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TCF7L2 gene polymorphisms and susceptibility to breast cancer: a meta-analysis

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ABSTRACT. Numerous studies have evaluated the association between TCF7L2 gene polymorphisms (rs12255372 and rs7903146) and breast cancer risk. However, the results have been inconsistent. Therefore, in the current study, we performed a meta-analysis. A systematically literature search of the PubMed and EMBASE databases was conducted in November 2013, and the reference lists of articles were retrieved. A summary odds ratio (OR) with its 95% confidence interval (CI) were calculated to evaluate the strength of association. Publication bias was investigated using Begg's funnel plot. Meta-analysis was performed using STATA package version 12.0. A total of 4 case-control studies met our inclusion criteria, including 4600 cases and 5289 controls. Overall, TCF7L2 gene polymorphisms were significantly associated with an increased risk of breast cancer in genetic comparison models (rs12255372 for GG *vs* GT: OR = 0.90, 95%CI = 0.83-0.98; rs7903146 for CC *vs* TT: OR = 0.75, 95%CI = 0.63-0.90, CC *vs* CT: OR = 0.88, 95%CI = 0.81-0.97, dominant model: OR = 1.16, 95%CI = 1.06-1.27, recessive model: OR = 0.79, 95%CI = 0.67-0.94). This meta-analysis demonstrated that TCF7L2 gene polymorphisms (rs12255372 and

rs7903146) are associated with an increased susceptibility to breast cancer. However, further studies including large sample sizes are needed to validate this association.

Key words: Breast cancer; Metal analysis; TCF7L2 gene polymorphism

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, accounting for 23% (1.38 million) of total new cancer cases and 14% of total cancer deaths in 2008. Approximately half of breast cancer cases and 60% of deaths are estimated to occur in economically developing countries (Jemal et al., 2011). Various factors may influence the development of breast cancer, including age at menarche, menopause, first birth age, and exogenous hormone use (Chen et al., 2013). In addition, epidemiological studies provide strong evidence that genetic factors are important in the pathogenesis of breast cancer, and approximately 27% of breast cancer cases are related to inherited susceptibility (Lichtenstein et al., 2000).

The transcription factor 7-like 2 (TCF7L2) gene is located on the long arm of chromosome 10q25.2, which was previously known as the TCF-4.TCF7L2 gene, and is part of the Wnt/β-catenin signaling pathway, which plays a critical role in cell development and growth regulation (Ravindranath et al., 2008). The TCF7L2 protein is involved in blood glucose homeostasis, and its gene variants rs12255372 and rs7903146 have been reported to be associated with risk of type 2 diabetes (Bodhini et al., 2007). In addition, epidemiological studies demonstrated that TCF7L2 gene polymorphisms were associated with susceptibility to cancer (Sun et al., 2006).

Various studies have demonstrated that TCF7L2 rs12255372 and rs7903146 gene polymorphisms were associated with susceptibility to prostate cancer, colon cancer, colorectal cancer, lung cancer, and ovarian cancer (Agalliu et al., 2008; Folsom et al., 2008). However, little is known regarding the association between rs12255372 or rs7903146 variant and susceptibility to breast cancer. Over the past decade, several case-control studies have focused on the association between TCF7L2 gene polymorphisms and breast cancer risk. However, the results were inconsistent conflicting. Therefore, we performed a meta-analysis to clarify the association between the TCF7L2 gene rs12255372 and rs7903146 variants and breast cancer risk.

MATERIAL AND METHODS

Selection of studies

Systematic literature searches of the PubMed and EMBASE databases were conducted to identify previously published clinical studies. All search queries were updated through November 2013 using the following search strategy: (“breast cancer” or “TCF7L2”) and (“rs12255372” or “rs7903146” or “genotype” or “polymorphism”). In addition, the reference lists of the included articles and relevant meta-analyses were manually searched. Studies reported by the same authors were evaluated for possible overlapping participant groups. No language restrictions were applied.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met the following criteria: i) case-control studies that addressed breast cancer cases and healthy controls; ii) studies that evaluated the association between TCF7L2 gene polymorphisms (rs12255372 and rs7903146) and breast cancer risk, and iii) studies that included sufficient genotype data for extraction. Studies were excluded when: i) they were not case-control studies that evaluated the association between TCF7L2 gene polymorphisms (rs12255372 and rs7903146) and breast cancer risk; ii) case reports, letters, reviews, meta-analysis, and editorial articles; iii) studies based on incomplete data and those with no usable data reported; iv) duplicate data were contained, and v) healthy controls were not in Hardy-Weinberg equilibrium (HWE).

Data extraction

Information was extracted independently by 2 investigators according to the inclusion criteria described above (X.P. Lu and G.N. Hu). For each study, the following characteristics were collected: first author, year of publication, area, race, source of cases and controls, number of cases and controls, sample, polymorphisms, genotype frequency, and evidence of HWE in controls. For conflicting evaluations, an agreement was reached following discussion.

Statistical analysis

Meta-analysis was performed using the STATA package version 12.0 (Stata Corporation, College Station, TX, USA). To test for control population selective bias, a chi-square test was used to determine if the genotype distribution of the control subjects of each individual population was reported conformed to HWE ($P < 0.05$ was considered to be significant). The strength of the associations between TCF7L2 gene polymorphisms (rs12255372 and rs7903146) and susceptibility to breast cancer estimated based on the odds ratio (OR) and 95% confidence interval (95%CI) under the co-dominant model (GG *vs* TT, GG *vs* GT or CC *vs* TT, CC *vs* CT), dominant model (TT+GT *vs* GG), and recessive model (GG+GT *vs* TT) were calculated by the fixed-effect model or random-effect model. Between-study heterogeneities were estimated using the I^2 test. I^2 represents the variability attributed to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. When a significant $I^2 > 50\%$ indicated heterogeneity across studies, the random-effect model was used for meta-analysis; otherwise, the fixed-effect model was used. Sensitivity analysis was performed by comparing random-effect model values to the fixed effect. Publication bias was investigated using Begg's funnel plot, and $P < 0.05$ was considered to be statistically significant publication bias.

RESULTS

Study characteristics

Based on the search criteria, 21 articles were identified. Of these, 13 studies were excluded after reading the title or abstract because these articles were irrelevant to our study. In addition, 2 duplicated publications and 1 review were excluded. One paper did not include a

control group, which is why it was excluded. Therefore, only 4 studies addressing the association between TCF7L2 gene polymorphisms (rs12255372 and rs7903146) and breast cancer were analyzed in this meta-analysis (Burwinkel et al., 2006; Naidu et al., 2012; Connor et al., 2012; Alanazi et al., 2013). A flow chart summarizing the process of study inclusion/exclusion is depicted in Figure 1. The characteristics of each study are listed in Table 1, including 4600 cases and 5289 controls. All 4 eligible studies were hospital-based case-control studies. Of the 4 included studies, 3 used the restriction fragment length polymorphism method (Burwinkel et al., 2006; Naidu et al., 2012; Connor et al., 2012) and 1 used TaqMan Assays (Alanazi et al., 2013). All control samples were consistent with HWE ($P > 0.05$).

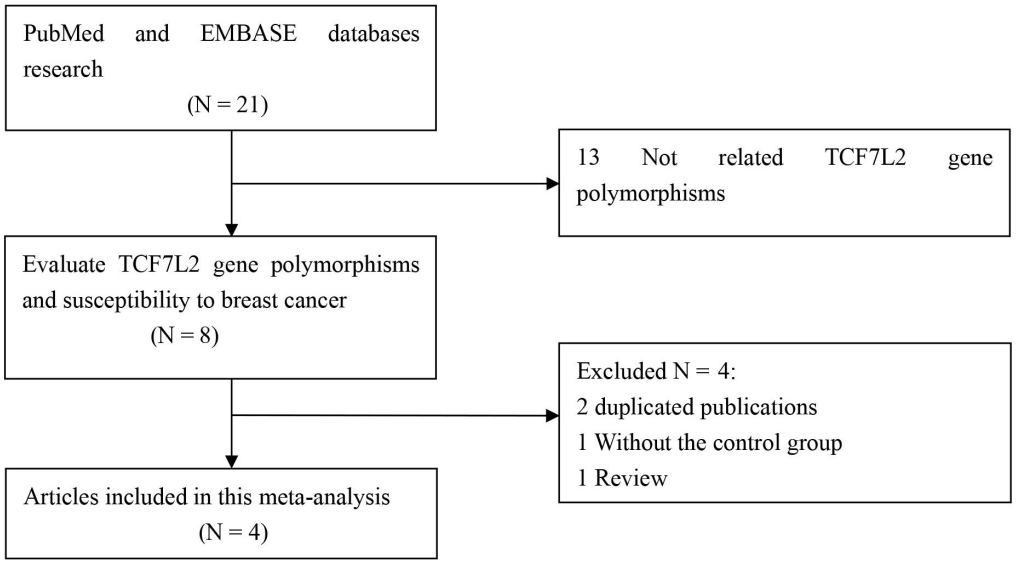

Figure 1. Flow chart of study searching and selection process.

Table 1. Characteristics of the included studies for meta-analysis.

Study included	Year	Area	Race	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test
rs12255372					GG	GT	TT	GG	GT	TT	
Burwinkel	2006	Germany	Caucasians	592/735	297	244	51	408	276	51	0.64
Naidu	2012	Malaysia	Asians	387/252	186	167	34	141	95	16	0.99
Connor	2012	USA	Caucasians	3522/4209	2041	1252	229	2552	1431	226	0.17
Alanazi	2013	Saudi Arabia	Asians	99/93	50	43	6	33	45	15	0.96
rs7903146					CC	CT	TT	CC	CT	TT	
Naidu	2012	Malaysia	Asians	390/252	187	163	40	140	93	19	0.52
Connor	2012	USA	Caucasians	3523/4209	1961	1304	258	2483	1476	250	0.12

Quantitative synthesis

A summary of the meta-analysis findings regarding the association between TCF7L2 gene polymorphisms and breast cancer risk is shown in Table 2. For the rs12255372 poly-

morphism, a total of 4600 cases and 5289 controls were identified. The meta-analysis results showed that the rs12255372 polymorphism was related to an increased risk of breast cancer in the general population (Table 2 and Figure 2: for GG *vs* GT: OR = 0.90, 95%CI = 0.83-0.98). A total of 3913 cases and 4461 controls were identified for the rs7903146 polymorphism. This meta-analysis suggested that the rs7903146 polymorphism was significantly associated with an increased risk of breast cancer in genetic comparison models (Table 2 and Figure 3: for CC *vs* TT: OR = 0.75, 95%CI = 0.63-0.90; CC *vs* CT: OR = 0.88, 95%CI = 0.81-0.97; dominant model: OR = 1.16, 95%CI = 1.06-1.27; recessive model: OR = 0.79, 95%CI = 0.67-0.94). Sensitivity analyses were conducted by altering the statistic models. No material alteration was detected, indicating that our results were statistically robust.

Table 2. Summary ORs and 95%CI of TCF7L2 gene polymorphism and breast cancer risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2	P	OR	95%CI	z	P
rs12255372	GG *vs* TT	4600	5289	Random	68.0%	0.03	0.88	0.58-1.34	0.00	1.00
	GG *vs* GT			Fixed	42.0%	0.16	0.90	0.83-0.98	0.00	1.00
	Dominant model			Random	64.5%	0.04	1.12	0.91-1.37	0.00	1.00
	Recessive model			Random	55.4%	0.08	0.89	0.63-1.25	0.00	1.00
rs7903146	CC *vs* TT	3913	4461	Fixed	0.0%	0.55	0.75	0.63-0.90	0.00	1.00
	CC *vs* CT			Fixed	0.0%	0.37	0.88	0.81-0.97	0.00	1.00
	Dominant model			Fixed	0.4%	0.32	1.16	1.06-1.27	0.00	1.00
	Recessive model			Fixed	0.0%	0.71	0.79	0.67-0.94	0.00	1.00

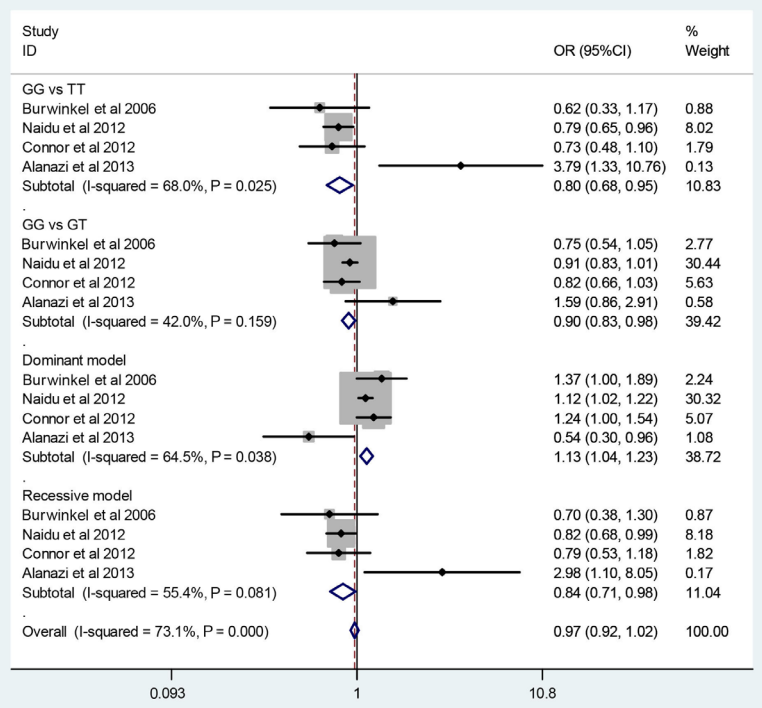

Figure 2. Association between the rs12255372 polymorphism and breast cancer risk.

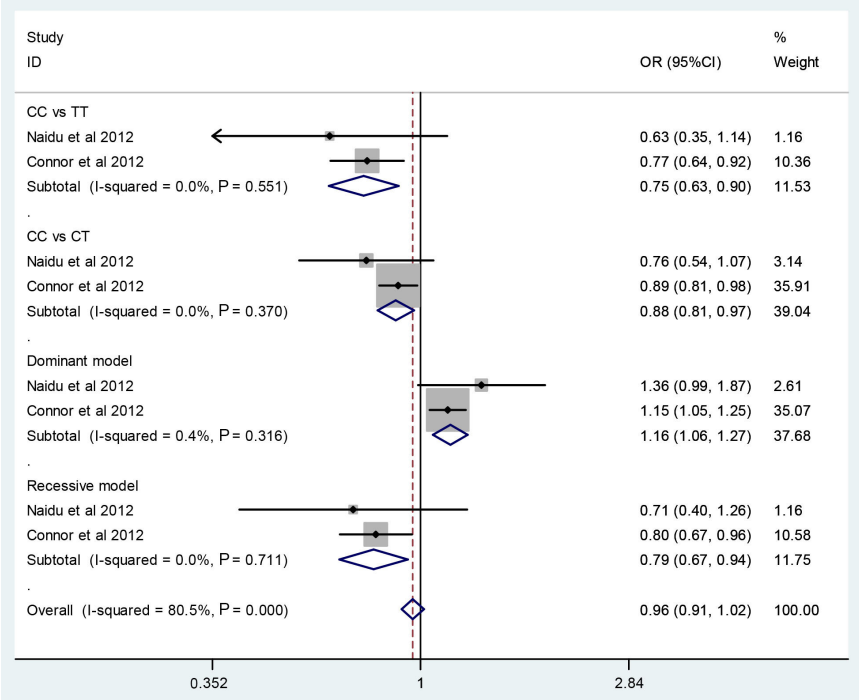

Figure 3. Association between the rs7903146 polymorphism and breast cancer risk.

Publication bias

Publication bias of the literature was assessed by Begg's funnel plot (Table 2). The funnel plot was used to measure the asymmetry of the funnel plot. The results of the Begg's funnel plot are shown in Table 2. Results showed that there was no publication bias (all $P > 0.05$).

DISCUSSION

TCF7L2 gene variants have been reported to be associated with risk of type 2 diabetes in different populations (Grant et al., 2006). In addition, TCF7L2 may affect cancer independently of diabetes, as the TCF7L2 gene product is involved the Wnt/-catenin signaling pathway. TCF7L2 forms an active nuclear complex with β-catenin that binds and induces the expression of target genes involved in cellular proliferation, evasion of apoptosis, tissue invasion, and metastasis (Reya and Clevers, 2005). Few epidemiological studies have examined the association between TCF7L2 gene polymorphisms and breast cancer risk with contradictory results. Naidu et al. (2012) reported that the rs7903146 (T) variant may elevate the risk of breast cancer, and thus is a potential candidate for breast cancer susceptibility, and rs12255372 was not associated with risk of breast cancer. Burwinkel et al. (2006) examined the association between rs12255372 and familial breast cancer risk and reported that the T allele was significantly associated with break cancer risk. In contrast, Goode et al. (2009) found no overall association. Meta-analysis is a method that examines related studies, published or

unpublished, and applying statistical methods to compare data and reach quantitative conclusions. In this study, we performed meta-analysis to investigate whether TCF7L2 variants are associated with breast cancer risk.

This is the first meta-analysis examining the association between TCF7L2 gene polymorphisms (rs12255372 and rs7903146) and breast cancer risk. Only 4 case-control studies were included in this analysis, and included 4600 patients and 5289 healthy controls. We found that the rs12255372 polymorphism was significantly associated with an increased risk of breast cancer (GG *vs* GT; OR = 0.90, 95%CI = 0.83-0.98). For rs7903146, the meta-analysis indicated a significant association between the rs7903146 polymorphism and breast cancer susceptibility among the overall population (CC *vs* TT: OR = 0.75, 95%CI = 0.63-0.90; CC *vs* CT: OR = 0.88, 95%CI = 0.81-0.97; dominant model: OR = 1.16, 95%CI = 1.06-1.27; recessive model: OR = 0.79, 95%CI = 0.67-0.94). We observed no publication bias in this meta-analysis regarding the association between TCF7L2 gene polymorphisms and susceptibility to breast cancer.

The mechanism of how TCF7L2 gene polymorphisms are related to breast cancer risk remains unclear. The TCF7L2 gene product is involved the Wnt/β-catenin signaling pathway, and deregulation of the Wnt pathway is involved in the mechanisms of carcinogenesis (Reya and Clevers, 2005). In addition, the potential function of TCF7L2 gene polymorphisms may be affected via gene-gene interactions, and the TCF7L2 rs7904519 (in intron 4 of TCF7L2), rs12255372, and rs7903146 alleles have been found to be in linkage disequilibrium. These haplotypes were associated with increased risk of breast cancer (Michailidou et al., 2013). Further studies of gene-gene interactions should be conducted to examine breast cancer risk.

There were some limitations to our meta-analysis. First, the random-effect model was used to calculate ORs, which may have affected the precision of the results. Second, there was not sufficient individual information regarding genotypes of both the TCF7L2 rs12255372 and rs7903146 polymorphisms, and we could not perform combined analysis of linkage disequilibrium. Therefore, more studies including a larger sample size and more detail information are needed. Finally, the genotype information stratified for the main confounding variables was not available in the original papers, such as age, gender, ethnicity, and exposures. These confounding factors may cause serious confounding bias.

In summary, this meta-analysis evaluated the effect of TCF7L2 gene polymorphisms on the risk of breast cancer. We found that TCF7L2 gene polymorphisms are associated with an increased susceptibility to breast cancer. Additional studies should be conducted to verify our results.

Conflicts of interest

The authors declare no conflict of interest.

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