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ORIGINAL ARTICLE

A meta-analysis of *MTRR* A66G polymorphism and colorectal cancer susceptibility

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Summary

Purpose: *A meta-analysis was performed to determine the association between MTRR A66G polymorphism and colorectal cancer (CRC) susceptibility.*

Methods: *Based on comprehensive searches of the MEDLINE, EMBASE and ISI Web of knowledge, China National Knowledge Infrastructure (CNKI) and Wanfang Database, we identified eligible studies about the association between MTRR A66G polymorphism and CRC susceptibility.*

Results: *A total of 6020 cases and 8317 controls in 15 studies were pooled together for evaluation of the overall association between MTRR A66G polymorphism and susceptibility of CRC. The allele model (G vs A: p=0.01; OR=1.07, 95% CI=1.02-1.12), and homozygous model (GG vs AA: p=0.006; OR=1.15, 95% CI=1.04-1.28) showed increased risk for CRC development. Similarly, the dominant model (GG+GA vs AA: p=0.04; OR=1.11, 95% CI=1.01-1.22) and the recessive model (GG vs GA+AA: p=0.04; OR=1.08, 95% CI=1.00-1.17) showed increased risk for CRC development. In the analysis stratified by ethnicity (Caucasian and East Asian), significant associations were found between MTRR A66G polymorphism and susceptibility to CRC among Caucasians.*

Conclusion: *Our pooled data suggest an association between MTRR A66G polymorphism and CRC susceptibility among Caucasians.*

Key words: *colorectal cancer, meta-analysis, MTRR, polymorphism*

Introduction

Folate is critical to one-carbon metabolism, also referred to as folate-mediated one-carbon metabolism, acting as a coenzyme in DNA methylation and synthesis [1]. Methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), and methione synthase reductase (MTRR) are key enzymes involved in folate metabolism, and play essential roles in nucleotide synthesis and the methylation of DNA, histones, and other proteins. For the MTRR, the most common polymorphism is an isoleucine-to-methionine change at position 22 (A66G; rs1801394), and it has been demonstrated that 66GG genotype is inversely associated with plasma homocysteine levels [2]. Several studies have evaluated the association between the *MTRR* A66G polymorphism and cancer risk [3-7]. However, the role of *MTRR* A66G polymorphism in the development of CRC has been investigated with conflicting results. A previous study has suggested an association between the *MTRR* A66G polymorphism and CRC [8]. However, other studies have failed to confirm such an association [9,10]. The exact relationship between the *MTRR* A66G polymorphism and susceptibility

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to CRC is not entirely established. Therefore, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the association between the *MTRR* A66G polymorphism and the susceptibility to CRC.

Methods

Publication search

The electronic databases MEDLINE, EMBASE and ISI Web of knowledge, China National Knowledge Infrastructure (CNKI) and Wanfang Database were searched for studies to be included in the present meta-analysis, using the following key words: ("one-carbon metabolism" or "methione synthase reductase" or "MTRR") and ("colorectal" or "colon" or "rectal") and ("cancer" or "carcinoma" or "adenocarcinoma"). An upper date limit of June 30, 2014 was used, but no earlier date limit was applied. The search was conducted without any restrictions on language but focused on studies that had been conducted on human subjects. Only published studies with full text articles were included.

Inclusion and exclusion criteria

Included studies in this meta-analysis met the following criteria: (a) a human study on the association between *MTRR A66G* polymorphism and the susceptibility to CRC; (b) containing available genotype data in cases and controls for estimating odds ratio (OR) and 95% confidence interval (CI); (c) genotype distributions of control population were consistent with Hardy-Weinberg equilibrium (HWE). The exclusion criteria were: (a) reviews, letters, editorial articles and case reports; (b) studies on the association between other gene polymorphisms and CRC susceptibility.

Data extraction

The following information was extracted from each study: first author, year of publication, ethnicity of study population, and the number of CRC cases and controls for the A66G genotype. We did not define a minimum number of patients as a criterion for a study's inclusion in our meta-analysis.

Statistics

The association between *MTRR A66G* polymorphism and CRC susceptibility was estimated by calculating pooled ORs and 95% CI in the allele model (G vs A), homozygous model (GG vs AA), dominant model (GG/GA vs AA), and recessive model (GG vs GA/AA). The effect of the association was indicated as an OR with its corresponding 95% CI. Pooled OR was estimated using fixed and random effects models. Heterogeneity between studies was tested using the Q statistics. Heterogeneity was considered statistically significant if $p<0.10$. Heterogeneity was quantified using the I^2 metric, which was independent of the number of studies in the meta-analysis ($I^2<25\%$ no heterogeneity; I^2 = 25-50% moderate heterogeneity; and $I^2>50\%$ large or extreme heterogeneity). Begg's funnel plot and Egger's test were performed to assess the publication bias in the literature. All calculations were performed using ReviewManager 5.0 and STATA10.0 software.

Results

Study characteristics

After reading the titles and abstracts of retrieved articles, 12 articles encompassing 15 studies were included for data extraction [8-19]. Le Marchand et al. sorted the data in East Asians, Caucasians and Hawaiians, respectively, therefore, each group in the study was considered separately for pooling analyses [12]. Steck et al. sorted the data in Caucasians and African-Americans, respectively, therefore, the research was considered as two separate studies [17]. These studies were published between 2002 and 2013 (Table 1). The 15 studies provided 6020 cases and 8317 controls for MTRR A66G polymorphism. Fifteen studies were conducted in populations of different ethnicities: 10 studies were conducted in Caucasian populations [8-13,16-19], 1 study was in African-American population [17], 1 study was in Hawaiian populations [12], and 3 studies were in East Asian populations [12,14,15]. For case groups, the frequency of A66G polymorphism among GG-homozygous individuals was 26.7%. However, 47.6% of GA-heterozygous individuals and 25.7% of AA-homozygous individuals displayed the A66G polymorphism. In control groups, the frequencies of A66G polymorphism among GG-homozygous individuals, GA-heterozygous individuals, and AA-homozygous individuals were 25.6, 47.5, and 26.9%, respectively. The G allelic frequencies in the case and control groups were 50.5% and 49.3%, respectively.

Meta-analysis results

A total of 6020 cases and 8317 controls in 15 studies were pooled together for evaluation of the overall association between *MTRR* A66G polymorphism and the susceptibility to CRC. The pooled OR indicated significant association between the *MTRR* A66G polymorphism and susceptibility to CRC. The allele model (G vs A: p=0.01; OR=1.07, 95% CI=1.02-1.12), and the homozygous model (GG vs AA: p=0.006; OR=1.15, 95% CI=1.04-1.28) showed increased risk of developing CRC. Similarly, the dominant model (GG+GA vs AA: p=0.04;

Table 1. Study characteristics

First author [Ref No.]	*Country*	*Ethnicity*	*No. of Cases/ Controls*	*Distribution of A66G genotype*						*HWE*
				GG		*GA*		*AA*		
				CRC	*Control*	*CRC*	*Control*	*CRC*	*Control*	
Burcos, 2010 [16]	Romania	Caucasian	120/60	45	18	64	35	11	7	0.11
Guimaraes, 2011 [9]	Brazil	Caucasian*	113/188	32	33	55	102	26	53	0.18
Jokic, 2011 [8]	Croatia	Caucasian	300/300	88	83	159	143	53	74	0.43
Koushik, 2006 [11]	USA	Caucasian*	357/807	116	245	159	399	82	163	0.98
Le Marchand, 2002(1) [12]	USA	East Asian	314/393	26	30	140	170	148	193	0.37
Le Marchand, 2002(2) [12]	USA	Caucasian	149/170	40	39	81	86	28	45	0.86
Le Marchand, 2002(3) [12]	USA	Hawaiin	76/87	12	9	34	38	30	40	0.99
Liu, 2013 [13]	USA	Caucasian	1420/1775	439	550	717	869	264	356	0.70
Morita, 2002 [15]	Japan	East Asian	685/778	65	74	278	343	342	361	0.56
Otani, 2005 [14]	Japan	East Asian	107/224	5	14	44	82	58	128	0.86
Pardini, 2011 [16]	Czech	Caucasian	661/1372	218	410	330	671	113	291	0.59
Steck, 2008(1) [17]	USA	Caucasian	307/533	99	168	155	256	53	109	0.53
Steck, 2008(2) [17]	USA	African-American	239/322	24	26	99	127	116	169	0.76
Theodoratou, 2008 [18]	UK	Caucasian*	995/1009	339	329	456	482	200	198	0.37
Wettergren, 2010 [19]	Sweden	Caucasian	177/299	61	97	94	152	22	50	0.46

*most of the subjects were Caucasians. CRC: colorectal cancer

Table 2. Odds ratios (ORs) and heterogeneity results for the genetic contrasts of MTRR A66G polymorphism for colorectal cancer

	Population	*OR*				*I^2 (%)*	*p value*
		Fixed effects (95% CI)	*p value*	*Random effects (95% CI)*	*p value*		*Q test*
Alleles	All	1.07 (1.02-1.12)	0.01	1.07 (1.02-1.12)	0.01	0	0.55
	Caucasian	1.08 (1.02-1.14)	0.006	1.08 (1.02-1.14)	0.006	0	0.53
	East Asian	0.97 (0.86-1.10)	0.64	0.97 (0.86-1.10)	0.65	0	0.55
GG to AA	All	1.16 (1.04-1.28)	0.005	1.15 (1.04-1.28)	0.006	0	0.55
	Caucasian	1.17 (1.05-1.31)	0.005	1.18 (1.05-1.33)	0.006	8	0.37
	East Asian	0.97 (0.72-1.30)	0.81	0.97 (0.72-1.30)	0.82	0	0.79
GG to GA+AA	All	1.08 (1.00-1.17)	0.04	1.08 (1.00-1.17)	0.04	0	0.89
	Caucasian	1.08 (1.00-1.18)	0.05	1.08 (1.00-1.18)	0.05	0	0.73
	East Asian	1.00 (0.75-1.32)	0.99	1.00 (0.75-1.33)	1.0	0	0.81
GG+GA to AA	All	1.09 (1.01-1.18)	0.03	1.11 (1.01-1.22)	0.04	20	0.23
	Caucasian	1.14 (1.03-1.25)	0.01	1.15 (1.02-1.30)	0.02	23	0.23
	East Asian	0.95 (0.81-1.12)	0.56	0.95 (0.81-1.12)	0.56	0	0.37

OR=1.11, 95% CI=1.01-1.22) and the recessive model (GG vs GA+AA: p=0.04; OR=1.08, 95% CI=1.00-1.17) showed increased risk of developing CRC. No heterogeneity (I^2=0%, p=0.55) was detected among 15 studies. In the analysis stratified by ethnicity (Caucasians and East Asians), significant associations were found between *MTRR* A66G polymorphism and susceptibility to CRC among Caucasians. Detailed results are shown in Table 2.

Publication bias

Begg-Mazumdar test and the Egger test were performed to assess the publication bias. All of the studies investigating the 66G allele versus the A allele yielded a Begg's test score of p=0.334 and an Egger's test score of p=0.423. These results did not indicate a potential for publication bias.

Discussion

CRC is the third most common cause of cancer-related mortality in the western world and its morbidity is high [20,21]. Over the past decades, the roles of folate and genetic polymorphisms of enzymes involved in folate metabolism have attracted considerable interest in the epidemiological research on CRC. Unfortunately, conflicting results were obtained ranging from strong links to no association. In the present meta-analysis, we summarized all of the available data on the association between *MTRR* A66G polymorphism and susceptibility to CRC. Our results indicate evidence for an association between *MTRR* A66G polymorphism and CRC susceptibility among Caucasians, which suggested that the effect of the *MTRR* A66G polymorphism on the susceptibility to CRC might differ based on ethnicity. Reasons for the conflicting results obtained from different studies about the association between *MTRR* A66G polymorphism and the susceptibility to CRC may be attributed to the genetic heterogeneity in different ethnicities and the clinical heterogeneity (age, gender, and lifestyle) in different studies.

MTRR is a key enzyme involved in folate metabolism, and play essential roles in nucleotide synthesis and the methylation of DNA, histones, and other proteins. The A66G single nucleotide polymorphism at codon 22 is one of the most common polymorphisms in the MTRR gene, and the variant MTRR enzyme has a lower affinity for MTR [22], and is inconsistently associated with elevated blood or plasma homocysteine levels [23]. More conceivable would be the relation between folate status and genotype in CRC, where folate status might be more conditional on the subject's own genotype and folate intake. High folate intake has been related to decreased risk of CRC in a series of meta-analyses [24-26]. These findings demonstrate that the risks associated with the MTRR genotype may vary depending on folate status. Genetic and/or environmental exposures are required for cancer to develop. None of the studies to date has assessed the dietary folate intake to evaluate whether overall folate status may have modified the relation between having the MTRR genotype and one's risk of developing CRC.

Considering the limitations of this meta-analysis, our results should be interpreted with caution. First, our results are based on unadjusted estimates. A more precise analysis should be conducted using individual data, which would allow researchers to adjust for covariates, including age, family history, lifestyle, and environmental factors. Second, only published studies were included in this meta-analysis. Although we did not find a potential for publication bias, nonsignificant or negative findings may not have been published.

In conclusion, our pooled data suggest an association between *MTRR* A66G polymorphism and CRC susceptibility among Caucasians.

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