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Original Article

Association between MTHFR A1298C polymorphism and digestive system cancer susceptibility: a meta-analysis based on sixty-five case-control studies

Xiaofan Deng[1*], Lingli Li[2*], Lingjun Xie[2], Shan Wu[2], Ning Ning[2], Xiaoling Hou[2]

[1]Center of Organ Transplantation, Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital, Chengdu, China; [2]West China Hospital, Sichuan University, No. 37, Guoxuexiang, Chengdu 610041, China. [*]Equal contributors.

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Abstract: Previous studies have explored the association between MTHFR A1298C polymorphism and digestive system cancers susceptibility but result still remains controversial. A meta-analysis was performed to clarify the effect of MTHFR A1298C polymorphism on the risk of digestive system cancers. PubMed, EMBASE, Cochrane library, Web of science and China Knowledge Resource Integrated Databases (until December 1, 2015) were searched. The overall odds ratio (OR) with the corresponding 95% confidence interval (95% CI) was used to assess the strength of the association between the MTHFR A1298C polymorphism and digestive system cancers susceptibility. Statistical heterogeneity, tests of publication bias and sensitivity analysis was performed. The software STATA (Version 13.0) was used for statistical analysis. Finally, sixty-five studies from sixty-one papers included a total of 18, 259 cases and 31, 161 controls were selected in this meta-analysis. The ORs for the homozygote comparison was 0.946, 95% CI [0.837, 1.069], for heterozygote comparison was 1.039, 95% CI [0.998, 1.082], for dominant model was 1.029, 95% CI [0.990, 1.069], for recessive model was 0.960, 95% CI [0.896, 1.029]. In conclusion, the overall results of this meta-analysis don't support a significant association of the MTHFR A1298C polymorphism with the risk of digestive system cancers. However, when a subgroup analysis stratified by subtypes of digestive system cancers was performed, a significant correlation between MTHFR A1298C polymorphism and esophagus cancer risk was observed.

Keywords: MTHFR, A1298C, polymorphism, digestive system cancer, meta-analysis

Introduction

Digestive system cancers, mainly including esophagus cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer, et al., are the most common malignant tumors worldwide, with three million new cases each year (nearly 30% of all cancers) [1]. It was reported that there were about 0.91 million new cases of digestive system cancers and 0.59 million deaths from these health care problems in 2008 in European countries [2]. Even the prevalence of digestive system cancers in developed countries was shown to be higher compared to that in developing countries, the upward trends have been observed in the majority of developing countries [3].

Although the exact mechanism of carcinogenesis remains to be fully understood, evidence from previous studies has indicated that certain risk factors (such as dietary, ethnic and socioeconomic factors) and interactions between genetic and environmental factors may play important roles in the pathogenesis of digestive system cancers [4]. 5, 10-methylenetetrahydrofolate reductase (MTHFR), a critical role in the folate metabolism pathway, irreversibly catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant.

circulatory form of folate and primary methyl donor for the remethylation of homocysteine to methionine [5]. Methionine, a substrate for s-adenosylmethionine (SAM), is the principal biological methyl group donor for the DNA methylation process implicated in many types of cancer. The MTHFR gene is mapped on chromosome 1 at the end of the short arm (1p36.6)

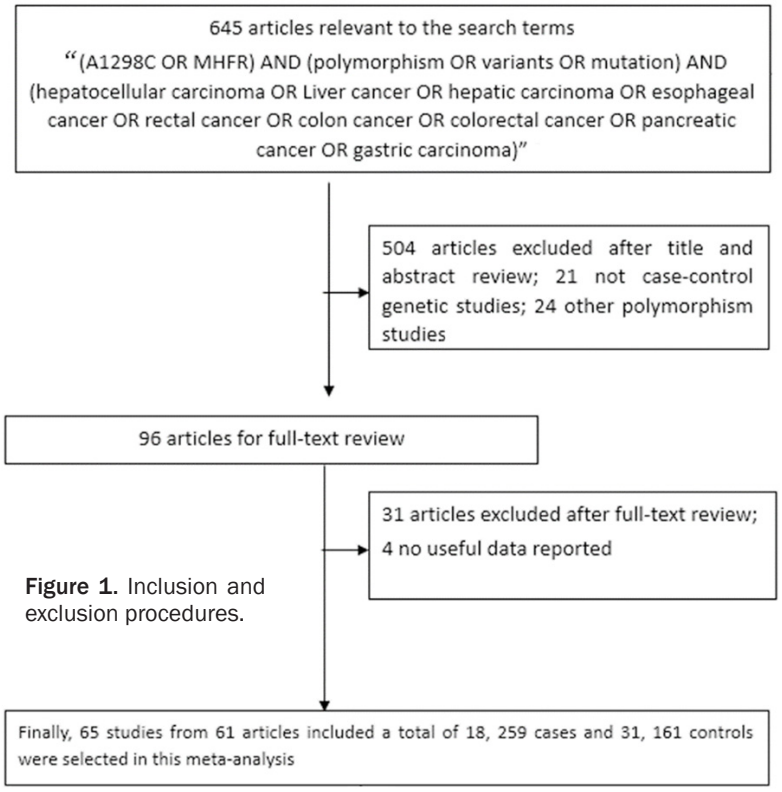

Figure 1. Inclusion and exclusion procedures.

and is 2.2 kb in length with a total of 11 exons. MTHFR gene A1298C (rs1801131) in exon 7, a glutamate to alanine substitution at codon 429 (E429A), could increase the serum folate levels, possibly influencing cancer risk.

The MTHFR A1298C polymorphism has been reported to be associated with several types of digestive system cancers, including esophagus cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer. However, the result remains controversial and the previous studies have generally been small-sized. Meta-analysis, a good statistical method to combine the results from multiple studies, is often used in recent years to increase statistical power, improve estimates of the magnitude of an effect and to resolve uncertainty across conflicting reports.

Based on the most up-to-date information and the current available evidences, a meta-analysis with subgroup analysis from all eligible case-control studies was performed in this study to clarify the effect of MTHFR A1298C polymorphism on the risk of digestive system cancers. To the best of our knowledge, this is the first meta-analysis concerning MTHFR A1298C polymorphism and digestive system cancers susceptibility.

Materials and methods

Search strategy

We attempted to include all the case-control studies published to date on the association between MTHFR A1298C polymorphism and digestive system cancers susceptibility. PubMed, EMBASE, Cochrane library, Web of science and China Knowledge Resource Integrated Databases (until December 1, 2015) were searched using search terms as "(A1298C OR MHFR) AND (polymorphism OR variants OR mutation) AND (hepatocellular carcinoma OR Liver cancer OR hepatic carcinoma OR esophageal cancer OR rectal cancer OR colon cancer OR colorectal cancer OR pancreatic cancer OR gastric carcinoma)". Case-control studies containing available genotype frequencies of A1298C were chosen. The reference lists of reviews andrelated reference articles were also searched to identify other relevant publications. Studies published in English or in Chinese language were selected. Unpublished data were not included.

Inclusion and exclusion criteria

Included studies had to satisfy the following criteria: 1) human case-control design; 2) MTHFR A1298C polymorphism and digestive system cancers susceptibility; 3) studies that reported the frequency of the MTHFR A1298C polymorphism as number of digestive system cancers and controls according to the three variant genotypes of either polymorphisms; 4) studies published in English or in Chinese; 5) studies contained at least one of the five main subtypes of digestive system cancers: esophagus cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer.

The major exclusion criterion are as follows: 1) not a primary case-control study; 2) using the MTHFR A1298C polymorphism to predict survival in cancers or considering it an indicator for the response to therapy; 3) not related to the

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

Author	Year	Region	Ethnicity	Types of cancer	Case group				Control group				H-W (P)#
					Total	AA	AC	CC	Total	AA	AC	CC	
Mu et al.	2007	China	Asians	Hepatocellular carcinoma	194	135	55	4	394	275	112	7	0.249
Yuan et al.	2007	USA	Caucasians	Hepatocellular carcinoma	118	65	44	9	209	104	85	20	0.666
Yuan et al.	2007	China	Asians	Hepatocellular carcinoma	247	136	101	10	248	136	91	21	0.305
Kwak et al.	2008	Korea	Asians	Hepatocellular carcinoma	96	67	28	1	201	155	41	5	0.261
Cui et al.	2012	China	Asians	Hepatocellular carcinoma	356	258	94	4	641	461	153	27	0.003
De Re et al.	2010	Italy	Caucasians	Gastric cancer	48	24	19	5	96	33	54	9	0.050
Vollset et al.	2007	Europea	Caucasians	Gastric cancer	244	103	116	25	614	315	246	53	0.615
Mu et al.	2007	China	Asians	Gastric cancer	196	147	49	0	394	275	112	7	0.249
Zhang et al.	2007	Poland	Caucasians	Gastric cancer	291	135	125	31	400	180	179	41	0.720
Boccia et al.	2007	Italy	Caucasians	Gastric cancer	102	50	43	9	254	125	107	22	0.894
Fu et al.	2007	China	Asians	Gastric cancer	169	96	73	0	169	125	44	0	0.052
Li et al.	2006	China	Asians	Gastric cancer	170	126	42	2	140	97	41	2	0.311
Weng et al.	2006	China	Asians	Gastric cancer	38	26	12	0	34	22	11	1	0.788
Kim et al.	2005	South Korea	Asians	Gastric cancer	133	98	34	1	445	308	129	8	0.185
Si et al.	2005	China	Asians	Gastric cancer	122	73	44	5	101	58	38	5	0.699
Stolzenberg-Solomon et al.	2003	China	Asians	Gastric cancer	90	69	21	0	398	294	104	0	0.003
Miao et al.	2002	China	Asians	Gastric cancer	217	150	64	3	468	324	139	5	0.018
Shen et al.	2001	China	Asians	Gastric cancer	187	130	55	2	166	111	50	5	0.825
Li et al.	2005	USA	Caucasians	Pancreatic cancer	303	129	145	29	310	133	137	40	0.613
Wang et al.	2005	China	Asians	Pancreatic cancer	163	124	37	2	337	243	86	8	0.904
Matsubayashi et al.	2005	USA	Caucasians	Pancreatic cancer	303	133	134	36	305	144	140	21	0.092
Ekiz et al.	2012	Turkey	Caucasians	Esophageal cancer	26	10	13	3	30	11	17	2	0.179
Ibiebele et al.	2011	Australia	Caucasians	Esophageal cancer	678	280	298	100	1303	610	572	121	0.429
zhang et al.	2008	China	Asians	Esophageal cancer	88	56	30	2	72	52	20	0	0.171
Gao et al.	2004	China	Asians	Esophageal cancer	141	90	48	3	224	164	60	0	0.021
Stolzenberg et al.	2003	China	Asians	Esophageal cancer	129	94	32	3	398	294	104	0	0.003
Song et al.	2001	China	Asians	Esophageal cancer	240	179	54	7	360	242	113	5	0.040
Keku et al.	2002	USA	Caucasians	Colorectal cancer	309	156	132	21	541	237	236	68	0.440
Pufulete et al.	2003	UK	Caucasians	Colorectal cancer	63	34	22	7	76	47	26	3	0.799
Plaschke et al.	2003	Germany	Caucasians	Colorectal cancer	287	134	124	29	346	154	151	41	0.669
Toffoli et al.	2003	Italy	Caucasians	Colorectal cancer	276	122	129	25	279	133	121	25	0.735
Landi et al.	2005	Spain	Caucasians	Colorectal cancer	360	189	146	25	319	170	127	22	0.794
Koushik et al.	2006	USA	Caucasians	Colorectal cancer	353	154	166	33	806	389	332	85	0.262

Van Guelpen et al.	2006	Sweden	Caucasians	Colorectal cancer	220	85	103	32	412	189	173	50	0.288
Osian et al.	2007	Romania	Caucasians	Colorectal cancer	69	33	32	4	67	41	25	1	0.192
Lima et al.	2007	Brazil	Caucasians	Colorectal cancer	102	68	28	6	300	191	93	16	0.297
Theodoratou et al.	2008	Scotland	Caucasians	Colorectal cancer	996	465	425	106	1009	462	445	102	0.733
Sharp et al.	2008	Scotland	Caucasians	Colorectal cancer	245	105	111	29	394	177	157	60	0.012
Küry et al.	2008	France	Caucasians	Colorectal cancer	1023	484	432	107	1121	577	443	101	0.231
De Vogel et al.	2009	Netherlands	Caucasians	Colorectal cancer	684	299	275	110	1767	735	774	258	0.021
Fernández-Peralta et al.	2010	Spain	Caucasians	Colorectal cancer	143	84	53	6	103	57	44	2	0.048
Eussen et al.	2010	Europe	Caucasians	Colorectal cancer	1330	605	574	151	2365	1099	1007	259	0.215
Pardini et al.	2011	Czech	Caucasians	Colorectal cancer	666	281	309	76	1377	583	638	156	0.349
Lee et al.	2012	USA	Caucasians	Colorectal cancer	175	72	82	21	355	181	136	38	0.108
Lee et al.	2012	USA	Caucasians	Colorectal cancer	153	73	73	7	312	147	133	32	0.812
Lee et al.	2012	USA	Caucasians	Colorectal cancer	213	101	100	12	365	167	154	44	0.358
Matsuo et al.	2002	Japan	Asians	Colorectal cancer	141	94	44	3	482	314	150	18	0.987
Yin et al.	2004	Japan	Asians	Colorectal cancer	672	428	218	26	1826	1300	488	38	0.320
Matsuo et al.	2005	Japan	Asians	Colorectal cancer	257	163	85	9	767	479	257	31	0.635
Jiang et al.	2005	China	Asians	Colorectal cancer	124	93	30	1	670	452	206	12	0.035
Otani et al.	2005	Japan	Asians	Colorectal cancer	106	73	32	1	224	156	63	5	0.643
Wang et al.	2006	India	Caucasians	Colorectal cancer	302	141	130	31	582	210	270	102	0.346
Chang et al.	2007	China	Asians	Colorectal cancer	195	120	65	10	195	127	55	13	0.046
Cao et al.	2008	China	Asians	Colorectal cancer	315	204	105	6	742	478	238	26	0.586
Promthet et al.	2010	Thailand	Asians	Colorectal cancer	130	43	84	3	130	54	71	5	0.002
Chandy et al.	2010	India	Caucasians	Colorectal cancer	100	22	70	8	86	22	50	14	0.109
Kim et al.	2011	Korea	Asians	Colorectal cancer	67	44	22	1	53	36	16	1	0.607
Li et al.	2011	China	Asians	Colorectal cancer	137	88	47	2	145	76	60	9	0.529
Keku et al.	2002	USA	Africans	Colorectal cancer	243	157	78	8	329	217	99	13	0.686
Lima et al.	2007	Brazil	Africans	Colorectal cancer	10	5	4	1	300	191	93	16	0.297
El Awady et al.	2009	Egypt	Africans	Colorectal cancer	35	5	21	9	78	26	37	15	0.777
Miranda Guimarães et al.	2011	Brazil	Africans	Colorectal cancer	113	67	38	8	374	252	98	24	0.001
Curtin et al.	2004	USA	Mixed	Colorectal cancer	1608	757	698	153	1972	929	827	216	0.119
Murtaugh et al.	2007	USA	Mixed	Colorectal cancer	742	360	317	65	970	436	424	110	0.653
Reeves et al.	2009	Australia	Mixed	Colorectal cancer	206	92	89	25	211	86	98	27	0.910

Table 2. Results of the overall meta-analysis

Contrast	OR, 95% CI	Heterogeneity	Z and P
CC vs. AA	0.946, [0.837, 1.069]	chi-squared = 116.07 (d.f. = 62) P = 0.000, I-squared = 46.6%	Z = 0.89, P = 0.375
AC vs. AA	1.039, [0.998, 1.082]	chi-squared = 88.19 (d.f. = 64) P = 0.024, I-squared = 27.4%	Z = 1.88, P = 0.060
AC + CC vs. AA	1.029, [0.990, 1.069]	chi-squared = 106.77 (d.f. = 64) P = 0.001, I-squared = 40.1%	Z = 1.45, P = 0.147
CC vs. AC + AA	0.960, [0.896, 1.029]	chi-squared = 105.59 (d.f. = 62) P = 0.000, I-squared = 41.3%	Z = 1.16, P = 0.247
C vs. A	1.010, [0.980, 1.040]	chi-squared = 124.99 (d.f. = 64) P = 0.000, I-squared = 48.8%	Z = 0.62, P = 0.534

MTHFR A1298C polymorphism and digestive system cancers susceptibility; 4) no usable or sufficient genotype data reported; 5) case reports, letter to Editor, book chapters or reviews; 6) duplicate of previous publication. The study inclusion and exclusion procedures are summarized in **Figure 1**.

Data extraction

Two investigators independently extracted the data from all qualified studies according to the inclusion and exclusion criteria listed above. Discrepancies were solved through discussion with another investigator until agreement was reached.

The following data was extracted: the first author's name, year of publication, the region in which the study was conducted, the source of control group evidence of Hardy-Weinberg equilibrium (HWE) in controls, the sample size, number of cases and controls with the AA/AC/CC genotypes. Different ethnic descentswere categorized as Caucasians, Africans, Asians and Mixed, which included more than one ethnic descent.

Statistical analysis

The overall odds ratio (OR) with thecorresponding 95% confidence interval (95% CI) was used to assess the strength of the association between the MTHFR A1298C polymorphism and digestive system cancers susceptibility [6]. For the control groups for each study, the observed genotype frequencies of the MTHFR A1298C polymorphism were evaluated for Hardy-Weinberg equilibrium using the χ^2 test (significant at the 0.05 level). The pooled ORs were calculated for the homozygous model (CC vs. AA), heterozygous model (AC vs. AA), dominant model (AC + CC vs. AA), recessive model (CC vs. AC + AA) and an additive model (C vs. A) [7, 8]. Heterogeneity assumption was checked by a chi square-based Q-test, $P < 0.10$ and $I^2 > 50\%$ were considered to indicate the existence of significant heterogeneity [9]. A *P* value of < 0.05 for the Q-test indicated a lack of heterogeneity among studies, so that the pooled OR estimate of each study was calculated by the fixed-effects model (the Mantel-Haenszel method). If the heterogeneity test result returned $P > 0.05$, the pooled ORs were using the random-effects model(the DerSimonian and Laird method) [9, 10]. Sensitivity analyses were also performed after sequential removal of each study [11]. Lastly, Begg's funnel plot and Egger's test were used to examine statistically any publication bias [12, 13]. All statistical analyses were performed using the STATA software 13.0 (StataCrop, College Station, TX). Two-sided *P* values less than 0.05 were considered statistically significant.

Result

Characteristics of the included studies

Finally, sixty-five studies from sixty-one papers included a total of 18, 259 cases and 31, 161 controls were selected in this meta-analysis [14-74]. Some articles may include two or three studies at the same time. Of these, all studies were case-control studies, including 6 esophagus cancer studies, 38 colorectal cancer studies, 13 gastric cancer studies, 5 hepatocellular carcinoma studies and 3 pancreatic cancer studies. Among these studies, 30 studies were conducted in Caucasian populations, 4 studies were conducted in Africans, 3 studies were conducted in Mixed populations and 28 involved Asian populations. The characteristics of all included studies were summarized in **Table 1**.

Results of the overall meta-analysis

The main results on the association between the MTHFR A1298C polymorphism and digestive system cancers risk were listed in **Table 2**.

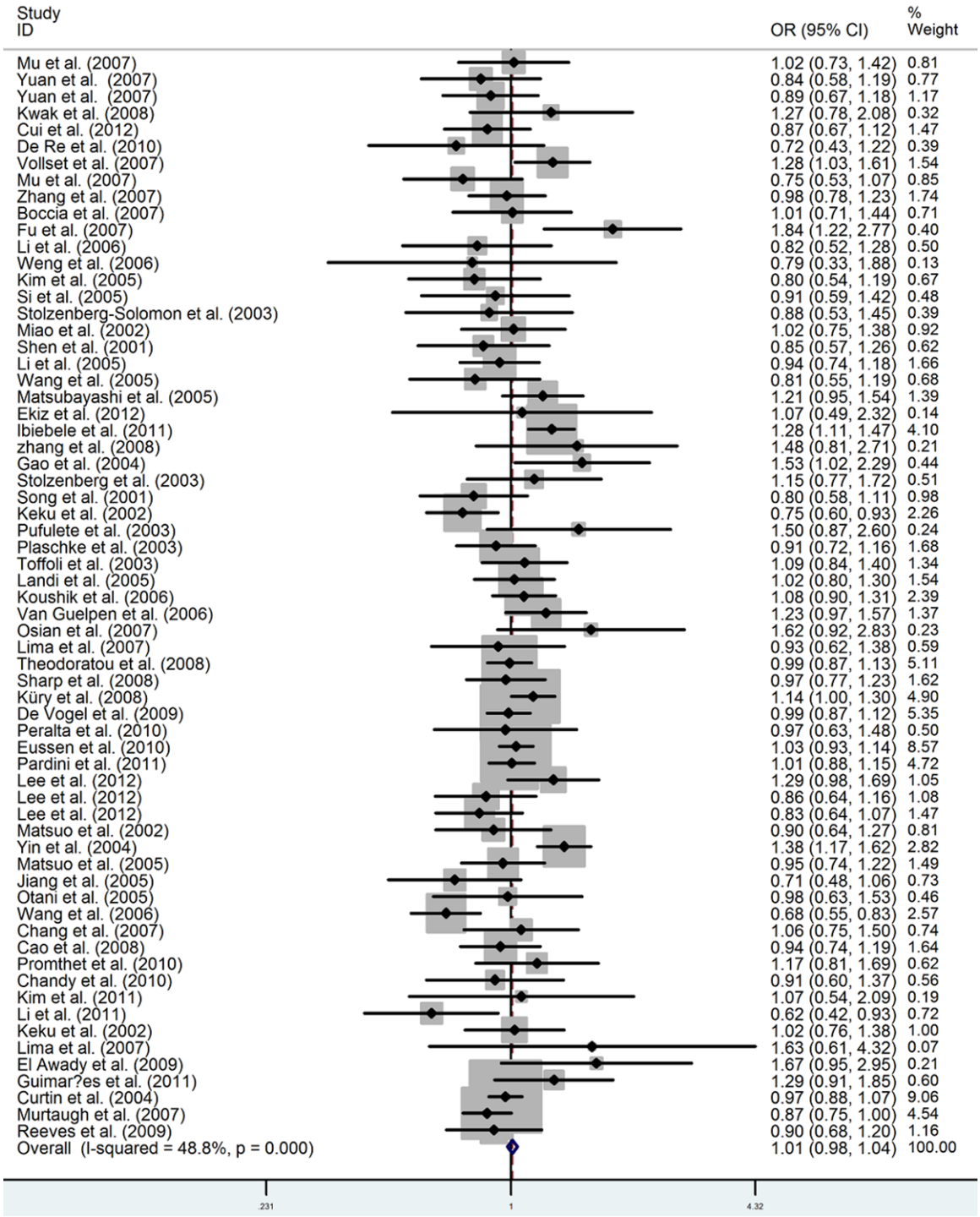

Figure 2. Fixed effectforest plot of additive model (C versus A) of MTHFR A1298C Polymorphism and digestive system cancers.

The MTHFR A1298C polymorphism showed pooled odds ratios for the homozygote comparison (CC versus AA: OR = 0.946, 95% CI [0.837, 1.069], chi-squared = 116.07, I-squared = 46.6%), heterozygote comparison (AC versus AA: OR = 1.039, 95% CI [0.998, 1.082], chi-squared = 88.19, I-squared = 27.4%), dominant model (AC + CC versus AA: OR = 1.029, 95% CI [0.990, 1.069] chi-squared = 106.77, I-squared = 40.1%), recessive model (CC versus AC + AA:

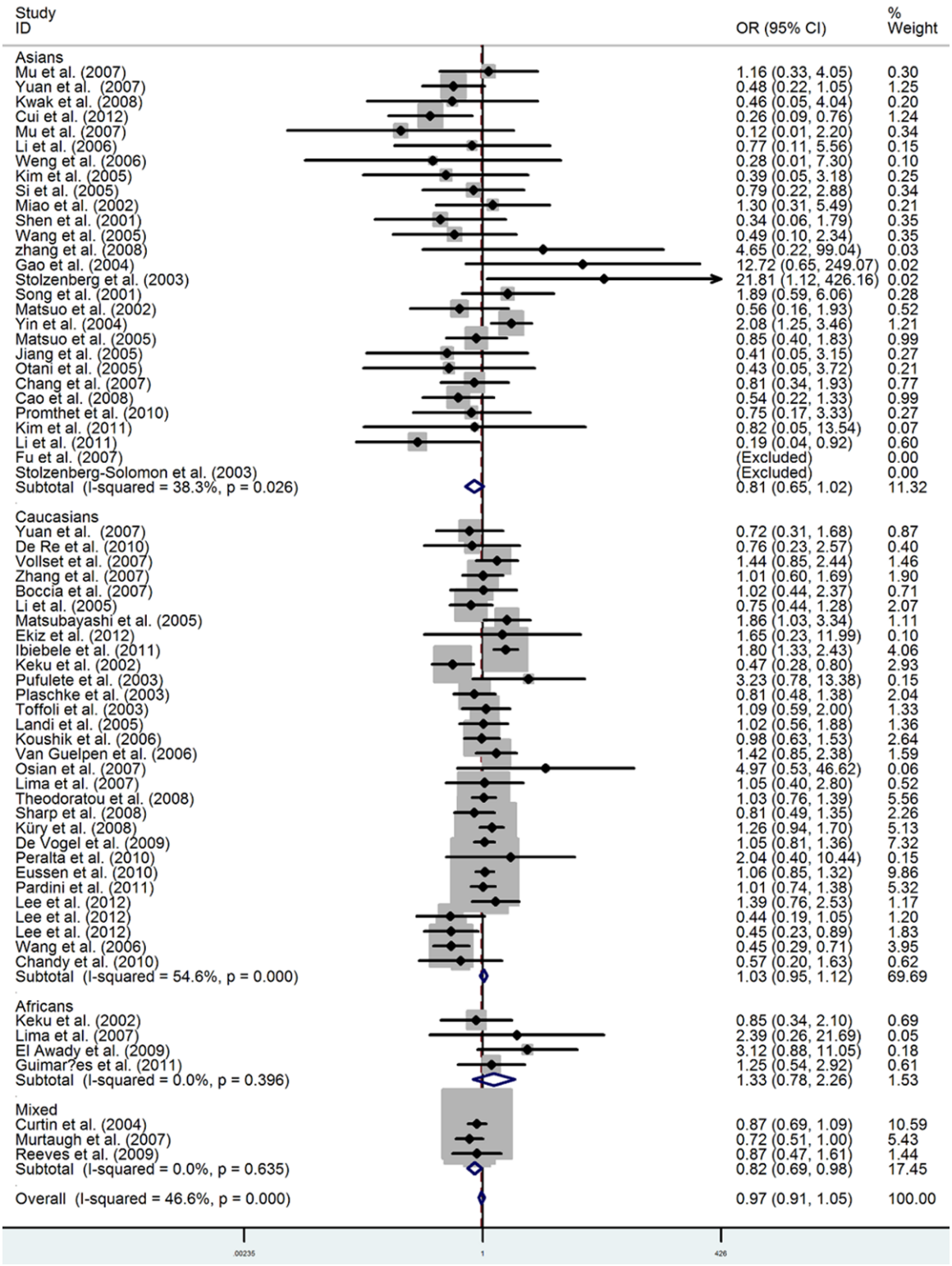

Figure 3. Fixed effect forest plot of homozygote comparison (CC versus AA) of MTHFR A1298C Polymorphism and digestive system cancers stratified by ethnicity.

OR = 0.960, 95% CI [0.896, 1.029], chi-squared = 105.59, I-squared = 41.3%), and an additive model (C versus A: OR = 1.010, 95% CI [0.980, 1.040], chi-squared = 124.99, I-squared =

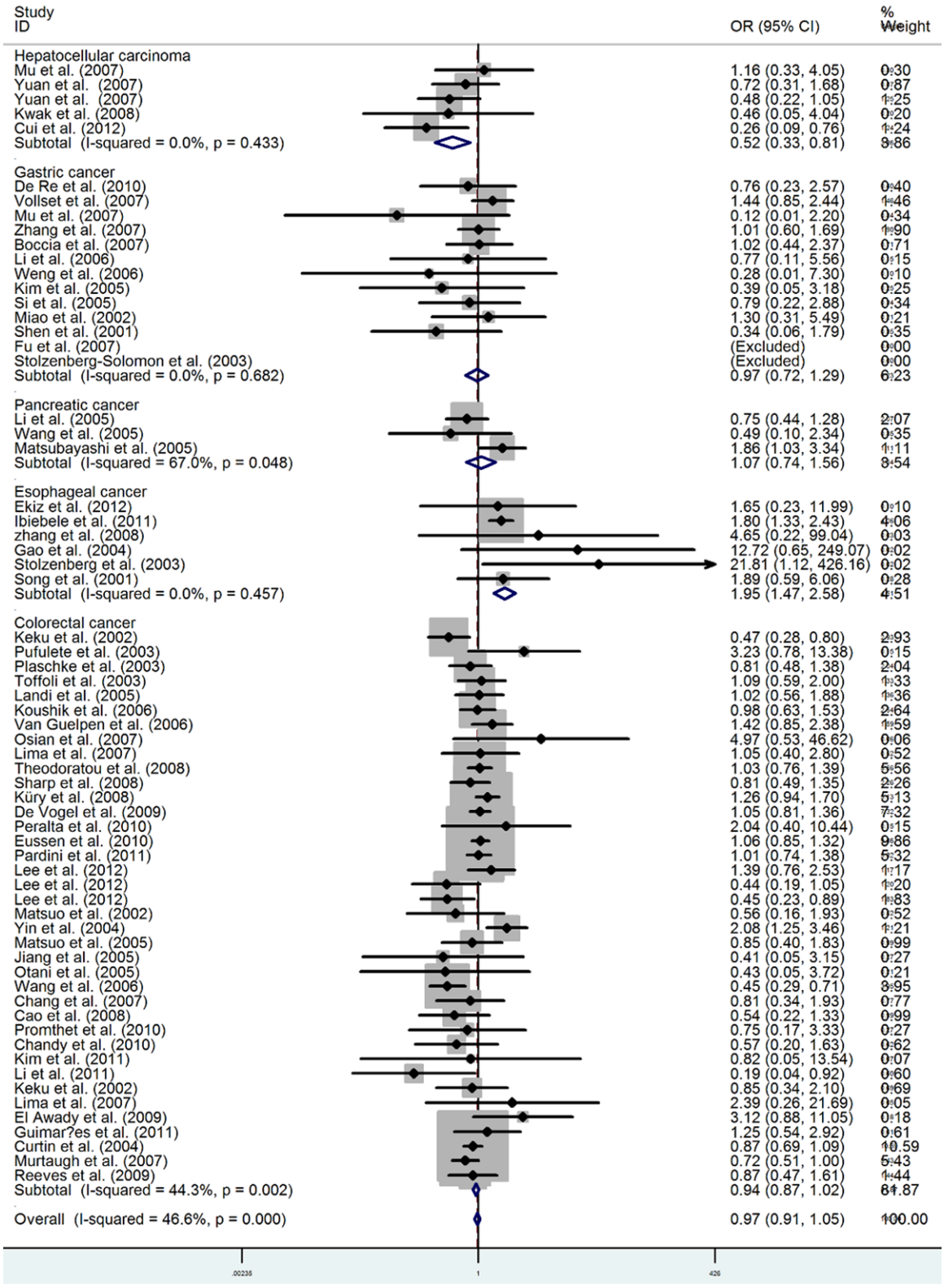

Figure 4. Fixed effect forest plot of homozygote comparison (CC versus AA) of MTHFR A1298C Polymorphism and digestive system cancers stratified by types of cancers.

48.8%). We found no association between MTHFR A1298C polymorphism anddigestive system cancers risk in the overall analysis (**Figure 2**).

Table 3. Sub-group analysis stratified by ethnicity and types of digestive system cancers

Ethnicity	Comparisons	CC vs. AA (OR, 95% CI)	AC vs. AA (OR, 95% CI)	AC + CC vs. AA (OR, 95% CI)	CC vs. AC + AA (OR, 95% CI)	C vs. A (OR, 95% CI)
Asians	28	0.753, [0.532, 1.066]	1.050, [0.973, 1.132]	1.030, [0.957, 1.109]	0.794, [0.633, 0.995]	1.010, [0.980, 1.040]
Caucasians	30	0.997, [0.862, 1.152]	1.039, [0.985, 1.096]	1.039, [0.988, 1.092]	1.013, [0.934, 1.098]	1.025, [0.987, 1.064]
Africans	4	1.339, [0.782, 2.293]	1.307, [1.000, 1.708]	1.287, [0.997, 1.662]	1.116, [0.678, 1.836]	1.205, [0.980, 1.481]
Mixed	3	0.822, [0.686, 0.984]	0.981, [0.878, 1.095]	0.948, [0.854, 1.052]	0.830, [0.699, 0.987]	0.932, [0.861, 1.009]
Overall	65	0.946, [0.837, 1.069]	1.039, [0.998, 1.082]	1.029, [0.990, 1.069]	0.960, [0.896, 1.029]	1.010, [0.980, 1.040]
Types of cancer	Comparisons	CC vs. AA (OR, 95% CI)	AC vs. AA (OR, 95% CI)	AC + CC vs. AA (OR, 95% CI)	CC vs. AC + AA (OR, 95% CI)	C vs. A (OR, 95% CI)
Hepatocellular carcinoma	5	0.543, [0.343, 0.860]	1.076, [0.904, 1.280]	0.996, [0.842, 1.179]	0.516, [0.331, 0.804]	0.923, [0.799, 1.065]
Gastric cancer	13	1.013, [0.755, 1.359]	1.015, [0.899, 1.146]	1.007, [0.895, 1.133]	0.965, [0.730, 1.276]	1.000, [0.907, 1.103]
Pancreatic cancer	3	1.011, [0.471, 2.171]	1.009, [0.819, 1.243]	1.012, [0.829, 1.236]	1.041, [0.729, 1.487]	1.015, [0.870, 1.184]
Esophageal cancer	6	1.893, [1.425, 2.514]	1.050, [0.905, 1.218]	1.148, [0.996, 1.324]	1.843, [1.414, 2.402]	1.213, [1.085, 1.358]
Colorectal cancer	38	0.924, [0.812, 1.051]	1.041, [0.993, 1.091]	1.024, [0.979, 1.071]	0.926, [0.857, 1.000]	0.998, [0.965, 1.033]
Overall	65	0.946, [0.837, 1.069]	1.039, [0.998, 1.082]	1.029, [0.990, 1.069]	0.960, [0.896, 1.029]	1.010, [0.980, 1.040]

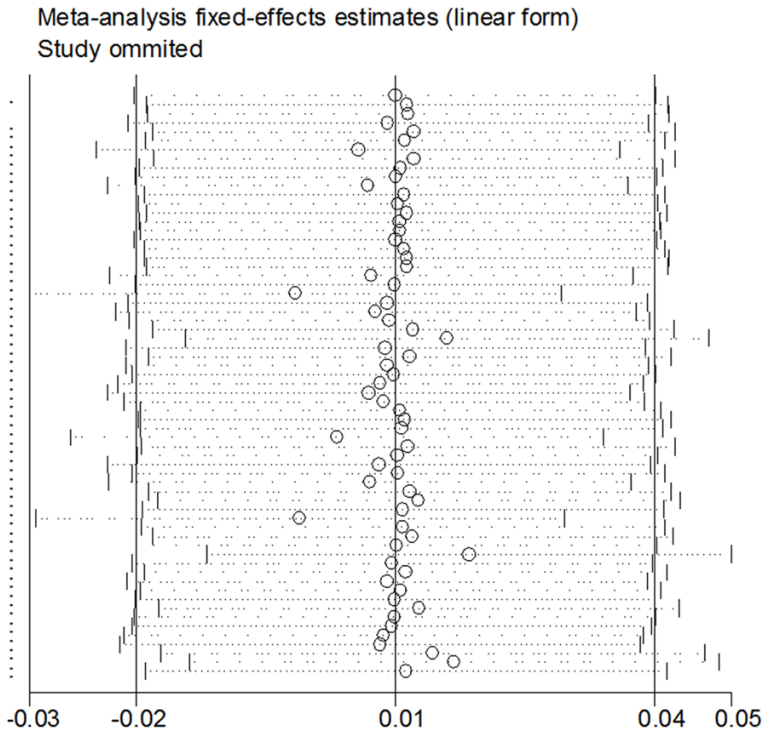

Figure 5. Sensitivity analysis forMTHFR A1298C Polymorphism and digestive system cancers (C versus A).

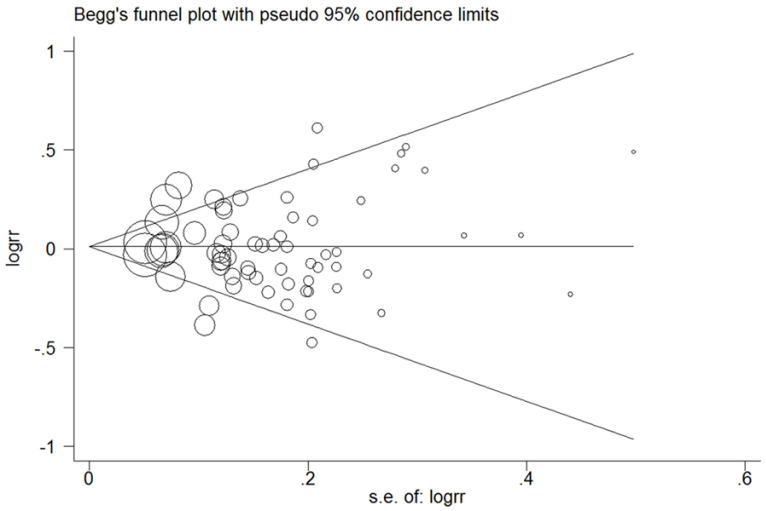

Figure 6. Tests of publication bias for MTHFR A1298C Polymorphism and digestive system cancers (C versus A).

Sub-group analysis

We performed a sub-group analysis stratified by ethnicity. However, we did not find an association between the A1298C polymorphism and digestive system cancers risk in Caucasians, Africans, Asians and Mixed groups in any genetic models (**Figure 3**). A sub-group analysis stratified by subtypes of digestive system cancers was also conducted. No association between MTHFR A1298C polymorphism and digestive system cancers risk was observed in colorectal cancer, gastric cancer, hepatocellular carcinoma and pancreatic cancer, whereas a significant correlation between MTHFR A1298C polymorphism and esophagus cancer risk was found (**Figure 4**). The meta-analysis results for the all genetic models are listed in detail in **Table 3**.

Test for heterogeneity

There was nosignificant heterogeneity: for the homozygote comparison (CC versus AA), chi-squared = 116.07, I-squared = 46.6%; heterozygote comparison (AC versus AA) chi-squared = 88.19, I-squared = 27.4%; dominant model (AC + CC versus AA), chi-squared = 106.77, I-squared = 40.1%; recessive model (CC versus AC + AA), chi-squared = 105.59, I-squared = 41.3% and an additive model (C versus A), chi-squared = 124.99, I-squared = 48.8%.

Sensitivity analysis

We conducted sensitivity analyses to ascertain the primary origin of the heterogeneity. When we omitted every study at each time, the results of reanalyse for A1298C polymorphism was stable. Through sensitivity analysis, this result showed that no individual study had marked effect on the pooled ORs (**Figure 5**).

Publication bias

Begg's funnel plot and the Egger's test were conducted to estimate the publication bias of articles. Both the results of Begg's and Egger's

test did not show any evidence of publication bias: Begg's test: Pr > |z| = 0.647 and Egger's test: P > |t| =0.721 (**Figure 6**).

Discussion

MTHFR, coded by the MTHFR gene, is an important enzyme in folate metabolism [75-78]. Previous studies have explored the association between MTHFR A1298C polymorphism and digestive system cancers susceptibility but result still remains controversial. Considering the limitations of individual studies, a meta-analysis with subgroup analysis based on 65 case-control studies was performed in this study to clarify the effect of MTHFR A1298C polymorphism on the risk of digestive system cancers. To the best of our knowledge, this is the first meta-analysis concerning MTHFR A1298C polymorphism and digestive system cancers susceptibility.

The overall results of this meta-analysis did not support a significant association between MTHFR A1298C polymorphism and digestive system cancers susceptibility in all genetic models. Results from sub-group analysis stratified by ethnicity showed no significant association between the A1298C polymorphism and digestive system cancers risk in Caucasians, Africans, Asians and Mixed groups. However, when a subgroup analysis stratified by subtypes of digestive system cancers was performed, a significant correlation between MTHFR A1298C polymorphism and esophagus cancer risk was observed. Significant association between MTHFR A1298C polymorphism and digestive system cancers risk was notfound in colorectal cancer, gastric cancer, hepatocellular carcinoma and pancreatic cancer when stratified by subtypes of digestive system cancers. By means of meta-analysis, we drew a more reliable conclusion on the influence of MTHFR A1298C polymorphism ondigestive system cancers risk. However, cancer is a "multi-factorial" result, with many factors, genetic and/or environmental. Future research should investigate not only individual genes, but also gene-gene interactions, genetic-nutritional interactions, and other SNPs [79-83].

Although the funnel plot and Begg's test showed no publication bias in this study, selection bias may have occurred since only studies in English or Chinese were included. The second limitation of this study is that we just included five main subtypes of digestive system cancers (esophagus cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma and pancreatic cancer). Failing to include all types of digestive system cancers may potentially have an impact on the overall results of this meta-analysis. The third limitation of this meta-analysis is that colon cancer and rectum cancer were not analyzed separately as most of the original studies included in this meta-analysisregarded colon cancer and rectum cancer as colorectal cancer.

Our meta-analysis also has some clear advantages: 1) this is the first meta-analysis concerning the association between the MTHFR A1298C polymorphism and digestive system cancersrisk and sixty-five studies from sixty-one papers included a total of 18, 259 cases and 31, 161 controls were selected; 2) we performed sub-group analysis stratified by ethnicity and by types of digestive system cancers; 3) the well-designed search and selection method significantly increased the statistical power of this meta-analysis; 4) sensitivity analysis did not show any single study strongly affecting the combined results and no publication bias was detected, indicating that our pooled results are likely to be reliable.

Conclusion

In conclusion, the overall results of this meta-analysis don't support a significant association of the MTHFR A1298C polymorphism with the risk of digestive system cancers. However, when a subgroup analysis stratified by subtypes of digestive system cancers was performed, a significant correlation between MTHFR A1298C polymorphism and esophagus cancer risk was observed.

Disclosure of conflict of interest

None.

Address correspondence to: Lingli Li, West China Hospital, Sichuan University, No. 37, Guoxuexiang, Chengdu 610041, Sichuan Province, China. Tel: +8618980602161; E-mail: lilingli2000@126.com; lilingli20000@qq.com

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