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META-ANALYSIS

Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and gastric cancer susceptibility

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Abstract

AIM: To identify the association between methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms and gastric cancer (GC) susceptibility.

METHODS: Systematic searches were performed on the electronic databases PubMed, ISI, Web of knowledge, CNKI and Wanfang, as well as manual searching of the references of the identified articles. A total of 26 papers were included in this meta-analysis. Overall and subgroup analyses were performed. Odds ratio (OR) and 95%CI were used to evaluate the associations between *MTHFR* polymorphisms and GC risk. The I^2 statistics were used to evaluate between-study heterogeneity. Sensitivity analysis was also performed.

RESULTS: Increased risk was found for the MTHFR C677T polymorphism under four genetic models (TT + CT *vs* CC: OR = 1.23, *P* = 0.002; T *vs* C: OR = 1.15, *P* = 0.001; TT *vs* CC: OR = 1.37, *P* = 0.0005; TT *vs* CT + CC: OR = 1.17, *P* = 0.0008). Subgroup analysis by ethnicity suggested that C677T polymorphism conferred a risk of GC in eastern but not in western populations. Stratification by tumor site showed an association between the C677T polymorphism and gastric cardia cancer and non-cardia GC in the worldwide population and in eastern populations. Regardless of comparisons with controls or diffuse-type GC, a positive association was found for the C677T polymorphism and an increased risk of intestinal-type GC in the whole population and in western populations. With regard to the A1298C polymorphism, we found that genotype CC was significantly decreased and conferred protection against GC in eastern populations (CC *vs* AA: OR = 0.44, *P* = 0.03; CC *vs* AC + AA: OR = 0.46, *P* = 0.04).

CONCLUSION: MTHFR C677T polymorphism is a risk factor for GC, and the A1298C polymorphism may be a protective factor against GC in eastern populations.

Key words: Methylenetetrahydrofolate reductase; Polymorphism; Gastric cancer; Meta-analysis

Core tip: Many studies have reported associations of methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms with susceptibility to gastric cancer (GC). There are several relevant published meta-analyses about this subject. Nevertheless, these articles failed to analysis *MTHFR* polymorphisms and GC risk *per se* in detail as follows. They failed to investigate the difference between gastric cardia cancer and non-cardia GC, and the distinction between diffuse and intestinal subtypes. Consequently, we performed a meta-analysis to clarify the roles of MTHFR C677T and A1298C polymorphisms in GC susceptibility among the eligible studies.

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INTRODUCTION

The incidence of gastric cancer (GC) has decreased worldwide, but it remains the fourth most common cancer diagnosis in men and the fifth in women[1], and the second leading cause of cancer-related death[2,3]. The etiology of GC is believed to be multi-stage and multifactorial. Although the decrease in the incidence of GC[4] in recent decades can be explained by changing lifestyles, diet habits, and reduced *Helicobacter pylori* infection, the fact that some individuals develop GC while others do not under similar environmental circumstances suggests that genetic predisposition plays an important role in the pathogenesis of GC.

Methylenetetrahydrofolate reductase (MTHFR), whose gene maps to chromosome 1p36.3[5] and encodes a 77-kDa protein[6], plays a key role in folate metabolism by irreversibly catalyzing the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant circulatory form of folate, which serves as both a cofactor and substrate for the regeneration of methionine. The latter leads to production of *S*-adenosylmethionine (SAM); the universal methyl donor in humans for DNA methylation[7]. Reduced enzyme activity may result in lower levels of SAM and an increased risk of cancer, including GC, as a consequence of gene hypomethylation[8]. Two common single nucleotide polymorphisms (SNPs) of MTHFR have been indicated: C677T (rs1801133), which results in the amino acid product changing from alanine to valine[9]; and A1298C (rs1801131), which results in the amino acid product changing from glutamic acid to alanine[8]. Studies have confirmed that the variant genotypes are associated with a significant reduction of enzyme activity[10,11], suggesting that the polymorphisms of C677T and A1298C may be related to the risk of GC.

Until now, many studies have reported associations of MTHFR C677T and A1298C polymorphisms with susceptibility to GC with controversial results[12-37]. Additionally, there have been several relevant meta-analyses published on this subject[38-44]. Nevertheless, these studies failed to analyze *MTHFR* polymorphisms and GC risk *per se* in detail as follows. They failed to address the difference between gastric cardia cancer (GCC) and non-cardia gastric cancer (NCGC) as well as the distinction between diffuse and intestinal subtypes. Consequently, we performed a meta-analysis to clarify the roles of MTHFR C677T and A1298C polymorphisms in GC susceptibility among the eligible studies.

MATERIALS AND METHODS

Search strategy

Two researchers independently performed a computerized search in four databases - PubMed, ISI Web of Knowledge (Version 4.5), Chinese National Knowledge Infrastructure, and Wanfang (Chinese) - up to May 2013. Moreover, an additional search was carried out for relevant studies on scholar.google.com.hk. The search terms were "methylenetetrahydrofolate reductase" or MTHFR, "gastric or stomach or cardia" and "cancer or carcinoma or neoplasm" in various combinations, with the language limited to English and Chinese. The reference list of each relevant publication was also reviewed to ensure that all appropriate studies were included in the meta-analysis.

Inclusion and exclusion criteria

Studies were included according to the following criteria: (1) case-control or cohort studies determining the distribution of MTHFR C677T and/or A1298C genotypes; (2) cases with GC were diagnosed by histopathological biopsy, and the controls were free of cancer; and (3) the numbers of cases and controls reported for each genotype should be sufficient for calculation. If multiple studies from the same case series were available, the one including the most individuals was used in the analysis. We excluded the studies if they were: (1) meeting abstracts, case reports, reviews, or editorials; (2) not written in English or Chinese; or (3) not in Hardy-Weinberg equilibrium (HWE) with the controls. The final included studies were based on discussion among the researchers.

Data extraction

Two investigators independently extracted data from the published reports using a standardized protocol and a reporting form with the following information: first author's last name, year of publication, country and ethnicity of participants (classified into eastern and western), sample size, detailed genotype information (genotype distribution and allele frequency), anatomical site of tumor (cardia or non-cardia GC) and Lauren classification (intestinal or diffuse subtype).

Statistical analysis

The MTHFR C677T genotypes include TT, CT and CC, and A1298C comprises CC, AC and AA genotypes. The pooled odds ratios (ORs) were calculated for the dominant model [C677T: (TT + CT) *vs* CC; A1298C: (CC + AC) *vs* AA], the allelic model (C677T: T allele *vs* C allele; A1298C: C allele *vs* A allele), the additive model (C677T: TT *vs* CC; A1298C: CC *vs* AA), and the recessive model (C677T: TT *vs* (CT + CC); A1298C: CC *vs* (AC + AA), respectively. Given that the potential causes of heterogeneity among studies were ethnicity, tumor site and classification, subgroup analyses were conducted according to different ethnic groups (Eastern/Western), tumor site (cardia/non-cardia), and Lauren classification (intestinal/diffuse).

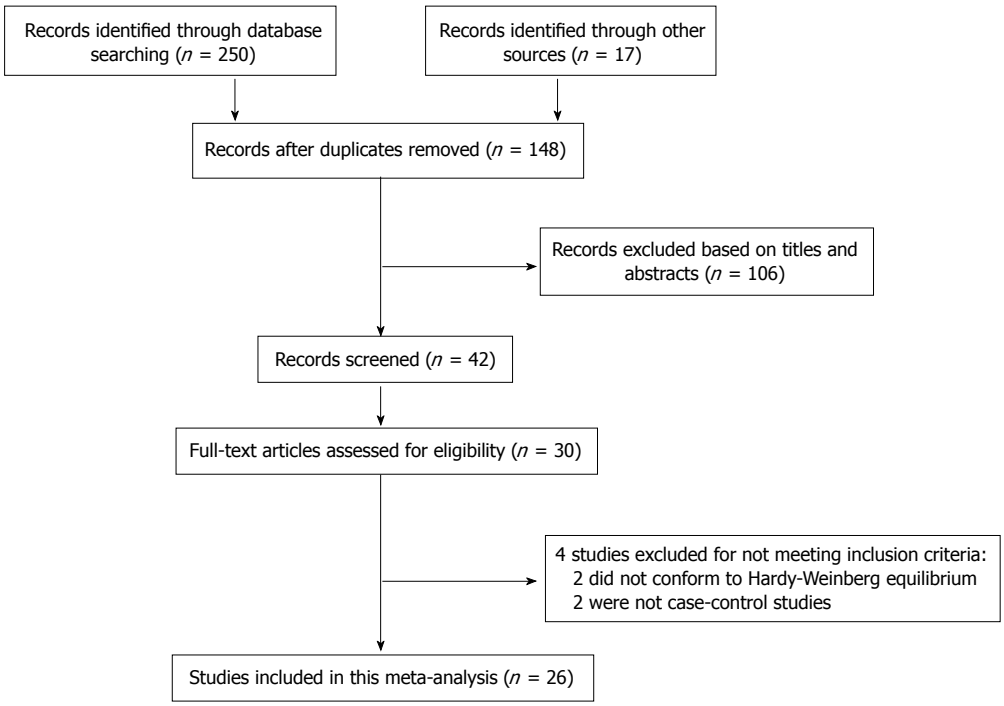

Figure 1 Flowchart of the literature selection process.

RevMan software (Review Manager, Version 5.1; Cochrane Collaboration, 2011) was used for this meta-analysis. The between-study heterogeneity (*i.e.*, the variation in findings not compatible with chance alone) was tested with the χ^2-based Cochran's statistic and the inconsistency index (I^2). Statistically significant heterogeneity was considered to be present when $P_{\text{heterogeneity}} < 0.05$ and $I^2 > 50\%$. If there was no statistical heterogeneity among studies ($I^2 < 50\%$ and $P_{\text{heterogeneity}} > 0.05$), the OR and 95%CI were estimated for each study in a fixed-effects model (FEM). Otherwise, a random effect model (REM) was used. A funnel plot was performed to look for evidence of publication bias; the funnel plot should be asymmetric when there is publication bias and symmetric in the case of no publication bias. Additionally, the publication bias was quantitatively estimated by Begg's and Egger's tests.

RESULTS

Study characteristics

Figure 1 summarizes the selection process of eligible studies. After a thorough literature search, 26 qualified publications[12-37] were included in this meta-analysis according to the inclusion criteria. Among these, 24 were included for the MTHFR C677T polymorphism and GC, and 11 were included for the MTHFR A1298C polymorphism and GC. The characteristics of the included studies, the variant genotypes and allele frequencies are listed in Table 1. Table 2 shows the available data on GCC and NCGC for MTHFR C677T and A1298C in detail. Additionally, data on intestinal and diffuse subtype GC for C677T were accessible in four studies (Table 3). According to the size of the heterogeneity, FEM or REM was adopted to analyze every comparison (Table 4).

Overall analysis

MTHFR C677T polymorphism and GC: Table 4 lists the main results of this meta-analysis. A total of 6266 cases and 8250 controls were identified for analysis of the association between the MTHFR C677T polymorphism and GC. The overall results showed that there was a significant association between C677T and GC [TT + CT *vs* CC: OR = 1.23 (1.08, 1.40), $P = 0.002$], and a T allele was associated with a 15.0% increased risk of GC compared to a C allele [T *vs* C: OR = 1.15 (1.06, 1.25), $P = 0.001$]. Similar results were obtained in the analysis for the additive model [TT *vs* CC: OR = 1.37 (1.15, 1.63), $P = 0.0005$] and the recessive model [TT *vs* CT + CC: OR = 1.17 (1.07, 1.28), $P = 0.0008$].

MTHFR A1298C polymorphism and GC: As shown in Table 4, 11 studies including a total of 2007 cases and 3679 controls were performed to analyze the relationship between the MTHFR A1298C polymorphism and GC. The risk for GC conferred by the MTHFR A1298C polymorphism did not reach significance under the four genetic models ($P > 0.05$).

Subgroup analysis

When stratifying the data by ethnicity, stronger significance between the MTHFR C677T polymorphism and GC was shown when restricted to eastern populations [TT + CT *vs* CC: OR = 1.26 (1.08, 1.47), $P = 0.003$; T *vs* C: OR = 1.21 (1.08, 1.34), $P = 0.0005$; TT *vs* CC: OR = 1.42 (1.15, 1.76), $P = 0.001$; TT *vs* CT + CC: OR = 1.22

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

Ref.	Country	Ethnicity	Sample size		C677T											A1298C										
					Genotypes distribution						Alleles frequency				*P* HWE	Genotypes distribution						Alleles frequency				*P* HWE
			Case	Control	Case			Control			Case		Control			Case			Control			Case		Control		
					CC	CT	TT	CC	CT	TT	C	T	C	T		AA	AC	CC	AA	AC	CC	A	C	A	C	
Gao *et al*[12]	China	Eastern	264	535	115	105	44	277	207	51	335	193	761	309	0.19											
Guo *et al*[13]	China	Eastern	97	114	22	48	27	32	57	25	92	102	121	107	0.97											
Saberi *et al*[14]	Iran	Eastern	405	780	198	172	35	422	308	50	578	242	1152	408	0.54											
Yang *et al*[15]	China	Eastern	139	165	44	80	15	62	75	28	168	110	197	131	0.5											
Cui *et al*[16]	South Korea	Eastern	2213	1700	778	1052	382	540	863	297	2608	1816	1943	1457	0.13											
De Re *et al*[17]	Italy	Western	48	96	12	23	13	37	46	13	47	49	120	72	0.73	24	19	5	33	54	9	67	29	120	72	0.08
Galvan-Portillo *et al*[18]	Mexico	Western	248	478	37	132	79	89	217	172	216	290	395	561	0.17											
Gotze *et al*[19]	Germany	Western	106	106	46	45	12	41	49	16	137	69	131	81	0.74											
Zeybek *et al*[20]	Turkey	Eastern	35	144	18	12	5	64	65	15	48	22	193	95	0.76											
Vollset *et al*[21]	Europea[1]	Western	247	631	109	104	32	248	277	94	322	168	773	465	0.27	103	116	25	315	246	53	322	166	876	352	0.61
Mu *et al*[22]	China	Eastern	196	397	50	106	38	135	199	57	206	182	469	313	0.23	147	49	0	275	112	7	343	49	662	126	0.25
Zhang *et al*[23]	Poland	Western	305	427	146	116	33	185	178	36	408	182	548	250	0.48	135	125	31	180	179	41	395	187	539	261	0.72
Boccia *et al*[24]	Italy	Western	102	254	29	51	22	98	115	41	109	95	311	197	0.43	50	43	9	125	107	22	143	61	357	151	0.89
Fu *et al*[25]	China	Eastern	169	169												96	73	0	125	44	0	265	73	294	44	0.12
Graziano *et al*[26]	Italy	Western	162	164	34	86	42	67	68	29	154	126	202	126	0.10											
Li *et al*[27]	China	Eastern	170	140	61	78	31	67	56	17	200	140	190	90	0.32	126	42	2	97	41	2	294	46	235	45	0.32
Weng *et al*[28]	China	Eastern	38	34	14	19	5	15	11	8	47	29	41	27	0.06	26	12	0	22	11	1	64	12	55	13	0.79
Kim *et al*[29]	South Korea	Eastern	133	445	42	64	27	143	239	63	148	118	525	365	0.02[2]	98	34	1	308	129	8	230	36	745	145	0.19
Si *et al*[30]	China	Eastern	122	101	58	48	16	49	43	9	164	80	141	61	0.92	73	44	5	58	38	5	190	54	154	48	0.70
Sarbia *et al*[31]	Germany	Western	332	255	138	153	41	107	115	33	429	235	329	181	0.81											
Bi *et al*[32]	China	Eastern	309	188	139	150	20	97	76	15	428	190	270	106	0.99											
Wang *et al*[33]	China	Eastern	129	315	25	45	59	74	143	98	95	163	291	339	0.12											
Stolzenberg-Solomon *et al*[34]	China	Eastern	90	398	17	36	37	65	209	124	70	110	339	457	0.14	69	21	0	294	104	0	159	21	692	104	0.003[2]
Miao *et al*[35]	China	Eastern	217	468	47	107	63	151	217	100	201	233	519	417	0.18	150	64	3	324	139	5	364	70	787	149	0.02[2]
Gao *et al*[36]	China	Eastern	107	200	22	61	24	63	99	38	105	109	225	175	0.93											
Shen *et al*[37]	China	Eastern	187	166	55	90	42	60	80	26	200	174	200	132	0.96	130	55	2	111	50	5	315	59	272	60	0.83

[1]Study involving Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom; [2]Studies with the controls not in Hardy-Weinberg equilibrium (HWE).

(1.09, 1.35), $P = 0.0003$], although the result for western populations was not significant (Table 4). With regard to the A1298C polymorphism, the results showed that there was a significant association between the A1298C polymorphism and a decreased risk of GC in eastern populations in the additive and recessive models [CC *vs* AA: OR = 0.44 (0.21, 0.93), $P = 0.03$; CC *vs* AC + AA: OR = 0.46 (0.22, 0.96), $P = 0.04$] (Table 4).

Stratification analyses were performed to consider tumor sites. The results suggested that the MTHFR C677T polymorphism was significantly associated with an increased GC risk for both GCC [TT *vs* CT + CC: OR = 1.38 (1.15, 1.67), $P = 0.0006$] and NCGC [TT + CT *vs* CC: OR = 1.38 (1.18, 1.63), $P < 0.0001$; T *vs* C: OR = 1.24 (1.10, 1.40), $P = 0.0003$; TT *vs* CC: OR = 1.44 (1.09, 1.91), $P = 0.01$] in the whole population. When further analyzed by ethnicity, similar positive results were found only in eastern but not in western populations. We also obtained no significant results for the association between A1298C and both GCC and NCGC (Table 4).

In view of the Lauren classification, we divided the studies into two subgroups. The results showed that the MTHFR C677T polymorphism was significantly associated with an increased risk for intestinal-type GC [TT *vs* CC: OR = 1.88 (1.22, 2.89), $P = 0.004$; TT *vs* CT + CC: OR = 1.45 (1.07, 1.95), $P = 0.02$] in the whole population. When further

Table 2 Distribution of MTHFR C677T and A1298C genotypes and alleles frequency in gastric cardia cancer, non-cardia cancer and controls

Ref.	Sample size			Genotypes distribution									Alleles frequency					
	Cardia	Non-cardia	Control	Cardia			Non-cardia			Control			Cardia		Non-cardia		Control	
MTHFR C677T polymorphism				CC	CT	TT	CC	CT	TT	CC	CT	TT	C	T	C	T	C	T
Saberi *et al*[14]	152	210	780	77	60	15	99	98	13	422	308	50	214	90	296	124	1152	408
Gotze *et al*[19]	27	76	106	13	13	1	33	32	11	41	49	16	39	15	98	54	131	81
Graziano *et al*[26]	43	119	164	7	25	11	27	61	31	67	68	29	39	47	115	123	202	126
Weng *et al*[28]	NA	38	34		NA		14	19	5	15	11	8	NA		47	29	41	27
Sarbia *et al*[31]	119	213	255	65	45	9	73	108	32	107	115	33	175	63	254	172	329	181
Si *et al*[30]	29	93	101	21	7	1	37	41	15	49	43	9	49	9	115	71	141	61
Bi *et al*[32]	155	154	188	74	73	8	65	77	12	97	76	15	211	89	207	101	270	106
Wang *et al*[33]	129	NA	315	25	45	59		NA		74	143	98	95	163	NA		291	339
Stolzenberg-Solomon *et al*[34]	90	NA	398	17	36	37		NA		65	209	124	70	110	NA		339	457
Miao *et al*[35]	217	NA	468	47	107	63		NA		151	217	100	201	233	NA		519	417
Shen *et al*[37]	82	105	166	22	38	22	33	52	20	60	80	26	82	82	118	92	200	132
MTHFR A1298C polymorphism				AA	AC	CC	AA	AC	CC	AA	AC	CC	A	C	A	C	A	C
Weng *et al*[28]	NA	38	34		NA		26	12	0	22	11	1	NA		64	12	55	13
Si *et al*[30]	29	93	101	15	12	2	58	32	3	58	38	5	42	16	148	38	154	48
Shen *et al*[37]	82	105	166	64	17	1	66	38	1	111	50	5	145	19	170	40	272	60

NA: Not available.

Table 3 Distribution of MTHFR C677T and A1298C genotypes and alleles frequency in intestinal, diffuse gastric cancer and controls

Ref.	Sample size			Genotypes distribution									Alleles frequency					
	Intestinal	Diffuse	Control	Intestinal			Diffuse			Control			Intestinal		Diffuse		Control	
				CC	CT	TT	CC	CT	TT	CC	CT	TT	C	T	C	T	C	T
MTHFR C677T polymorphism																		
Saberi *et al*[14]	142	80	780	69	59	14	39	34	7	422	308	50	197	87	112	48	1152	408
Galvan-Portillo *et al*[18]	88	152	454	50		38	113		39	291		163	NA		NA		NA	
Gotze *et al*[19]	53	37	106	21	24	8	18	15	4	41	49	16	66	40	51	23	131	81
Graziano *et al*[26]	91	71	164	19	47	25	15	39	17	67	68	29	85	97	69	73	202	126

NA: Not available.

analyzed by ethnicity, similar positive results were found only in western populations but not in eastern populations. No significant relationship was found between the MTHFR C677T polymorphism and diffuse-type GC (Table 4).

Relationships between GCC and NCGC, and intestinal-type and diffuse-type GC

When comparing GCC with NCGC, no significant results were observed in any of the four models for C677T or A1298C (Table 5), and ORs of 1.71 (95%CI: 1.13-2.59, $P = 0.01$) and 1.60 (95%CI: 1.09-2.35, $P = 0.02$) were found in the TT *vs* CC model in western populations and total populations, respectively, when comparing intestinal-type with diffuse-type GC for C677T. None of the other models produced significant results for eastern, western or overall populations (Table 5).

Sensitivity analysis and publication bias evaluation

A sensitivity analysis was performed by excluding one study each time to reflect the influence of the individual data set on the ORs; the analysis did not alter the pattern of the results (data not shown), which confirmed the stability of the above results. The funnel plot (data not shown) provided no evidence of publication bias. Consistent results were drawn from Begg's and Egger's tests.

DISCUSSION

Regarding the MTHFR C677T and A1298C polymorphisms and their association with GC, definite conclusions cannot be drawn. Therefore, we performed a meta-analysis to estimate the relationships between the two SNPs in the *MTHFR* gene and the risk of GC.

In the present meta-analysis, the overall analysis suggested that MTHFR 677TT and CT genotype carriers had a higher risk of developing GC; in addition, an elevated risk of GC was also found among the MTHFR 677T allele carriers. It is well known that individuals who are MTHFR 677T carriers have reduced MTHFR activity[10], and the low enzyme activity of MTHFR C677T variant genotypes is associated with DNA hypomethylation, which may induce genomic instability and thereby affect the expression of oncogenes or tumor suppressor genes, leading to the development of malignancies[45,46]. No significant association was found between the MTH-

Table 4 Comparisons of MTHFR C677T and A1298C polymorphisms for whole and stratified analysis

	n	Case/control	OR (95%CI)	*P*	$P_{Heterogeneity}$	OR (95%CI)	*P*	$P_{Heterogeneity}$	OR (95%CI)	*P*	$P_{Heterogeneity}$	OR (95%CI)	*P*	$P_{Heterogeneity}$
			(TT + CT)/CC			T/C			TT/CC			TT/(CT + CC)		
C677T														
Total	24	6266/8250	1.23 (1.08, 1.40)	0.002	< 0.0001	1.15 (1.06, 1.25)	0.001	0.0004	1.37 (1.15, 1.63)	0.0005	0.0005	1.17 (1.07, 1.28)	0.0008	0.01
Eastern	16	4716/5839	1.26 (1.08, 1.47)	0.003	0.002	1.21 (1.08, 1.34)	0.0005	0.002	1.42 (1.15, 1.76)	0.001	0.005	1.22 (1.09, 1.35)	0.0003	0.03
Western	8	1550/2411	1.20 (0.92, 1.56)	0.180	0.002	1.05 (0.91, 1.21)	0.53	0.05	1.28 (0.91, 1.82)	0.16	0.009	1.05 (0.88, 1.25)	0.55	0.11
Tumor site														
Cardia														
Total	10	1043/2941	1.09 (0.81, 1.48)	0.560	0.0005	1.16 (0.95, 1.41)	0.14	0.002	1.28 (0.85, 1.95)	0.24	0.003	1.38 (1.15, 1.67)	0.0006	0.05
Eastern	7	854/2416	1.16 (0.89, 1.52)	0.280	0.05	1.24 (1.04, 1.48)	0.02	0.06	1.57(1.23, 2.00)	0.0003	0.16	1.53 (1.25, 1.87)	< 0.0001	0.31
Western	3	189/525	1.09 (0.38, 3.12)	0.870	0.001	1.00 (0.52, 1.91)	1.00	0.004	0.78 (0.15, 4.16)	0.77	0.003	0.73 (0.27, 1.99)	0.54	0.07
Non-cardia														
Total	8	1008/1794	1.38 (1.18, 1.63)	< 0.0001	0.42	1.24 (1.10, 1.40)	0.0003	0.42	1.44 (1.09, 1.91)	0.01	0.31	1.19 (0.93, 1.52)	0.16	0.61
Eastern	5	600/1269	1.35 (1.10, 1.66)	0.004	0.99	1.21 (1.04, 1.41)	0.01	0.87	1.30 (0.87, 1.95)	0.20	0.48	1.10 (0.79, 1.55)	0.57	0.44
Western	3	408/525	1.41 (0.83, 2.38)	0.400	0.03	1.26 (0.91, 1.76)	0.16	0.06	1.55 (0.86, 2.78)	0.14	0.12	1.29 (0.91, 1.83)	0.16	0.53
Lauren's classification														
Intestinal														
Total	4	374/1504	1.46 (0.86, 2.47)	0.160	0.05	1.33 (0.97, 1.84)	0.08	0.10	1.88 (1.22, 2.89)	0.004	0.19	1.45 (1.07, 1.95)	0.02	0.76
Eastern	1	142/780	1.25 (0.87,1.87)	0.230	NA	1.25 (0.95, 1.64)	0.12	NA	1.71 (0.90, 3.26)	0.10	NA	1.60 (0.86, 2.97)	0.14	NA
Western	3	232/724	1.61 (0.60,4.29)	0.340	0.03	1.37 (0.74, 2.52)	0.32	0.04	2.01 (1.13, 3.59)	0.02	0.07	1.41 (1.00, 1.98)	0.05	0.58
Diffuse														
Total	4	340/1504	1.31 (0.66,2.58)	0.440	0.03	1.19 (0.78, 1.82)	0.42	0.06	1.46 (0.66, 3.21)	0.35	0.13	0.94 (0.56, 1.58)	0.82	0.09
Eastern	1	80/780	1.24 (0.78,1.96)	0.360	NA	1.21 (0.85, 1.73)	0.29	NA	1.51 (0.64, 3.57)	0.34	NA	1.40 (0.61, 3.20)	0.80	NA
Western	3	260/724	1.33 (0.35,5.01)	0.670	0.008	1.14 (0.50, 2.60)	0.76	0.02	1.31 (0.29, 5.83)	0.72	0.04	0.85 (0.46, 1.55)	0.59	0.1
A1298C			(CC + AC)/AA			C/A			CC/AA			CC/(AC + AA)		
Total	11	2007/3679	0.98 (0.79, 1.21)	0.840	0.008	0.97 (0.83, 1.14)	0.73	0.03	0.95 (0.71, 1.28)	0.76	0.60	0.95 (0.72, 1.27)	0.75	0.78
Eastern	7	1015/1452	0.96 (0.72, 1.29)	0.790	0.02	0.93 (0.73, 1.19)	0.56	0.04	0.44 (0.21, 0.93)	0.03	0.84	0.46 (0.22, 0.96)	0.04	0
Western	4	702/1408	1.00 (0.71, 1.41)	0.990	0.04	1.07 (0.93, 1.23)	0.36	0.15	1.13 (0.82, 1.57)	0.46	0.69	1.11 (0.81, 1.51)	0.53	0.98
Tumor site														
Cardia														
Total	2	111/267	0.80 (0.37, 1.74)	0.240	0.13	0.83 (0.41, 1.69)	0.61	0.10	0.76 (0.21, 2.83)	0.69	0.28	0.80 (0.22, 2.93)	0.73	0.36
Eastern	2	111/267	0.80 (0.37, 1.74)	0.240	0.13	0.83 (0.41, 1.69)	0.61	0.10	0.76 (0.21, 2.83)	0.69	0.28	0.80 (0.22, 2.93)	0.73	0.36
Western	0	0	NA			NA			NA			NA		
Non-cardia														
Total	3	236/301	0.98 (0.69, 1.41)	0.930	0.59	0.93 (0.68, 1.26)	0.62	0.69	0.45 (0.15, 1.40)	0.17	0.86	0.46 (0.15, 1.40)	0.17	0.82
Eastern	3	236/301	0.98 (0.69, 1.41)	0.930	0.59	0.93 (0.68, 1.26)	0.62	0.69	0.45 (0.15, 1.40)	0.17	0.86	0.46 (0.15, 1.40)	0.17	0.82
Western	0	0	NA			NA			NA			NA		

NA: Not available; $P_{Heterogeneity}$: *P* value of *Q* test for heterogeneity test.

Table 5 Comparisons of MTHFR C677T and A1298C polymorphisms for gastric cardia and non-cardia cancers, intestinal-type and diffuse-type gastric cancers

	n	Case/control	OR (95%CI)	*P*	$P_{Heterogeneity}$	OR (95%CI)	*P*	$P_{Heterogeneity}$	OR (95%CI)	*P*	$P_{Heterogeneity}$	OR (95%CI)	*P*	$P_{Heterogeneity}$
C677T			(TT + CT)/CC			T/C			TT/CC			TT/(CT + CC)		
Cardia and non-cardia														
Total	7	607/970	0.74 (0.51, 1.08)	0.12	0.01	0.80 (0.59, 1.09)	0.2	0.002	0.82 (0.49, 1.38)	0.46	0.01	0.71 (0.36, 1.39)	0.31	0.06
Eastern	4	418/562	0.76 (0.47, 1.21)	0.24	0.04	0.85 (0.56, 1.27)	0.4	0.01	1.04 (0.52, 2.06)	0.91	0.05	0.89 (0.39, 2.03)	0.78	0.10
Western	3	189/408	0.75 (0.35, 1.61)	0.46	0.04	0.73 (0.45, 1.20)	0.2	0.05	0.59 (0.35, 1.00)	0.05	0.08	0.52 (0.17, 1.59)	0.25	0.26
Intestinal-type and diffuse-type														
Total	4	374/340	1.09 (0.74, 1.62)	0.67	0.76	1.10 (0.84, 1.45)	0.5	0.78	1.60 (1.09, 2.35)	0.02	0.87	1.24 (0.68, 2.27)	0.48	0.50
Eastern	1	142/80	1.01 (0.58, 1.74)	0.98	NA	1.03 (0.68, 1.57)	0.9	NA	1.14 (0.44, 2.95)	0.79	NA	1.13 (0.42, 3.04)	0.81	NA
Western	3	232/260	1.19 (0.68, 2.09)	0.55	0.54	1.16 (0.81, 1.66)	0.4	0.57	1.71 (1.13, 2.59)	0.01	0.64	1.32 (0.62, 2.80)	0.48	0.41
A1298C			(CC + AC)/AA			C/A			CC/AA			CC/(AC + AA)		
Cardia and non-cardia														
Total	2	111/198	0.83 (0.26, 2.64)	0.75	0.03	0.90 (0.34, 2.34)	0.8	0.03	1.87 (0.39, 9.03)	0.44	0.59	1.85 (0.39, 8.69)	0.43	0.75
Eastern	2	111/199	0.83 (0.26, 2.64)	0.75	0.03	0.90 (0.34, 2.34)	0.8	0.03	1.87 (0.39, 9.03)	0.44	0.59	1.85 (0.39, 8.69)	0.43	0.75
Western	0	0	NA			NA			NA			NA		

NA: Not available; $P_{Heterogeneity}$: *P* value of *Q* test for heterogeneity test.

FR A1298C polymorphism and overall GC risk; a possible explanation for which could be that the reduction of MTHFR functional activity caused by the A1298C mutation is significantly less than that caused by the C677T mutation[9].

In subgroup analyses stratified by the ethnicity, gastric tumor site and Lauren classification, we found that the MTHFR C677T polymorphism was associated with susceptibility to both GCC and NCGC in eastern populations compared with controls. No positive association was found between the MTHFR C677T polymorphism and the risk of intestinal or diffuse types of GC compared with controls. With regard to the A1298C polymorphism, we found that the CC genotype conferred protection against GC in eastern but not in Western populations; however, the inconsistent results among Western and Eastern populations are difficult to explain. Moreover, irrespective of comparison with controls or diffuse-type GC, a positive association was found that the C677TT polymorphism increased the risk of intestinal-type GC in the whole population and in the western population. No significant difference was found between GCC and NCGC. Because a small sample size was included, this conclusion remains to be confirmed. To the best of our knowledge, the distribution of the *MTHFR* polymorphism differs among various ethnic populations[47], which may have led to the different results for eastern and western populations.

Although several related meta-analyses have been published previously[38-44], our current research still has some advantages. First, because it involved 26 studies conforming to HWE and provided 6390/8515 cases/controls, our meta-analysis included a larger number of studies than the previous studies, and the results are more reliable. Second, our study is the first to include stratification according to tumor site and Lauren classification.

There was a certain degree of heterogeneity among the studies assessed here, which may be attributed to design quality, sample size, noncomparable measures of genotyping, and variation of the covariate. To clarify the sources of heterogeneity, we conducted a sensitivity analysis, and this analysis confirmed the stability of the null association between *MTHFR* polymorphisms and GC after excluding any one study at a time.

No significant publication bias was found herein given the symmetry shown in the funnel plots, and consistent results were drawn from Begg's and Egger's tests (data not shown). Nevertheless, unpublished data from conference abstracts and dissertations and unpublished pharmaceutical company data were not extracted, which could introduce a distinct possibility of publication bias. Moreover, we followed the inclusion and exclusion criteria strictly to reduce selection bias. In addition, the test of HWE for the distribution of the genotypes in the control groups suggested that there were no individuals with significantly aberrant genetic backgrounds among the participants.

Nevertheless, this meta-analysis had several limitations that may have affected the conclusions. First, we selected only the MTHFR C677T and A1298C polymorphisms

because these were the most extensively studied polymorphisms, although several other SNPs in the *MTHFR* gene have been identified. Meta-analyses that investigate the association of other polymorphisms in the *MTHFR* gene with GC should be performed in the future. Second, study design, small sample size and environmental factors may have affected the results; many studies did not use an appropriate design or neglected to consider important environmental factors. Third, the results drawn from subgroup analyses might be limited because of the small sample size. Moreover, it was difficult to obtain full papers published in various languages; we included studies published only in English and Chinese.

In summary, data from our meta-analysis support that the MTHFR C677T polymorphism increases the risk of developing GC in the general population, as well as the risk of GCC and NCGC in eastern populations and intestinal-type GC in western populations. The A1298C polymorphism may be a protective factor against GC in eastern populations. GC is a disease resulting from complex interactions between genes and the environment. Therefore, further well-designed studies with larger sample sizes should be performed to assess other genetic and environmental factors in the development of GC.

COMMENTS

Background

Currently, the incidence of gastric cancer (GC) has decreased worldwide, but it remains the fourth most common cancer diagnosis in men, and the fifth in women, and the second leading cause of cancer-related death. Methylenetetrahydrofolate reductase (MTHFR) encodes a 77-kDa protein that plays a key role in DNA methylation. Many studies have explored the association between *MTHFR* polymorphisms and GC risk, but the results remain either controversial or inconclusive. Consequently, the authors performed a meta-analysis to clarify the role of *MTHFR* polymorphisms in GC susceptibility among the eligible studies.

Research frontiers

Until now, many studies have reported associations of *MTHFR* polymorphisms with susceptibility to GC; however, the results have been inconsistent and inconclusive.

Innovations and breakthroughs

This meta-analysis indicates that the MTHFR C677T polymorphism is a risk factor in GC and that the A1298C polymorphism may be a protective factor against GC in eastern populations. Moreover, this study is the first to include stratification according to tumor site and Lauren classification.

Applications

This meta-analysis showed that the C677T and A1298C polymorphisms of the *MTHFR* gene could alter susceptibility to GC. The findings may provide valuable information about the etiology of GC for both researchers and clinicians.

Terminology

MTHFR encodes a 77-kDa protein that plays a key role in folate metabolism by irreversibly catalyzing the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant circulatory form of folate, which serves as both a cofactor and substrate for the regeneration of methionine. The latter leads to the production of *S*-adenosylmethionine (SAM), the universal methyl donor in humans for DNA methylation. Reduced enzyme activity may result in lower levels of SAM and an increased risk of cancer, including GC, as a consequence of gene hypomethylation.

Peer review

This meta-analysis was a well-written and well-conducted study that evaluated the association of *MTHFR* polymorphisms with susceptibility to gastric cancer. It had a large sample size, which allowed consistent conclusions in relation to the general population. Additionally, this study is the first to include stratification according to gastric cancer location and histological subtype. It is important to review these relevant reports systematically.

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