Int J Clin Exp Med 2016;9(3):6228-6236
www.ijcem.com /ISSN:1940-5901/IJCEM0020504

Original Article

Meta-analysis of *TNRC9* rs3803662 polymorphism and breast cancer risk

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Received November 25, 2015; Accepted February 13, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Background: As one important cancer in world, breast cancer is a hot topic for researchers. A large number of genome-wide association studies of persons with breast cancer have widely studied the association between rs3803662 and breast cancer risk. However, the results remain inconclusive. So, we want to clarify the association between them through a classical statistics method: a meta-analysis. Methods and results: We mined the literature for publications on the *TNRC9* rs3803662 polymorphism and breast cancer risk. We then performed a meta-analysis on the genotype data. To assess the association, we estimated odds ratios (ORs) with 95% confidence intervals (CIs). We performed sensitivity analysis, heterogeneity tests, cumulative meta-analysis, and bias assessment. Our meta-analysis confirmed that *TNRC9* rs3803662 polymorphisms increased breast cancer risk using thirteen case-control studies. These data are consistent for all genetic models: the allele model, the dominant model, the recessive model, and the additive model. The results of subgroup analysis suggest that the association in Caucasians appeared more significant than in Asians. Conclusions: Our study suggests that *TNRC9* rs3803662 polymorphisms may be a risk-conferring factor for breast cancer. Further functional studies on the role of rs3803662 in breast cancer pathogenesis are warranted.

Keywords: Breast cancer, *TNRC9*, genetic polymorphism, meta-analysis

Introduction

Breast cancer (BC) is one of the most common malignancies affecting women. So it is one of the hotspots of researchers. A large number of factors which including advanced age, female gender, and other environmental and inherit variants confer the increased risk of breast cancer [1]. Among them genetic factors plays a vital role in breast cancer etiology. Recently some susceptibility loci of breast cancer of which the masses are SNPs-that contribute a small effect on breast cancer risk have identified by many genome-wide association studies (GWAS) [2-6]. Because of only 5% of breast cancer incidence can be explained by these high-penetrance mutations [7], identification of low-penetrance genes/loci correlated with breast cancer susceptibility could have a significant impact on determining high-risk individuals. One of these isolated SNPs, rs3803662 of trinucleotide repeat containing 9 (*TNRC9*) located at 16q12, is a newly described risk factor for breast cancer; however, its function is unknown [8].

TNRC9, also known as *TOX3*, is a gene of encoding a putative, high-mobility group box motif, suggesting that it may be a transcription factor [9]. It has been implicated in the bone metastasis of breast cancer and involved in calcium dependent transcription regulation and interacts with cAMP-response-element-binding protein (CREB) and *CREB*-binding protein (CBP) [2, 10]. Moreover, TOX3 can interact with *CBP*/p300-interacting transactivator 1 (CITED1) and augment transcription levels [11, 12]. CITED1 is a transcriptional co-regulator that improves the activity of transcription factors such as the estrogen receptor (ER) and SMAD4 [13, 14].

The SNP rs3803662 is located 8 kb upstream of the *TNRC9* gene. There are studies researched it with an increased breast cancer risk in *BRCA1* and *BRCA2*-mutation carriers [15], men with breast cancer [16] and estrogen receptor positive breast cancer [17, 18]. Several epidemiological studies have suggested the association between *TNRC9* polymorphisms and breast cancer risk [17, 19, 20]. However, the association in different studies hold different conclusion. Liang J et al, Li L et al and Butt S et al [17, 19, 21] suggested that rs3803662 polymorphisms are not associated with breast cancer risk, the studies of Hutter CM et al, Slattery ML et al and Harlid S et al [22-24] got the opposite conclusion. Given these inconsistent conclusions and the defects of GWAS, we have performed a meta-analysis of the association between rs3803662 and breast cancer to clarify the risk estimation.

Materials and methods

Search strategy

To perform the meta-analysis, we mined publications from a number of electronic databases including PubMed, CNKI, Google Scholar database, and Excerpta Medica Database (Embase). The search terms "*TNRC9*", "*TOX3*", "rs3803662", "breast cancer", "genotype", and "polymorphism" were used to compile relevant publications. The search was also supplemented by reviewing the citations of the retrieved publications. The search was last updated on 20 June, 2014. The references included in the meta-analysis were all published in English as primary literature, used human subjects, and had no obvious overlap of subjects between studies. We selected articles that discussed the association between *TNRC9* rs3803662 polymorphisms and risk of breast cancer, and then looked for independent authors to prevent subject overlap which was verified this by checking the reference lists of all available publications for co-authorships. All the studies included have sufficient information to calculate odds ratio (OR) estimates and the corresponding 95% confidence intervals (CI).

Inclusion and exclusion criteria

For further meta-analysis, the following inclusion criteria were used to select literature: 1) the studies verified the association between rs3803662 and breast cancer risk, 2) the samples consisted of unrelated individuals, 3) the case sources and controls are described clearly with the diagnostic criteria meeting international standards, 4) the studies provided sufficient genotype data to calculate the ORs and corresponding 95% CIs, and 5) the genotype distribution was consistent with Hardy-Weinberg equilibrium (HWE). Studies were excluded using the following criteria: 1) lacking case-control studies, 2) incomplete genotype frequency data, and 3) studies using the same population across multiple publications. Thirteen studies met the criteria for meta-analysis (**Table 1**).

Data extraction

Two authors independently extracted the data from all eligible publications. Any disagreement regarding study inclusion was resolved by discussion between the two authors. The following data was extracted from each study: the first author's name, publication year, population ethnicity, source of controls, numbers of genotyped cases and controls (CC, CT, and TT genotypes for *TNRC9* rs3803662 polymorphism).

Statistical analyses

In this study all *p* values were two-sided and $P \leq 0.05$ was the standard for statistical significance. For the case and control groups of each study, we calculated the allelic frequency. The observed genotype frequencies for each polymorphism were assessed for HWE using a Chi-square test [25]. The pooled OR with a 95% confidence CI was employed to assess the association strength between *TNRC9* rs3803662 polymorphisms and breast cancer risk. We used the following models to calculate different ORs: the allele model (C vs. T), the dominant genetic model (TT/TC vs. CC), the recessive genetic model (TT vs. CC/CT), and the additive genetic model (TT vs. CC). Heterogeneities were estimated using Cochran's Q-statistic and $P < 0.100$ was considered to be statistically significant [26]. We also quantified the effect of heterogeneity using an I^2 test [27]. The I^2 values ranged from 0 to 100%, with an I^2 < 25%, 25-75%, and > 75% representing low, moderate, or high degrees of inconsistency,

Table 1. Details from the published studies on the relationship between *TNRC9* rs3803662 polymorphism and breast cancer risk included in the meta-analysis

ID	Author	Year	Ethnic group	Sample Size (case/control)	Source of controls[a]	Allele A/B	Control			Case			*p* for HWE
							AA	AB	BB	AA	AB	BB	
1	Mcinerney et al	2008	Caucasian (West of Ireland)	986/950	PB	C/T	532	396	58	486	382	82	0.16
2	Antoniou et al	2008	Caucasian	5092/4457	-	C/T	2244	1831	382	2422	2173	497	0.76
3	Latif et al	2009	Caucasian (British)	227/373	HB	C/T	217	137	19	106	103	18	0.66
4	Li et al	2009	Asian (Chinese)	291/291	HB	C/T	40	128	123	32	141	118	0.47
5	Liang et al	2010	Asian (Chinese)	1025/1046	PB	C/T	127	464	455	126	413	486	0.60
6	Gorodnova et al	2010	Caucasian (Russian)	140/174	PB	C/T	77	82	15	74	50	16	0.29
7	Slattery et al	2011	Caucasian (non-Hispanic)	1173/1328	PB	G/A	708	530	90	569	495	109	0.49
			Caucasian (Hispanic)	564/714	PB	G/A	270	332	112	209	260	95	0.55
8	Han et al	2011	Asian (Korean)	3285/3494	PB	G/A	516	1617	1361	369	1435	1481	0.32
9	Butt et al	2012	Caucasian (Swedish)	695/1387	PB	C/T	780	512	95	353	278	64	0.38
10	Harlid et al	2012	Caucasian (Sweden, Iceland, Poland)	3544/5018	PB	C/T	2768	1898	352	1794	1420	330	0.28
11	Ottini et al	2013	Caucasian (Italian)	412/745	PB	C/T	352	323	70	143	195	74	0.74
12	Mizoo et al	2013	Asian (Japanese women)	464/460	HB	C/T	91	227	142	74	230	160	0.99
13	Chen et al	2014	Asian (Chinese)	388/482	HB	C/T	217	227	38	159	178	51	0.04

[a]; HB: hospital-based; PB: population-based; HWE, Hardy-Weinberg equilibrium.

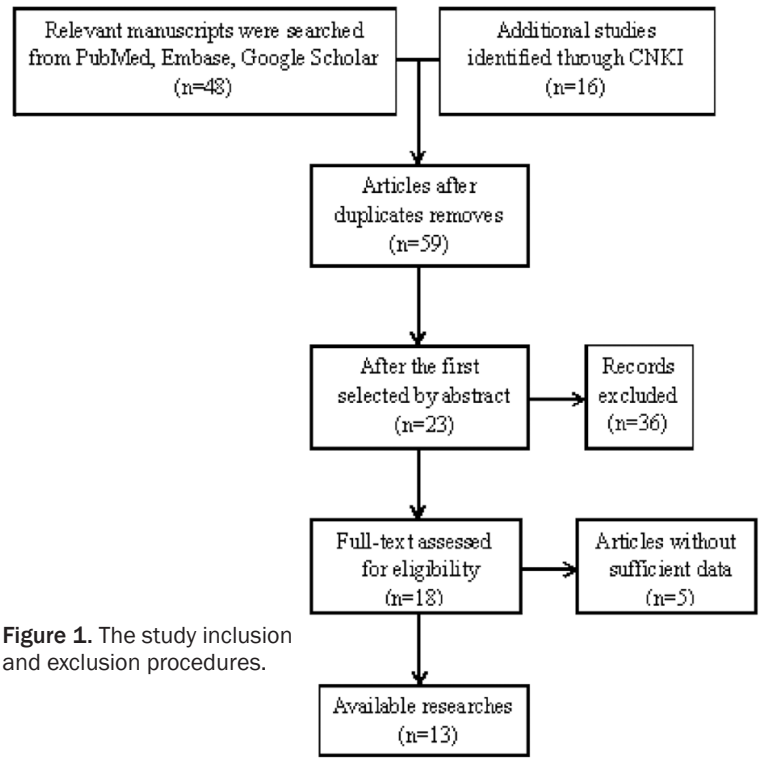

Figure 1. The study inclusion and exclusion procedures.

respectively. If the Q-test *p* value was greater than 0.100 and I^2 less than 25%, the data lacked heterogeneity and the overall OR estimate was calculated by the fixed-effects model (the Mantel-Haenszel method). Otherwise, the random-effects model (the DerSimonian-Laird method) was used [28]. To evaluate the heterogeneity, subgroup analyses were calculated by grouping studies with semblable characteristics, such as the control source. Sensitivity analysis was performed by individually removing each study and re-analyzing those remaining to identify potential outliers [29]. To assess publication bias the Begg's funnel plot was performed and the Egger's test was used to determine the funnel-plot symmetry. We built a regression model using the standardized estimate of the size effect as a dependent variable and the inverse of the standard error as an independent variable. If the intercept deviated significantly from zero, the effect estimate was considered biased. The combined OR significance was determined using the Z test ($P < 0.05$ was considered statistically significant). Analysis was performed using the STATA software (version 11.0; Stata Corporation, College Station, Texas, USA) for all the statistical tests.

Results

The characteristics of eligible studies

Following the initial literature search, 59 studies were identified. First, we reviewed all the articles and checked the titles, abstracts, and full texts against the defined criteria. And then we excluded the articles which haven't the sufficient data and wrote to authors the letter of request the specific data which hadn't list in articles. Finally, thirteen studies were included in the final meta-analysis [15, 17, 19-21, 23, 24, 30-35] (**Figure 1**). All of the selected studies conformed to HWE. **Table 1** shows the relevant publication details, including the first author, publication year, subject ethnicity, control source, the *P* for HWE, and the genotype distribution and frequency among cancer cases and controls.

Meta-analysis results

We analyzed the association between *TNRC9* rs3803662 genomic polymorphism and breast cancer risk. The eligible studies were pooled for the meta-analysis and included 18250 cases and 20955 controls. We observed a significant association between increased breast cancer risk and the rs3803662 variant genotypes for all genetic models. As shown in **Table 2**, the allele model has an OR of 1.170 (95% CI 1.135-1.206). The dominant model shows an OR of 1.190 (95% CI: 1.139-1.242). In the recessive model the OR equals 1.289 (95% CI: 1.186-1.401). Finally, in the additive model the OR is 1.422 (95% CI: 1.274-1.588). When stratified by ethnicity, our meta-analysis revealed a significant association between *TNRC9* rs3803662 polymorphisms and cancer risk in Asian and Caucasian populations. For Asian populations the OR is 1.176 (95% CI: 1.117-1.239) in allele model, 1.240 (95% CI: 1.092-1.407) in dominant model, 1.222 (95% CI: 1.081-1.381) in recessive model and 1.381

Table 2. Stratified analyses of *TNRC9* rs3803662 polymorphism on breast cancer risk

Variables	Allele model		Dominant model		Recessive model		Additive model	
	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a
Total	1.170 (1.135-1.206)[b]	0.009	1.190 (1.139-1.242)[b]	0.016	1.289 (1.186-1.401)[b]	0.083	1.422 (1.274-1.588)[b]	0.026
Ethnicity								
Asian	1.176 (1.117-1.239)[b]	0.330	1.240 (1.092-1.407)[b]	0.297	1.222 (1.081-1.381)[b]	0.168	1.381 (1.160-1.644)[b]	0.188
Caucasian	1.186 (1.102-1.276)[b]	0.003	1.195 (1.093-1.306)[b]	0.011	1.356 (1.199-1.535)[b]	0.103	1.458 (1.250-1.701)[b]	0.018

[a]*p* value of chi-squared from the heterogeneity test. [b]The fixed-effects model was used when the heterogeneity test *p* value > 0.100 and I^2 < 25%; the random-effects model was used for all other data. OR, odds ratio; CI, confidence interval.

Table 3. The test of heterogeneity degree in meta-analyses of TNRC9-rs3803662 polymorphism

Genetic model	λ^{2a}			Q-test *p*			I-squared (%)			Model[b]
	Asian	Caucasian	Overall	Asian	Caucasian	Overall	Asian	Caucasian	Overall	
Allele (C vs T)	4.61	22.91	27.99	0.330	0.003	0.009	13.2	65.1	53.6	R
Dominant (TT/TC vs. CC)	4.91	19.92	26.21	0.297	0.011	0.016	18.5	59.8	50.4	R
Recessive (TT vs. CC/CT)	6.45	13.28	20.50	0.168	0.103	0.083	38.0	39.8	36.6	R
Additive (TT vs. CC)	6.15	18.41	24.65	0.188	0.018	0.026	35.0	56.6	47.3	R

[a]Chi-square for heterogeneity test ($P \leq 0.05$). [b]Fix-effects model (F) was used when *P* value for heterogeneity test > 0.100 and I^2 < 25%; otherwise, random-effects model (R) was used.

(95% CI: 1.160-1.644) in additive model, respectively. In Caucasian populations the OR is 1.186 (95% CI: 1.102-1.276) in allele model, 1.195 (95% CI: 1.093-1.306) in dominant model, 1.356 (95% CI: 1.199-1.535) in recessive model and 1.458 (95% CI: 1.250-1.701) in additive model, respectively.

Heterogeneity tests

Table 3 lists the heterogeneity results. Random-effects model was performed to calculate the ORs in all genetic models. The recessive model is not statistically significant in the Asian and Caucasian populations. All genetic models also failed the Q-test in Asian populations. But overall, significant heterogeneity existed in the majority genetic models.

Sensitivity analysis

Sensitivity analysis was performed by removing each study individually and re-analyzing the remaining data. We calculated forest plots of the studies and the analysis results suggest that the pooled OR significance was not influenced by any single study in the allele genetic model. Sensitivity analyses indicated that the independent study contributing the most to heterogeneity was conducted by Ottini et al (**Figure 2**). These data indicate that the final results of this meta-analysis are statistically robust.

Publication bias

The Begg's funnel plot and Egger's test were performed to evaluate publication bias (**Figure 3**). The shape of the funnel plot shows no obvious asymmetry. Egger's test, based on a linear regression of the standard normal deviation against its precision, was carried out to verify the funnel plot symmetry. No statistically significant bias was found for any of the genetic models ($P > 0.05$).

Discussion

SNPs which could potentially increase an individual's susceptibility to cancer are the most pervasive source of human genetic variation. As a result, SNPs and their role in genetic susceptibility for cancer have been extensively studied in which including *TNRC9* rs3803662 and the risk of breast cancer. The result of current literatures on the association of rs3803662 and breast cancer risk is not definitive, in part due to the insufficient of sample. To remove the uncertainty regarding the evidence and ascertain the association between the *TNRC9* rs3803662 and breast cancer risk, the meta-analysis was carried out.

From the meta-analysis study indicates that there is a significant correlation between *TNRC9* rs3803662 polymorphism and breast cancer susceptibility. This result was observed

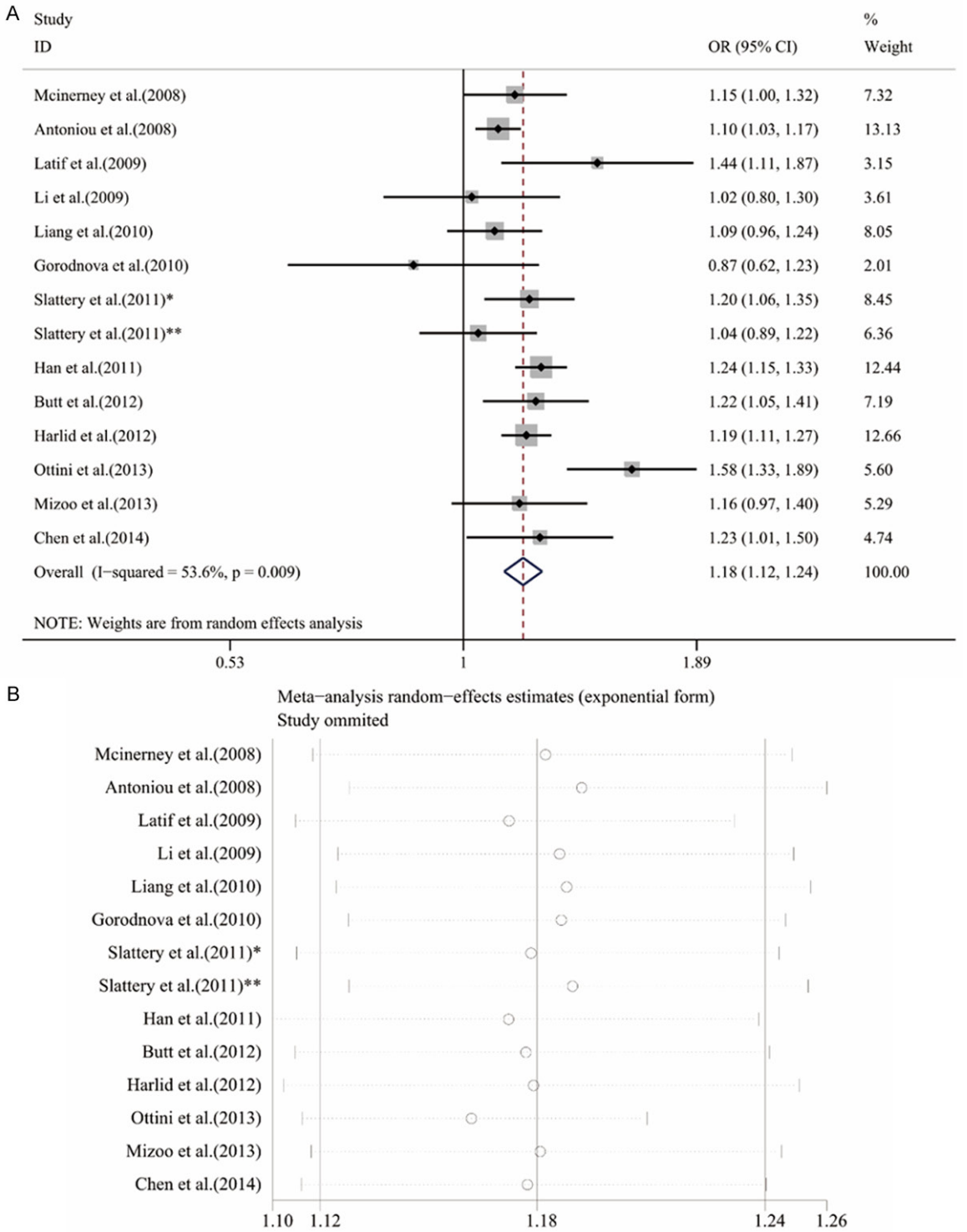

Figure 2. A: Forest plots for rs3803662 polymorphism and breast cancer risk using the allele model. Studies are represented by the odds ratio (OR) and 95% confidence interval (CI). B: Influence analysis of the individual studies in the overall meta-analysis. This figure shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate the 95% CI. Open circles indicate the pooled OR when the study indicated on the left is omitted from the meta-analysis. The lines indicate the 95% CI values when the study indicated is omitted from the meta-analysis.

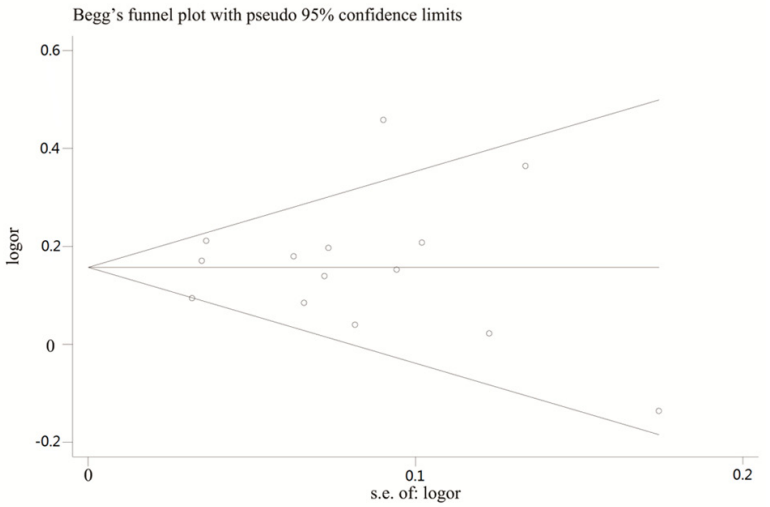

Figure 3. Begg's funnel plot to determine the publication bias for the studies included in the meta-analysis.

that the variants was a statistics significant risk factor for developing breast cancer in the allele, dominant, recessive, and additive models. In the statistical analysis of meta-analysis, heterogeneity evaluation can pose a potential problem for the interpretation of results. Through the heterogeneity in the overall comparisons was statistically significant in all genetic models, the tests have low power to detect it [36]. So, some subgroup meta-analyses were carried according to ethnicity and found the association in Caucasians appeared more significant than in Asians in racial subgroups. Many studies already obtained the thesis that different genetic adaptation exists in different environments. That is to say, environment pressure might play a role in the process of shaping genetic diversity [37-39]. From the history of human, the living environment of Asian and Caucasians is absolutely different, so the shaped genetic diversity of environment is different. Which is the reason of the different results about two groups must be cautious interpret.

TNRC9 belongs to the large and diverse family of HMG-box proteins. TNRC9 is differentially expressed in patients with breast cancer bone metastasis versus patients whose metastases occurred elsewhere [8, 10, 40]. The putative high-mobility group motif of it might be a transcription factor or is involved in the structural alterations of chromatin [40]. From the result of our analysis, we can propose the hypothesis that the rs3803662 variation may modulate *TNRC9* gene expression, and then change the structure of chromatin and transcriptional level, induce tumorigenesis and finally promote breast cancer enlargement, nearby tissues and lymph nodes infiltration which would ongoing to shorten the time to death.

We acknowledge that this meta-analysis has certain limitations due to the limited number of published studies in the literature. First, the results were obtained from unadjusted ORs estimates. If more individual data was available the adjusted ORs for age and sex could be calculated to provide exact summary estimates. Second, with more data this study could consider more refined subgroup analysis, environmental stresses, and gene-environment interactions.

However, this meta-analysis also has some advantages. The case and control subjects were from different populations and the subject enrollment was relatively large. This helps to eliminate publication bias, improving the accuracy of our findings.

Conclusions

The overall results of this meta-analysis provided reliable evidence showing that *TNRC9*-rs3803662 polymorphism is different extent to significantly correlate with increased breast cancer risk in Asian and Caucasian population. But the difference of different populations and the different extent among them aren't known. Further analyses conducted with a larger sample size and functional studies of the relationship between this polymorphism and cancer risk are warranted.

Acknowledgements

The authors are responsible for all the content. We are grateful to all the individuals in this study who made the work possible. This work was supported by 2013 Science and Technology Department of Shaanxi Province Natural

Science Foundation Project (No. 2013JM4035) and 2013 National Natural Science Foundation of China. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of conflict of interest

None.

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