Meta-Analysis of Observational Studies in Epidemiology

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Association between ABCB1 (3435C>T) polymorphism and susceptibility of colorectal cancer

A meta-analysis

Li-li Han, MD[a,b], Bai-le Zuo, PhD[c], Wei-liang Cai, PhD[d], Zhen-ni Guo[a], Bing-hua Tong[a], Hui-lian Wei, BE[a], Zheng Zhu, PhD[e,*], Guo-yin Li, PhD[a,*]

Abstract

Studies on the relationship between ABCB1 3435C>T polymorphism (rs1045642) and colorectal cancer (CRC)susceptibility have yielded inconclusive results. To clarify this issue, we undertook a meta-analysis to investigate the relationship between rs1045642 and CRC risk.

Three electronic scientific publication databases (Cochrane Library, Pubmed, Embase) were screened using specific search terms. Relevant literature was identified using literature traceability methods. Selected publications were evaluated according to the inclusion and exclusion criteria. Effect size information (odds ratio and the corresponding 95% confidence interval [CI]) was obtained following quality assessment and data extraction from the included publications, and a meta-analysis conducted. Statistical analysis was performed with the Stata sofz (Version 13.0) software.

Overall, 17 case-control studies involving 7129 CRC patients and 7710 healthy control subjects satisfied the criteria for inclusion in the meta-analysis. There was no significant association between ABCB1 3435C>T polymorphism and CRC risk in any of the genetic models. In the CC versus CT model (I^2 = 20.9%, $P_{heterogeneity}$ = .276), CC versus CT + TT model (I^2 = 45.6%, $P_{heterogeneity}$ = .102) and CT versus CC + TT model (I^2 = 17.8%, $P_{heterogeneity}$ = .298) analyses, between-study heterogeneities were detected as significant in Asian populations. In the CT versus TT model (I^2 = 24%, $P_{heterogeneity}$ = .254) and CC + CT versus TT model (I^2 = 0, $P_{heterogeneity}$ = .55), between-study heterogeneities were found to be significant in groups of different populations.

The meta-analysis described here suggests that the ABCB1 3435C>T polymorphism is not related to CRC susceptibility.

Abbreviations: 95% CI = 95% confidence interval, CRC = colorectal cancer, OR = odds ratio.

Keywords: ABCB1 gene, colorectal cancer, meta-analysis, polymorphism, susceptibility

1. Introduction

In a global context, colorectal cancer (CRC) represents a serious threat to human life and health. What is more, it confers an enormous economic burden on society. CRC is the third most commonly diagnosed cancer in the United States. Its estimated morbidity and mortality incidence will be the third among all carcinomas in the United States in 2019.[1] The incidence and mortality rates of CRC vary substantially by race/ethnicity.[2] Lifestyle difference is also a vital factor leading to the striking variation in CRC morbidity globally.[3] Differences in access to prevention, the quality of treatment technology, and the economic level of the patients greatly affect the mortality rate of CRC patients.[4] Although the incidence of CRC in the United States has been tapering off in recent years, worldwide, the outlook does not give grounds for optimism.[1,5,6]

"The adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also known as multidrug resistance gene 1 (MDR1), is located on the chromosomal region 7q21.1 and encodes the P-glycoprotein (P-gp). P-gp is a 1280-amino acid transporter that serves as a genetically polymorphic efflux transporter that removes foreign substances from cells.[7] P-gp mediates multiple drug resistance in cancer cells through various signaling pathways, such as the cyclic adenosine monophosphate/protein kinase A pathway,[8,9] the phosphatidylinositol 3-kinase/protein kinase B pathway,[10–12] the Y-box binding protein

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[a] College of Life Science and Agronomy, Zhoukou Normal University, [b] Department of Respiratory, Zhoukou Central Hospital, Zhoukou, [c] Tumor Molecular Immunology and Immunotherapy Laboratory, School of Laboratory Medicine, Xinxiang Medical University, Xinxiang, [d] Department of Orthopedics Surgery, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China, [e] Department of Internal Medicine, Division of Hematology/Oncology, University of California Davis, Sacramento, CA, USA.

[*] Correspondence: Guo-yin Li, College of Life Science and Agronomy, Zhoukou Normal University, 6 Changle Wenchang Road, Zhoukou 466000, China (e-mail: guoyin060410@163.com); Zheng Zhu, Department of Internal Medicine, Division of Hematology/Oncology, University of California Davis, Sacramento, CA, USA (e-mail: zegzhu@ucdavis.edu).

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1,[13,14] the phosphatase and tensin homolog,[15,16] p53,[17] protein kinase C,[18] and other protein kinases.[19] Previous studies have shown that ABCB1 is overexpressed in a variety of tumors, such as breast cancer, acute myeloid leukemia, hematological malignancies, childhood tumors, and other solid tumors.[20]

Single nucleotide polymorphisms (SNPs) of ABCB1 affect its expression and function.[21] Up to now, numerous SNPs, including some synonymous ones, have been identified in the coding region.[21] Three SNPs in the coding sequence (rs1128503, rs1045642, and rs2032582) are the most widely studied in ABCB1; these are relevant to the substrate and inhibitor-dependent functional modifications observed in vitro and reduced expression in tissues.[21] The distributions of rs1128503, rs1045642, and rs2032582 differ significantly among races and ethnicities. It is reported that Africans and African-Americans harbor the lowest frequencies of polymorphic alleles and Asians and Caucasians possess the highest.[21]

The ABCB1 3435C>T polymorphism is a synonymous SNP with no impact on the structural contribution of the amino acid at position 1145 (Ile) in the second ATP binding domain but does affect the expression of P-gp in tissues.[22] So far, numerous epidemiological studies have been performed to assess the association between rs1045642 and risk for CRC. However, due to the limitations of individual studies, the results are inconsistent. To help resolve this matter, we performed a meta-analysis based on a total of 17 independent studies, to obtain a more precise estimation of the association between rs1045642 and the risk of CRC. This meta-analysis suggested ABCB1 3435C>T polymorphism is not related to CRC susceptibility.

2. Materials and methods

2.1. Literature search

We queried the Cochrane Library, Pubmed, and Embase databases on August 1, 2019. Keyword combinations for colorectal neoplasms (colorectal, colorectal tumor, colorectal neoplasm, colorectal tumors, tumor colorectal, neoplasms colorectal, neoplasm colorectal, cancers colorectal, cancer colorectal, CRC, carcinomas colorectal, colorectal carcinoma, carcinoma colorectal, colorectal carcinomas) or colonic neoplasms (colonic neoplasm; colon neoplasm; neoplasms colonic, neoplasm colon, colon neoplasms, neoplasms colon, neoplasm colonic, cancer colonic, cancers colon, cancer of the colon, colonic cancer, colon cancer, colon cancers, colonic cancers, cancers colonic, cancer colon, cancer of colon) and gene symbols, and synonyms for the ABCB1 gene (ABCB1, MDR1, CLCS, P-GP, PGY1, ABC20, CD243, and GP170) and polymorphism (polymorphism, SNP, and variant) were used to form a Boolean query formula. Two reviewers (L.H. and Z.Z.), independently and in duplicate, screened titles and abstracts using a standardized data form tested in pilot runs. Inconsistencies regarding inclusion were resolved through consensus. The meta-analysis did not involve data related to patient personal information and therefore does not require ethical approval.

2.2. Inclusion and exclusion criteria

The criteria for inclusion in the study were as follows:

(1) manuscripts from peer-reviewed journals;
(2) case-control studies assessing the association between the ABCB1 3435C>T polymorphism (rs1045642) and CRC;
(3) studies focusing on CRC or colonic cancer;
(4) no inconsistencies in genotype data for either cases or controls; and
(5) studies with enough genotype data to estimate the odds ratio (OR) and 95% confidence interval (CI) in at least one genetic comparison model.

The exclusion criteria were:

(1) not case-control studies,
(2) control population including malignant tumor patients, and
(3) duplicate publications.

Two individual authors (L.H. and Z.Z.) performed the literature selection process. Another author (B.Z.) performed an investigation to reach an eventual agreement if the first 2 reviewers came to contradictory conclusions.

2.3. Data extraction

Two investigators reviewed and extracted information from all qualified publications based on the inclusion and exclusion criteria listed above. When there was a conflict, the 2 reviewers reached an agreement through discussion. The following information was extracted from each included study: first author's surname, year of publication, ethnicity, total numbers of cases and controls, as well as numbers of cases and controls with CC, CT, and TT genotypes. Individuals of different descent were categorized as Caucasian and Asian. Individuals of different descent were categorized as Caucasian and Asian.

2.4. Methodological quality assessment

The quality of the included studies was evaluated by the total score of quality assessment (TSQA).[23] Studies were scored according to TSQA standards (Supplementary Table S1, http://links.lww.com/MD/D781). Studies of high quality were given scores of greater than 9.

2.5. Statistical analysis

The measure of effect in these studies was the OR with 95% CI. Summary measures were pooled using random-effects models, with the estimate of heterogeneity taken from the Mantel-Haenszel model. All statistical analyses were conducted in the Stata 13 environment. The aggregated estimate of the OR and corresponding 95% CI were calculated for the dominant model (CC + CT vs TT, with C standing for cytosine and T for thymine), the recessive model (CC vs CT + TT), and the overdominant model (CT vs CC + TT). Cochran's Chi-square-based Q test was used to test the heterogeneity assumption. A value of $P < .1$ in the Q test indicated that the between-study heterogeneity was significant.[24] However, when $P \geq .1$, the pooled ORs and 95% CIs should be measured using a fixed-effect model employing the Mantel–Haenszel algorithm.[25] To explore the effect of heterogeneity among the studies on the conclusions of this meta-analysis, we performed subgroup analyses by ethnicity. We examined the ABCB1 3435C>T genotypes using dominant (CC + CT vs TT), recessive (CC vs CT + TT), and overdominant (CT vs CC + TT) genetic models, as well as the allelic model (C vs T). The estimated OR and 95% CI were obtained from Forest plots. Publication bias was graphically detected by funnel plots. The symmetry of the funnel plot was further evaluated by Egger linear regression test. The significance of the intercept was determined

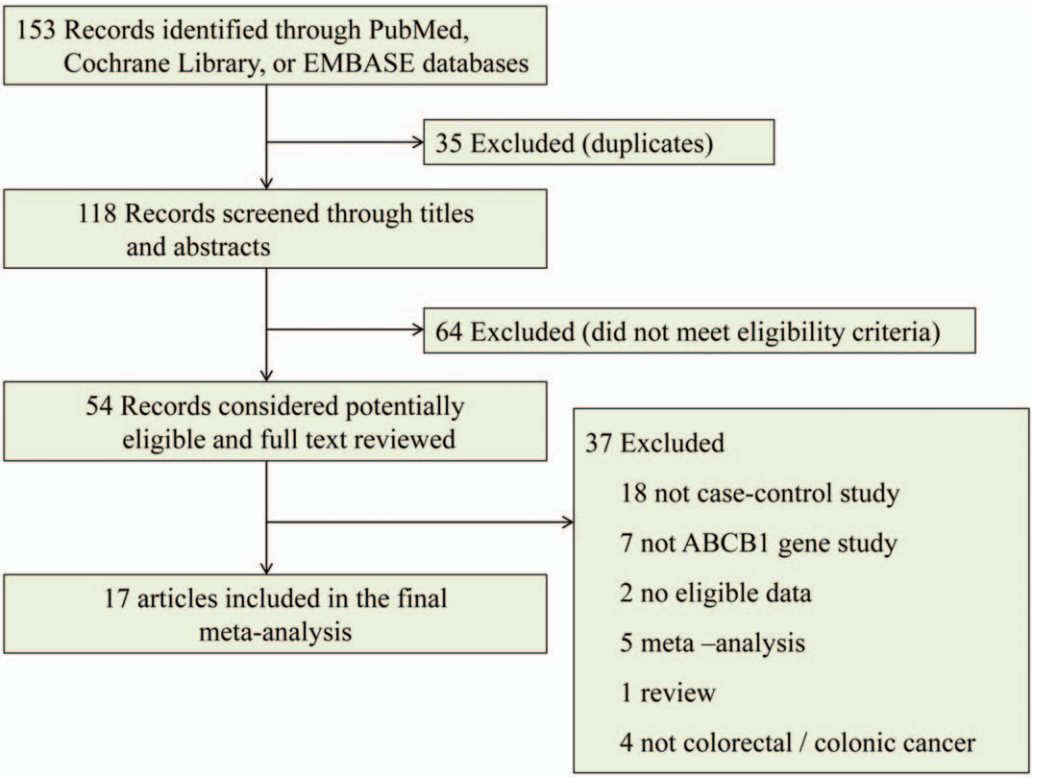

Figure 1. Flow diagram of literature search and screen.

by the *t* test suggested by Egger, where $P < .05$ was considered representative of statistically significant publication bias.

3. Results

3.1. Retrieval of studies and their characteristics

From the searches for studies on colorectal neoplasms or colonic neoplasms and C3435T genotypes, 153 potentially eligible records were identified. Titles and abstracts of these records were screened for inclusion. Seventeen independent studies met the inclusion criteria, consisting of six Asian and eleven Caucasian populations (Fig. 1).[26–42] In total, 7,179 CRC cases and 7,710 controls were included in the meta-analysis. The characteristics of the selected studies are summarized in Table 1.

3.2. Association of rs1045642 C>T and CRC

A total of 17 independent studies consisting of 7129 CRC patients and 7710 healthy controls were included in the analysis of the

Table 1

Main characteristics of studies included in this meta-analysis.

					Sample size		Cases			Controls				
Firstauthor [reference]	yr	Ethnicity	Genotyping method	Source	Cases	Controls	CC	CT	TT	CC	CT	TT	HWE	Score
Kurzawski	2005	Caucasian	PCR-RFLP	HB	184	188	41	18	62	48	94	46	1	8
Lee	2006	Asian	TaqMan PCR	HB	64	64	19	35	10	24	34	6	0.22	7
Komoto	2006	Asian	TaqMan PCR	HB	48	154	14	28	6	55	73	26	0.83	6
Bae	2006	Asian	PCR-RFLP	HB	111	93	32	63	16	22	55	16	0.07	7
Osswald	2007	Caucasian	TaqMan PCR	HB	285	275	86	129	70	57	140	78	0.69	10
Potocnik	2008	Caucasian	TaqMan PCR	PB	38	355	5	18	15	81	173	101	0.64	9
Petrova	2008	Caucasian	TaqMan PCR	HB	146	160	36	79	31	43	71	46	0.16	9
Andersen	2009	Caucasian	TaqMan PCR	PB	359	765	73	173	112	118	385	262	0.23	13
Panczyk	2009	Caucasian	PCR-RFLP	HB	95	95	25	50	20	33	44	18	0.63	7
Khedri	2011	Caucasian	PCR-RFLP	HB	118	137	20	46	52	24	77	36	0.12	7
Sainz	2011	Caucasian	PCR	PB	1765	1784	366	908	491	444	859	481	0.12	13
Campa	2012	Caucasian	TaqMan PCR	PB	2169	1634	659	1607	883	780	1657 965	0.18	12	
Kim	2013	Asian	PCR-RFLP	HB	193	200	88	80	25	85	90	25	0.87	8
Wu	2013	Asian	PCR-RFLP	HB	1028	1230	349	548	133	422	569	239	0.06	12
Özhan	2013	Caucasian	PCR	PB	103	150	46	34	23	35	87	28	0.05	12
Stańko	2015	Caucasian	PCR-RFLP	PB	107	110	17	53	37	17	57	35	0.47	8
Wang	2015	Asian	PCR-RFLP	HB	316	316	49	168	99	77	163	76	0.57	10

HB = hospital based, PB = population based.

Table 2

Main results of rs1045642 polymorphism and colorectal cancer risk in this meta-analysis.

Variables	Study number	Statistic model	Test of association		Test of heterogeneity	
			OR (95% CI)	*P*	I^2	P_h
CC versus TT						
Total	17	Random	0.969 (0.801–1.172)	.744	64.7%	.000
Caucasian	11	Random	0.972 (0.795–1.188)	.779	57.1%	.01
Asian	6	Random	0.94 (0.571–1.546)	.807	74.1%	.002
HB	11	Random	0.931 (0.678–1.281)	.662	67.3%	.001
PB	6	Random	0.978 (0.781–1.226)	.849	59.3%	.031
CC versus CT						
Total	17	Random	1.074 (0.884–1.304)	.473	76.8%	.000
Caucasian	11	Random	1.227 (0.926–1.627)	.155	83.7%	.000
Asian	6	Random	0.861 (0.708–1.047)	.133	20.9%	.276
HB	11	Random	1.058 (0.79–1.416)	.706	74.5%	.000
PB	6	Random	1.108 (0.813–1.509)	.516	82.7%	.000
CT versus TT						
Total	17	Random	0.877 (0.712–1.08)	.215	79.7%	.000
Caucasian	11	Random	0.789 (0.614–1.014)	.064	82.2%	.000
Asian	6	Random	1.013 (0.734–1.657)	.637	68.3%	.008
HB	11	Random	0.844 (0.548–1.299)	.441	86.2%	.000
PB	6	Random	1.008 (0.894–1.136)	.902	24%	.254
CC versus CT + TT (recessive model)						
Total	17	Random	1.013 (0.866–1.185)	.872	67.4%	.000
Caucasian	11	Random	1.093 (0.88–1.358)	.421	74.9%	.000
Asian	6	Random	0.888 (0.898–1.130)	.336	45.6%	.102
HB	11	Random	0.983 (0.803–1.204)	.869	52.7%	.02
PB	6	Random	1.072 (0.81–1.418)	.629	81.2%	.000
CC + CT versus TT (dominant model)						
Total	17	Random	0.914 (0.767–1.09)	.318	74.1%	.000
Caucasian	11	Random	0.863 (0.709–1.05)	.142	73.5%	.000
Asian	6	Random	1.045 (0.686–1.592)	.837	73.2%	.002
HB	11	Random	0.882 (0.614–1.266)	.496	82.7%	.000
PB	6	Random	0.995 (0.918–1.079)	.911	0	.55
CT versus CC + TT (overdominant model)						
Total	17	Random	0.899 (0.759–1.065)	.218	80.3%	.000
Caucasian	11	Random	0.796 (0.63–1.007)	.057	85.8%	.000
Asian	6	Random	1.153 (0.098–1.358)	.087	17.8%	.298
HB	11	Random	0.889 (0.656–1.203)	.445	83.6%	.000
PB	6	Random	0.899 (0.759–1.065)	.487	75%	.001
C allele versus T allele						
Total	17	Random	0.972 (0.886–1.066)	.543	64.3%	.000
Caucasian	11	Random	0.973 (0.87–1.088)	.702	65.7%	.001
Asian	6	Random	0.962 (0.789–1.173)	.636	65.5%	.013
HB	11	Random	0.939 (0.805–1.094)	.418	67.2%	.001
PB	6	Random	0.997 (0.886–1.121)	.959	63.4%	.018

95% CI = 95% confidence interval, HB = hospital based, OR = odds ratio, PB = population based.

association of ABCB1 3435C>T polymorphism with susceptibility to CRC. All possible genetic models were analyzed to seek potential differences in genotypic and allelic frequencies regarding ABCB1 3435 C>T polymorphism amongst CRC cases and controls. We used the random effect model for the analysis of all genetic models: we did not find a significant association between the different genotypes of SNP rs1045642 C>T and susceptibility to CRC in any of the models (Table 2; Fig. S1, http://links.lww.com/MD/D782). Moreover, we found no association between ABCB1 3435 C>T polymorphism and CRC when comparing the C and T alleles (Table 2; Fig. S2, http://links.lww.com/MD/D783).

3.3. Subgroup analysis based on ethnicity

In general, between-study heterogeneities were not significant in any of the genetic models for the association between ABCB1 3435C>T polymorphism and CRC, but in the stratified analysis by ethnicity, they were present in some genetic models (Table 2). Eleven studies consisting of 5369 CRC cases and 5653 controls were included in the Caucasian group, while six studies comprising 1760 CRC cases and 2057 controls were enrolled in the Asian group. We used the random-effect model for examining heterogeneity using the genetic models described above. For the Caucasian group, no significant between-study heterogeneity was detected (Figs. 2–4; Fig. S3, http://links.lww.com/MD/D784). For the Asian group, the between-study heterogeneities increased strikingly. In the CC versus CT model ($I^2 = 20.9\%$, $P_{\text{heterogeneity}} = 0.276$), CC versus CT + TT model ($I^2 = 45.6\%$, $P_{\text{heterogeneity}} = 0.102$), and CT versus CC + TT model ($I^2 = 17.8\%$, $P_{\text{heterogeneity}} = 0.298$), between-study heterogeneities were determined to be significant (Table 2; Fig. 2). Moreover, there was no significant association detected for the C allele

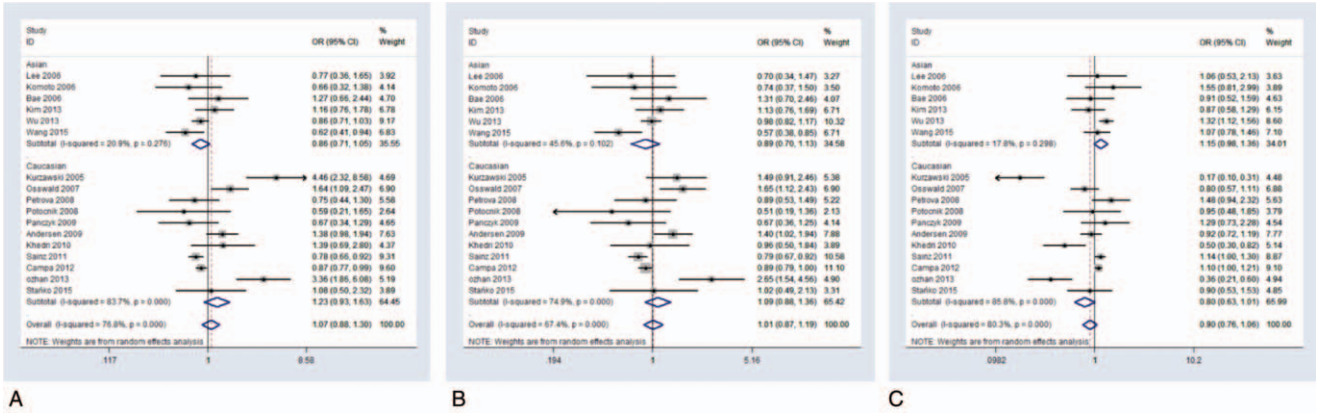

Figure 2. Forest plot on association between rs1045642 polymorphism and colorectal cancer risk, stratified by ethnicity. (A) CC versus CT model, random-effect pooled OR = 1.074, 95% CI: 0.884–1.304, $P = .473$, $I^2 = 76.8\%$, $P_{heterogeneity} = .000$. (B) CC versus CT + TT model, random-effect pooled OR = 1.013, 95% CI: 0.866–1.185, $P = .872$, $I^2 = 67.4\%$, $P_{heterogeneity} = .000$. (C) CT versus CC + TT random-effect pooled OR = 0.899, 95% CI: 0.759–1.065, $P = .218$, $I^2 = 80.3\%$, $P_{heterogeneity} = .000$. 95% CI = 95% confidence interval, OR = odds ratio.

versus T allele comparison (Table 2; Fig. S4, http://links.lww.com/MD/D785).

3.4. Subgroup analysis based on the characteristics of patients used as study controls

To further explore other potential sources of heterogeneity, we stratified all the studies according to attributes of study controls. In eleven studies, the participants were 2588 patients with CRC and 2912 people who were in the hospital for unrelated problems (hospital-based (HB) group), while in six studies the participants were 4541 patients with CRC and 4798 healthy individuals who were selected from the general population (population-based (PB) group). All genetic models were evaluated using the random-effect statistical model. For the PB group, the striking between-study heterogeneities were minimized. For all genetic models except for the CT versus TT model ($I^2 = 24\%$, $P_{heterogeneity} = .254$) and CC + CT versus TT model ($I^2 = 0$, $P_{heterogeneity} = .55$), between-study heterogeneities were found not to be significant (Table 2; Fig. 3). For the HB group, there was no significant between-study heterogeneity detected (Table 2; Fig. 3; Fig. S5, http://links.lww.com/MD/D786). Moreover, there was no significant association detected for the comparison of the C and T alleles (Table 2; Fig. S6, http://links.lww.com/MD/D787).

3.5. Sensitivity analyses

The leave-one-out sensitivity analysis confirmed the robustness and reliability of our drawn conclusion. The association between

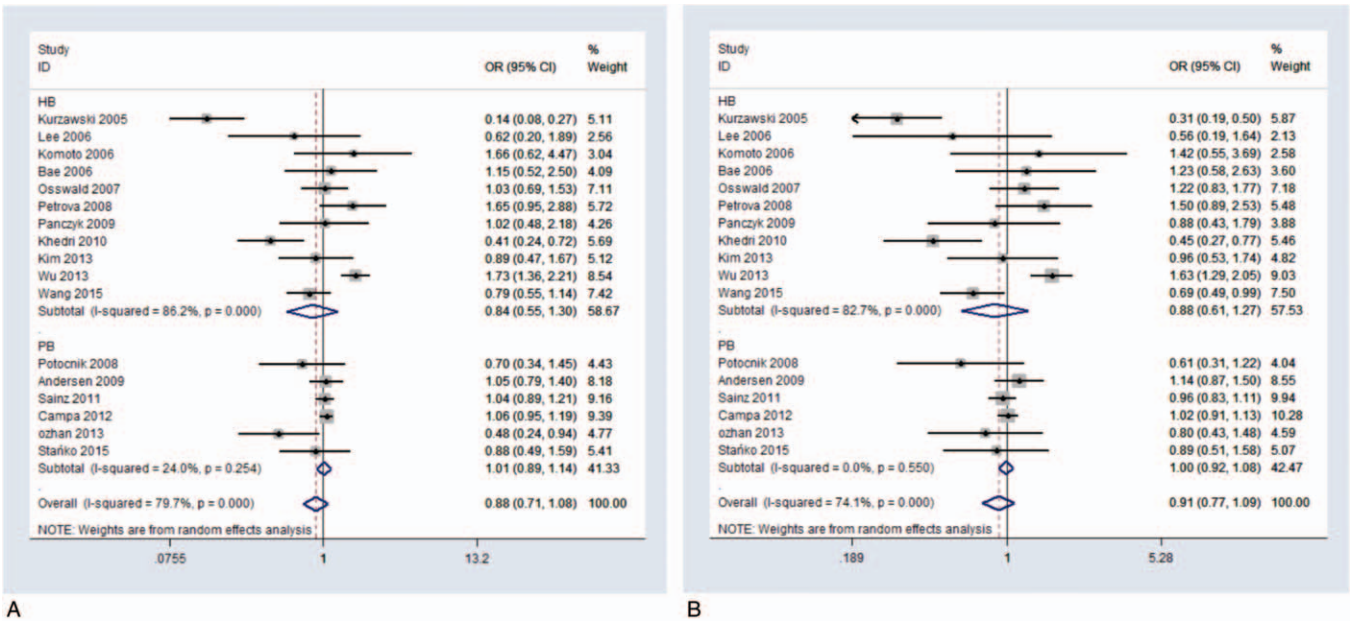

Figure 3. Forest plot on association between rs1045642 polymorphism and colorectal cancer risk, stratified by source. (A) CT versus TT model, random-effect pooled OR = 0.877, 95% CI: 0.712–1.08, $P = .215$, $I^2 = 79.7\%$, $P_{heterogeneity} = .000$. (B) CC + CT versus TT model, random-effect pooled OR = 0.914, 95% CI: 0.767–1.09, $P = .318$, $I^2 = 74.1\%$, $P_{heterogeneity} = .000$. 95% CI = 95% confidence interval, OR = odds ratio.

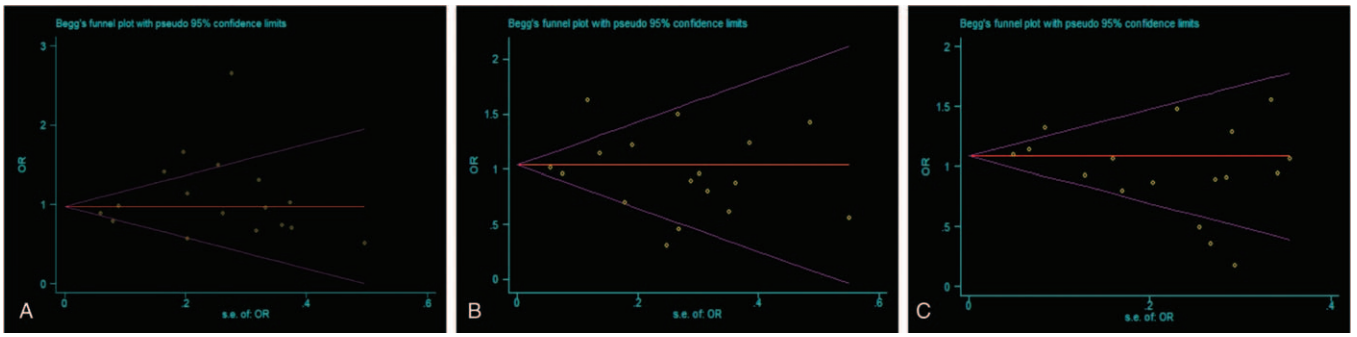

Figure 4. Funnel plot analysis to detect publication bias for rs1045642 polymorphism. (A) Recessive model. (B) Dominant model. (C) Overdominant model. Each point represents a separate study for the indicated association.

SNP rs1045642 C>T and CRC remained insignificant after the removal of any included study (detailed data not shown).

3.6. Publication bias

Begg funnel plot and Egger test were performed to assess the publication bias. No apparent asymmetry of funnel plots was detected on visual inspection. Egger test was used to provide statistical evidence for the funnel plot. In the recessive, dominant, and overdominant models, the *P* values for Begg funnel plot were .201, .57, and .104, respectively, indicating that there was no significant publication bias (Fig. 4). There was also no publication bias in comparisons of any of the other genetic models (Fig. S7, http://links.lww.com/MD/D788).

4. Discussion

Although the pathogenesis of CRC is multifactorial and mostly unclear, both internal and external factors are considered to contribute to its etiology. The multifactorial nature of the pathology of CRC calls for the quantitation of the independent risk factors. Due to the leading role of genetic factors in the pathogenesis of CRC, an in-depth understanding of the correlation of gene polymorphisms to CRC will help predict the course of the disease and take preventive measures, as well as identify potential targets for specific drug therapy. According to the findings of our present study, there was no statistically significant correlation between ABCB1 3435C>T polymorphism and the risk of CRC, regardless of the ethnicity of the study subjects and the environment of the healthy controls.

In recent years, researchers have carried out a number of studies on the association between ABCB1 gene polymorphisms and the susceptibility to various tumors. As a systematic approach that uses statistical analysis, meta-analysis is an effective way to come to conclusions about different studies that are inconsistent due to the limitations of the individual studies. A meta-analysis performed by Razi et al suggested that ABCB1 3435C>T polymorphism was not associated with the risk of multiple myeloma.[43] The meta-analysis carried out by Sharif et al suggested that ABCB1 3435C>T polymorphism might be a genetic risk factor and a potential biomarker for breast cancer,[44] but Tazzite et al reported that it was not associated with breast cancer risk in Morocco.[45] Research by Wu et al showed that the ABCB1 C3435T polymorphism was not associated with susceptibility to gastric cancer.[46] The study executed by He et al indicated that ABCB1 3435C>T polymorphism was associated with CRC risk in Asians, but Zhang et al found there was no significant association between them.[47,48]

In recent years, we have been concerned with the study of ABCB1 C3435T polymorphism and the risk of CRC. In the present work, 17 case-control studies were selected from Cochrane Library, PubMed, Embase databases.[26–42] The results of these studies are inconsistent. Patients' gender, age, race/ethnicity, pathological type, pathological grade, attributes of study controls, and other factors may account for inconsistencies in the results of the studies. Unfortunately, we did not get full information about patients and controls. Despite that, a comprehensive analysis was performed to identify the possible association between ABCB1 3435C>T polymorphism and CRC susceptibility. Several potential limitations can be noted in the present analysis that are inherent to any meta-analysis. First, the total sample size was not large enough, and subgroup analysis could only be performed on the basis of ethnicity and the selection of study controls. Second, only studies written in English were included in this meta-analysis. Third, some studies were of poor quality. Thus, a larger meta-analysis containing more studies, other ethnicities, and gender should be conducted in the future to improve the reliability of the conclusions.

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Author contributions

Guo-yin Li designed the study and drafted the initial manuscript. Li-li Han, Bai-le Zuo and Wei-liang Cai contributed to initial data analysis and interpretation. Zhen-ni Guo, Bing-hua Tong and contributed to the production of the pictures. Guo-yin Li and Zheng zhu supervised all aspects of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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