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Increased risk of breast cancer in individuals carrying the *TNRC9* rs3803662 C>T polymorphism: a meta-analysis of case-control studies

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ABSTRACT. Currently, the relationship between the trinucleotide repeat containing 9 (*TNRC9*) rs3803662 C>T polymorphism and risk of breast cancer (BC) is uncertain. Here, we attempted to obtain a more accurate assessment of this association by conducting a meta-analysis of all eligible case-control investigations, comprising 44,820 cases and 58,316 controls. A comprehensive search was performed to identify all suitable studies involving the *TNRC9* rs3803662 polymorphism and BC risk. Pooled odds ratios (ORs) and 95% confidence intervals (95%CIs)

were estimated using fixed- or random-effect models. Heterogeneity, publication bias, and sensitivity analyses were also carried out. We found that the variant T allele of rs3803662 C>T greatly increases BC risk (CT *vs* CC: OR = 1.14, 95%CI = 1.07-1.22, P < 0.001; TT *vs* CC: OR = 1.38, 95%CI = 1.25-1.53, P < 0.001; CT/TT *vs* CC: OR = 1.19, 95%CI = 1.11-1.28, P < 0.001; TT *vs* CT/CC: OR = 1.28, 95%CI = 1.19-1.38, P < 0.001). Stratified analysis based on ethnicity also revealed a markedly increased risk in Asian and Caucasian populations. Moreover, studies with hospital-based control groups showed elevated risk under the four genetic models employed, as did those using population-based controls, except under heterozygote comparison. The *TNRC9* rs3803662 C>T polymorphism is greatly related to increased risk of BC, in both Asian and Caucasian populations.

Key words: Genetic polymorphism; *TNRC9*; rs3803662 C>T; Breast cancer; Meta-analysis

INTRODUCTION

Breast cancer (BC) is the most common malignancy affecting women worldwide. Despite an overall 5-year survival rate of 83-92% among women with stages I and II BC (Guo et al., 2012), the 10-year risk of recurrence is 20-40% (Early Breast Cancer Trialists' Collaborative Group, 2005). Aspects such as tumor stage, grade, and size, and lymph node metastasis status remain the most important prognostic factors for BC; however, we know little of the influence of inherited genetic variation on recurrence and overall survival rates.

It seems likely that a combination of environmental factors and susceptibility genes may contribute to the pathogenesis and progression of BC (Lichtenstein et al., 2000). In addition to the well-defined, highly penetrant modifications to genes such as *BRCA1* and *BRCA2*, which are only observed in a limited number of cases, certain common, low-penetrance variations have been identified in other genes potentially implicated in BC (Dong et al., 2008). Recently, several genome-wide association studies (GWAS; Antoniou et al., 2008; Garcia-Closas et al., 2008; Mcinerney et al., 2009; Latif et al., 2010) have revealed multiple BC-associated loci, of which the majority are single nucleotide polymorphisms (SNPs). However, these contribute only insignificant effects to BC risk.

One important locus is the trinucleotide repeat containing 9 (*TNRC9*) gene, also termed *TOX3*. This gene, on chromosome 16q12, contains a presumed high-mobility group (HMG), suggesting that it may act as a transcription factor. Moreover, it is related to bone metastasis in BC (Smid et al., 2006). Recently, Easton et al. (2007) provided strong evidence that rs3803662 C>T, which lies 8 kb upstream of *TNRC9/LOC643714*, confers even greater BC risk than mutations in both *BRCA1* and *BRCA2*. The rs3803662 polymorphism is either restricted to or more strongly associated with estrogen receptor (ER)-positive BC than ER-negative cases (Stacey et al., 2007; Garcia-Closas et al., 2008; Dittmer et al., 2011). Several GWAS have evaluated the relationship between this variant and BC risk, but their results

remain to be verified in different ethnic groups (Li et al., 2009; Zheng et al., 2009; Ruiz-Narváez et al., 2010). Hence, we performed a meta-analysis of 18 eligible studies, involving 44,820 cases and 58,316 controls, to achieve an accurate estimation of this association and better understand BC risk factors.

MATERIAL AND METHODS

Identification of relevant studies

We searched PubMed and Embase (last update: June 30, 2014) using the following terms: "rs3803662", "*TNRC9*", "*TOX3*", "16q12", "genetic susceptibility", "SNP", "polymorphism" or "variation", and "breast cancer". The search was conducted in English. A manual search of references included in retrieved papers was performed to identify additional studies. Articles in our meta-analysis conformed to the following criteria: i) they evaluated the *TNRC9* rs3803662 polymorphism and BC risk, ii) they used a case-control design, and iii) they contained genotype data.

Data extraction

Two investigators independently extracted data and reached a consensus in cases of disagreement. The following data were recorded: first authors' names, year of publication, nationality, control source, and genotype frequencies. Ethnicity was categorized as Caucasian or Asian (one study of an African population was excluded). Data were extracted separately.

Statistical analysis

All analyses were carried out with the Stata software (version 8.2; StataCorp. LP, College Station, TX, USA), using two-sided P values. The relationship between the *TNRC9* rs3803662 polymorphism and BC risk was assessed by odds ratios (ORs) and 95% confidence intervals (95%CIs). The significance of pooled ORs was assessed by the *Z*-test. Pooled ORs were generated from the respective studies using heterozygote (CT *vs* CC) and homozygote comparisons (TT *vs* CC), and dominant (CT/TT *vs* CC) and recessive models (TT *vs* CT/CC). Bonferroni correction was adopted for multiple comparisons. Since such comparisons were carried out four times, P values below 0.05/4 (0.0125) were considered statistically significant. Both the Cochran *Q*-test of heterogeneity and the I^2 statistic, which quantifies the proportion of overall variation due to heterogeneity, were calculated (Cochran, 1950; Higgins et al., 2003). Where the *Q*-test P value of at least 0.05 indicated a lack of heterogeneity, the OR of each dataset was calculated using a fixed-effect model (the Mantel-Haenszel method; Mantel and Haenszel, 1959). Otherwise, a random-effect model (the DerSimonian-Laird method; DerSimonian and Laird, 1986) was applied. Stratified analyses were also carried out based on ethnicity. A funnel plot and the Egger linear regression test were used to assess potential publication bias (Egger et al., 1997). In addition, sensitivity analysis was undertaken to verify the reliability of our results, by sequentially removing single studies from the meta-analysis to determine their individual effects on the pooled OR.

RESULTS

Study characteristics

In total, 18 studies involving 44,820 cases and 58,316 controls met the inclusion criteria and were used in pooled analyses (Antoniou et al., 2008; Garcia-Closas et al., 2008; Li et al., 2009; Mcinerney et al., 2009; Gorodnova et al., 2010; Latif et al., 2010; Liang et al., 2010; Tamimi et al., 2010; Campa et al., 2011; Han et al., 2011; Slattery et al., 2011; Butt et al., 2012; Harlid et al., 2012; Shan et al., 2012; Mizoo et al., 2013; Ottini et al., 2013; Chen et al., 2014; Elematore et al., 2014). The primary features of these investigations are shown in Table 1. All were case-control studies concerning BC. Five involved Asian subjects, 12 focused on Caucasians, while one comprised African participants. Twelve and six studies were population- and hospital-based, respectively.

Table 1. Characteristics of the studies included in our meta-analysis.

First author	Year	Country/Region	Ethnicity	Source	Cases (44,820)			Controls (58,316)		
					CC	CT	TT	CC	CT	TT
Antoniou	2008	Europe	Caucasian	Hospital	2422	2173	497	2244	1831	382
Garcia-Closas	2008	Europe	Caucasian	Hospital	7759	7132	1848	13,295	9705	2026
Mcinerney	2009	UK	Caucasian	Population	486	382	82	532	396	58
Latif	2010	UK	Caucasian	Hospital	106	103	18	217	137	19
Li	2009	China	Asian	Hospital	32	141	118	40	128	123
Tamimi	2010	Sweden	Caucasian	Population	333	300	54	415	273	50
Gorodnova	2010	Russia	Caucasian	Population	74	50	16	77	82	15
Liang	2010	China	Asian	Population	126	413	486	127	464	455
Han	2011	Korea	Asian	Population	369	1435	1481	516	1617	1361
Campa	2011	Europe	Caucasian	Population	3706	3528	1071	5721	4724	1150
Slattery	2011	America	Caucasian	Population	569	495	109	708	530	90
Harlid	2012	Europe	Caucasian	Population	1794	1420	330	2768	1898	352
Butt	2012	Sweden	Caucasian	Population	353	278	64	780	512	95
Shan	2012	Tunisia	African	Population	190	271	141	126	165	78
Chen	2014	China	Asian	Population	159	178	51	217	227	38
Ottini	2013	Italy	Caucasian	Hospital	143	195	74	352	323	70
Mizoo	2013	Japan	Asian	Hospital	74	230	160	91	227	142
Elematore	2014	Chile	Caucasian	Population	330	371	100	100	185	62

Quantitative synthesis

The variant T allele of rs3803662 C>T markedly increased BC risk under heterozygote (CT *vs* CC: OR = 1.14, 95%CI = 1.07-1.22, P < 0.001, I^2 = 68.3%) and homozygote comparisons (TT *vs* CC: OR = 1.38, 95%CI = 1.25-1.53, P < 0.001, I^2 = 71.2%), as well as under dominant (CT/TT *vs* CC: OR = 1.19, 95%CI = 1.11-1.28, P < 0.001, I^2 = 74.9%) and recessive models (TT *vs* CT/CC: OR = 1.28, 95%CI = 1.19-1.38, P < 0.001, I^2 = 58.8%; Figure 1 and Table 2).

In our stratified analysis based on ethnicity, each genetic model also revealed obviously enhanced risk in the Asian group (CT *vs* CC: OR = 1.16, 95%CI = 1.04-1.29, P = 0.010, I^2

= 18.0%; TT *vs* CC: OR = 1.42, 95%CI = 1.26-1.59, P < 0.001, I^2 = 35.0%; CT/TT *vs* CC: OR = 1.26, 95%CI = 1.13-1.40, P < 0.001, I^2 = 18.5%; TT *vs* CT/CC: OR = 1.24, 95%CI = 1.15-1.34, P < 0.001, I^2 = 38.0%; Figure 2). Moreover, similar results were obtained using the Caucasian dataset (CT *vs* CC: OR = 1.15, 95%CI = 1.06-1.24, P = 0.001, I^2 = 77.2%; TT *vs* CC: OR = 1.40, 95%CI = 1.22-1.59, P < 0.001, I^2 = 78.6%; CT/TT *vs* CC: OR = 1.19, 95%CI = 1.09-1.29, P < 0.001, I^2 = 82.3%; TT *vs* CT/CC: OR = 1.32, 95%CI = 1.19-1.46, P < 0.001, I^2 = 64.1%; Figure 3). Likewise, we noted that data from studies with hospital-based control groups showed elevated risk under these same four models (CT *vs* CC: OR = 1.25, 95%CI = 1.13-1.38, P < 0.001, I^2 = 57.3%; TT *vs* CC: OR = 1.53, 95%CI = 1.25-1.87, P < 0.001, I^2 = 74.4%; CT/TT *vs* CC: OR = 1.32, 95%CI = 1.17-1.49, P < 0.001, I^2 = 73.2%; TT *vs* CT/CC: OR = 1.31, 95%CI = 1.10-1.55, P = 0.002, I^2 = 73.2%). Data from population-based investigations demonstrated an interesting and clear association under homozygote comparison (TT *vs* CC: OR = 1.31, 95%CI = 1.14-1.51, P < 0.001, I^2 = 69.7%) and dominant (CT/TT *vs* CC: OR = 1.13, 95%CI = 1.03-1.24, P = 0.007, I^2 = 73.1%) and recessive models (TT *vs* CT/CC: OR = 1.27, 95%CI = 1.16-1.39, P < 0.001, I^2 = 48.3%), but not using heterozygote comparison (CT *vs* CC: OR = 1.09, 95%CI = 1.00-1.19, P = 0.058, I^2 = 66.4%; Table 2).

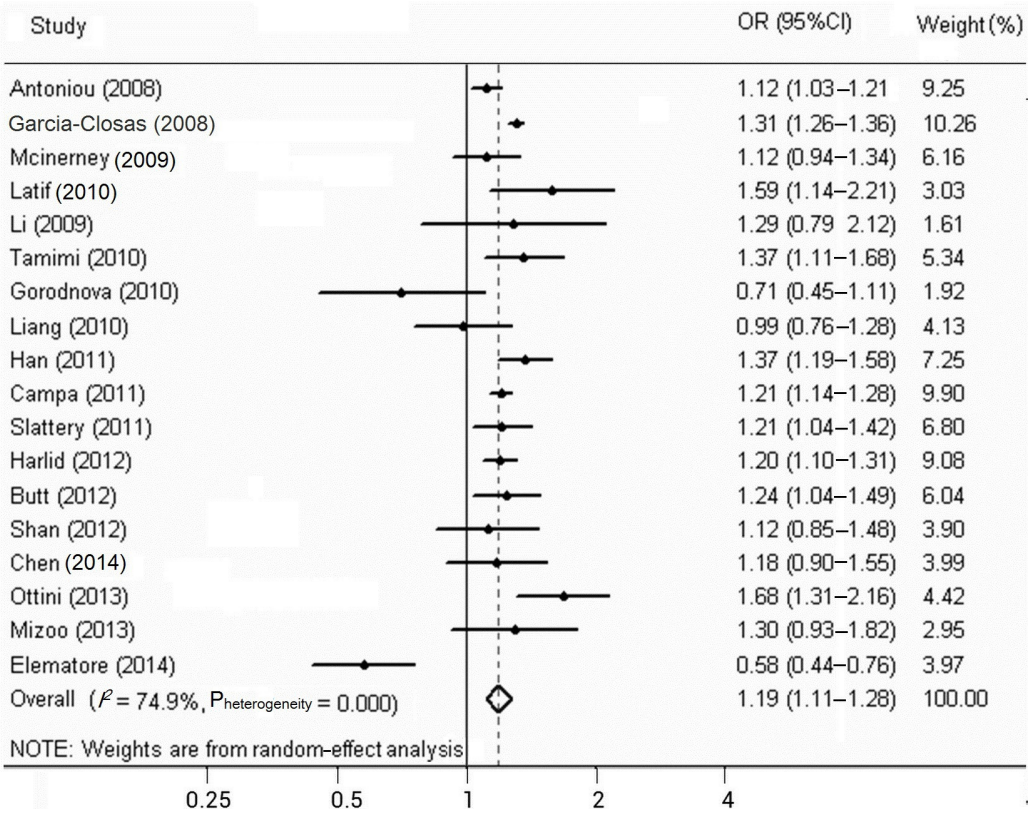

Figure 1. Forest plot concerning our meta-analysis of the relationship between the *TNRC9* rs3803662 C>T polymorphism and breast cancer risk under the dominant genetic model. OR = odds ratio, CI = confidence interval.

Table 2. Stratified analysis of the relationship between the *TNRC9* rs3803662 C>T polymorphism and breast cancer risk.

Variable	N[a]	Cases/controls	CT vs CC				TT vs CC				CT/TT vs CC				TT vs CT/CC			
			OR (95%CI)	P (*Z*)	P (*Q*)	I^2 (%)	OR (95%CI)	P (*Z*)	P (*Q*)	I^2 (%)	OR (95%CI)	P (*Z*)	P (*Q*)	I^2 (%)	OR (95%CI)	P (*Z*)	P (*Q*)	I^2 (%)
Total	18	44,820/58,316	1.14 (1.07-1.22)[b]	<0.001	<0.001	68.3	1.38 (1.25-1.53)[b]	<0.001	<0.001	71.2	1.19 (1.11-1.28)[b]	0.001	<0.001	74.9	1.28 (1.19-1.38)[b]	<0.001	0.001	58.8
Ethnicity																		
Caucasian	12	38,765/52,174	1.15 (1.06-1.24)[b]	0.001	<0.001	77.2	1.40 (1.22-1.59)[b]	<0.001	<0.001	78.6	1.19 (1.09-1.29)[b]	<0.001	<0.001	82.3	1.32 (1.19-1.46)[b]	<0.001	0.001	64.1
Asian	5	5453/5773	1.16 (1.04-1.29)	0.010	0.300	18.0	1.42 (1.26-1.59)	<0.001	0.188	35.0	1.26 (1.13-1.40)	<0.001	0.297	18.5	1.24 (1.15-1.34)	<0.001	0.168	38.0
Control source																		
Population	12	21,595/26,964	1.09 (1.00-1.19)[b]	0.058	0.001	66.4	1.31 (1.14-1.51)[b]	<0.001	<0.001	69.7	1.13 (1.03-1.24)[b]	0.007	<0.001	73.1	1.27 (1.16-1.39)[b]	<0.001	0.030	48.3
Hospital	6	23,225/31,352	1.25 (1.13-1.38)[b]	<0.001	0.039	57.3	1.53 (1.25-1.87)[b]	<0.001	0.002	74.4	1.32 (1.17-1.49)[b]	<0.001	0.002	73.2	1.31 (1.10-1.55)[b]	0.002	0.002	73.2

[a]Number of datasets. The single African study was excluded in the stratified analysis based on ethnicity. [b]A random-effect model was used when the heterogeneity test P value was <0.05, otherwise, a fixed-effect model was employed. P (*Q*): P value for the *Q*-test of heterogeneity. P (*Z*): P value for the *Z*-test of overall odds ratio. P < 0.0125 was defined as the significance threshold after Bonferroni correction. OR = odds ratio, CI = confidence interval.

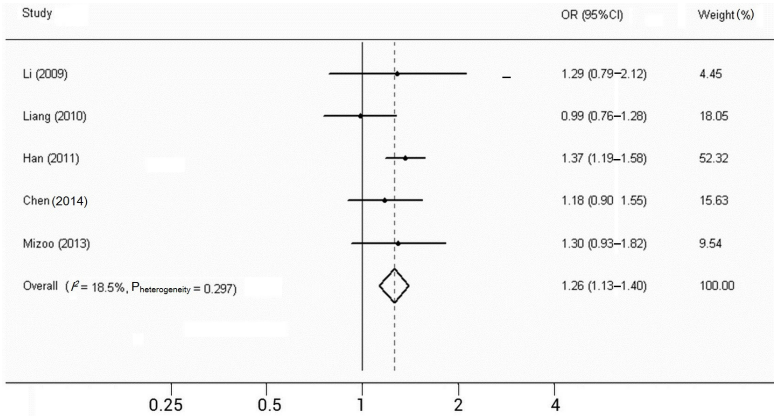

Figure 2. Forest plot concerning our meta-analysis of the relationship between the *TNRC9* rs3803662 C>T polymorphism and breast cancer risk among Asians, under the dominant genetic model. OR = odds ratio, CI = confidence interval.

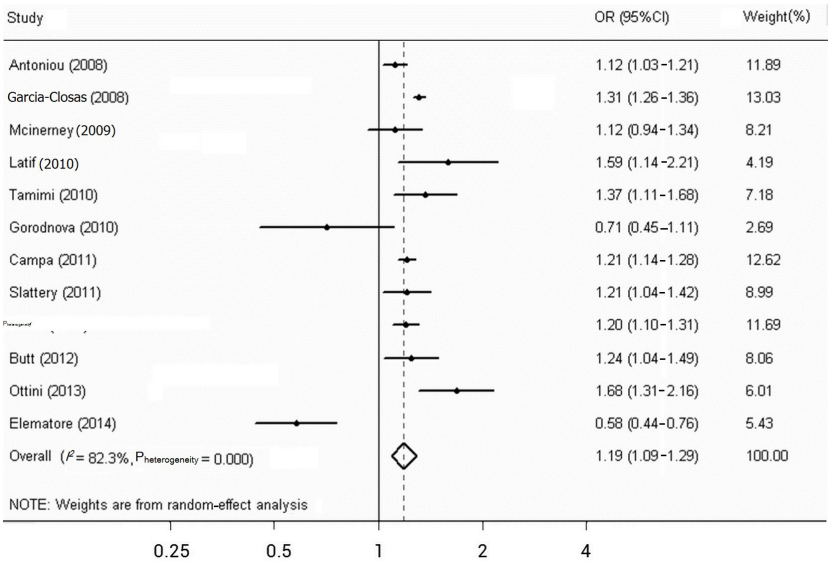

Figure 3. Forest plot concerning our meta-analysis of the relationship between the *TNRC9* rs3803662 C>T polymorphism and breast cancer risk among Caucasians, under the dominant genetic model. OR = odds ratio, CI = confidence interval.

Heterogeneity tests

We found obvious heterogeneity in data regarding the relationship between the *TNRC9* rs3803662 polymorphism and susceptibility to BC under heterozygote (CT *vs* CC: $P_{heterogeneity} < 0.001$, $I^2 = 68.3\%$) and homozygote comparisons (TT *vs* CC: $P_{heterogeneity} < 0.001$, $I^2 = 71.2\%$), and dominant (CT/TT *vs* CC: $P_{heterogeneity} < 0.001$, $I^2 = 74.9\%$) and recessive models (TT *vs* CT/CC: $P_{heterogeneity} < 0.001$, $I^2 = 58.8\%$). We assessed the source of this heterogeneity

by subgroup analysis, which showed no significant level in the Asian dataset, but revealed a significant presence in the Caucasian group, under all genetic models. One possible reason for this is that the Caucasian subjects derived from various countries associated with different genetic backgrounds.

Sensitivity analysis

We attempted to test the influence of single datasets on the pooled ORs by excluding each study included in our meta-analysis in turn. The corresponding results were not materially altered (data not shown), suggesting that our findings were statistically robust.

Publication bias

Begg's funnel plot and the Egger test were used to assess publication bias. The former revealed no evidence of obvious asymmetry (the funnel plot of the overall CT/TT *vs* CC comparison is shown in Figure 4). Furthermore, application of the Egger test to provide statistical evidence of funnel plot symmetry also suggested the absence of publication bias (CT/TT *vs* CC: P = 0.218).

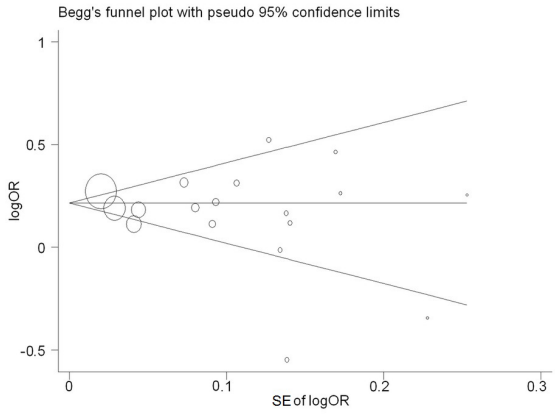

Figure 4. Begg's funnel plot testing publication bias under the dominant genetic model. Each point represents a separate study for the indicated association. The horizontal line represents mean effect size. LogOR = natural logarithm of the odds ratio, SE = standard error.

DISCUSSION

We believe, based on the present meta-analysis, that the *TNRC9* rs3803662 C>T polymorphism is clearly connected with increased BC risk. To the best of our knowledge, this is the first report to explore the connection between this polymorphism and risk of BC in different ethnicities.

The *TNRC9* gene, also known as *TOX3* and *CAGF9*, contains a trinucleotide repeat motif (Margolis et al., 1997) and an HMG-box (O'Flaherty and Kaye, 2003). It is involved in the regulation of calcium-dependent transcription and interacts with cAMP response element-binding protein (Yuan et al., 2009). In addition, TNRC9 can interact

with CITED1 to increase transcription (Yuan et al., 2009; Dittmer et al., 2011). CITED1 is a transcription coregulator that enhances the activity of transcription factors such as ERs (Yahata et al., 2001). A correlation between the rs3803662 genotype and decreased *TNRC9* mRNA has been observed in breast tumors, in which transcription of this gene decreases in an allele-dependent manner (Riaz et al., 2012). To date, one study has shown an effect of *TNRC9* expression on BC, showing that increased levels of *TNRC9* mRNA predict bone metastasis in this disease (Smid et al., 2006).

Recently, Easton et al. (2007) found that the *TNRC9* polymorphisms rs3803662 C>T, rs8051542 C>T, and rs12443621 A>G demonstrate a convincing connection with heightened BC risk. Moreover, another GWAS of 1600 Icelandic BC patients and 11,563 controls, followed by a replication study of 4554 affected individuals and 17,577 control subjects, showed the rs3803662 C>T *TNRC9* variant to be associated with increased ER-positive BC risk (Stacey et al., 2007). However, in a Japanese study, the rs3803662 T allele exhibited no connection with risk of BC (Mizoo et al., 2013). As conflicting results have been obtained, the clinical importance of this polymorphic gene is uncertain. Thus, this meta-analysis was conducted to establish the possible risk of BC conferred by the *TNRC9* rs3803662 C>T polymorphism. Based on 44,820 cases and 58,316 controls, the present study did reveal a connection between the *TNRC9* polymorphism and BC, in that the rs3803662 variant was found to be strongly associated with increased risk of this disease. The stratified analysis according to ethnicity also returned a similar result, using both Caucasian and Asian datasets. Our meta-analysis demonstrates that the T allele of the *TNRC9* rs3803662 C>T variant constitutes a minor risk factor for the development of BC.

The interpretation of our results may be limited by certain factors. First, the published studies were not sufficiently numerous to enable a comprehensive analysis, and the lack of data in some articles restricted further investigation of potential interactions with, for example, ER/progesterone receptor status, menopause, and pathological subtype. Second, although every effort was made to identify studies for use in our meta-analysis, we believe that some eligible investigations were not included. Third, our results were based on unadjusted data, whereas a more precise analysis could be conducted if detailed individual information were available, such as age, histological type, and *BRCA1*/*2* status.

Nevertheless, the present meta-analysis has several advantages. First, we extensively explored the connection between the *TNRC9* rs3803662 C>T polymorphism and BC risk, and our research further established an obvious association in Asian and Caucasian groups. This study attempted to reveal the role of genetic ancestry in BC etiology. Second, we pooled several datasets comprising a substantial number of cases and controls from different studies, which greatly aided our statistical analysis.

In conclusion, our meta-analysis suggests that the *TNRC9* rs3803662 C>T polymorphism is associated with elevated BC risk among both Asians and Caucasians. This polymorphism is an independent factor in the development of BC, and represents a potential therapeutic target for new drugs. However, well-designed, multicenter studies of other potential BC risk factors, such as gene-gene and gene-environment interactions, should be conducted to validate our findings.

Conflicts of interest

The authors declare no conflict of interest.

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