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Polymorphisms of tumor necrosis factor-alpha and breast cancer risk: a meta-analysis

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Abstract We conducted a meta-analysis to assess the association between tumor necrosis factor-alpha (TNF-alpha) gene *TNFA* −308 (G>A), *TNFA* −238 (G>A), *TNFA* −857 (C>T), *TNFA* −863 (C>A), *TNFA* −1031 (T>C), *TNFA* −1210 (A>T) polymorphisms and breast cancer(BC) susceptibility. We also performed subgroup analyses based on ethnicity (Caucasian, Asian, and African). An extensive search was performed to identify all case–control studies investigating such association. Thirteen eligible studies, including 10,236 BC patients and 13,143 controls, were identified. No significant association was observed in all genotypes in worldwide populations, but stratification by ethnicity indicated that the *TNFA* −308 A allele was associated with a decreased risk of BC compared with the G allele in Caucasian individuals (OR = 0.927, 95%CI = 0.879–0.978). Similar results were obtained when the A/A +A/G genotype was compared with the G/G genotype. In addition, meta-analysis results indicated that the A/A genotype of *TNFA* −308 was a risk factor for BC in African (A/A vs. G/G OR = 4.085 95%CI = 1.460–11.425; A/A vs. G/A OR = 4.861 95%CI = 1.746–13.527; A/A vs. G/A + G/G OR = 4.246 95%CI = 1.551–11.625), but not in Caucasian or Asian individuals. In conclusion, the results of this meta-analysis indicate that the *TNFA* −308 A allele may be an important protective factor for BC in European individuals, but it is not likely to confer susceptibility to BC in worldwide populations. In addition, the AA genotype of *TNFA* −308 may be a risk factor for BC in African individuals. Besides, other polymorphisms were not associated with BC susceptibility.

Keywords Tumor necrosis factor-alpha · Breast cancer · Polymorphisms · Meta-analysis

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Introduction

Breast cancer (BC) is the most common cancers worldwide and a major cause of mortality in women in developed countries. Over the past several years, breast cancer incidence rates have increased by approximately 30% in Westernized counties owing to changes in reproductive patterns and, more recently, to increased screening [1]. BC pathogenesis is a multistep and multifactorial process owing to a complex series of interactions among genetic, environmental, and endocrine factors [2]. Among the former, genetic polymorphisms, such as variants of pro- and anti-inflammatory cytokines such as -interleukin (IL) and tumor necrosis factors (TNF), have been most extensively investigated.

TNF-alpha is a potent pro-inflammatory cytokine initially identified as a serum factor that induces necrosis of transplanted tumors in mice [3]. It is one of the earliest cytokines to be produced in inflammatory response [4]. This production initiates a cytokine cascade involving the production of IL-1, IL-6, and other mediators, as well as TNF itself. High levels of TNF-alpha may cause organ

dysfunction [5]. It has been shown that the blood level of *T* TNF-alpha is increased in solid tumors [6]. Therefore, it seems likely that the expression level of TNF-alpha may be involved in cancer pathogenesis and progression.

Several single-nucleotide polymorphisms in the *TNFA* promoter can greatly influence the expression level of TNF-alpha [7]. Among these, a common polymorphism in the promoter, a G to A substitution at position −308, has been studied intensively as a putative determinant of susceptibility to various disease, including rheumatoid arthritis, psoriasis, and BC; although the effect is small, the A allele of the *TNFA* −308 polymorphism is significantly associated with increased TNF-alpha production [8]. Similarly, the T allele of *TNF*-A 857 polymorphism located in the 5′-flanking region also shows higher transcriptional activity [9].

In fact, numerous studies have investigated genetic polymorphisms and BC susceptibility or progression. However, the association between BC risk and polymorphisms found in *TNFA* is still controversial. Many studies have found that pro-inflammatory genotypes of *TNFA* were associated with BC risk [10, 11]. However, other studies have suggested that polymorphisms of *TNFA* may not be significantly associated with BC risk. These mixed results were likely due to small sample sizes and low statistical power. The low statistical power of individual studies to detect small differences between cases and controls is one factor to explain the lack of conclusive results.

To better address the association between *TNFA* polymorphisms and BC risk, we performed a meta-analysis of all eligible studies, including a subgroup analysis based on ethnicity.

Materials and methods

Identification of eligible studies

We performed an extensive search of studies that examined the association of the *TNFA* polymorphisms with BC. All eligible studies were identified by searching the PubMed database. The following terms were used: ("lacteal gland" OR "mammary gland" OR "breast") AND ("cancer" OR "carcinoma") AND ("polymorphism" OR "polymorphisms") AND ("tumor necrosis factor-alpha" OR "TNF-alpha" OR "TNFA"OR "TNF-A"). References of cited articles were reviewed to identify additional studies not indexed by Medline. No language or country restrictions were applied. Included studies were required to meet the following criteria: (a) based on unrelated individuals, pedigree data were excluded; (b) genotype distributions of both cases and controls were available; and (3) genotype distribution of the control population must be in Hardy–Weinberg equilibrium (HWE).

Data extraction

Information was carefully extracted from all eligible publications independently by two of the authors, according to the inclusion criteria. Disagreement was resolved by discussion between the authors. If these two authors could not reach a consensus, a third author was consulted to resolve the dispute and a final majority decision was made. For each study, the following information was collected: the first author's last name, year of publication, country in which the study was performed, ethnicity of the study population, numbers of genotyped cases and controls, source of control groups (population-or hospital-based), source of DNA, and other variables that could be sources of bias. Patient ethnicity was categorized as Caucasian, Asian, and African.

Statistical analysis

Meta-analysis

We calculated summary odd ratios (ORs) corresponding to a 95% confidence interval (CI) to assess the strength of association between *TNFA* polymorphisms and breast cancer. We examined the association between *TNFA* −308 allele A and BC risk compared with that for allele G (A vs. G); homozygote AA was contrasted with GG. Recessive (AA vs. GA + GG) and dominant (AA + GA vs. GG) models for allele A were also used. The same contrasts were performed for allele T of the *TNFA* −857 polymorphism, allele C of the *TNFA* −1031 polymorphism, and allele C of the *TNFA* −1210 polymorphism, respectively. As the AA genotypes of *TNFA* −238 were much less frequent than GA and GG genotypes, so we just examined the contrast of the allelic effect of A (minor allele) versus G (common allele), and also examined the contrast of A/A + G/A versus G/G genotypes. The same contrasts were performed for allele A of the *TNFA* −863 polymorphism.

We used the Cochrane *Q*-test to assess the heterogeneity among studies. If the *Q*-test revealed a *P* value of more than 0.05, the fixed-effects model (the Mantel–Haenszel method) was selected to pool the data [12]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used [13]. For sensitivity analysis, we excluded smaller studies and recalculated the summary ORs (95% CIs) using only larger studies to reflect the influence of the individual data. The potential publication bias was estimated by visual inspection of funnel plots [14], in which the standard error of log (OR) of each study was plotted against its log (OR); an asymmetric plot indicates a possible publication bias. We also used the method of Begg and Mazumdar [15] to calculate *P* values for rank

correlation and Egger's weighted regression method [16] to calculate P values for bias ($P < 0.05$ was considered representative of statistical significance). All statistical analyses were performed using STATA (v.10.1; Stata Corporation, College Station, TX).

Results

Included studies

Thirteen relevant studies with a total number of 10,236 cases and 13,143 controls were included in this analysis [10, 11, 17–27]. Characteristics of the included studies are shown in Table 1. The most commonly investigated genotypes were *TNFA* −308, −238, −863, −1031, −1210, and −857, which were reported in 13, 3, 2, 3, 2, and 2 studies, respectively. All studies used healthy volunteers or blood donors as control subjects. Populations were categorized into Caucasian, Asian, and African.

Effect of allele and subgroup analysis

TNF-A −308

Summary results of this meta-analysis for the association between the *TNFA* −308 polymorphism and BC are shown in Table 2. The meta-analysis did not reveal an association

Table 1 Characteristics of individual studies included in the meta-analysis

TNFA First author	Year	Country	Ethnicity	Number of cases/controls	Source of control	Case			Control			*P*-HWE controls
						G/G	G/A	A/A	G/G	G/A	A/A	
TNFA −308 polymorphism												
Kohaar	2009	Indian	Asian	40/150	Clinic based	21	16	3	137	13	0	1
Scola L	2006	Italian	Caucasian	84/106	Clinic based	71	12	1	79	26	1	0.69
Gaudet MM	2007	USA and Polish	Caucasian	5159/4986	Healthy volunteers	3681	1346	132	3490	1369	127	0.61
Kamali-Sarvestani E	2005	Iranian	Asian	223/235	Healthy volunteers	192	31	0	203	32	0	0.61
Azmy IA	2004	UK	Caucasian	705/498	Clinic based	475	208	22	313	167	18	0.57
Giordani L	2003	Italian	Caucasian	125/100	Healthy volunteers	104	19	2	84	15	1	0.52
Park KS	2002	Koreans	Asian	95/190	Healthy volunteers	75	20	0	134	54	2	0.26
Mestiri S	2001	Tunisian	African	243/174	Healthy volunteers	167	53	23	117	53	4	0.6
Chouchane L	1997	Tunisian	African	40/106	Healthy volunteers	15	24	1	72	33	1	0.29
Ostashkin AS	2008	Russians	Caucasian	167/139	Healthy volunteers	126	39	2	108	28	3	0.43
Gallicchio	2007	USA	Caucasian	59/907	Clinic based	44	14	1	593	273	41	0.19
Sirotkovic-Skerlev	2007	Croatia	Caucasian	158/76	Clinic based	136	22	0	68	8	0	0.63
MARIE-GENICA	2009	Germany	Caucasian	3138/5476	Healthy volunteers	2238	822	78	3795	1527	154	0.98
TNFA −238 polymorphism												
Kohaar	2009	Indian	Asian	40/150	Clinic based	34	6	0	145	5	0	1
Azmy IA	2004	UK	Caucasian	708/495	Clinic based	621	84	3	434	59	2	0.43
Sirotkovic-Skerlev	2007	Croatia	Caucasian	158/76	Clinic based	148	9	1	72	4	0	0.67
TNFA −857 polymorphism												
Kohaar	2009	Indian	Asian	40/150	Clinic based	26	11	3	76	64	10	1
Park KS	2002	Koreans	Asian	95/190	Healthy volunteers	65	27	3	138	46	6	0.3
TNFA −863 polymorphism												
Kohaar	2009	Indian	Asian	40/150	Clinic based	27	9	4	96	45	9	1
Park KS	2002	Koreans	Asian	95/190	Healthy volunteers	66	29	0	133	51	6	0.31
TNFA −1031 polymorphism												
Kohaar	2009	Indian	Asian	40/150	Clinic based	19	17	4	94	49	7	1
Park KS	2002	Koreans	Asian	95/190	Healthy volunteers	56	34	5	110	71	9	0.29
Sirotkovic-Skerlev	2007	Croatia	Caucasian	158/76	Clinic based	93	56	9	49	24	3	0.6
TNFA −1210 polymorphism												
Gaudet MM	2007	USA and Polish	Caucasian	5288/5006	Healthy volunteers	3323	1730	235	3199	1602	205	0.71
Gallicchio	2007	USA	Caucasian	58/916	Clinic based	34	20	4	584	285	47	0.23

Note: G/G, G/A, A/A represent homozygotes for common alleles, heterozygotes and homozygotes for rare alleles, respectively

Table 2 Summary results of various comparisons

	Subgroup	OR (95%CI)	*P-heterogeneity*	*P value*	*P-Publication bias*
TNFA −308					
A vs. G	All	1.050 (0.889,1.241)	0	0.565	0.393
	Caucasian	0.927 (0.879,0.978)	0.556	0.005	0.621
	Asian	1.731 (0.450,6.654)	0	0.424	0.602
	African	1.642 (0.827,3.261)	0.045	0.156	0.317
AA vs. GG	All	0.976 (0.824,1.155)	0.069	0.776	0.532
	Caucasian	0.904 (0.760,1.077)	0.902	0.259	0.881
	Asian	4.027 (0.035,466.292)	0.026	0.566	NA
	African	4.085 (1.460,11.425)	0.909	0.007	0.317
AA vs. GA	All	1.063 (0.893,1.265)	0.259	0.495	0.211
	Caucasian	0.992 (0.829,1.188)	0.931	0.934	0.881
	Asian	1.933 (0.338,11.060)	0.281	0.459	NA
	African	4.861 (1.746,13.527)	0.355	0.002	0.317
AA + GA vs. GG	All	1.023 (0.851,1.229)	0	0.809	0.18
	Caucasian	0.915 (0.861,0.972)	0.526	0.004	0.805
	Asian	1.774 (0.447,7.037)	0	0.415	0.602
	African	1.746 (0.476,6.408)	0.003	0.401	0.317
AA vs. GA + GG	All	1.003 (0.848,1.186)	0.112	0.976	0.532
	Caucasian	0.928 (0.781,1.104)	0.92	0.402	0.652
	Asian	3.305 (0.796,13.729)	0.05	0.1	NA
	African	4.246 (1.551,11.625)	0.742	0.005	0.317
TNFA −238					
A vs. G	All	1.187 (0.871,1.618)	0.065	0.278	0.419
AA + GA vs. GG	All	1.617 (0.639,4.091)	0.046	0.31	0.437
TNFA −857					
T vs. C	All	0.947 (0.657,1.363)	0.177	0.768	NA
TT vs. CC	All	0.960 (0.360,2.561)	0.849	0.935	NA
TT vs. TC	All	1.198 (0.428,3.351)	0.493	0.73	NA
TT + TC vs. CC	All	0.915 (0.596,1.405)	0.084	0.686	NA
TT vs. TC + CC	All	1.068 (0.404,2.822)	0.898	0.895	NA
TNFA −863					
A vs. C	All	0.947 (0.650,1.378)	0.773	0.774	NA
AA + AC vs. CC	All	0.963 (0.624,1.486)	0.699	0.865	NA
TNFA −1031					
C vs. T	All	1.209 (0.922,1.585)	0.287	0.169	0.039
CC vs. TT	All	1.575 (0.761,3.259)	0.563	0.221	0.451
CC vs. CT	All	1.325 (0.629,2.794)	0.927	0.459	0.555
CC + CT vs. TT	All	1.219 (0.877,1.694)	0.319	0.24	0.076
CC vs. CT + TT	All	1.480 (0.724,3.024)	0.716	0.283	0.525
TNFA −1210					
C vs. T	All	1.048 (0.980,1.121)	0.494	0.171	NA
CC vs. TT	All	1.112 (0.919,1.346)	0.615	0.275	NA
CC vs. CT	All	1.066 (0.876,1.297)	0.818	0.525	NA
CC + CT vs. TT	All	1.051 (0.970,1.137)	0.54	0.222	NA
CC vs. CT + TT	All	1.096 (0.908,1.324)	0.676	0.34	NA

NA not available

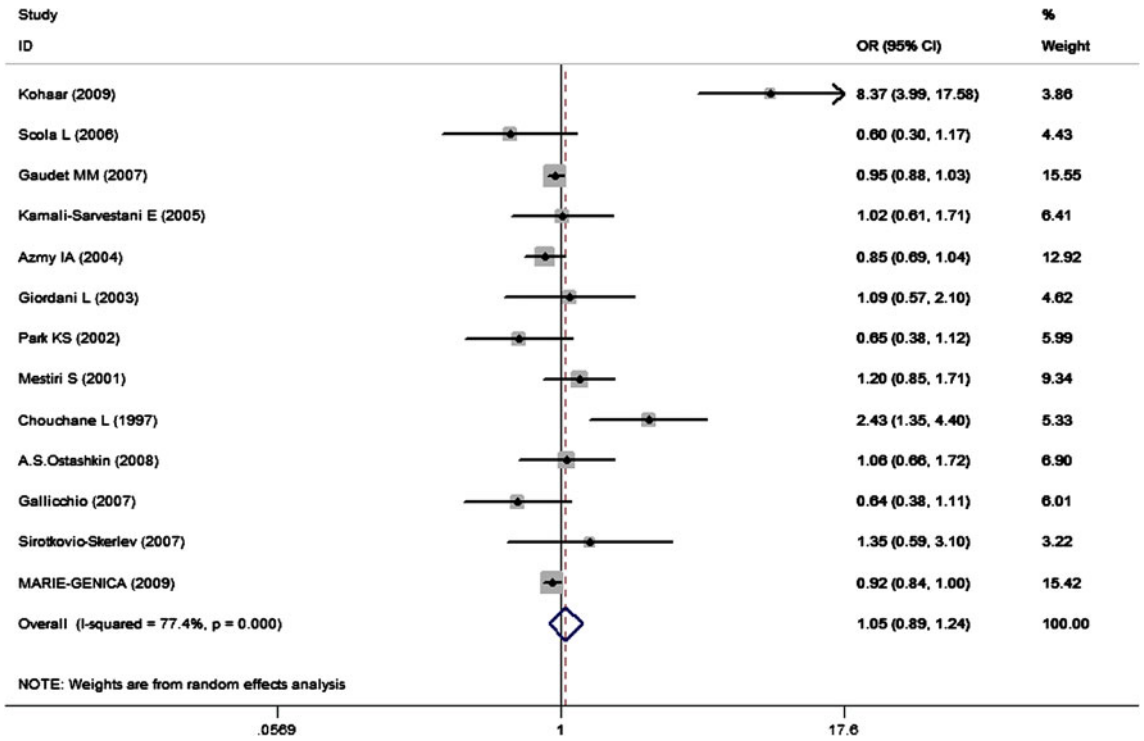

Fig. 1 OR and 95% CI of individual studies and pooled data for the association between the *TNFA* −308 allele A and BC in overall populations

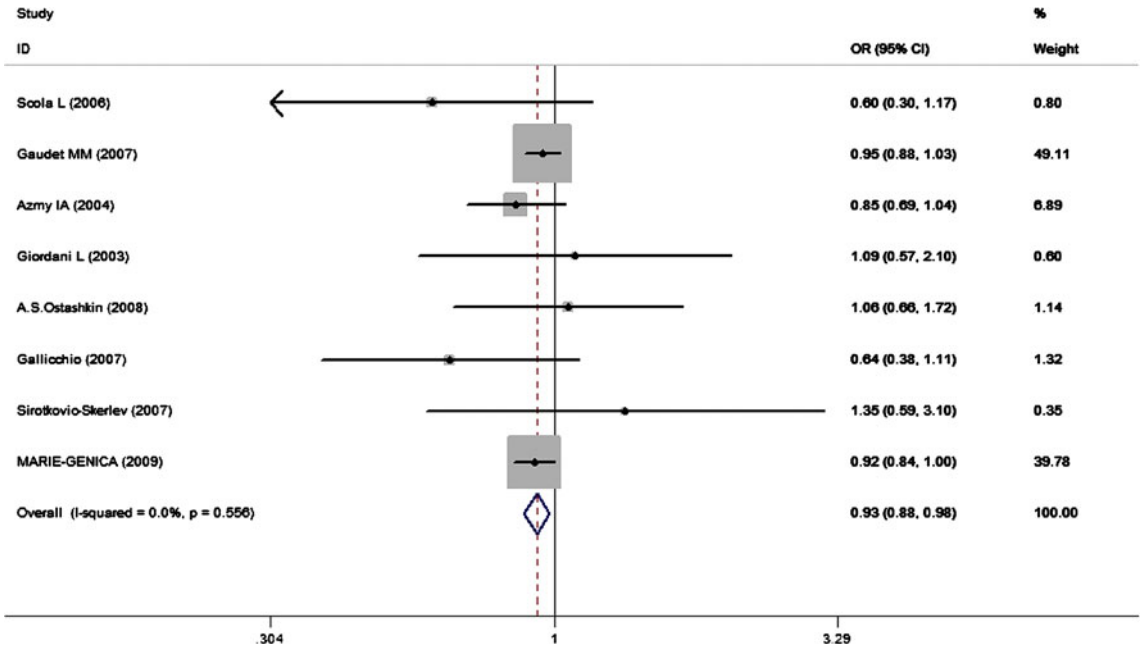

Fig. 2 OR and 95% CI of individual studies and pooled data for the association between the *TNFA* −308 allele A and BC in European populations

between BC and the *TNFA* −308 A allele in the overall population (OR = 1.050, 95%CI = 0.889–1.241; Fig. 1). However, stratification by ethnicity indicated that the *TNFA* −308 A allele was associated with a decreased risk of BC compared with the G allele in Caucasian individuals (OR = 0.927, 95%CI = 0.879–0.978; Fig. 2). The overall OR for the A/A versus G/G genotype of the *TNFA* promoter −308 was 0.976(95%CI 0.824–1.155), and an association was not found. However, stratification by ethnicity indicated that the AA genotype was a risk factor for BC in African, but

not in Caucasian or Asian populations. The same results were seen when we compared the A/A and G/A genotypes or the A/A and G/A + G/G genotypes. For the A/A + G/A versus GG genotype, the OR was 1.203 (95%CI 0.851–1.229), 0.915 (95%CI 0.861–0.972), 1.774 (95%CI 0.447–7.037), and 1.746 (95%CI 0.476–6.048) in the overall, Caucasian, Asian, and African populations, respectively.

Other genotypes

The meta-analysis did not reveal an association between BC and *TNFA* −238 G>A polymorphism, and the same results were obtained between BC and any other polymorphisms in the overall population (Table 2). As these genotypes were investigated in small number of studies, we did not perform subgroup analysis. And more studies were needed to examine whether BC is associated with these polymorphisms.

Sensitivity analysis

With regard to *TNFA* −308 polymorphism, the results pattern was not impacted by any single study in all subgroup studies (data not shown).

Publication bias

Funnel plot from comparisons of A versus G of *TNFA* −308 was generated to assess publication bias (Fig. 3). The Begg's and Egger's Test was performed to statistically evaluate funnel plot symmetry; the results indicated no significant publication bias (Table 2).

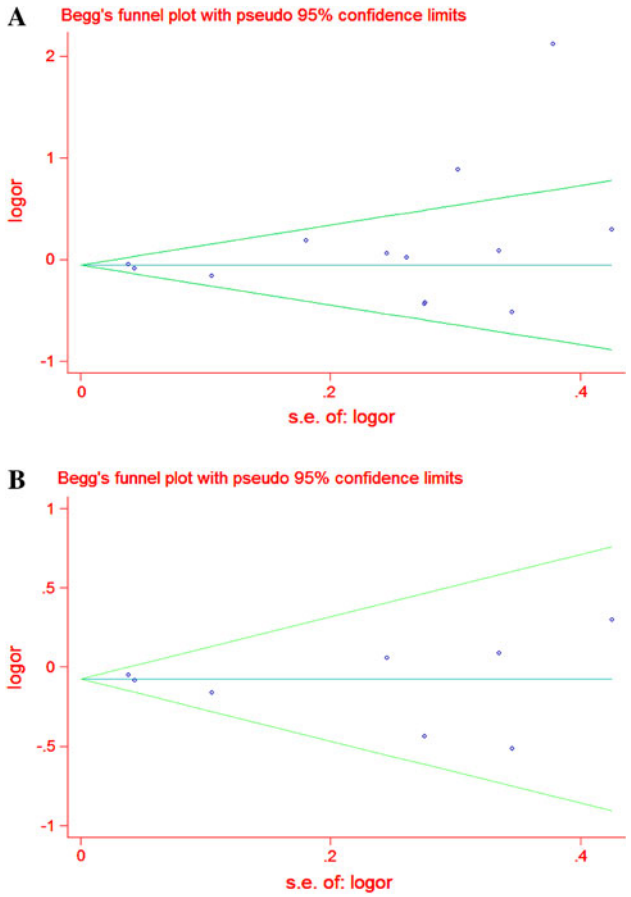

Fig. 3 Begg's funnel plots for the associations: (**a**) allele A versus allele G in the overall populations; (**b**) allele A versus allele G in European populations

Discussion

TNFA is located within the HLA class III region in chromosome 6p21.3, and contains several sites of single-nucleotide polymorphisms, which modify gene expression. TNF-alpha has shown an anti-tumor activity in a variety of tumor cell lines, including BC cell lines [28]. TNF-alpha causes arrest of the cell cycle in the transition from G1 to S phase in mammary carcinoma cells [29] and induces apoptosis in tumor cells, similar to the Fas ligand [30]. −238 G/A and −308 G/A promoter polymorphisms of *TNF* are shown to be associated with the TNF expression both in vivo and in vitro [31–33]. *TNFA* −857T, −863A, and −1031C are also found to increase TNF promoter activity [9] and lipopolysaccharide-induced TNFA production [34], although contradictory findings have also been reported [35, 36].

This study investigated the relationship between *TNFA* polymorphisms and BC susceptibility. For TNFA −308 genotypes, the overall results of this meta-analysis showed no significant BC susceptibility with the *TNFA* −308 promoter A/G polymorphism. However, stratification by ethnicity revealed a significant association between BC risk and the *TNFA* polymorphism in the European study populations. The available data indicate that the *TNFA* −308 A allele is an ethnic-specific protective factor for BC, and the A/A genotype is a risk factor for BC in African individuals, although the small number of Caucasian and African studies available to date reduces the confidences of this conclusion. There was no heterogeneity among the Caucasian and African studies, suggesting a strong association of the *TNFA* −308 A/G polymorphism with BC by ethnicity.

This meta-analysis of the A allele and A/A + A/G genotype of *TNFA* −308 locus revealed a significant association with BC in European populations, but no such association with the A/A versus G/G, A/A versus G/A genotype, and A/A versus A/G + G/G genotypes. Contrasting results were seen in African individuals. As only eight Caucasian and two African population studies were included, these results should be interpreted with caution. More Caucasian and African studies are needed to confirm this possible association.

The ORs of the A/A versus G/G genotype and AA versus A/G + G/G genotype of *TNFA* −308 locus were decreased in European populations, versus African and Asian populations, although the difference did not reach statistical significance. This finding may be due to low statistical power owing to the low frequency of the A/A genotype. The meta-analysis consistently showed no heterogeneity among studies in European populations. Taken together, these findings suggest that the *TNFA* −308 A/G polymorphism may protect against for BC in European individuals. However, because only eight studies in European populations were included, this result should be interpreted with caution. More European studies are needed to determine this possible association.

The finding that the association between the *TNFA* −308 A/G polymorphism and BC differs according to ethnicity is somewhat surprising; however, many factors may contribute to this difference. First, genetic heterogeneity for BC may exist in different ethnic populations. Second, clinical heterogeneity may be involved, and the contribution of differences in patient populations may cause different results. Third, different linkage disequilibrium (LD) patterns may contribute to the discrepancy. This polymorphism may be in LD with a nearby causal variant in one ethnic group, but not in another. Fourth, the difference might arise from chance, such as type I error, or due to multiple testing that inflates the type I error.

No association was found between BC and *TNFA* −238, −863, −857, −1031, and −1210 genotypes. As studies investigated these genotypes were not much enough, these results should be interpreted with caution, and more studies are needed.

In conclusion, results of this meta-analysis indicate that the *TNFA* −308 A allele may protect against BC in European individuals, but it is not likely to confer susceptibility to BC in worldwide populations. In addition, the AA genotype may be a risk factor for BC in African individuals. *TNFA* −238, −863, −857, −1031, and −1210 genotypes were not association with BC risk. Further detailed investigation with large numbers of worldwide participants is needed to clarify the role of these polymorphisms in BC.

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