen.
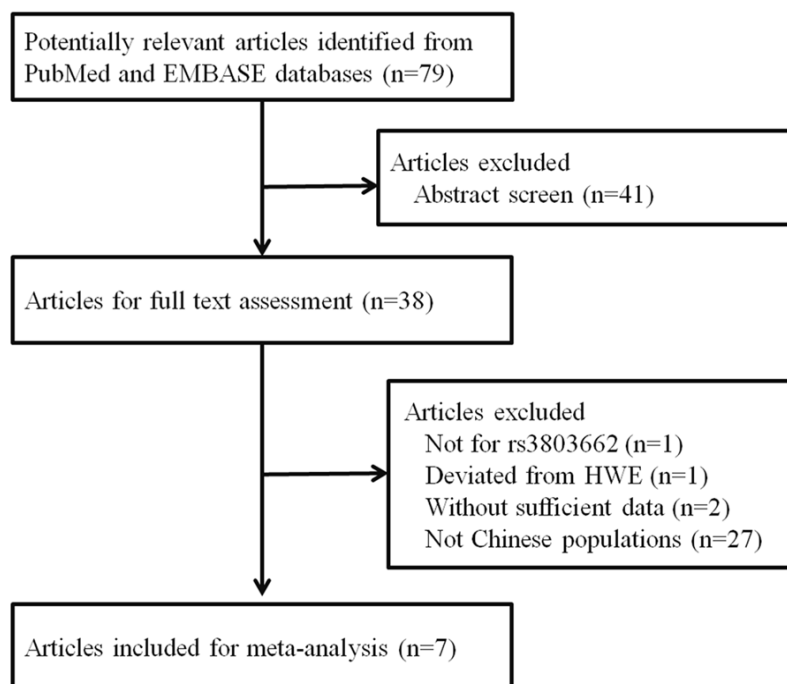
Data extraction

Information was extracted by two investigators independently. Disagreements between the two investigators were resolved by discussion. The following data were extracted: first author's surname, year of publication, country of origin, ethnicity, genotyping method, numbers of cases and controls and the genotype counts of cases and controls for *TOX3* rs3803662 C > T polymorphism.

Statistical analysis

HWE calculation for genotype frequency distributions was conducted in the control group for each selected study, using chi-squared goodness-of-fit test. A *P* value > 0.05 was applied for HWE. The strength of the association of *TOX3* rs3803662 C > T polymorphism with the risk of breast cancer in the Chinese population was measured by crude OR with corresponding 95% CI. The pooled ORs (95% CIs) were estimated for *TOX3* rs3803662 C > T polymorphism genotypes under the homozygous (TT vs. CC), heterozygous (CT vs. CC), recessive (TT vs. CT + CC), and dominant models (CT + TT vs. CC). Moreover, comparison of allele frequency was also carried out (T vs. C). The heterogeneity between studies was quantified with Chi square-based Q-test. A *P* value > 0.10 was considered the absence of significant heterogeneity. In the case of no heterogeneity we chose the fixed-effects model (the Mantel-Haenszel method) [22]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used [23]. Furthermore, the heterogeneity was also assessed by I^2 statistics. Values of I^2 range from 0 to 100%, with higher score suggesting a greater degree of heterogeneity [24]. Potential publication bias was evaluated using both Begg's funnel plots and Egger's linear regression test [25, 26]. A *P* value < 0.05 was considered a significant publication bias. We also conducted sensitivity test by recalculating the ORs (95% CIs) after consecutively excluding individual studies. All statistical analyses were performed using the STATA software (version 11.0; Stata Corporation, College Station, TX).

Potentially relevant articles identified from PubMed and EMBASE databases (n=79)

Articles excluded
  Abstract screen (n=41)

Articles for full text assessment (n=38)

Articles excluded
  Not for rs3803662 (n=1)
  Deviated from HWE (n=1)
  Without sufficient data (n=2)
  Not Chinese populations (n=27)

Articles included for meta-analysis (n=7)

Figure 1. Flow chart of studies included procedure in this meta-analysis.

Results

Study characteristics

As shown in **Figure 1**, a total of 79 potentially relevant articles were retrieved from PubMed and EMBASE databases. After title and abstract screening, 41 studies were removed because they did not investigate the association between *TOX3* gene polymorphisms and breast cancer risk. We assessed full texts of the remaining 38 studies. Among them, 27 publications were ruled out for not analyzing the Chinese population. In addition, one publication was excluded for not focusing on *TOX3* rs3803662 C > T polymorphism; two articles were excluded because genotyping data were not reported. Finally, one study was removed because of deviation from HWE [27]. Thus, seven eligible studies with 12,800 cases and 11,550 controls [18-21, 28-30] were ultimately involved in the meta-analysis (**Table 1**). All the selected studies were in agreement with HWE.

Meta-analysis results

The association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population was summarized in **Table 2**. Overall, a significantly increased risk of developing breast cancer in the Chinese population was indentified under all genetic models (homozygous model: OR = 1.28, 95% CI = 1.17-1.39, *P* < 0.001; heterozygous model: OR = 1.12, 95% CI = 1.03-1.22, *P* = 0.009; recessive model: OR = 1.17, 95% CI = 1.11-1.23, *P* < 0.001; dominant model: OR = 1.20, 95% CI = 1.10-1.30, *P* < 0.001, **Figure 2**; and comparison of allele frequency: OR = 1.13, 95% CI = 1.09-1.18, *P* < 0.001).

Heterogeneity and sensitivity analyses

No significant heterogeneity was observed under all genetic models: *P* = 0.580 for homozygous model, *P* = 0.694 for heterozygous model, *P* = 0.541 for recessive model, *P* = 0.649 for dominant model, and *P* = 0.528 for comparison of allele frequency (**Table 2**). Moreover, sensitivity analysis indicated that no single study affected the pooled ORs qualitatively.

Publication bias

Begg's funnel plots test and Egger's linear regression test were used to evaluate the potential publication bias. As shown in **Table 2** and **Figure 3**, there was no evidence of publication bias under all genetic models (homozygous model: *P* = 0.167; heterozygous model: *P* = 0.659; recessive model: *P* = 0.070; and dominant model: *P* = 0.352; as well as allele comparison: *P* = 0.079). The absence of publication bias further proved the reliability and accuracy of the present assessment of the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population.

Discussion

The etiology of breast cancer has not been fully clarified. The association of the high- and moderate-penetrance susceptibility genes with breast cancer risk has been well documented.

Table 1. Characteristics of eligible studies in the meta-analysis

Surname	Year	Country	Ethnicity	Genotyping method	Cases				Controls				MAF	HWE
					All	CC	CT	TT	All	CC	CT	TT		
Li	2009	China	Chinese	PCR-ligation detection reaction	291	32	141	118	291	40	128	123	0.64	0.470
Liang	2010	China	Chinese	SNP stream high-throughput 12-plex	1025	126	413	486	1046	127	464	455	0.66	0.603
Long	2010	USA	Chinese	Affymetrix	6345	650	2761	2934	3795	465	1727	1603	0.65	0.996
Zheng	2010	USA	Chinese	Affymetrix	3039	313	1325	1401	3082	386	1410	1286	0.65	0.987
Jiang	2011	China	Chinese	SNaPshot	493	48	212	233	510	54	224	232	0.67	0.995
Barzan	2013	Germany	Chinese	Sequenom MassArray	984	89	413	482	2206	255	990	961	0.66	0.999
He	2014	China	Chinese	Sequenom MassArray	623	72	280	271	620	72	278	270	0.66	0.973

MAF, Minor Allele Frequency; HWE: Hardy-Weinberg equilibrium.

Table 2. Meta-analysis results of the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population

Genetic comparison	OR (95% CI)	P^{het}	I^2 (%)	P value	Model	Publication bias (P for Begg's test)
Homozygous model (TT vs. CC)	1.28 (1.17-1.39)	0.580	0.0	< 0.001	Fixed-effects	0.167
Heterozygous model (CT vs. CC)	1.12 (1.03-1.22)	0.694	0.0	0.009	Fixed-effects	0.659
Recessive model (TT vs. CT + CC)	1.17 (1.11-1.23)	0.541	0.0	< 0.001	Fixed-effects	0.070
Dominant model (CT + TT vs. CC)	1.20 (1.10-1.30)	0.649	0.0	< 0.001	Fixed-effects	0.352
Allele comparison (T vs. C)	1.13 (1.09-1.18)	0.528	0.0	< 0.001	Fixed-effects	0.079
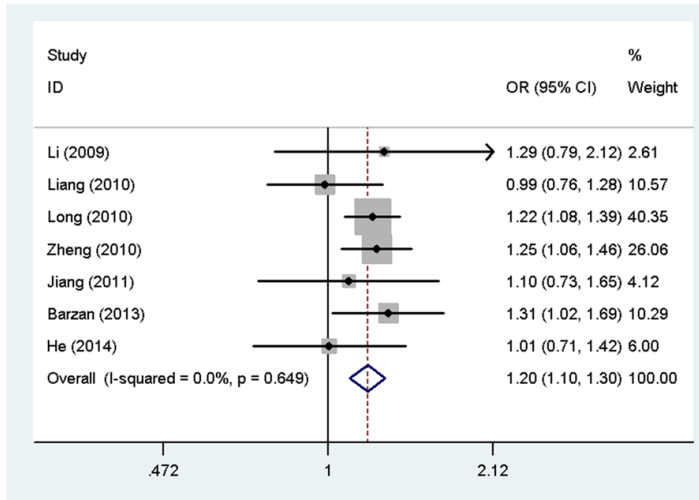
Figure 2. Forest plot for the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk under dominant model.

However, these susceptibility genes account for only a small proportion of individuals who are at high risk of breast cancer [7-9]. *TOX3*, a low-penetrance gene, had been found to be implicated in breast cancer in GWASs since 2007 [10, 13]. But, the role of *TOX3* in the development of breast cancer is unclear. *TOX3* is located on chromosome 16q12 and its protein product contains a putative high-mobility-group box motif. Such motif suggests that TOX3 may act as a transcription factor, which has been reported to be involved in bone metastasis of breast cancer [11]. *TOX3* rs3803662 C > T polymorphism has been widely studied in breast cancer. However, association studies on its association with breast cancer susceptibility yielded conflicting result.
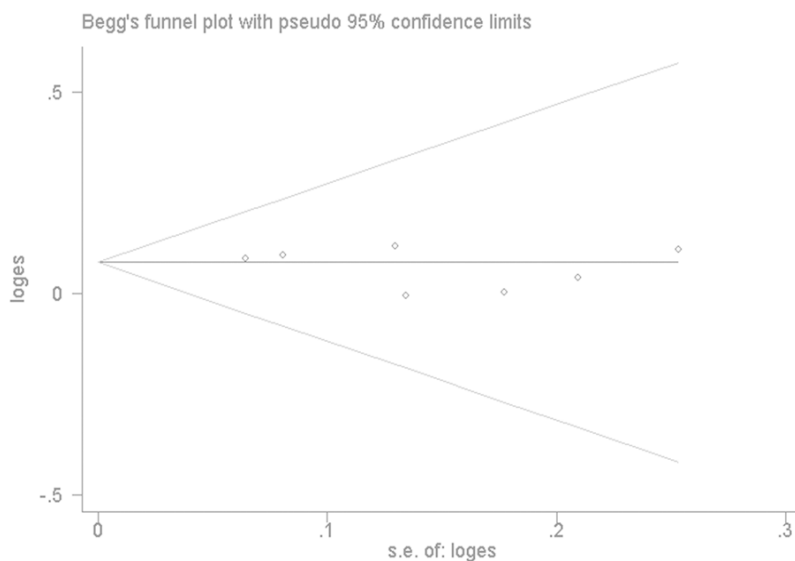
In this meat-analysis, we evaluated the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population by pooling together seven studies comprising 12,800 cases and 11,550 controls [18-21, 28-30]. Overall, our risk estimates indicated that *TOX3* rs3803662 C > T polymorphism was associated with 1.12- to 1.28-fold increased risk of breast cancer in the Chinese population under all genetic models. Meanwhile, no heterogeneity and publication bias was observed, indicating the reliability and accuracy of the current meta-analysis. In summary, these results suggested that *TOX3* rs3803662 C > T polymorphism was linked to the risk of breast cancer in the Chinese population.

To data, no previous meta-analysis has assessed the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population. There was two published meta-analyses investigating the relationship of this polymorphism and breast cancer risk [17, 31]. Chen et al. found that *TOX3* rs3803662 C > T polymorphism was associated with the risk of breast cancer in all the studied populations under the homozygous and recessive models, and in comparison of allele frequency [31]. However, they did not perform the subgroup analysis by ethnicity; therefore the association was not clear in the Chinese population. In the other meta-analysis, authors carried out the stratified analysis by ethnicity and observed that *TOX3* rs3803662 C > T polymorphism was associated with increased risk of breast cancer in Asians under all genetic models [17]. However, individuals harboring *TOX3* rs-3803662 T allele are common in Chinese, while C allele is prevalent among Koreans [32]. Due to the discrepancy in the genotype distri-

Figure 3. Funnel plot analysis for publication bias for *TOX3* rs3803662 C > T polymorphism and breast cancer risk under dominant model.

bution of *TOX3* rs3803662 among different ethnic groups, it is indispensible to understand the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population. Our meta-analysis results was in accordance with the previous meta-analysis [17]. The present meta-analysis, with the lager sample size (24,350 subjects) revealed that *TOX3* rs3803662 C > T polymorphism contributed to the increased risk of breast cancer in the Chinese population.

Despite the advantage of large sample size and the lack of heterogeneity and publication bias in our meta-analysis, several limitations should be addressed. First, the source of control groups was not uniformly defined. Some were population-based studies, whereas others were hospital-based studies. Second, the estimation of the association between *TOX3* rs3803662 C > T polymorphism and breast cancer risk in the Chinese population was solely dependent on crude without adjustment for other risk factors, such as age, obesity, smoking and estrogen receptor status. Third, the sample sizes of some included studies were relatively small. Finally, we failed to conduct stratified analysis by some risk factors and explore gene-environment interaction because of insufficient data in some eligible studies.

In conclusion, our meta-analysis suggested that *TOX3* rs3803662 C > T polymorphism was associated with increased susceptibility to breast cancer in the Chinese population. Future large sample size studies should be warranted to solidify these conclusions.

Disclosure of conflict of interest

None.

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