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Methionine synthase A2756G polymorphism and lymphoma risk: a meta-analysis

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Abstract. – OBJECTIVE: The association between methionine synthase (MS) A2756G polymorphism and lymphoma risk was studied with conflicting results. The present meta-analysis aimed to investigate the overall association between MS A2756G polymorphism and lymphoma risk.

MATERIALS AND METHODS: We searched PubMed and Embase databases until March 30, 2017, for articles that assessed the association between MS A2756G polymorphism and lymphoma risk. Statistical analyses were performed using the Revman 5.0 software.

RESULTS: A total of 14 articles involving 4,156 cases and 6,407 controls were included in this meta-analysis. Combined analysis revealed no association between this polymorphism and lymphoma susceptibility (OR = 0.92, 95% CI: 0.74-1.16, *p* = 0.50 for GG *vs.* GA+AA). Subgroup analysis by ethnicity showed decreased lymphoma risk with the MS A2756G gene polymorphism among Caucasians in GG+GA vs. AA and G *vs.* A models, but not among Asians. Subgroup analysis by disease type suggested that GG homozygous and G alleles were not associated with risks of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), the subtype of NHL including the diffuse large B-cell lymphoma and follicular lymphoma.

CONCLUSIONS: The results in this meta-analysis suggest no association between the MS A2756G polymorphism and lymphoma risk; however, the GG homozygous and G alleles could decrease the lymphoma risk in Caucasians.

Key Words:
Methionine synthase A2756G, Lymphoma, Polymorphism, Meta-analysis.

Introduction

Lymphomas (non-Hodgkin lymphoma [NHL] and Hodgkin lymphoma [HL]) are malignant neoplasms that mainly affect systemic lymphoid tissue[1]. The possibility of misdiagnosis and missed diagnosis is high owing to atypical clinical symptoms and the limited positive rate of pathological diagnosis in lymphomas. These unfavorable factors result in the diagnosis of patients at advanced stages (III and IV), and such patients have low treatment efficiency and poor disease prognosis[2]. Although EBV, Bcl2 and p53 contribute to the pathogenesis of lymphomas[3], the etiology of the disease remains unclear. Besides various infections, a possible risk factor for the development of lymphomas is individual genetic susceptibility. Even with the same environmental exposure, individual susceptibility to lymphomas differs. In the past decade, genetic susceptibility of patients due to multiple single nucleotide polymorphisms (SNPs) was extensively studied, and the methionine synthase (MS or MTR) gene was one of the assessed genes. Tetrahydrofolate and methionine contribute to cellular activities, such as synthesis of DNA and essential amino acids. MS plays a key role in the maintenance of adequate intracellular methionine concentration by catalyzing the transfer of the methyl group from 5-methyltetrahydrofolate to homocysteine and generating tetrahydrofolate and methionine[4]. The MS A2756G polymorphism was recently identified to have a close association with modest homocysteine reduction and DNA hypomethylation[5]. A large number of studies found a relation between MS polymorphisms and cancer risk. Additionally, numerous studies were performed to evaluate the association of MS A2756G polymorphism with lymphoma risk; however, the results were inconclusive. A meta-analysis was performed to assess the overall association between NHL risk and the polymorphism of MSA2756G[6]; however, this article had minor limitations. First, the me-

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ta-analysis did not evaluate the Hardy-Weinberg equilibrium (HWE) test, which is important for the reliability of the results. Furthermore, the included articles were incomplete. To obtain a more reliable and precise conclusion about the association between MS A2756G polymorphism and lymphoma risk, we performed this meta-analysis for all eligible studies.

Materials and Methods

Study Identification and Selection

Two authors performed up to date systematic search from PubMed and Embase databases to identify articles that evaluated the association between polymorphism of MS A2756G and lymphoma risk (Last search was updated on March 30, 2017). The search terms were as follows: "lymphoma" in combination with "polymorphism or variant or mutation" and in combination with "methionine synthase or MTR". The languages were limited to English. Articles were included if they satisfied the inclusion criteria: (1) they had evaluated the association between MS A2756G polymorphism and lymphoma risk; (2) they were case-control studies; (3) genotype distributions for cases and controls must be available to estimate an odds ratio (OR) with its 95% confidence interval (CI); and (4) the distribution of genotypes in the control group was consistent with Hardy-Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were also used: (1) studies in which genotype frequency was not reported; (2) abstracts, letters and reviews; (3) publications involved the repeated and overlapping data, and only studies with the largest participants were included.

Data Extraction

Two reviewers independently checked all potentially relevant studies and reached a consensus on all items. The following data were collected from each study: first author, year of publication, ethnicity, definition of cases, source of control, total number of cases and controls, genotyping methods, and genotype distributions in cases and controls.

Statistical Analysis

All statistical tests were performed using Revman 5.0 software and STATA 12.0 software. HWE was tested by Pearson's χ^2-test ($p<0.05$ means deviated from HWE). The strength of association between MS A2756G polymorphism and lymphoma risk was assessed by OR with the corresponding 95% CI. The genetic model evaluated for pooled OR of the polymorphism was a recessive genetic model (GG *vs.* GA+AA). The dominant genetic model (GG+AG *vs.* AA) and allele model (G *vs.* A) were also used to assess the association with the risk of lymphoma. Heterogeneity among studies was assessed by a χ^2-based Q statistic, with statistical significance at $p < 0.05$. The OR was calculated by a fixed-effects model or a random-effects model according to the heterogeneity. When the p-value was < 0.10, the pooled OR was calculated by the fixed-effects model; otherwise a random-effects model was used. The significance of the pooled OR was determined by a Z-test and $p < 0.05$ was considered statistically significant. To evaluate ethnicity-specific effects, subgroup analyses were performed by an ethnic group. Publication bias was analyzed by Begg's funnel plots and Egger's test.

Results

Characteristics of the Included Studies

A total of 198 articles were identified after an initial search of the PubMed and Embase databases (Figure 1). Of these, 14 articles[7-20] that evaluated the association between MS A2756G polymorphism and lymphoma risk were included in the meta-analysis. These articles included 4,156 cases and 6,407 controls. Three articles[21-23] were excluded because the distribution of genotypes in the control group was inconsistent with HWE. Seven[9-13,17,19] of the 14 included articles described case-control studies involving Caucasians, whereas three[7,8,16]articles described studies involving Asians. Eleven of these articles reported on NHL[10-17,19,20], whereas one reported on HL[18]. Six[9,11,12,14-16] of the NHL studies were about diffuse large B-cell lymphoma (DLBCL) and five[9,12-15] were about follicular lymphoma (FL). The characteristics of each case-control study are summarized in Table I, and the genotypes and allele distributions for each case-control study are listed in Table II.

Quantitative Data Synthesis

We analyzed the heterogeneity of the GG *vs.* GA+AA model for all 14 studies to select the most suitable calculation model. The value of χ^2 was 10.43 with 13 degrees of freedom and p=0.66, and thus, we selected the fixed-effects

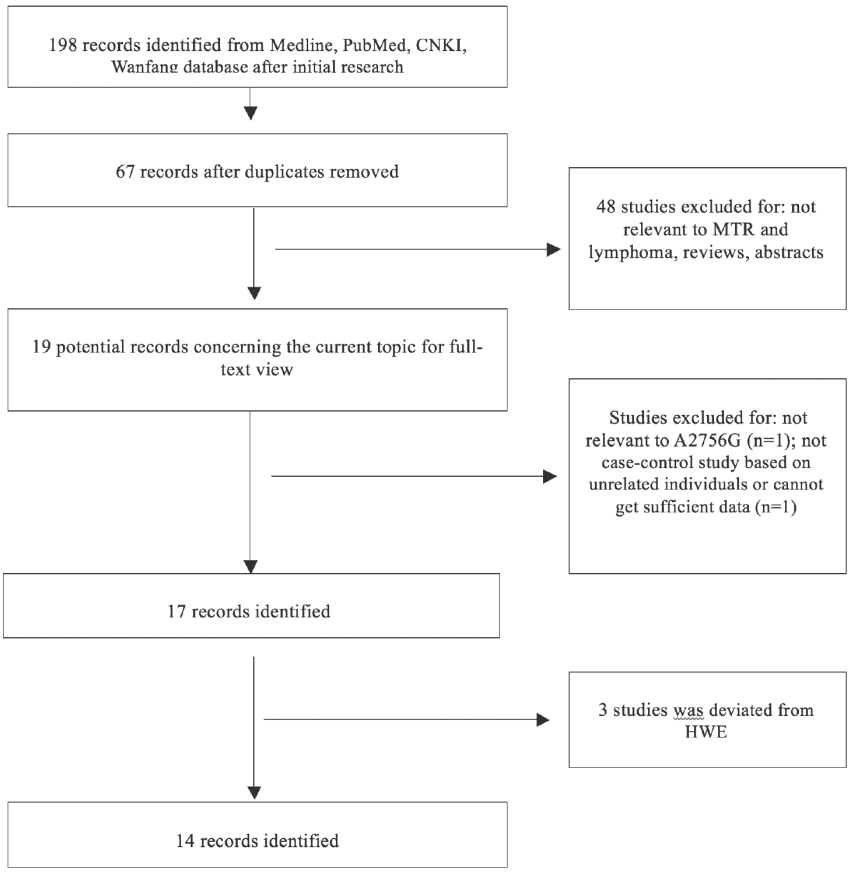

Figure 1. The flow diagram of included and excluded studies.

model to synthesize the data. Overall, the odds ratio (OR) was 0.92 (95% CI=0.74-1.16), and the test for overall effect, Z-value, was 0.68 (p=0.50) for the GG *vs*. GA+AA model (Figure 2), which showed no relation with lymphoma risk. We also analyzed the GG+GA *vs*. AA, GG *vs*. AA, and G *vs*. A models for further evaluation. These results showed no association, and the data are shown in Table III. In subgroup analysis according to ethnicity, OR

Table I. Characteristics of the case-control studies included in the present meta-analysis.

Author	Year	Country	Ethnicity	Cases	Controls	Genotyping method	Lymphoma type	HWE
Matsuo	2001	Japan	Asian	96	243	PCR-RFLP	NHL and HL	0.23
Lincz	2003	USA	Caucasian	149	298	PCR-RFLP	NHL	0.81
Gemmati	2004	Italy	Caucasian	200	257	PCR-RFLP	NHL	0.56
Linnebank	2004	Germany	Caucasian	31	142	PCR	NHL	0.96
Matsuo	2004	Japan	Asian	273	500	PCR-RFLP	NHL and HL	0.72
Lightfoot	2005	England	Caucasian	589	755	PCR-RFLP	NHL	0.78
Niclot	2006	France	Caucasian	171	206	PCR	NHL	0.52
Lim	2006	USA	Mixed	272	241	PCR	NHL	0.17
Lee	2007	Australia	Mixed	559	505	PCR	NHL	0.38
Kim	2008	Korea	Asian	584	1700	PCR	NHL	0.52
Kurzwelly	2010	Germany	Caucasian	185	212	PCR	NHL	0.64
Kasperzyk	2011	USA	Mixed	450	360	PCR	HL	0.24
Weiner	2011	Russia	Caucasian	141	456	PCR-RFLP	NHL	0.47
Li	2013	USA	Mixed	456	532	PCR	NHL	7.28

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. HEW: Hardy-Weinberg equilibrium. NHL: non-hodgkin lymphoma. HL: hodgkin lymphoma.

Table II. Distributions of MS A2756G genotype and allele among cancer patients and controls.

Author	Case			Control			Case		Control	
	AA	AG	GG	AA	AG	GG	A	G	A	G
Matsuo	63	26	7	156	81	6	152	40	393	93
Lincz	110	34	5	187	99	12	254	44	473	123
Gemmati	129	65	6	158	89	10	323	77	405	109
Linnebank	26	5	0	83	51	8	57	5	217	67
Matsuo	172	88	13	335	150	15	432	114	820	180
Lightfoot	382	190	17	507	222	26	954	224	1236	274
Niclot	144	24	3	149	51	6	312	30	349	63
Lim	186	79	7	169	62	10	451	93	400	82
Lee	364	173	22	304	180	21	901	217	788	222
Kim	442	133	9	1282	392	26	1017	151	2956	444
Kurzwelly	132	46	7	132	72	8	310	60	336	88
Kasperzyk	305	131	14	234	108	18	741	159	576	144
Weiner	96	40	5	297	139	20	232	50	733	179
Li	291	150	15	363	153	16	732	180	879	185

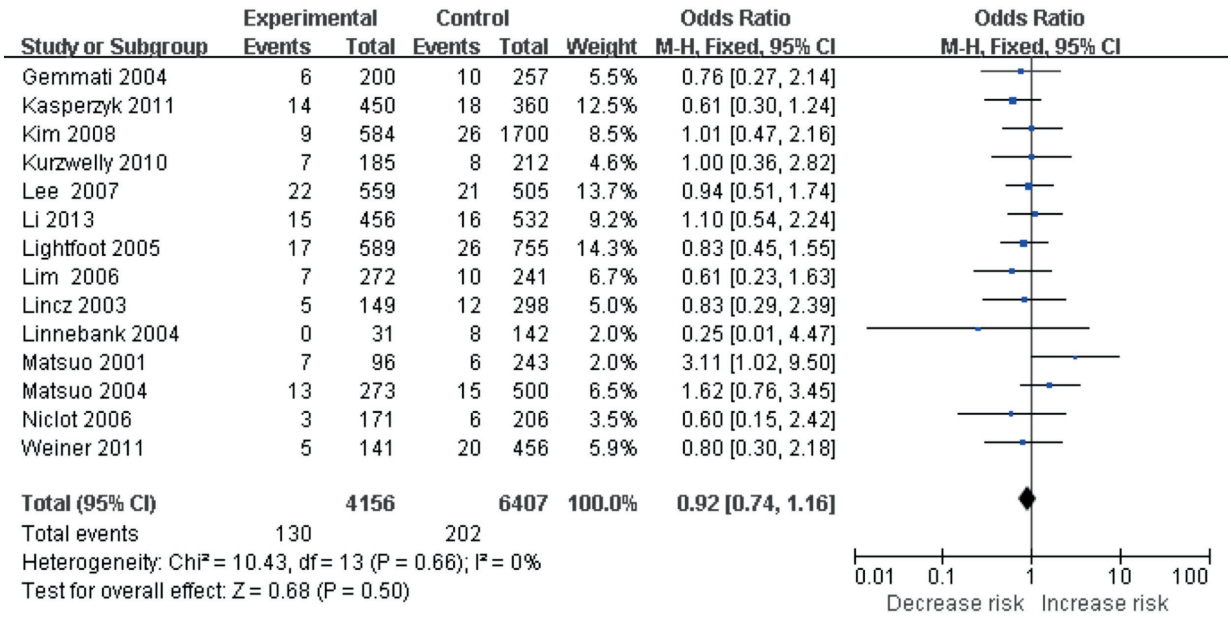

Figure 2. Meta-analysis for the association between lymphoma risk and the MS A2756G polymorphism (GG *vs.* GA+ AA, fixed-effects model).

was 0.72 (95% CI = 0.55-0.95, $p = 0.02$) for the GG+GA *vs.* AA model, and the OR was 0.76 (95% CI = 0.61-0.96, $p = 0.02$) for the G *vs.* A model among Caucasians (Figure 3). These results suggested that the GG homozygous and G alleles decreased the lymphoma risk in Caucasians. For the Asians, the results showed no association. In the subgroup analysis according to lymphoma type and subtype for NHL, results also suggested no association between MS A2756G polymorphism and lymphoma risk. A summary of the results from other comparisons is listed in Table III.

Sensitivity Analysis and Publication Bias

Sensitivity analysis was assessed to evaluate the stability of the individual data to the pooled OR (GG *vs.* GA+AA). After sequentially excluding each study, statistically similar results were obtained, suggesting that the results of this

Table III. Summary of results from different comparative genetic models.

MS A2756G	N	GG+GA *vs.* AA		GG *vs.* GA+AA		GG *vs.* AA		G *vs.* A	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Total	14	0.89 (0.78, 1.02)	0.10	0.92 (0.74, 1.16)	0.50	0.90 (0.72, 1.13)	0.37	0.91 (0.81, 1.03)	0.12
By ethnicity									
Caucasian	7	**0.72 (0.55, 0.95)**	**0.02**	0.79 (0.54, 1.15)	0.22	0.75 (0.51, 1.09)	0.13	**0.76 (0.61, 0.96)**	**0.02**
Asian	3	1.04 (0.88, 1.23)	0.67	1.49 (0.93, 2.40)	0.10	1.49 (0.93, 2.41)	0.10	1.07 (0.92, 1.24)	0.39
By lymphoma type									
NHL	11	0.85 (0.72, 1.01)	0.07	0.86 (0.66, 1.12)	0.26	0.83 (0.64, 1.09)	0.18	0.88 (0.76, 1.01)	0.06
HL	1	0.88 (0.66, 1.18)	0.41	0.61 (0.30, 1.24)	0.17	0.60 (0.29, 1.22)	0.16	0.86 (0.67, 1.10)	0.23
By NHL lymphoma type									
DLBCL	6	0.89 (0.75, 1.06)	0.18	1.07 (0.69, 1.64)	0.77	1.01 (0.65, 1.56)	0.97	0.92 (0.79, 1.07)	0.29
FL	5	0.77 (0.53, 1.12)	0.16	0.79 (0.48, 1.31)	0.36	0.76 (0.46, 1.26)	0.28	0.78 (0.56, 1.08)	0.14

DLBCL: diffuse large B-cell lymphoma. FL: follicular lymphoma

meta-analysis were stable. Publication bias was assessed by Begg's funnel plots and Egger's test. The shape of the funnel plots appeared symmetrical for the GG *vs.* GA+AA model, suggesting the absence of publication bias (Figure 4). Egger's test was performed to provide statistical evidence of funnel plot asymmetry. The results indicated the presence of publication bias ($p = 0.594$), indicating an absence of publication bias.

Discussion

Lymphomas are severe malignant tumors with unidentified causes and aggressive properties. Even with advanced pathological methods, the missed diagnosis is still remarkable. Results from epidemiological, immunological, and genetic studies indicated that complex interactions between genetic and environmental factors contribute to lymphoma pathogenesis[24]. Studies have attempted to identify genetic factors associated with lymphomas and have accumulated evidence indicating that certain genetic events during cell differentiation, such as chromosomal translocation, play a critical role in lymphoma pathogenesis[7,25]. Furthermore, gene variants exert a vital influence on individual susceptibility to lymphomas through alteration of protein function[9,10]. Many susceptibility genes (P52, P50, HLA-DPB1, MTHFR, MS) have been identified in genome-wide and genetic association studies[26-28]. Additionally, the MS gene has been extensively studied. MS is an important vitamin B12-dependent enzyme in one-carbon metabolism. A previous case-control study discovered gene-diet interactions and nutrient involvement in one-carbon metabolism (including folate, vitamin B12, and MS)[17]. A common polymorphism in MS gene (A2756G, rs1805087) was believed to be associated with lower enzyme activity than polymorphism in MS 2756 AA genotype, causing homocysteine elevation and DNA hypomethylation. Therefore, an increasing number of studies have researched the relationship between MS A2756G polymorphism and lymphoma risk. However, the results were inconsistent among different published studies. Thus, we performed this meta-analysis to comprehensively analyze the association. The relation between cancer risk and MS A2756G polymorphism has already been analyzed, and no relation with lymphoma risk was noted[29]. However, in this meta-analysis, we collected more studies and found that the G allele

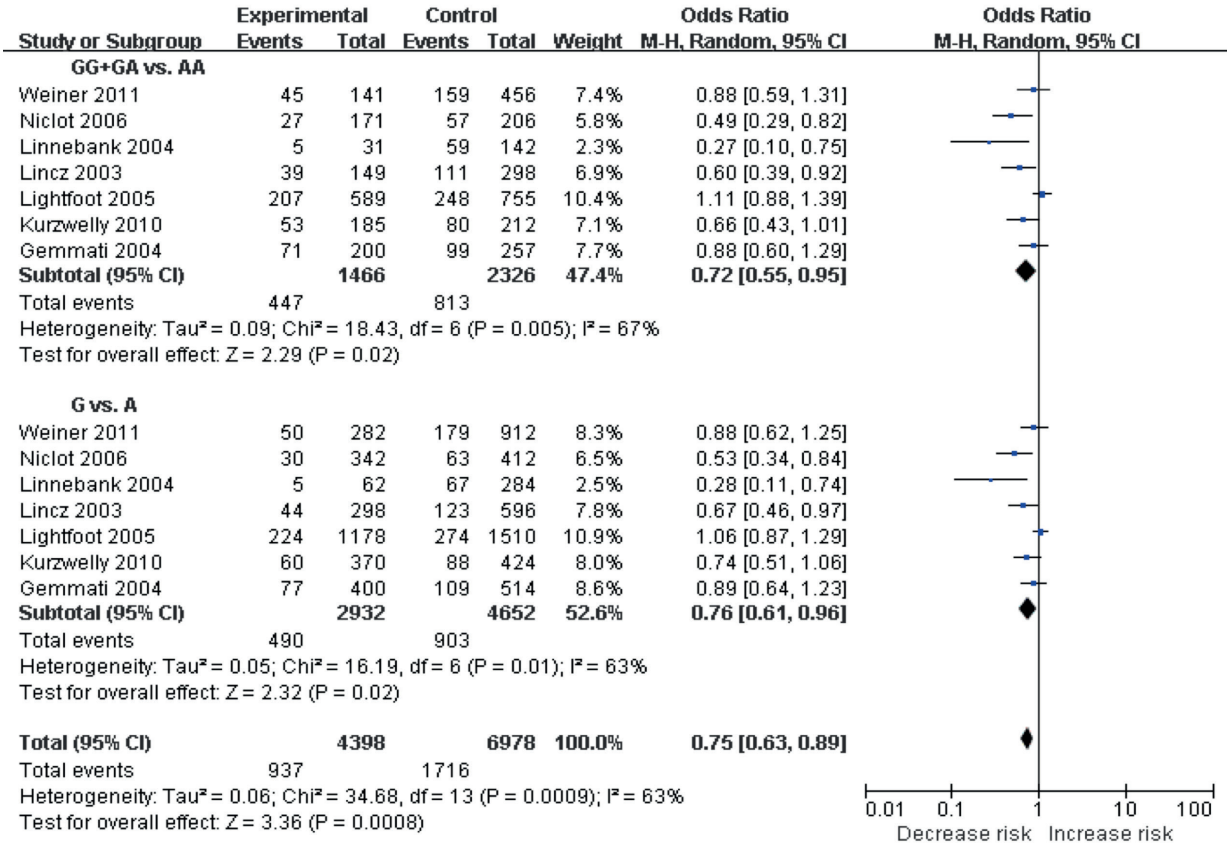

Figure 3. Meta-analysis for the association between lymphoma risk and the MS A2756G polymorphism in Caucasians (GG+GA *vs.* AA, G *vs.* A, random-effects model).

could decrease the lymphoma risk in Caucasians. We performed this meta-analysis to integrate the results from comparable studies in order to increase the statistical power and draw more valid conclusions. Multicenter studies with a large sample size are essential for a meta-analysis, and they can help provide a better prediction of the lymphoma risk. Our meta-analysis involved articles studying Caucasians and Asians, as it is known that SNPs differ among different ethnicities. Accordingly, ethnicity is one of the important factors for the development of lymphomas, and genetic inheritance decides the pathogenesis of different lymphomas among different ethnicities. In this meta-analysis, data was stratified according to ethnicity. A significant association of the G allele was found with susceptibility to lymphomas among Caucasians but not among Asians, indicating that ethnicity is an important factor that affects this association. The pathogenesis of lymphomas is complicated. Lymphomas could be divided into NHL and HL pathologically. The present study included both types (11 articles on NHL and only one on HL), which may have influenced the results; therefore, we performed subgroup analysis. The results indicated no association between MS A2756G polymorphism and lymphoma risk. NHL can be pathologically divided into subtypes, including DLBCL and FL. We also assessed the association for MS A2756G polymorphism and DLBCL/FL risk, and

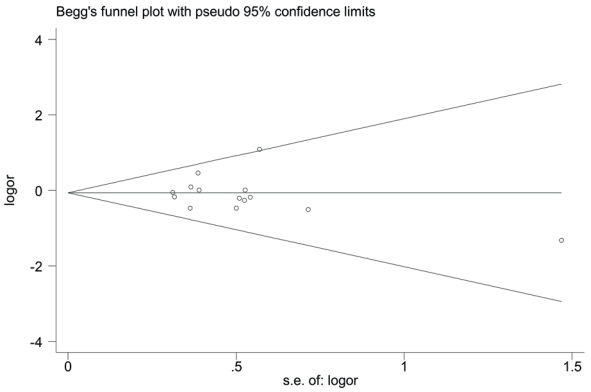

Figure 4. Begg's funnel plot for publication bias in selection of studies on the MS A2756G polymorphism (GG *vs.* GA+AA).

the results were the same as the overall analysis. More studies are needed for further evaluation, especially for that of HL. Although a meta-analysis aims to integrate comparable results on a particular topic, several confounding factors may influence the results of a meta-analysis. In this meta-analysis, an article was excluded, as it was not in accordance with HWE. Publication bias and study quality were important factors for the analysis. Therefore, strict inclusion and exclusion criteria were used in order to reduce selection bias. In this study, publication bias was analyzed using Begg's funnel plots and Egger's test. The results indicated the absence of publication bias. The results for sensitivity and publication bias showed the reliability of our meta-analysis. We should also mention the importance of heterogeneity. Heterogeneity may affect the reliability of the results; significant heterogeneity was detected in some comparisons, and this maybe because of ethnicities, different types of lymphoma, and sample selections. The heterogeneity among different populations reduced after ethnic subgroup analysis, and this may have resulted because of different genetic backgrounds and desperate living environments. Although this is an up-to-date meta-analysis, some limitations should be discussed. First, only published studies were included. Unpublished studies with unidentified null results were not included in the study. For HL, only one study was included in the subgroup analysis, and the results may differ greatly if more studies are included. Second, the included studies only consisted of Asians and Caucasians. Thus, our results may be applicable to only these ethnic groups. The lack of other ethnicities, especially Africans, may cause induced bias. A multi-ethnic study with a larger sample size should be performed to assess the association between MS A2756G polymorphism and lymphoma risk. Nevertheless, there were some advantages in this meta-analysis. Although there have been previous meta-analyses for the assessment of the correlation between MS A2756G polymorphism and lymphoma risk[6,29], this is the most comprehensive and reliable analysis.

Conclusions

To our knowledge, this is the most comprehensive meta-analysis to assess the relationship between MS A2756G polymorphism and lymphoma risk. Our results indicated that MS A2756G polymorphism was significantly associated with a decreased lymphoma risk among Caucasians. In the future, additional case-control studies should be performed to validate our findings.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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