The association between methionine synthase A2756G polymorphism and hematological cancer
A meta-analysis
Bing Wu, MS\textsuperscript{a}, Kang Liu, MD\textsuperscript{b}, Jun-Ping Yang, MD\textsuperscript{c,*}, Yan Hu, MS\textsuperscript{a}, Jun Zhang, MS\textsuperscript{c}, Jun-xiang He, MS\textsuperscript{a}

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, \(P = 0.62\)), heterozygote (GG vs AA: OR = 0.99, 95% CI = 0.85–1.15, \(P = 0.91\)), dominant (AG+GG vs AA: OR = 0.99, 95% CI = 0.90–1.08, \(P = 0.93\)), and recessive (GG vs AG+AA: OR = 1.00, 95% CI = 0.86–1.16, \(P = 0.97\)) 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.\textsuperscript{1} Hematological cancer is common, being the fourth most frequently diagnosed cancer in both males and females in the United States. Among newly diagnosed, 171,350 hematological cancer patients and 58,310 deaths were estimated in the United States in 2016.\textsuperscript{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.\textsuperscript{[1–6]} 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.\textsuperscript{[7–10]} So far, more and more evidence indicates that these folate-dependent polymorphisms are associated with malignant tumors, including the risk of blood cancers.\textsuperscript{[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
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.[14–18] 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 “hematological 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 hematological cancer risk; 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 I² metric (I² < 25% no heterogeneity; I² = 25–50% moderate heterogeneity; I² > 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.[43] 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 3 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<.01, I² = 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          |
| Nikuakht     | 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        |
| Bohancic     | 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            |
| Nicot        | 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            |
| Linicz       | 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.
it was found Lightfoot et al. [16]. Linz et al. [18], Niclot et al. [19], and Gemmati et al. [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 ($P_{het} = 0.20, I^2 = 20\%$), 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.lw.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 2

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

| First author | Year | Cancer types | Sample size | Cases | Controls | AA | GA | GG | ORs (95% CI) | P value |
|--------------|------|--------------|-------------|-------|----------|----|----|----|-------------|---------|
| Rahimi       | 2014 | Leukemia     | 73           | 128   | 5        | 75 | 47 | 6  | .32         |         |
| Niksaheht    | 2012 | Leukemia     | 125          | 100   | 7        | 58 | 35 | 7  | .45         |         |
| Lightfoot    | 2010 | Leukemia     | 870          | 759   | 531      | 51 | 223| 26 | .98         |         |
| Kim          | 2009 | Leukemia     | 108          | 1700  | 77       | 3  | 1282|392 | .30         |         |
| De Jonge     | 2009 | Leukemia     | 245          | 489   | 162      | 9  | 340|137 | .69         |         |
| Gast         | 2007 | Leukemia     | 446          | 547   | 280      | 13| 375|151 | .59         |         |
| Bohanec      | 2007 | Leukemia     | 68           | 258   | 51       | 16 | 161| 82  | .47         |         |
| Gemmati      | 2013 | Leukemia     | 118          | 257   | 88       | 1  | 158| 89  | .79         |         |
| Skibola      | 2002 | Leukemia     | 70           | 114   | 50       | 1  | 75  | 39  | .82         |         |
| Linz         | 2003 | Lymphoma     | 149          | 298   | 110      | 5  | 187| 99  | .52         |         |
| Gemmati      | 2004 | Lymphoma     | 200          | 257   | 129      | 6  | 158| 89  | .68         |         |
| Skibola      | 2004 | Lymphoma     | 330          | 731   | 201      | 489 |242 | 0.32    |         |
| Lightfoot    | 2005 | Lymphoma     | 589          | 755   | 382      | 190 |157 | 222 | .52         |         |
| Niclot       | 2006 | Lymphoma     | 171          | 206   | 144      | 24 | 149| 51  | .24         |         |
| Lee          | 2007 | Lymphoma     | 559          | 505   | 364      | 173 |22  | 304 | .30         |         |
| Lim          | 2007 | Lymphoma     | 739          | 628   | 481      | 239 |19  | 422 | .38         |         |
| Kim          | 2008 | Lymphoma     | 584          | 1700  | 442      | 133 |9  | 1282| .99        |         |
| Benglund     | 2009 | Lymphoma     | 260          | 437   | 170      | 11 | 302| 126 | .13         |         |
| Kurzweilly   | 2010 | Lymphoma     | 185          | 212   | 131      | 46 | 8  | 131| 72  | .23         |         |
| Weiner       | 2011 | Lymphoma     | 141          | 456   | 96       | 5  | 297| 139 | .52         |         |
| Li           | 2013 | Lymphoma     | 456          | 532   | 291      | 150 |15  | 363 | .78         |         |
| Ruiz-Cosano  | 2013 | Lymphoma     | 192          | 214   | 135      | 48 | 9  | 151| 84  | .56         |         |
| Milne        | 2015 | Lymphoma     | 391          | 514   | 251      | 130 |10  | 337 | .56         |         |
| Kim          | 2007 | Myeloma      | 174          | 1700  | 91       | 14 | 857| 718 | .25         |         |
| Lima         | 2007 | Myeloma      | 123          | 188   | 63       | 28 | 53 | 102 | .31         |         |
| Martino      | 2014 | Myeloma      | 1275         | 1813  | 858      | 372 |45 | 1201| .99  |         |

HWE = Hardy-Weinberg equilibrium.
GA = GG.

### 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 | Cases | Controls | ORs (95% CI) | P value |
|------------------|----|--------------------|-------|----------|--------------|---------|
| Cancer types     |    |                    |       |          |              |         |
| Leukemia         | 9  | 21233              | 0.98 | 0.89 | 1.15 | .25 | 15 | 0.99 | 0.00  | 0.00  | 1.00 | 0.54 |
| Lymphoma         | 14 | 4846              | 0.85 | 0.88 | 1.06 | .20 | 13 | 0.10 | 0.82 | 0.24 | 0.79 | 0.58 |
| Myeloma          | 3  | 1572              | 0.85 | 0.88 | 1.06 | .60 | 14 | 0.00 | 0.85 | 1.09 | 0.67 | 0.54 |
| Ethnicity        |    |                    |       |          |              |         |
| Asian            | 5  | 1064              | 0.98 | 0.84 | 1.16 | .83 | 0  | 0.00 | 0.86 | 1.16 | 0.98 | 0.00 |
| Caucasian        | 17 | 5868              | 0.91 | 0.79 | 1.24 | .47 | 24 | 0.00 | 0.85 | 1.04 | 0.82 | 0.64 |
| Mixed            | 4  | 1709              | 0.98 | 0.82 | 1.06 | .83 | 0  | 0.00 | 0.86 | 1.16 | 0.98 | 0.11 |
| Design of study  |    |                    |       |          |              |         |
| PB               | 19 | 7422              | 0.98 | 0.84 | 1.16 | .32 | 11 | 0.00 | 0.49 | 1.42 | 0.23 | 0.05 |
| FH               | 2  | 313               | 0.98 | 0.89 | 1.10 | .23 | 0  | 0.00 | 0.86 | 1.16 | 0.98 | 0.11 |
| HB               | 5  | 906               | 0.83 | 0.86 | 1.24 | .45 | 0  | 0.00 | 0.87 | 1.12 | 0.45 | 0.00 |

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, PH=probability of heterogeneity, fixed-effects model was used when $P_{het}$=1, otherwise, random model was used.
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 ($P_{\text{Egger}} = .58$) (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 (A\(^{2756}G\)) 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 A\(^{2756}G\) 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 A\(^{2756}G\) polymorphism and susceptibility with hematological cancer under the homozygote, heterozygote, dominant, and recessive models, respectively.
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 representative 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...
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.

References

[1] Campbell V, Copland M. Hedgehog signaling in cancer stem cells: a focus on hematological cancers. Stem Cells Cloning 2015:8:27–38.
[2] Segel RL, McMillan KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
[3] Chiu BC, Weißenburger DD, Zahm SH, et al. Agricultural pesticide use, familial cancer, and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2004;13:525–31.
[4] Ekstroem-Smedby K. Epidemiology and etiology of non-Hodgkin lymphoma: a review. Acta Oncol 2006;45:258–71.
[5] Schiffman JD. Applying molecular epidemiology in pediatric leukemia. J Pediatr Hematol Oncol 2003;25:97–102.
[6] Segel GB, Lichtman MA. Familial (inherited) leukemia, lymphoma, and myeloma: an overview. Blood Cells Mol Dis 2004;32:246–61.
[7] Duthe SJ, Narayanan S, Brand GM, et al. Impact of folate deficiency on DNA stability. J Nutr 2002;132:suppl:2444s–9s.
[8] Ly A, Hoyt L, Crowell J, et al. Folate and DNA methylation. Antioxid Redox Signal 2012;17:302–26.
[9] Matsuo K, Suzuki R, Hamajima N, et al. Association between polymorphisms of folate- and methionine-metabolizing enzymes and susceptibility to malignant lymphoma. Blood 2001;97:3205–9.
[10] Peterson LG, Janez J, Vita D. Gene–gene interactions in the folate metabolic pathway influence the risk for acute lymphoblastic leukemia in children. Leuk Lymphoma 2007;58:786–92.
[11] Harmon DL, Shields DC, Woolside JV, et al. Methionine synthase D919G polymorphism is a significant but modest determinant of circulating homocysteine concentrations. Genet Epidemiol 1999;17:298–309.
[12] Wilson A, Leclerc D, Sabin F, et al. Functionally null mutations in patients with the chl variant form of methionine synthase deficiency. Am J Hum Genet 1998;63:409–14.
[13] Novotna B, Topinka J, Solansky I, et al. Impact of air pollution and genotype variability on DNA damage in Prague policemen. Toxicol Lett 2007;172:37–47.
[14] Rahimi Z, Rahimi Z, Ahmadian Z, et al. Thymidylate synthase and methionine synthase polymorphisms are not associated with susceptibility to childhood acute lymphoblastic leukemia in Iranian children. Leuk Lymphoma 2012;53:2195–200.
[15] Nikbakht M, MalekZadeh K, Kumar Jha A, et al. Polymorphisms of MTHFR and MTR genes are not related to susceptibility to childhood ALL in North India. Exp Oncol 2012;34:43–8.
[16] Lightfoot TJ, Johnston WT, Painter D, et al. Genetic variation in the folate metabolic pathway and risk of childhood leukemia. Blood 2010;115:3923–9.
[17] Kim HN, Kim YK, Lee IK, et al. Association between polymorphisms of folate-metabolizing enzymes and hematological malignancies. Leuk Res 2009;33:82–7.
[18] de Jonge R, Tissing WJE, Hoogberg JB, et al. Polymorphisms in folate-related genes and risk of pediatric acute lymphoblastic leukemia. Blood 2009;113:2284–9.
[19] Gemmatt D, Ongaro A, Scapoli GL, et al. Common gene polymorphisms in the metabolic folate and methylation pathway and the risk of acute lymphoblastic leukemia and non-Hodgkin’s lymphoma in adults. Cancer Epidemiol Biomarkers Prev 2004;13:787–94.
[20] Skibola CF, Smith MT, Hubbard A, et al. Polymorphisms in the thymidylate synthase and serine hydroxymethyltransferase genes and risk of adult acute lymphocytic leukemia. Blood 2002;99:3786–91.
[21] Bohannan GF, Jazbec J, Dolzan V. Gene–gene interactions in the folate metabolic pathway influence the risk for acute lymphoblastic leukemia in children. Leuk Lymphoma 2007;48:786–92.
[22] Milne E, Greenop KR, Scott RJ, et al. Folate pathway gene polymorphisms, maternal folic acid use, and risk of childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev 2015;24:48–56.
[23] Martino A, Campa D, Jurczyszyn A, et al. Genetic variants and multiple myeloma risk: IMMEnSE validation of the best reported associations—an extensive replication of the associations from the candidate gene era. Cancer Epidemiol Biomarkers Prev 2014;23:670–4.
[24] Ruiz-Cosano J, Torres-Moreno D, Conesa-Zamora P. Influence of polymorphisms in ERCC3, XPA and MTR DNA repair and synthesis genes in B-cell lymphoma risk. A case-control study in Spanish population. J BUON 2013;18:486–90.
[25] How C, Hui AB, Alajez NM, et al. MicroRNA-196b regulates the homeobox B7-vascular endothelial growth factor axis in cervical cancer. PLoS One 2013;8:e67846.
[26] Weiner AS, Beresina OV, Voronina EN, et al. Polymorphisms in folate-metabolizing genes and risk of non-Hodgkin’s lymphoma. Leuk Res 2011;35:508–15.
[27] Gast A, Bermejo JL, Floth T, et al. Folate metabolic gene polymorphisms and childhood acute lymphoblastic leukemia: a case-control study. Leukemia 2007;21:320–5.
[28] Kurzwelly D, Knop S, Guenther M, et al. Genetic variants of folate and methionine metabolism and PCNSL incidence in a German patient population. J Neurooncol 2010;100:187–92.
[29] Berglund M, Enblad G, Turesson I, et al. Folate-metabolizing genes in lymphoma patients from Sweden. Scand J Immunol 2009;70:408–10.
[30] Lima CS, Ortega MM, Ozel MC, et al. Polymorphisms of methyltetrahydrofolate reductase (MTHFR), methionine synthase (MTR), methionine reductase (MTRR), and thymidylate synthase (TYMS) in multiple myeloma risk. Leuk Res 2008;32:401–5.
[31] Kim HN, Lee IK, Kim YK, et al. Association between folate-metabolizing pathway polymorphism and non-Hodgkin lymphoma. Br J Haematol 2008;140:287–94.
[32] Lim U, Wang SS, Hantage P, et al. Gene-nutrient interactions among determinants of folate and one-carbon metabolism on the risk of non-Hodgkin lymphoma: NCI-SEER case-control study. Blood 2007;109:3050–9.
[33] Lee KM, Lan Q, Kricker A, et al. One-carbon metabolism gene polymorphisms and risk of non-Hodgkin lymphoma in Australia. Hum Genet 2007;122:525–33.
[34] Kim HN, Kim YK, Lee IK, et al. Polymorphisms involved in the folate metabolizing pathway and risk of multiple myeloma. Am J Hematol 2007;82:798–801.
[35] Niclot S, Pruvot Q, Besson C, et al. Implication of the folate-methionine metabolism pathways in susceptibility to follicular lymphomas. Blood 2006;108:2788–85.
[36] Lightfoot TJ, Skibola CF, Willett EV, et al. Risk of non-Hodgkin lymphoma associated with polymorphisms in folate-metabolizing genes. Cancer Epidemiol Biomarkers Prev 2005;14:2999–3003.
[37] Skibola CF, Forrest MS, Coppede F, et al. Polymorphisms and haplotypes in folate-metabolizing genes and risk of non-Hodgkin lymphoma. Blood 2004;104:2155–62.
[38] Lincz LF, Scorgie FE, Kerridge I, et al. Methionine synthase generic polymorphism MS A2756G alters susceptibility to follicular but not diffuse large B-cell non-Hodgkin’s lymphoma or multiple myeloma. Br J Haematol 2003;120:1051–4.
[39] Thakkinian A, McLelllP F, D’Este C, et al. A method for meta-analysis of molecular association studies. Stat Med 2005;24:1291–306.
[40] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[41] Rax L, Reda N, Fukui N, et al. More than numbers: the power of graphs in meta-analysis. Am J Epidemiol 2009;169:249–55.
[42] Soeken KL, Srivastanap A. Assessing publication bias in meta-analysis. Nurs Res 2003;52:57–60.
[43] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315:629–34.
[44] Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer 2006;6:193–203.