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Association between MDR1 C3435T polymorphism and colorectal cancer risk
A meta-analysis

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Abstract

Background: The multidrug resistance gene 1(MDR1) C3435T polymorphism has been reported to be associated with colorectal cancer (CRC) risk in Asians, however the results were inconsistent. Thus, we performed a meta-analysis to generate large-scale evidence on the association between C3435T polymorphism and CRC risk in Asian populations.

Methods: The PubMed, Web of Science, Embase, CNKI, and Chinese Biomedicine databases were searched up to January 15, 2017. The odd ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by a fixed-effects or random-effects model. Sensitivity and cumulative meta-analysis were also performed.

Results: A total of 7 studies involving 4818 individuals were included in this pooled-analysis. The results suggested that persons carrying a T allele at the C3435T polymorphism had a significantly decreased risk of CRC in Asian population (T vs C: OR = 0.897, 95%CI = 0.826–0.975, $P = .01$), and the significant association was also observed in another 2 genetic models (TT vs CC: OR = 0.721, 95%CI = 0.605–0.861, $P < .001$; TT vs TC+CC: OR = 0.679, 95%CI = 0.579–0.795, $P < .001$). Moreover, the results of sensitivity and cumulative meta-analysis indicated the stable of our results. Finally, funnel plot and Egger's test showed no evidence of publication bias.

Conclusions: In summary, this meta-analysis provided evidence that MDR1 C3435T polymorphism is associated with a decreased risk of CRC in Asian population.

Abbreviations: ABCB1 = ATP-binding cassette sub-family B member 1, CI = confidence interval, CRC = colorectal cancer, HWE = Hardy–Weinberg equilibrium, MDR1 = multidrug resistance gene 1, MTRR = methionine synthase reductase, OR = odds ratio, P-gp = P-glycoprotein, SNPs = single nucleotide polymorphisms, XRCC1 = x-ray repair cross-complementing group 1.

Keywords: colorectal cancer, MDR1, meta-analysis, polymorphism

1. Introduction

Colorectal cancer (CRC) is one of the most common cancer in worldwide.[1,2] In 2015, colorectal cancer leaded to 753,000 deaths worldwide and was the fourth leading cause of cancer mortality.[2] Previous epidemiological studies have shown that genetic susceptibility factors together with environmental factors —in particular, diet, cigarette smoke, drugs, and bacterial toxins —might increase the risk of colorectal cancer.[3–6] However, the exact mechanisms underlying the development of this malignant digestive tumor remain unclear.

The multidrug resistance gene 1 (MDR1, also named as ATP-binding cassette sub-family B member 1, ABCB1) encodes a 170Kd ATP transmembrane glycoprotein, P-glycoprotein (P-gp).[7] Recent studies indicated MDR1 gene seemed to play an important role in tumor progression, especially in the carcinogenesis of colorectal.[8–10] In 2005, Kurzawski et al[11] reported the first study that demonstrated carriers of MDR1 3435TT genotype were at 2.7-fold higher risk of the colon cancer development in Polish. Following the first report of the association, a growing number of studies focused on the association between MDR1 C3435T polymorphism and colorectal cancer risk in Asian population, however, these genetic studies have produced inconclusive results.[12–14] These contradictions might be due the small sample sizes and inadequate statistical power.

A meta-analysis is a proper method to overcome the problem of small sample sizes and inadequate statistical power in different genetic studies. A recent meta-analysis suggested that there were no significant associations between MDR1 C3435T and colorectal cancer risk in Caucasians.[15] However, to date, there was no meta-analysis which investigated the association between MDR1 C3435T polymorphism and colorectal cancer risk in Asians. Thus, we performed a meta-analysis to clarify the effect of C3435T polymorphism on susceptibility to colorectal cancer, by systematically summarizing all eligible data in Asian population.
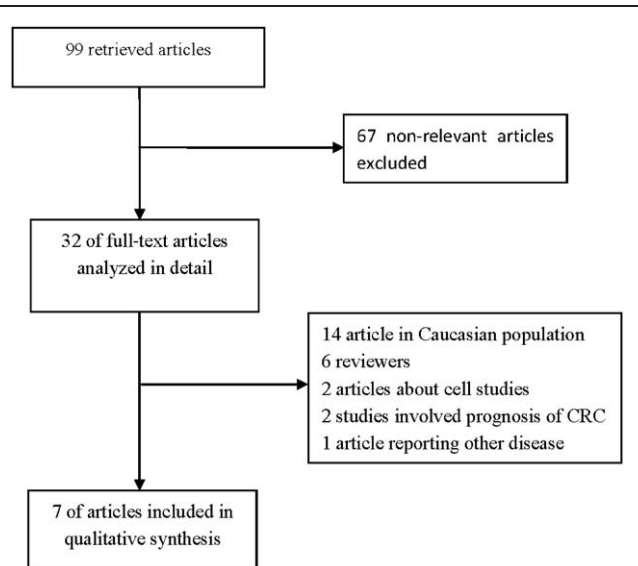
Figure 1. Flowchart of search strategy for the meta-analysis.

2. Methods

2.1. Search strategy

A comprehensive electronic search in PubMed, Embase, Medline, Web of Science database was performed to identify the association between MDR1 C3435T variant and colorectal cancer by using the following search terms: "multidrug resistance 1 gene" or "ABCB1" or "MDR1" or "rs1045642," "polymorphism" or "variant," and "colorectal cancer" (the last update was January 15, 2017). Moreover, the references of all retrieved articles were checked by hand-search for additional potential studies.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used to select eligible studies for the meta-analysis: case-control studies; population of ethnic descent was Asians; reporting the association between MDR1 C3435T polymorphism and colorectal cancer risk. Exclusion criteria for studies were as follows: no control population; incomplete genotype data; duplicate publications; comments, review articles, or articles only with an abstract.

2.3. Data extraction

Two independent reviewers extracted the following data from each eligibly study: name of first author, country of origin, publication

year, sex ratio, and mean age in individuals, and number of genotypes or allele frequency in cases and controls. Finally, any disagreement was resolved by discussion or through a third investigator. Moreover, this study was based on previously published studies; thus, no ethical approval was required.

2.4. Statistical methods

The odds ratio (OR), and its 95% confidence interval (CI) was estimated for assess the strength of the association between MDR1 C3435T and colorectal cancer risk. The significance of the pooled OR was determined by the Z-test; a P value of .05 was considered significant. We examined pooled OR for T versus C, TT versus CC, TC versus CC, the dominant model (TT+TC vs CC), as well as the recessive model (TT vs TC+CC). Moreover, data in the control group of each study were used to assess the Hardy–Weinberg equilibrium (HWE), and a $P < .05$ was considered as disequilibrium.

The heterogeneity between studies was evaluated by chi-squared based Q test and I^2 test.[16] When a P value was <.5, obvious heterogeneity exists and a random effects model was used. Otherwise, a fixed effects model was used to calculate pooled effect estimates.[17,18] I^2 takes values between 0% and 100% with higher values denoting a greater degree of heterogeneity.[19]

Cumulative meta-analysis was carried out to evaluate the trend and the stability of the genetic risk effect as evidence accumulating over time. Additionally, we also performed sensitivity analysis by sequential removal of each study to assess the stability of the results.[20] Publication bias was assessed by the symmetry of the funnel plot, which was further evaluated by Egger linear regression test.[21] A P value of <.05 from the Egger test was considered significant publication bias. All statistical analyses were performed by using STATA software, version 12 (StataCorp LP, College Station, TX).

3. Results

3.1. Characteristics of the eligible studies

A total of 99 studies involving the relationship between the MDR1 C3435T polymorphism and colorectal cancer risk met the search criteria. After a preliminary screening, full texts of 32 studies were reviewed in detail. Of which, 14 reported in Caucasian population, 6 were reviews, 2 were about cell studies, 2 investigated the prognosis of CRC, and 1 reported other disease. Finally, a total of 7 articles comprising 4818 individuals (2128 patients and 2690 controls) were included in this meta-analysis.[12–14,22–25] The distribution of the genotypes in control group of all included studies was in HWE except for one.[23] The flow chart for the process of study selection is shown in Fig. 1, and the detailed characteristics of all eligible studies are shown in Table 1.

Table 1

Characteristics of eligible studies in a meta-analysis of the MDR1 C3435T polymorphism and CRC risk.

First author	Year	Country	Genotyping method	In cases Age	In cases Males%	In controls Age	In controls Males%	In cases TT	In cases TC	In cases CC	In controls TT	In controls TC	In controls CC	HWE in controls
Bae[12]	2006	Korea	PCR–RFLP	62.5 (10.6)	54.1	49.2 (12.8)	59.1	16	63	32	16	55	22	Yes
Lee[14]	2006	Korea	TaqMan PCR	61.0 (11.0)	50.0	61.0 (6.0)	50.0	10	35	19	6	34	24	Yes
Komoto[13]	2006	Japan	TaqMan PCR	66.4 (11.5)	70.8	26.3 (7.5)	30.5	6	28	14	26	73	55	Yes
Wu[22]	2013	China	PCR–RFLP	60.2 (10.5)	57.1	59.9 (10.5)	58.8	133	546	349	239	569	422	Yes
Yue[23]	2013	China	PCR–RFLP	58.1 (12.2)	61.4	nr	nr	57	230	141	89	198	163	No
Wang[24]	2015	China	PCR–RFLP	63.5 (10.9)	38.6	62.8 (11.7)	38.6	49	168	99	77	163	76	Yes
Jiang[25]	2015	China	PCR–RFLP	63.6 (9.0)	53.4	55.7 (16.3)	55.4	22	62	49	46	195	142	Yes

Data are number (%), mean (SD),CRC = colorectal cancer, HWE = Hardy–Weinberg equilibrium, MDR1 = multidrug resistance gene 1, nr = not report.

Table 2

Pooled analysis for the associations between the MDR1 C3435T polymorphism and the risk of CRC.

Variant	Comparison	Variables	Data	Sameple size		Test of association		Model	Test of heterogeneity	
				Case	Control	OR (95% CI)	P value		I² (%)	P value
MDR1	T vs C	Overall	7	2128	2690	0.897 (0.826–0.975)	.010	F	33.1	.175
C3435T		All in HWE	6	1700	2240	0.888 (0.810–0.974)	.012	F	42.7	.120
	TT vs CC	Overall	7	2128	2690	0.721 (0.605–0.861)	<.001	F	44.7	.093
		All in HWE	6	1700	2240	0.717 (0.589–0.873)	.001	F	53.9	.055
	TC vs CC	Overall	7	2128	2690	1.111 (0.976–1.264)	.111	F	21.9	.263
		All in HWE	6	1700	2240	1.062 (0.920–1.226)	.414	F	12.4	.335
	TT+TC vs CC	Overall	7	2128	2690	1.001 (0.885–1.131)	.989	F	20.0	.277
		All in HWE	6	1700	2240	0.967 (0.843–1.108)	.627	F	19.6	.285
	TT vs TC+CC	Overall	7	2128	2690	0.679 (0.579–0.795)	<.001	F	51.1	.056
		All in HWE	6	1700	2240	0.805 (0.570–1.138)	.219	R	58.3	.035

CI = confidence interval, CRC = colorectal cancer, F = fixed-model, HWE = Hardy–Weinberg equilibrium, MDR1 = multidrug resistance gene 1, OR = odds ratio, R = random model.

3.2. Quantitative synthesis

The summary of meta-analysis for MDR1 C3435T polymorphism and colorectal cancer susceptibility is shown in Table 2 and Fig. 2. The results of pooled analysis demonstrated a significant association of MDR1 C3435T variant with colorectal cancer risk (T vs C: OR = 0.897, 95%CI = 0.826–0.975, P = .01; TT vs CC: OR = 0.721, 95%CI = 0.605–0.861, P < .001; TT vs TC+CC: OR = 0.679, 95%CI = 0.579–0.795, P < .001). Non-significant association was observed in the other genetic models. (TC vs CC: OR = 1.111, 95%CI = 0.976–1.264, P = .111; TT+TC vs CC: OR = 1.001, 95%CI = 0.885–1.131, P = .989). Overall, there was no significant between-study heterogeneity was found in all genetic models.

3.3. Sensitivity analysis and cumulative meta-analysis

We performed sensitivity analysis to assess the stability of the results by sequential omission of each eligible study. The results showed that no single study qualitatively changed the pooled ORs, indicating the results were highly stable (Fig. 3). Moreover, sensitivity analysis limited to studies in HWE also showed significant association between MDR1 C3435T polymorphism and colorectal cancer risk. In the cumulative meta-analysis, the results demonstrated that the pooled OR tended stable and significant with accumulation of more data over time (Fig. 4).

3.4. Publication bias

The potential publication bias of eligible literatures was assessed by funnel plot and Egger test. As shown in Fig. 5, the shapes of the funnel plots did not indicate any evidence of obvious asymmetry. In addition, the Egger test, which was used to provide statistical evidence of funnel plot symmetry, also did not show any
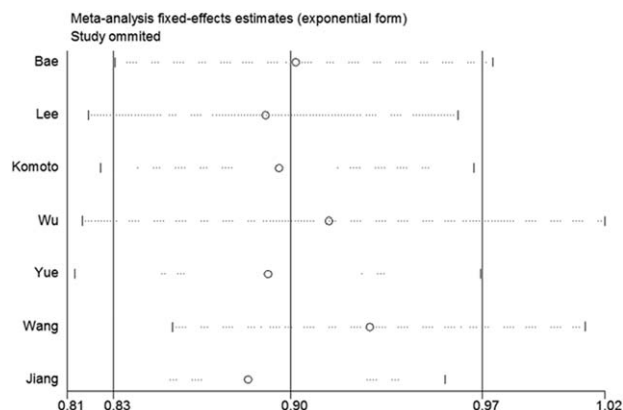

Figure 3. Sensitivity analysis on the associations between MDR1 C3435T polymorphism and CRC risk. Results were computed by omitting each study (left column) in turn. Bars = 95% confidence interval, CRC = colorectal cancer.
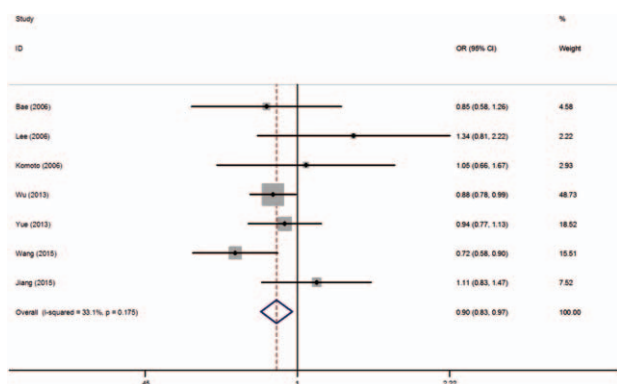

Figure 2. Forest plot of CRC risk associated with the MDR1 C3435T polymorphism in Asians (T vs C). CI = confidence interval, CRC = colorectal cancer, OR = odds ratio.
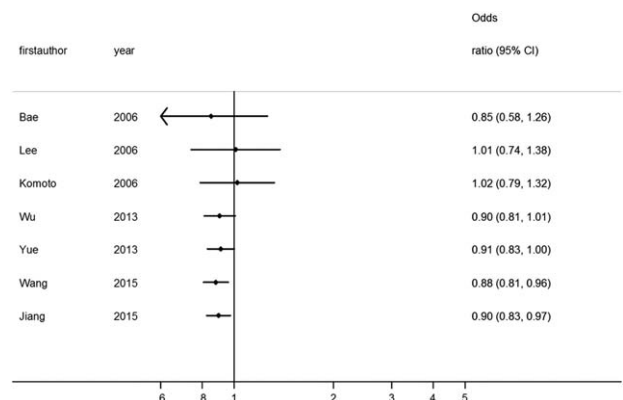

Figure 4. Odds ratio (OR) estimates for the results of cumulative meta-analysis of the association between MDR1 C3435T polymorphism and CRC risk. Bars represent 95% confidence intervals (CIs); CRC = colorectal cancer.
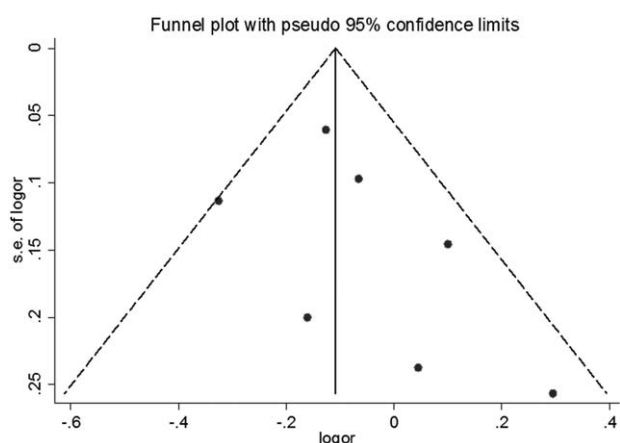
Figure 5. Funnel plots of the association between MDR1 C3435T polymorphism and CRC risk. CRC = colorectal cancer; Logor = natural logarithm of the OR, SE of logor = standard error of the logor.

significant publication bias. (T vs C: P = .322; TT vs CC: P = .227; TC vs CC: P = .642; TT+TC vs CC: P = .947; TT vs TC+CC: P = .124)

4. Discussion

Colorectal cancer (CRC), occurring in the colon and the rectum, is a multifactorial disease resulting from genetic, environmental, socioeconomic, and lifestyle factors.[26] Vogelstein et al[27] initially described the model of colorectal tumorigenesis, which showed the genetic alterations involved in the development of colorectal cancer. Recently, an accumulating number of studies provided evidence that genetic factors played an important role in the pathogenesis of CRC development. For example, methionine synthase reductase (MTRR) A66G polymorphism and rs12970291 on chromosome 18q22 were significantly associated with decreased CRC risk,[28,29] whereas, GSTM1 null polymorphism, CASC8 rs7837328 variant, and TLR4 Asp299Gly were proved to confer the susceptibility to CRC.[30–32]

The MDR1 gene, located on chromosomal region 7q21, encoded an ATP-dependent efflux transporter (P-gp) that protected the body from environmental toxins and xenobiotics.[33] To date, >50 single nucleotide polymorphisms (SNPs) have been identified for MDR1 gene. Recent study indicated that C3435T mutation, one of the most researched polymorphisms in MDR1, was associated with an altered structure of substrate and inhibitor interaction sites of P-gp.[34] In Asian population, studies that investigated the association of MDR1 C3435T polymorphism with CRC risk produced inconclusive results. For instance, some studies suggested a significant association between MDR1 C3435T and susceptibility to CRC[22,24], which, whereas, could not be confirmed in several studies.[12–14,23] Thus, the possible role of MDR1 polymorphism in carcinogenesis of CRC remains unclear. Here, we aimed to perform a meta-analysis to explore the correlation between MDR1 C3435T polymorphism and CRC susceptibility.

The present study involved 4818 individuals is the first meta-analysis to investigate the relationship between MDR1 C3435T polymorphism and CRC susceptibility in Asian population. The results of our meta-analysis suggested that persons carrying T allele had a significantly decreased CRC risk, which was also observed in homozygote comparison (TT vs CC) and recessive

model (TT vs TC+CC). A previous meta-analysis indicated that there were no significant associations of MDR1 C3435T polymorphism with colorectal cancer in Caucasian population, which included 10 studies of Caucasians.[15] It is widely accepted that the relative contribution of genetic markers in predisposition to CRC may vary across different ethnic groups. For instance, MDM2 SNP309 and x-ray repair cross-complementing group 1 (XRCC1) Arg399Gln polymorphisms were significantly associated with CRC risk in Asians but not among European populations.[35,36] Moreover, for MDR1 C3435T polymorphism, a recent study showed a significant difference in the prevalence of the MDR1 3435TT allele among healthy individuals of Asians (27.8%) and Caucasians (49.4%).[37] Taken together, these results suggested that the relative contribution of MDR1 C3435T polymorphism might vary across different populations.

Non between-study heterogeneity was observed in most genetic models. When excluding the study departed from HWE, the pooled ORs were not materially altered. The sensitivity analysis also showed that no single study qualitatively changed the pooled ORs. Also, cumulative meta-analysis suggested that the pooled ORs tended stable and significant as evidence accumulating over time. In addition, to assess the publication bias, we also performed funnel plot and Egger test, which did not show any evidence of publication bias. Thus, these results indicated that the results of this meta-analysis are highly stable.

Several limitations should be acknowledged for interpretation of our results. First, CRC is a complex disease and different environments existed among different countries, whereas, in this meta-analysis, the subgroup analysis stratified by countries was not performed due to the insufficient data. Second, our study was designed to analyze single polymorphism, however, a haplotype analysis may be more powerful to find a significant association between MDR1 polymorphisms and CRC risk. Finally, our meta-analysis was based on published articles, and there was no sufficient data for adjustment for individual level factors including sex, obesity, and smoking, which might affect the genetic effect.[4,38]

In conclusion, despite these limitations, our results were still significant. The present meta-analysis involved 4818 individuals demonstrated that MDR1 C3435T polymorphism might be significantly associated with decreased risk of CRC in Asian population. Moreover, further studies with larger sample size are required to clarify exact role of MDR1 C3435T polymorphism in the pathogenesis of CRC, especially the gene–gene and gene–environment interactions

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