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The association between methionine synthase A2756G polymorphism and hematological cancer

A meta-analysis

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Abstract

Background: Numerous studies have focused on the association of methionine synthase (MS) A2756G polymorphism and acute hematological cancer risk. However, the results remain inconsistent. Therefore, a meta-analysis was performed to derive a more precise estimate of the association between them.

Methods: This meta-analysis involved 25 articles (26 studies) including 8641 hematological cancer patients and 15,498 controls. The pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) of the association between MS A2756G polymorphism and the risk of hematological cancer were calculated.

Results: Overall, no significant increased risks were found between MS A2756G polymorphism and hematological cancer risk under allelic homozygote (GA vs AA: OR = 0.98, 95% CI = 0.89–1.07, $P = .62$), heterozygote (GG vs AA: OR = 0.99, 95% CI = 0.85–1.15, $P = .91$), dominant (AG+GG vs AA: OR = 0.99, 95% CI = 0.90–1.08, $P = .93$), and recessive (GG vs AG+AA: OR = 1.00, 95% CI = 0.86–1.16, $P = .97$) models, respectively. In the stratified analyses by ethnicity and source of controls, there were still no significant associations between them in all genetic models.

Conclusions: Therefore, these findings demonstrate that MS A2756G polymorphism may not be a risk factor for hematological cancer.

Abbreviations: CIs = confidence intervals, HWE = Hardy-Weinberg equilibrium, MS = methionine synthase, MTHFR = methylenetetrahydrofolate reductase, MTRR = methionine synthase reductase, ORs = odds ratios, SNPs = single nucleotide polymorphisms.

Keywords: hematological cancer, meta-analysis, methionine synthase, polymorphism

1. Introduction

Hematological cancer includes leukemia, lymphoma, myeloma, myelodysplastic syndromes, and myeloproliferative diseases, which derive from 2 major blood cell lineages: myeloid and lymphoid cell lines. Among hematological cancer, acute lymphocytic leukemia is the most common pediatric malignancy, and the main cause of death of all cancers among children.[1] Hematological cancer is common, being the fourth most frequently diagnosed cancer in both males and females in the United States. Among newly diagnosed, 171,550 hematological cancer patients and 58,310 deaths were estimated in the United States in 2016.[2] However, exact mechanism involved in the development of hematological cancer remains unclear. It is well accepted that the development of hematological cancer is associated with environmental exposure to some chemicals, family history, dietary factors, immune dysfunction, and viral infection.[3–6] One of the most important dietary factors is folic acid intake. Folate is a key element in one-carbon metabolism. It is a coenzyme in both nucleotide synthesis and the methylation of DNA, histones, and other proteins. And folate metabolism in normal cell is complex and involves several enzymes such as methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MS), and methionine synthase reductase (MTRR), and so on.[7,8] So far, more and more evidence indicates that these folate-dependent polymorphisms are associated with malignant tumors, including the risk of blood cancers.[9,10]

MS, a key gene in the folate metabolism pathway, encodes a vitamin B12-dependent enzyme that catalyzes the methylation of homocysteine and methionine. It locates on chromosome 5p15.3-15.2, and has at least 2028 single nucleotide polymorphisms (SNPs) (http://www.ncbi.nlm.nih.gov/SNP). Among these SNPs, the A2756G is one of the most commonly studied polymorphisms, and the A-to-G transition at position 2756 in the open

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reading frame of the *MS* gene converts an aspartic acid to a glycine residue, so this polymorphism results in decreasing enzyme activity, which is considered as a main cause of elevation of homocysteine and subsequently DNA hypomethylation.[11,12] In addition, previous studies also suggested that the MS 2756G polymorphism may be associated with an increased flux of one-carbon moieties available for DNA synthesis and repair.[13]

Thus, the A2756G polymorphism of MS may be associated with susceptibility to hematological cancer. A large number of epidemiological studies were conducted to investigate the relationship between A2756G polymorphism of MS and blood cancers.[14–38] However, the results remain conflicting. To derive a more precise estimation of the association between them, we performed this meta-analysis with all eligible published studies.

2. Materials and methods

2.1. Publication search

We searched the PubMed, EMBASE, and ISI Web of Science databases for all articles on the association between the MS A2756G polymorphism and hematological cancer risk up to January 10, 2016. The following keywords were used: "methionine synthase", "MS", "5-methyltetrahydrofolate-homocysteine methyltransferase", "MTR" and "polymorphism", "allele", "variant", "mutation", "leukemia", "lymphoma", "myeloma", "hematological tumour", and "hematologic neoplasm". There was no language restriction. The electronic search was supplemented by checking reference lists from the identified articles and reviews for additional original reports.

2.2. Data extraction

Two investigators (BW and KL) searched the literature and extracted data independently.

All selected studies met the following 3 criteria: the diagnosis of hematological cancer was determined histologically or pathologically; a case-control study on the MS A2756G polymorphism and the risk of hematological cancer; and sufficient published data to estimate the odds ratio (OR) with 95% confidence interval (CI). For each of the eligible case-control studies, the following information was collected: first authors, year of publication, country of subjects, ethnicities (Caucasian, Asian and Mixed), source of controls (hospital-based studies: HB, population-based studies: PB, and hospital and population-based studies: PH), genotyping methods, the number of cases and control genotypes, and Hardy-Weinberg equilibrium (HWE). The differences between the 2 investigators are resolved through discussion.

2.3. Statistical analysis

For the control group of each study, the observed genotype frequencies of MS A2756G polymorphism were assessed for HWE. The strength of association between MS A2756G polymorphism and hematologic neoplasm risk was assessed by calculating ORs with the corresponding 95% CIs for homozygote (GA vs AA), heterozygote (GG vs AA), dominant (AG+GG vs AA), and recessive (GG vs AG+AA) models, respectively.[39,40] Heterogeneity was assessed by a chi-square-based Q-statistic test ($P < .10$ was considered significant). Heterogeneity was quantified using the I^2 metric ($I^2 < 25\%$ no heterogeneity; $I^2 = 25–50\%$ moderate heterogeneity; $I^2 > 50\%$ large or extreme heterogeneity).[41,42] When heterogeneity was present, the random effects model (the DerSimonian and Laird method) was used to calculate the pooled ORs, whereas the fixed effects model (the Mantel-Haenszel method) was used. The main source of heterogeneity was determined by Galbraith plot.[41] Subgroup analysis was controlled by cancer type, race, and source of controls. To assess the effect of individual studies on the overall risk of cancers, sensitivity analyses were performed by excluding each study individually and recalculating the ORs and the 95% CIs.

We carried out a cumulative meta-analysis of the effect of the MS A2756G polymorphism on hematologic neoplasm risk based on the date of publication. Analysis of publication bias was shown with the funnel plot and Egger's linear regression asymmetry test; $P < .05$ suggested statistically significant publication bias.[42,43] All statistical analyses were performed using STATA statistical software (version 12.0; STATA Corporation, College Station, TX), and all tests were 2 tailed.

3. Results

3.1. Study characteristics

Following flow diagram (Fig. 1), 169 articles were found. And 47 studies were included in further analysis. Among them, we excluded 21 articles, of which 18 articles did not provide detailed data and 3 articles had overlapped data. Finally, 25 relevant articles (26 studies)[14–38] addressing the relationship between the MS A2756G polymorphism and hematologic neoplasm risk were included. Among the 26 studies, there were 9 studies of leukemia, 14 studies of lymphoma, and 3 studies of myeloma. Additionally, there were 5 studies of Asians, 17 studies of Europeans, and 4 studies of Mixed. And 19 studies were population based (PB), 5 studies were hospital based (HB), and 2 studies were population and hospital based (HB). The distribution of genotypes in all studies was consistent with HWE except for Kim et al's and Martino et al's studies[17–23,27] (Tables 1 and 2).

3.2. Quantitative synthesis

The main results of the current study on the association between the MS A2756G polymorphism and hematological cancer risk are shown in Table 3.

Overall, no significant association between the MS A2756G polymorphism and hematological cancer risk was observed under homozygote (GA vs AA: OR = 0.98, 95% CI = 0.89–1.07, $P = .62$), heterozygote (GG vs AA: OR = 0.99, 95% CI = 0.85–1.15, $P = .91$), dominant (AG+GG vs AA: OR = 0.99, 95% CI = 0.90–1.08, $P = .93$), and recessive (GG vs AG+AA: OR = 1.00, 95% CI = 0.86–1.16, $P = .97$) models, respectively (Fig. 2)

In the subgroup of cancer types, there were no significantly increased risks between the MS A2756G polymorphism and hematological cancer risk in all hematological cancer types (leukemia, lymphoma, and myeloma) in all genetic models. In the stratified analysis by races, no significantly increased risks were found between the MS A2756G polymorphism and hematological cancer risk in all genetic models. In addition, in further stratification analysis by source of controls, no significant effects were observed between the MS A2756G polymorphism and hematological cancer risk in PB, HB, and PB studies.

3.3. Test for heterogeneity

For the MS A2756G polymorphism and hematological cancer risk, significant heterogeneity existed in the dominant ($P_{het} < .01$, $I^2 = 51\%$) genetic models (Table 3). Galbraith plot analyses of all included studies were used to assess the potential sources of heterogeneity, and

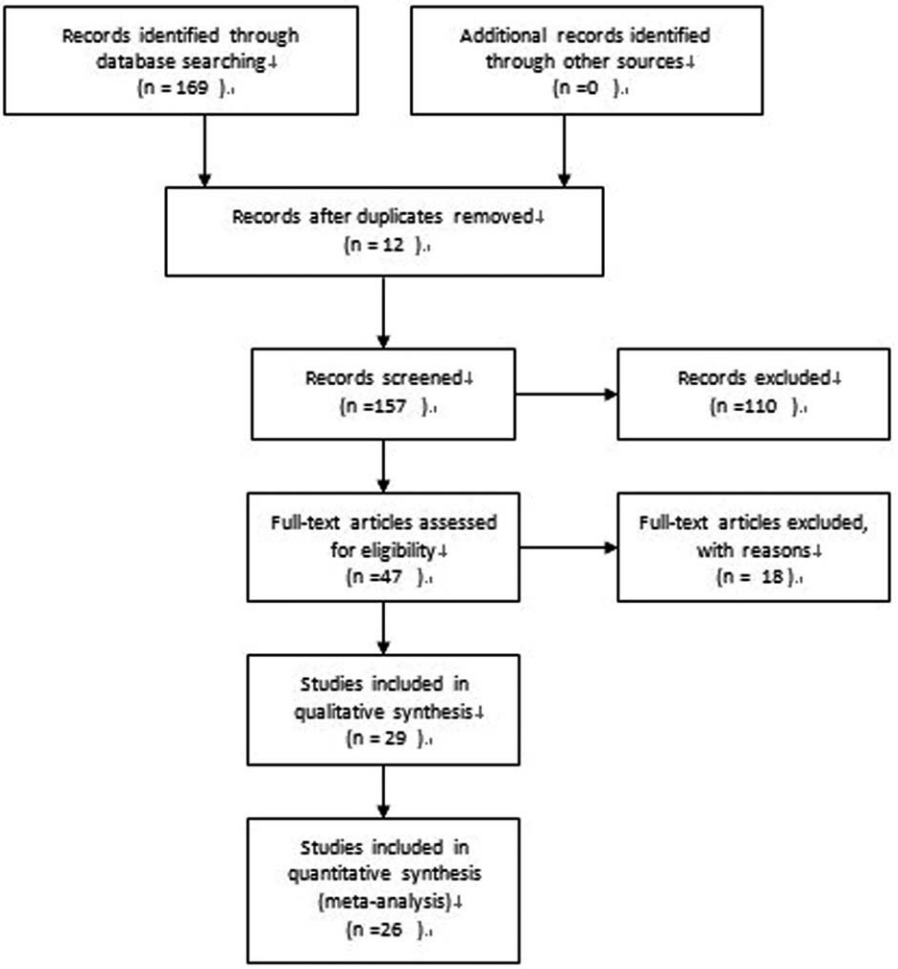

Figure 1. Flow diagram of selection process in the meta-analysis.

Table 1

Characteristics of the studies for the association of the MS A2756G polymorphism and the risk of hematological cancer.

First author	Year	Country	Ethnicity	Cancer types	Source	Genotyping method
Milne	2015	Australia	Mixed	Lymphoma	PB	TaqMan
Martino	2014	Brazil	Caucasian	Myeloma	PB	TaqMan
Li	2013	USA	Mixed	Lymphoma	PB	TaqMan
Ruiz-Cosano	2013	Spain	Caucasian	Lymphoma	PB	TaqMan
Rahimi	2012	Iran	Asian	Leukemia	PB	PCR-RFLP
Nikbakht	2012	India	Asian	Leukemia	PB	PCR-RFLP
Weiner	2011	Russia	Caucasian	Lymphoma	PB	TaqMan
Lightfoot	2010	United Kingdom	Caucasian	Leukemia	PB	TaqMan
Kurzwelly	2010	Germany	Caucasian	Lymphoma	PB	PCR-RFLP
Kim	2009	Korea	Asian	Leukemia	PB	PCR-RFLP
De Jonge	2009	Netherland	Caucasian	Leukemia	PH	PCR-RFLP
Berglund	2009	Sweden	Caucasian	Lymphoma	PB	Sequencing
Kim	2008	Korea	Asian	Lymphoma	PB	PCR-RFLP
Gast	2007	Sweden	Caucasian	Leukemia	HB	Sequencing
Bohanec	2007	Slovenia	Caucasian	Leukemia	PH	PCR-RFLP
Lee	2007	Australia	Caucasian	Lymphoma	PB	TaqMan
Lim	2007	USA	Mixed	Lymphoma	PB	TaqMan
Kim	2007	Korea	Asian	Myeloma	PB	PCR-RFLP
Lima	2007	Brazil	Mixed	Myeloma	HB	TaqMan
Niclot	2006	France	Caucasian	Lymphoma	PB	PCR-RFLP
Lightfoot	2005	United Kingdom	Caucasian	Lymphoma	PB	TaqMan
Gemmati	2004	Italy	Caucasian	Leukemia	HB	PCR-RFLP
Gemmati	2004	Italy	Caucasian	Lymphoma	PB	PCR-RFLP
Skibola	2004	USA	Caucasian	Lymphoma	PB	TaqMan
Lincz	2003	Australia	Caucasian	Lymphoma	HB	PCR-RFLP
Skibola	2002	United Kingdom	Caucasian	Leukemia	HB	PCR-RFLP

HB = hospital-based studies, HWE = Hardy-Weinberg equilibrium, Mixed = Caucasian, Asian, and blank, PB = population-based studies, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, PH = hospital and population-based studies.

Table 2

Distribution of the MS A2756G polymorphism among hematological cancer included in the meta-analysis.

First author	Year	Cancer types	Sample size		Cases			Controls			*P* for HWE
			Cases	Controls	AA	GA	GG	AA	GA	GG	
Rahimi	2012	Leukemia	73	128	42	26	5	75	47	6	.32
Nikbakht	2012	Leukemia	125	100	74	44	7	58	35	7	.45
Lightfoot	2010	Leukemia	870	759	531	288	51	510	223	26	.98
Kim	2009	Leukemia	108	1700	77	28	3	1282	392	26	.30
De Jonge	2009	Leukemia	245	489	162	74	9	340	137	12	.69
Gast	2007	Leukemia	446	547	280	153	13	375	151	21	.59
Bohanec	2007	Leukemia	68	258	51	16	1	161	82	15	.47
Gemmati	2004	Leukemia	118	257	88	29	1	158	89	10	.79
Skibola	2002	Leukemia	70	114	50	19	1	75	39	0	.82
Lincz	2003	Lymphoma	149	298	110	34	5	187	99	12	.52
Gemmati	2004	Lymphoma	200	257	129	65	6	158	89	10	.68
Skibola	2004	Lymphoma	330	731	201	129*	489	242*	0.32		
Lightfoot	2005	Lymphoma	589	755	382	190	17	507	222	26	.52
Niclot	2006	Lymphoma	171	206	144	24	3	149	51	6	.24
Lee	2007	Lymphoma	559	505	364	173	22	304	180	21	.30
Lim	2007	Lymphoma	739	628	481	239	19	422	172	34	.38
Kim	2008	Lymphoma	584	1700	442	133	9	1282	392	26	.00
Berglund	2009	Lymphoma	260	437	170	79	11	302	126	9	.13
Kurzwelly	2010	Lymphoma	185	212	131	46	8	131	72	9	.23
Weiner	2011	Lymphoma	141	456	96	40	5	297	139	20	.52
Li	2013	Lymphoma	456	532	291	150	15	363	153	16	.78
Ruiz-Cosano	2013	Lymphoma	192	214	135	48	9	151	55	8	.56
Milne	2015	Lymphoma	391	514	251	130	10	337	158	19	.56
Kim	2007	Myeloma	174	1700	91	69	14	857	718	125	NA
Lima	2007	Myeloma	123	188	32	63	28	53	102	33	.81
Martino	2014	Myeloma	1275	1813	858	372	45	1201	549	63	.03

HWE = Hardy-Weinberg equilibrium.
* GA+GG.

it was found Lightfoot et al's,[16] Lincz et al's,[38] Niclot et al's,[35] and Gemmati et al's[19] studies were the main contributors of heterogeneity under the dominant model (Fig. 3). After removing these studies, heterogeneity decreased in the dominant genetic model (P_{het} = .20, I^2 = 20%), and main results were not changed.

3.4. Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset to the pooled ORs. For the MS A2756G polymorphism susceptible to hematological cancer, the corresponding pooled ORs were not materially altered in the dominant models (Fig. 4), indicating that our results were statistically robust. In addition, Figure S1, http://links.lww.com/MD/B814 showed the results of the cumulative meta-analysis. Although subsequent studies have increased the precision of the point estimate, no substantive change has occurred in the direction or magnitude of the effect of the MS A2756G polymorphism on risk of hematologic neoplasm in all genetic models.

Table 3

Summary of the ORs and 95% CIs between the association of the MS A2756G polymorphism and hematological cancer risk in the meta-analysis.

Subgroup	N	Number of patients		GA versus AA (homozygote)						GG versus AA (heterozygote)						AG+GG versus AA (dominant)						GG versus AG+AA (recessive)					
		Cases	Controls	OR	(95% CI)		P_{value}	P_{het}	I^2 (%)	OR	(95% CI)		P_{value}	P_{het}	I^2 (%)	OR	(95% CI)		P_{value}	P_{het}	I^2 (%)	OR	(95% CI)		P_{value}	P_{het}	I^2 (%)
Total	26	8641	15498	0.98	0.89	1.07	.62	.01	46	0.99	0.85	1.15	.91	.25	15	0.99	0.90	1.08	.93	.00	51	1.00	0.86	1.16	.97	.30	11
Cancer types																											
Leukemia	9	2123	4352	1.03	0.85	1.24	.80	.06	47	1.22	0.90	1.64	.20	.13	36	1.01	0.82	1.24	.79	.01	58	1.18	0.87	1.59	.28	.18	30
Lymphoma	14	4946	7445	0.95	0.83	1.08		.01	55	0.85	0.68	1.06	.14	.60	0	0.96	0.85	1.09	.67	.01	54	0.85	0.68	1.06	.15	.57	0
Myeloma	3	1572	3701	0.95	0.82	1.09	.42	.93	0	1.08	0.81	1.45	.60	.69	0	0.96	0.96	0.84	1.09	.82	0	1.12	0.85	1.48	.44	.68	0
Ethnicity																											
Asian	5	1064	5328	0.99	0.84	1.16	.88	.92	0	1.09	0.74	1.61	.67	.83	0	1.00	0.86	1.16	.99	.88	0	1.11	0.76	1.62	.60	.85	0
Caucasian	17	5868	8308	0.91	0.79	1.04	.37	.00	61	1.03	0.85	1.25	.74	.24	19	0.96	0.89	1.04	.82	.00	65	1.04	0.86	1.26	.67	.40	5
Mixed	4	1709	1862	1.17	0.99	1.36	.05	.89	0	0.86	0.52	1.42	.54	.09	55	1.12	0.98	1.29	.11	.91	0	0.83	0.49	1.42	.23	.05	63
Design of study																											
PB	19	7422	13347	1.01	0.92	1.10	.68	.07	35	1.01	0.85	1.19	.93	.28	15	1.03	0.96	1.10	.40	.03	41	1.00	0.85	1.18	.96	.32	11
PH	2	313	747	0.89	0.49	1.59		.09	65	0.72	0.11	4.92	.85	.07	71	0.98	0.73	1.30	.86	.03	78	0.77	0.14	4.37	.89	.09	64
HB	5	906	1404	0.83	0.56	1.24	.55	.00	74	0.92	0.61	1.39	.70	.27	23	0.93	0.78	1.12	.45	.00	74	0.97	0.66	1.43	.88	.27	23

CI = confidence interval, HB = hospital-based studies, Mixed = Caucasian, Asian, and blank, N = number of study, OR = odds ratio, PB = population-based studies, PH = hospital and population-based studies, P_{het} = probability of heterogeneity; fixed-effects model was used when $P_{het} \geq .1$, otherwise, random model was used.

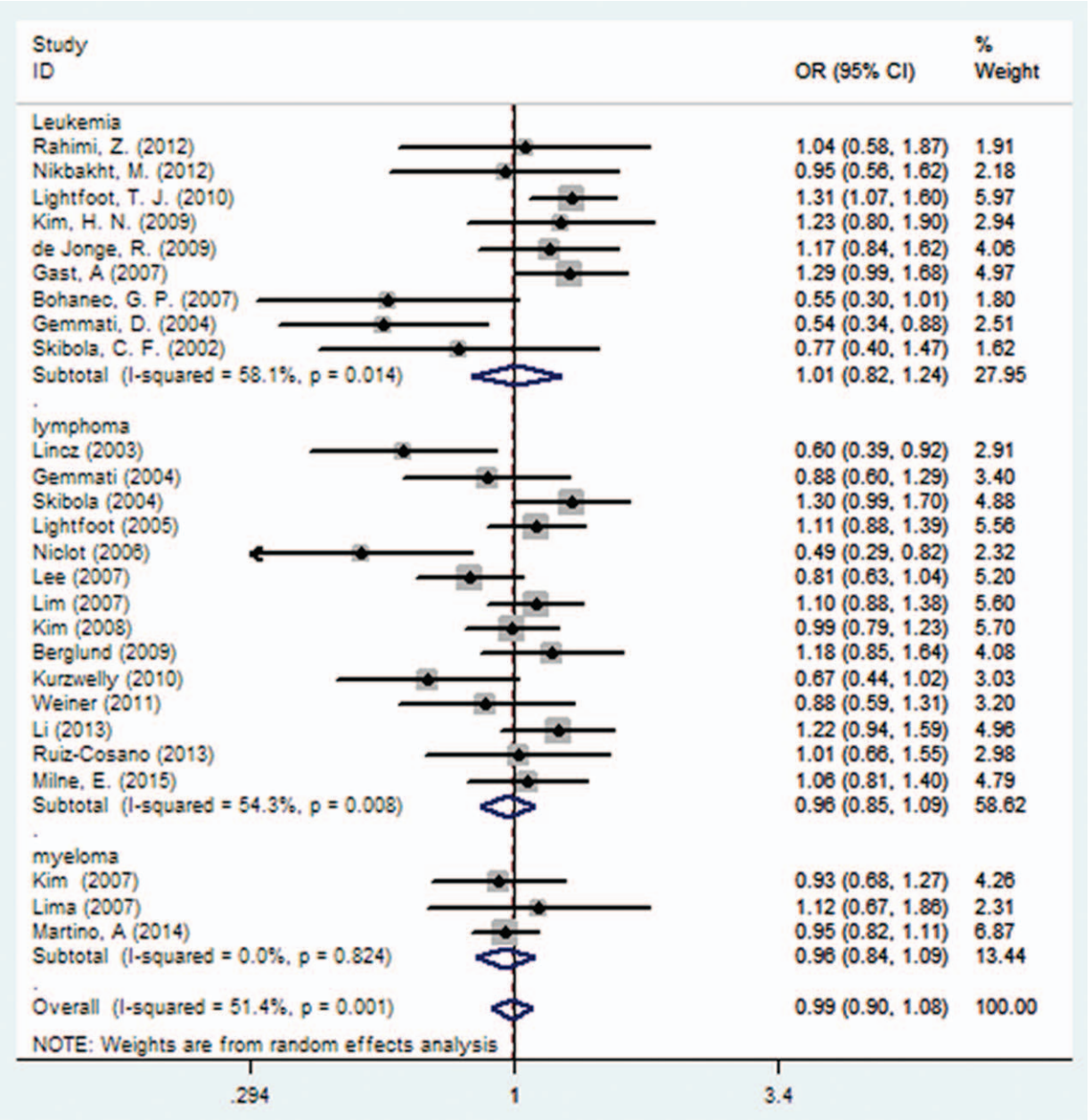

Figure 2. Forest plot of hematological cancer associated with the MS A2756G polymorphism under the dominant genetic models.

3.5. Publication bias

Begg's funnel plot and Egger's test were constructed to assess the publication bias of the literature. We found no publication bias in the dominant model ($P_{\text{Egger's test}} = .58$) (Fig. 5).

4. Discussion

Dietary factors may modulate the risk of hematological cancer.[9,44] The folate metabolic pathway is critical for the synthesis, repair, and methylation of DNA. It is suspected to be in the susceptibility of cancer, including cancers of the blood system.[9] The MS in folate metabolic pathway is considered as a critical factor for DNA integrity and DNA hypomethylation. A common polymorphism (A2756G) of MS may decrease the enzymatic activity and induce modest homocysteine reduction, and subsequently increase DNA hypermethylation and damage DNA integrity, which plays an important role in the development of hematological cancer.[11]

Although numerous studies have investigated the association between the MS A2756G polymorphism and hematological cancer, [12–36] the results were inconsistent. Some studies have found an increased risk of hematological cancer was associated with the 2756G allele,[16,37] some studies identified a reduced risk,[19,21,28,35,38] and another did not detect the association between them.[14,15,17,18,20,22–27,29–34,36] To resolve these conflicting findings, we conducted a meta-analysis including 26 studies. Overall, we failed to find any statistical evidence for the MS A2756G polymorphism and susceptibility with hematological cancer under the homozygote, heterozygote, dominant, and recessive models, respectively.

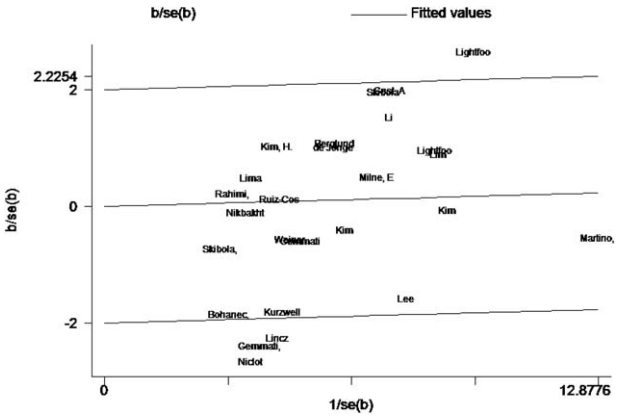

Figure 3. Galbraith plots for heterogeneity test of the MS A2756G polymorphism in the dominant genetic models.

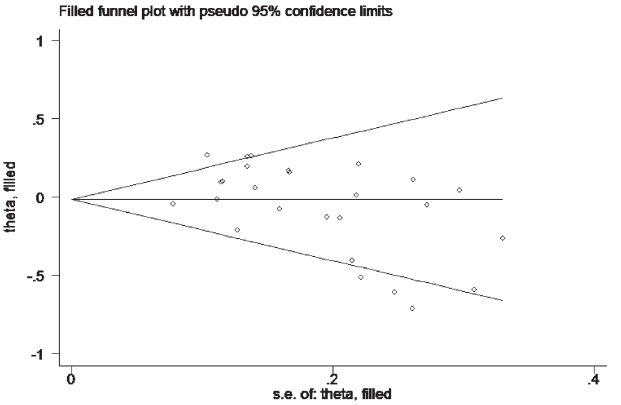

Figure 5. Funnel plot of association between the MS A2756G polymorphism and hematological cancer risk under the dominant genetic models.

Because the data might be confounded by the factors, such as types of cancer, ethnicities, and sources of controls, so we subsequently conducted stratified analyses by these factors. We found there were no significantly increased risks between the MS A2756G polymorphism and hematological cancer among any types of hematological cancer including leukemia, lymphomas, and myeloma in all genetic models. What was more, the significant association of the MS A2756G polymorphism and risk of hematological cancer could not be found in Asians or Caucasians under various models, indicating that different ethnicities did not influence the association between them. Additionally, hospital-based studies may have inherent selection biases, for the genotype distribution in HB studies may not be reprehensive of the general population. Therefore, we performed the stratified analysis by these factors. We still could not find any positive results in the subgroup analysis.

Significant heterogeneity existed in the dominant ($P_{het} < .01, I^2 = 51\%$) genetic models between MS A2756G polymorphism and risk of hematological cancers. And the identification of heterogeneity source was very important, so we detected source of heterogeneity using Galbraith plot. Lightfoot et al's,[16] Lincz et al's,[38] Niclot et al's,[35] and Gemmati et al's[19] studies were the main contributors of heterogeneity under dominant models. Moreover, after deleting these studies, heterogeneity was obviously decreased in the dominant genetic models; however, the corresponding pooled ORs were not materially altered after deleting these studies, indicating that our results were statistically robust.

However, some potential limitations existed in our meta-analysis. First, although under the premise of the inclusion criteria, the variations of the quality of the included studies remained a potential source of bias, which may affect the outcome. Second, in the subgroup analysis, a relatively small number of studies were used to analyze MS A2756G polymorphism and susceptibility of myeloma, which might lack the adequate statistical power, so these results should be interpreted

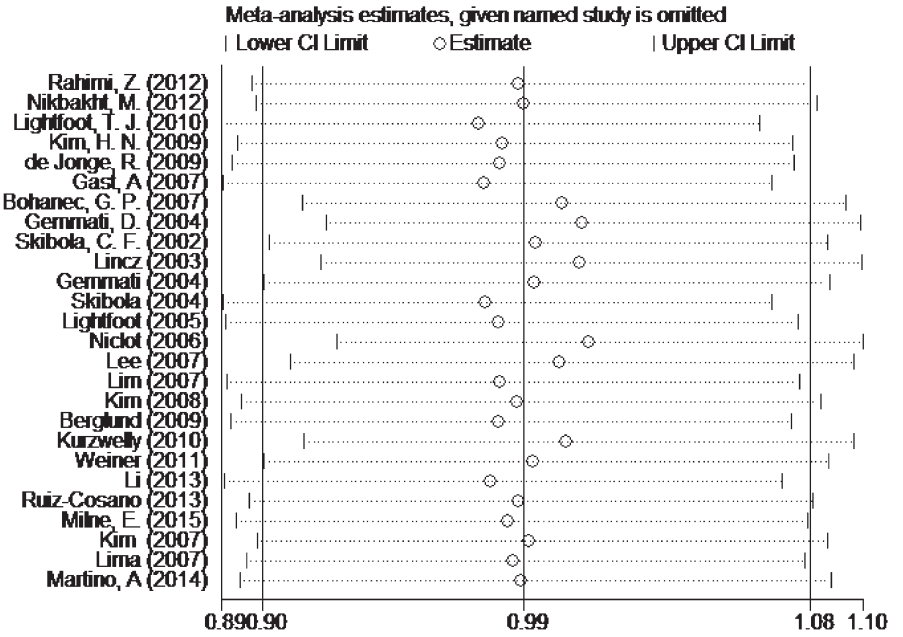

Figure 4. Sensitivity analyses performed between the MS A2756G polymorphism and hematological cancer risk in the dominant genetic models to assess the influence of each study on the pooled OR by individual studies omission.

with caution. Therefore, a further investigation is expected to have a larger sample size. Finally, when we evaluated the effect of MS A2756G polymorphism on the risk of hematological cancer, we did not take into account the other factors such as age, sex, ethnicity, and dietary factors such as the intake of folate due to lacking individual original data.

Despite these aforesaid limitations, our meta-analysis also had some advantages. First, the relationship between *MS* gene A2756G polymorphism and hematological cancer risk and the systematic review of statistics was more powerful than any single study. Second, the well-designed search and selection method had greatly improved the reliability of this meta-analysis.

In conclusion, our meta-analysis suggested that the MS A2756G polymorphism was not a candidate for susceptibility to hematological cancer. Considering the aforementioned limitations, further larger studies assessing gene-environment interactions should be performed to clarify the association of MS A2756G polymorphism and hematological cancer risk.

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