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Original Article

Meta-analysis on the association between CYP1A1 T3801C polymorphism and breast cancer in the Chinese population

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Abstract: Although many publications have evaluated the correlation between Cytochrome P450 1A1 (CYP1A1) T3801C polymorphism and breast cancer risk, the results remain inconclusive. In order to derive a more precise estimation of the association, a meta-analysis was performed in the Chinese population. Related studies were identified from PubMed and Chinese databases through December 2015. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the associations. A total of 14 studies including 2910 BC cases and 3018 controls were involved in this meta-analysis. Overall, significant association was found between CYP1A1 T3801C polymorphism and BC risk when all studies in the Chinese population pooled into this meta-analysis (C vs. T: OR = 1.29, 95% CI = 1.07-1.56; CC vs. TT: OR = 1.71, 95% CI = 1.20-2.45; CC vs. CT: OR = 1.21, 95% CI = 1.03-1.42; CC + CT vs. TT: OR = 1.40, 95% CI = 1.09-1.80; CC vs. TT + CT: OR = 1.46, 95% CI = 1.11-1.92). In subgroup analyses stratified by geographical areas and source of controls, significantly increased risk was found in North China and in population-based studies. In conclusion, this meta-analysis provides the evidence that CYP1A1 T3801C polymorphism may contribute to the BC development in the Chinese population, especially in North China, and further studies in other ethic groups are required for definite conclusions.

Keywords: Meta-analysis, CYP1A1 T3801C, polymorphism, breast cancer, Chinese

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458400) of the total cancer deaths in 2008 [1]. About half the BC cases and 60% of the deaths are estimated to occur in economically developing countries [1]. The mechanisms of BC have not been fully illustrated. Reproductive factors including a long menstrual history, nulliparity, recent use of postmenopausal hormone therapy or oral contraceptives, and late age at first birth, all can increase the risk of breast cancer [2]. Alcohol consumption also has been identified as one of the risk factors for BC [3, 4]. However, only a subset of individuals exposed to these risk factors eventually develop BC, indicating an important role of genetic factors in the BC development.

Many common low-penetrant genes have been identified as potential BC susceptibility genes. Among these, an important one is cytochrome P450 1A1 (CYP1A1), which plays an essential role in the metabolic activation of major classes of tobacco procarcinogen such as aromatic amines and polycyclic aromatic hydrocarbons (PAHs). So it may affect the metabolism of the environmental carcinogens and alter susceptibility to BC. CYP1A1 enzyme is a member of the CYP superfamily and prone to mutation [5]. Agundez [5] revealed an association between CYP1A1 enzyme activity and the risk of developing several types of cancers, including BC. CYP1A1 T3801C polymorphism (MspI, rs4646903), also known as the m1 allele, is most studied. An association between CYP1A1 T3801C polymorphism and BC was first reported by Bailey and co-workers in 1998 in Caucasians and African Americans [6]. As a consequence, many studies have attempted to clarify this relationship, but there has been no

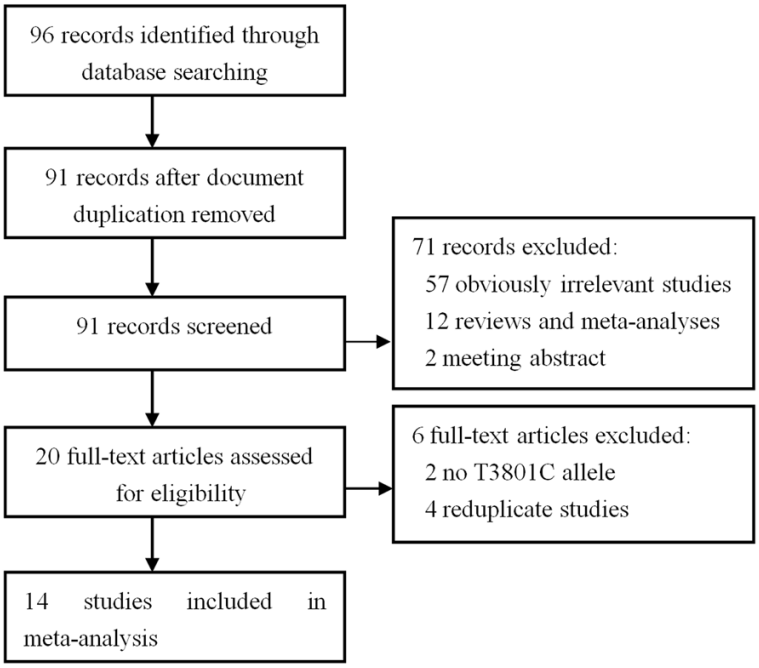

Figure 1. Flow diagram of the literature search.

definite consensus to date. Differences in results may be related to the ethnic and clinical heterogeneity of the patients studied or to the relatively small numbers of patients in each study. Meta-analysis is a good way to summarize the available evidence to provide a robust result. For addressing the association between CYP1A1 T3801C polymorphism and BC risk better, we performed a meta-analysis of all eligible studies in the Chinese population to lessen the impact of different genetic background.

Materials and methods

Search strategy and selection criteria

A comprehensive literature search was performed in the PubMed, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine for relevant articles published with the following Mesh terms: ("Breast Neoplasms" [MeSH] or "breast cancer" or "breast tumor" or "breast carcinoma") and ("P4501A1" or "CYP1A1") and (China or Chinese or Taiwan). An upper date limit of December 2015 was applied and no lower date limit was used. The search was performed without any restrictions on language and focused on studies conducted in humans. Concurrently, the reference lists of reviews and retrieved articles were searched manually.

Inclusion criteria: (1) case-control or cohort studies describing the association of CYP1A1 T3801C polymorphism and BC, (2) all patients with the diagnosis of BC confirmed by pathological or histological examination; (3) provides the distribution of CYP1A1 T3801C polymorphism in patients and controls, (4) Chinese participants only. Exclusion criteria: (1) duplicate publications, (2) incomplete data, (3) no control, (4) meta-analyses, letters, reviews, meeting abstract, or editorial articles.

Data extraction

Xu ZY independently extracted data from all included publications. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following data was collected from each study: first author's surname, year of publication, geographical areas, source of controls, total numbers of cases and controls, and the numbers of cases and controls who harbored the CYP1A1 T3801C genotypes.

Statistical analysis

The strength of associations between haplotypes of XRCC1 T3801C and risk of breast cancer was assessed according to the odds ratio (OR). The pooled ORs were performed for allele model (C versus T), dominant model (CT + CC versus TT), recessive model (CC versus CT + TT), heterozygous model (CC versus CT) and homozygous model (CC versus TT), respectively. The significance of the pooled OR was determined by the z test. The presence of between-study heterogeneity was investigated using the chi-square-based Cochran's Q statistic test with *P*-values < 0.1. Hardy-Weinberg equilibrium (HWE) of controls was calculated by using the goodness-of-fit test, and deviation was considered when $P < 0.05$. We used the fixed-effects model and the random-effects model

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

Reference	Source of controls	Geographical areas	Case no.	Control no.	Case			Control			HWE	
					TT	CT	CC	TT	CT	CC	χ^2	*P*
Huang 1999	PB	Taiwan	141	145	49	60	32	48	80	17	3.54	0.06
Wu 2002	PB	Taiwan	60	60	50		10	49		11		
Boyapati 2005	PB	Shanghai	1120	1196	433	517	170	453	556	187	0.57	0.450
Shen 2006	PB	Shanghai	250	268	83	125	42	128	109	31	1.10	0.295
Guo 2007	PB	Ningxia	144	155	47	72	25	65	72	18	0.08	0.774
Li 2008	PB	Sichuan	96	136	22	60	14	53	69	14	1.52	0.218
Chen 2009	PB	Guizhou	135	112	35	78	22	30	61	21	1.04	0.308
Bai 2009	HB	Jilin	160	124	72	74	14	76	44	4	0.62	0.431
Cui 2010	PB	Tianjin	315	360	138	120	57	214	114	32	8.02	0.005
Li 2010	HB	Hebei	70	70	15	55		32	38			
Huang 2013	PB	Sichuan	144	152	78	55	11	59	79	14	2.95	0.086
Wang 2013	PB	Guangdong	80	60	21	46	13	16	33	11	0.70	0.404
Zhang 2014	PB	Yunnan	51	60	15	20	16	28	24	8	0.60	0.439
Tuerxun 2015	PB	Xinjiang	144	120	62	63	19	65	49	6	0.71	0.399

PB, Population-based; HB, hospital-based.

Table 2. Main results in the total and subgroup analysis

Analysis model	Study groups	n	Random-effect model	Fixed-effect model	Heterogeneity	
			OR (95% CI)	OR (95% CI)	χ^2	P
C vs. T	Total analysis	12	1.29 (1.07-1.56)	1.19 (1.10-1.28)	51.65	0.000
	PB	11	1.26 (1.04-1.53)	1.17 (1.08-1.26)	47.46	0.000
	South China	8	1.15 (0.93-1.42)	1.07 (0.98-1.17)	27.02	0.000
	North China	4	1.65 (1.41-1.93)	1.65 (1.41-1.93)	1.86	0.603
CC vs. TT	Total analysis	12	1.71 (1.20-2.45)	1.41 (1.20-1.66)	36.77	0.000
	PB	11	1.64 (1.14-2.35)	1.38 (1.17-1.62)	33.99	0.000
	South China	8	1.36 (0.92-2.02)	1.16 (0.97-1.40)	18.97	0.008
	North China	4	2.66 (1.87-3.78)	1.68 (1.89-3.81)	1.33	0.721
CC vs. CT	Total analysis	12	1.31 (1.05-1.65)	1.21 (1.03-1.42)	15.71	0.152
	PB	11	1.29 (1.03-1.63)	1.20 (1.02-1.41)	14.85	0.138
	South China	8	1.17 (0.90-1.53)	1.10 (0.92-1.32)	9.92	0.193
	North China	4	1.72 (1.20-2.46)	1.73 (1.21-2.47)	0.98	0.806
CC + CT vs. TT	Total analysis	13	1.40 (1.09-1.80)	1.25 (1.12-1.39)	50.46	0.000
	PB	11	1.29 (1.00-1.67)	1.20 (1.07-1.33)	40.85	0.000
	HB	2	2.24 (1.46-3.42)	2.22 (1.49-3.32)	1.08	0.298
	South China	8	1.16 (0.85-1.59)	1.07 (0.94-1.21)	27.40	0.000
	North China	5	1.82 (1.50-2.22)	1.83 (1.50-2.22)	3.13	0.536
CC vs. TT + CT	Total analysis	13	1.46 (1.11-1.92)	1.29 (1.11-1.50)	27.54	0.006
	PB	12	1.42 (1.08-1.87)	1.27 (1.09-1.47)	25.54	0.008
	South China	9	1.22 (0.93-1.61)	1.12 (0.95-1.32)	13.94	0.083
	North China	4	2.17 (1.55-3.04)	2.19 (1.57-3.06)	1.46	0.693

PB, Population-based; HB, hospital-based; South China including Taiwan, Shanghai, Sichuan, Yunnan and Guizhou; North China including Xinjiang, Jilin, Ningxia, Tianjin and Hebei.

based on the Mantel-Haenszel method and the DerSimonian and Laird method, respectively, to evaluate the sensitivity analysis. Possible causes of heterogeneity were investigated by subgroup analyses based on geographic areas and source of controls. Begg's funnel plots and

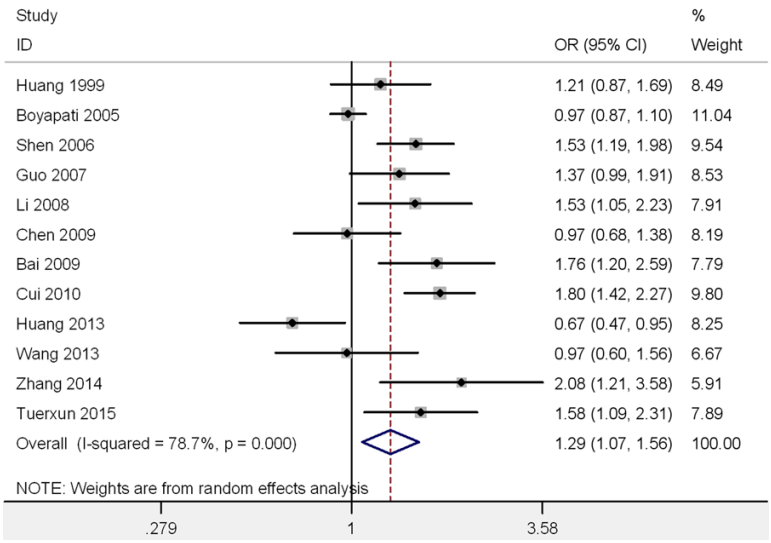

Figure 2. Forest plot (random-effects model) of BC risk associated with CYP1A1 T3081C polymorphism using the allele genetic model.

Egger's linear regression test were used to assess publication bias. All the statistical analysis was conducted using STATA statistical package (version 10, STATA, College Station, TX) and a significance level of $\alpha = 0.05$ was applied.

Results

Eligible studies

Figure 1 graphically illustrates the trial flow chart. A total of 91 articles that examined the association between CYP1A1 polymorphism and risk of BC were identified after document duplication removed in different databases. After screening the titles and abstracts, 71 articles were excluded because they were review articles, meeting abstracts and irrelevant to the current study. Of the 20 potentially relevant articles [7-26] identified for full study retrieval, six [7-12] were excluded due to duplicate studies or no T3801C allele. Finally, 14 studies [13-26] met the inclusion criteria. The publication year of involved studies ranged from 1999 to 2015. In total, 2910 BC cases and 3018 controls were involved in this meta-analysis, which evaluated the relationship between CYP1A1 T3801C polymorphism and BC risk in Chinese. The characteristics of the included studies are summarized in **Table 1**.

Meta-analysis results

Table 2 lists the primary results. In the total analyses, a significantly elevated risk of BC was associated with all variants of CYP1A1 T3801C (for CC vs TT: OR = 1.71, 95% CI = 1.20-2.45; (for CC vs CT: OR = 1.21, 95% CI = 1.03-1.42; for CC and CT combined vs TT: OR = 1.40, 95% CI = 1.09-1.80; for CC vs TT and CT: OR = 1.46, 95% CI = 1.11-1.92). For the allele C versus allele T, the pooled OR was 1.29 (95% CI = 1.07-1.56) (**Figure 2**). However, there was significant heterogeneity between studies. Hence, we then performed subgroup analyses by geographical areas and source of controls. In the stratified analysis by geographical areas, significantly increased risks were found in the population from North China (C vs. T: OR = 1.65, 95% CI = 11.41-1.93; CC vs. TT: OR = 1.68, 95% CI = 1.89-3.81; CC vs. CT: OR = 1.73, 95% CI = 1.21-2.47; CC + CT vs. TT: OR = 1.83, 95% CI = 1.50-2.22; CC vs. TT + CT: OR = 2.19, 95% CI = 1.57-3.06), but not found in the South China. In the stratified analysis by source of controls, significantly increased risks were found in the population-based studies (C vs. T: OR = 1.26, 95% CI = 1.04-1.53; CC vs. TT: OR = 1.64, 95% CI = 1.14-2.35; CC vs. CT: OR = 1.20, 95% CI = 1.02-1.41; CC vs. TT + CT: OR = 1.42, 95% CI = 1.08-1.87) and hospital-based studies (CC + CT vs. TT: OR = 2.22, 95% CI =1.49-3.32).

Sensitive analysis and bias diagnosis

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we used both models (the fixed-effects model and random-effects model) to evaluate the stability of the meta-analysis. All the significant results were not materially altered (**Table 2**). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible.

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plots did reveal obvious asymmetry (**Figure 3**). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The Egger's test indicated that there was publication bias under

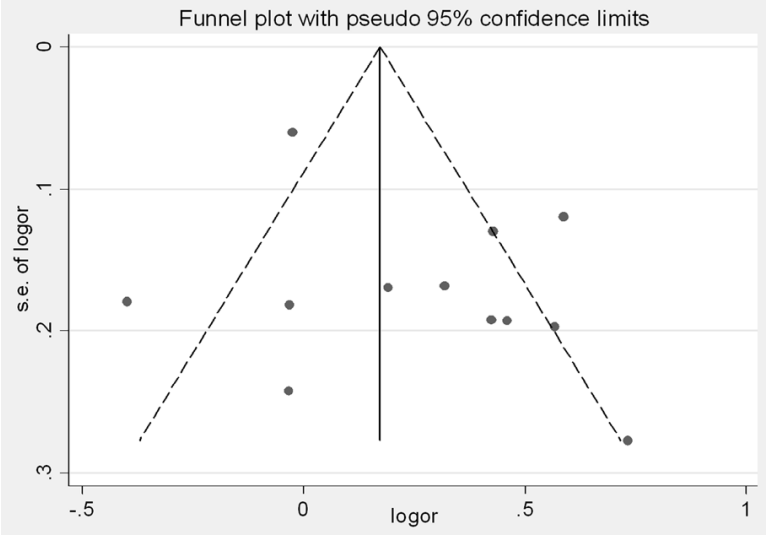

Figure 3. Begg's funnel plot of CYP1A1 T3081C polymorphism and BC risk under the allele genetic model.

the allele model in overall analyses (t = 2.60, *P* = 0.026).

Discussion

Although the multifactorial nature of cancer is well known, genetic factors are considered to be strong determinants of these diseases, thus encouraging researchers to search for the responsible genes. Since the first negative association between CYP1A1 T3801C and BC was reported [6], many studies have been undertaken to investigate the association. However, results of individual studies were inconclusive. Recently, one meta-analysis has reported that there was significant association between CYP1A1 T3801C polymorphism and BC risk only in South Indian [27], while another three meta-analyses reported that CYP1A1 T3801C polymorphism is not associated with BC risk [28-30]. Regional and racial differences is one likely reason for the conflict results. Therefore, we conducted this meta-analysis to derive a more precise estimate of the association between CYP1A1 T3801C and susceptibility to BC in the Chinese population, in order to lessen the impact of regional and racial differences.

Our meta-analysis involved 14 case-control studies, including 2910 BC cases and 3018 controls. Results showed a significant association between the CYP1A1 T3801C polymorphism and BC in the total analyses. In the subgroup analyses stratified by geographical areas and source of controls, significantly increased association was found in North China, in population-based and hospital-based studies, but not found in South China. This result suggested the differences in genetic backgrounds, the environment they lived in may influence the association between CYP1A1 T3801C polymorphism and BC risk.

Compared to the previous meta-analyses [27-30], they did not search Chinese databases, and included a smaller number of studies, which were conducted in Chinese populations than ours did. Therefore, our study has higher statistical power than other meta-analyses conducted in other ethnic groups. The effects of gene-environment interactions with respect to BC risk were also conducted by subgroup analyses in this meta-analysis. To our knowledge, this study represents the first meta-analysis of the association of CYP1A1 T3801C variants with BC in the Chinese population using such a large sample size. In addition, the test of the HWE for distribution of the genotypes in control groups suggested that there was no significantly different genetic background among the participants. The sensitivity analysis confirmed the reliability and stability of the meta-analysis. Therefore, the findings from our meta-analysis provide a strong evidence for the association between CYP1A1 T3801C polymorphism and BC in the Chinese population, especially in North China.

Although our study has obvious strengths, several limitations should be considered. First, the ethnic-specific meta-analysis only included data from Chinese patients with BC, and thus, our results are only applicable to this ethnic group. Second, since this meta-analysis was based primarily on unadjusted effect estimates and CIs, confounding factors were not controlled. Third, although we minimized this likelihood by searching all the databases related, publication bias nevertheless existed in our study.

In conclusion, this meta-analysis demonstrates that CYP1A1 T3801C polymorphism might contribute to individual susceptibility to BC in the Chinese population. Further studies are needed to determine if the CYP1A1 T3801C gene confers a risk of BC in other ethnic groups. BC is a multifactorial disease caused by not only genetic factors but also environmental factors, and studies analyzing gene-gene and gene-environment interactions are required to confirm our results. Such studies may eventually lead to have a better, comprehensive understanding of the association between the CYP1A1 T3801C polymorphism and BC risk.

Disclosure of conflict of interest

None.

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