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Methionine synthase reductase A66G polymorphism contributes to tumor susceptibility: evidence from 35 case–control studies

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Abstract Methionine synthase reductase (*MTRR*) gene is involved in tumorigenesis by regulating DNA methylation through activation of methionine synthase (*MTR*). *MTRR* is polymorphic at nucleotide 66 (*A*-to-*G*) and the resulting variant enzyme has a lower affinity for MTR. The reported associations of *MTRR A66G* polymorphism with cancer risk are contradictory. Therefore, we performed a meta-analysis to better assess the associations, including 18,661 cases and 27,678 controls from 35 studies. Crude ORs with 95% CIs were used to assess the strength of association between the *MTRR A66G* polymorphism and cancer risk. The pooled ORs were performed for homozygote model (GG vs. AA), heterozygote model (GG vs. GA), recessive genetic model (GG vs. GA + AA), and dominant genetic model (GG + GA vs. AA), respectively. Overall, results indicated that the G allele and GG variant genotypes were associated with a significantly increased cancer risk (G vs. A: OR, 1.039; 95% CI, 1.009–1.078; homozygote model: OR, 1.094; 95% CI, 1.006–1.191). In subgroup analysis by ethnicity, significant increased risks were found among Asians with G allele (G vs. A: OR, 1.063; 95% CI, 1.011–1.119; homozygote model: OR, 1.189; 95% CI, 1.055–1.341; recessive model: OR, 1.197; 95% CI, 1.068–1.341). For stratification analysis, the cancer types with fewer than three studies were categorized into "other cancers", and the results indicated that there was a significant elevated cancer risk in "other cancers" in all genetic models, not in colorectal cancer, lymphoid leukemia or breast cancer. In summary, our study suggests that the *MTRR A66G* polymorphism is a potential biomarker for cancer risk.

Keywords Methionine synthase reductase (MTRR) · Gene polymorphism · Cancer risk · Meta-analysis

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Introduction

One-carbon metabolism, also referred as folate-mediated one-carbon metabolism, is a network of biological reactions with a critical role in DNA methylation and synthesis, and an impact on both epigenetic and genetic pro-carcinogenic processes [1]. DNA methylation is critical for regulating gene expression. The mechanism by which abnormal DNA methylation leads to carcinogenesis is complex. Methionine is an essential amino acid and a precursor of *S*-adenosylmethionine, a universal methyl-group donor involved in methylation reactions, including DNA methylation [2]. Both methionine synthase reductase (MTRR) and methionine synthase (MTR) regulate the reaction that produces methionine through the irreversible transfer of a methyl group from 5-methyltetrahydrofolate. MTR is maintained in its active form by MTRR, an enzyme that regenerates a functional MTR via reductive methylation.

A genetic polymorphism at nucleotide 66 (*A*-to-*G*) of the MTRR gene is functional, but the variant enzyme has a lower affinity for MTR [3]. Several case–control studies have evaluated the association between the genetic

polymorphism and cancer risk, with inconclusive or controversial results. For *MTRR A66G*, some studies have reported elevated homocysteine levels for carriers of the homozygote wildtype genotype (*AA*), compared to other genotypes [4, 5], while others have not [6]. However, in subsequent investigations, the *66GG* genotype was associated with an increased risk of colorectal cancer among Japanese compared to the *GA* + *AA* genotype [7], and another study found an increased risk for the *GG* genotype among white populations only [8]. Moreover, it was shown that carrying the G allele was associated with a marginally decreased risk of acute lymphoblastic leukemia (ALL) [9], but another study suggested that the MTRR polymorphism was less clearly associated with susceptibility to ALL [10].

A large number of molecular epidemiological studies have been conducted to evaluate the role of *MTRR* polymorphisms in different kinds of neoplasm. However, the association between the polymorphisms and cancer risk is still controversial. To clarify this issue, we performed a meta-analysis with subgroup analysis from all eligible studies, to assess the association of the *MTRR A66G* polymorphism with cancer risk.

Materials and methods

Study identification and selection

Before the study, inclusion criteria were defined as: (a) articles evaluating the association between *MTRR A66G* polymorphism and cancer risk; (b) studies with case–control design; (c) sufficient data to estimate an odds ratio (OR) with its 95% confidence interval (95% CI).

A literature search of PubMed and China National Knowledge Infrastructure (updated to 2010/07/16) was conducted using the terms: "MTRR" or "methionine synthase reductase", "polymorphism(s)", and "cancer" or "carcinoma" or "neoplasm", without restriction on language. All the searched studies were retrieved by two of the authors, and their bibliographies were checked for other relevant publications. Reference lists of reviews and retrieved articles were also searched to find additional eligible studies. When an article reported results on different racial descent subpopulations or tumor types, we treated each subpopulation or tumor as a separate comparison. Any disagreement was resolved by discussion between the two authors.

Data extraction

Information was carefully and independently extracted from all eligible publications by two of the authors, according to the inclusion criteria. For each study, the collected characteristics were: first author's last name, journal, year of publication, ethnicity and country of study population (mixed or unknown populations were categorized as an "others" group), source of control groups (population- or hospital-based controls), demographics, numbers of genotyped cases and controls, methods for genotyping, *MTRR* polymorphism genotyping information.

Statistical analysis

The strength of association between the *MTRR A66G* and cancers was measured by OR with 95% CI. The statistical significance of the pooled OR was determined using the *Z*-test. The meta-analysis assessed association between allele G and cancer risk compared to allele A (G vs. A), as well as homozygote comparison (GG vs. AA), heterozygote comparison (GG vs. GA), recessive genetic model (GG vs. GA + AA), and dominant genetic model (GG + GA vs. AA) comparison. Stratification analysis was performed by cancer type (if one cancer type contained fewer than three individual studies, it was combined into an "other cancers" group), ethnicity and study designs (hospital-based studies and population-based studies).

A chi-square test was used to determine if the distribution of genotypes among controls conformed to Hardy–Weinberg equilibrium (HWE), with P value <0.05 signifying a departure from HWE. Weighted mean was used to calculate mean allele prevalence in controls using SPSS 13.0 software for Windows. The Q-test was used to investigate the degree of heterogeneity between studies, with a P value >0.05 indicating lack of heterogeneity. In cases of no statistical heterogeneity, a fixed-effects model was used to estimate the summery OR (Mantel–Haenszel method) [11]; otherwise, the random-effects model (the DerSimonian–Laird method) was used [12].

Potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry tested by Egger's test ($P < 0.05$ was significant publication bias) [13]. Sensitivity analysis was performed by omitting each study in turn to assess the results stability. We also did cumulative meta-analysis to evaluate the trend of summary ORs (95% CIs) by year of publication. All statistical tests were two-sided. Software STATA version 10.0 (Stata Corporation, College Station, TX, USA) was used for all analyses.

Results

Study characteristics

We obtained 61 articles after searching and screening based on our eligibility criteria. During data extraction, 26

articles were excluded because they did not provide allele frequencies needed for OR calculation, leaving 35 eligible studies that had assessed the association between *MTRR A66G* and cancer risk using human genomic DNA samples. Overall, 18,661 cancer patients and 27,678 controls were distributed among the 35 eligible studies.

We established a database from the extracted information from each eligible article (Table 1). All were case–control studies, including seven colorectal cancer studies, six lymphoid leukemia studies, and six breast cancer studies, with the rest in the "other cancers" group. Cancers were confirmed histologically or pathologically in most studies. Age-matching was performed by 29 articles and sex-matching in 28. Of the 35 studies, only 19 discussed quality control of genotyping, such as blindness to the case–control status, randomly repeated assays, or validation using a different genotyping method. In addition, 17 studies investigated interactions between polymorphisms and environmental factors or the combined effect with other genes.

Quantitative synthesis

Significant differences were found in the variant 66G allele frequency between the two major ethnicities (Asian, 28.9%; 95% CI, 28.4–29.5%; European, 53.0%; 95% CI, 52.4–53.6%; $P = 0.001$). Table 2 summarizes results of the *MTRR A66G* polymorphism and cancer risk. A significant association between the *MTRR A66G* polymorphism and cancer risk was found, for an overall OR for the allele G versus allele A of 1.039 ($P = 0.043$; 95% CI, 1.009–1.078; $P_{\text{heterogeneity}} = 0.021$; Fig. 1). In addition, individuals carrying the *MTRR 66GG* genotype had a significantly increased cancer risk compared to individuals with the *66AA* genotype (OR, 1.094; $P = 0.037$; 95% CI, 1.006–1.191; $P_{\text{heterogeneity}} = 0.004$; Fig. 2).

We also performed subgroup analysis stratified by ethnicity, study design, and cancer type. By ethnicity, the G allele was associated with a significantly increased cancer risk in Asian populations (OR, 1.063; $P = 0.018$; 95% CI, 1.011–1.119; $P_{\text{heterogeneity}} = 0.328$; Fig. 3). A marginally significant association between the *A66G* polymorphism and increased cancer risk was also detected in Asians under homozygote (GG vs. AA: OR, 1.189; $P = 0.005$; 95% CI, 1.055–1.341; $P_{\text{heterogeneity}} = 0.191$), and recessive model comparison (GG vs. GA/AA: OR, 1.197; $P = 0.002$; 95% CI, 1.068–1.341; $P_{\text{heterogeneity}} = 0.106$). By different study designs for Asian populations, the 66GG genotype led to a significantly increased cancer risk in population-based studies under allelic frequency (OR, 1.089; $P = 0.011$; 95% CI, 1.020–1.163; $P_{\text{heterogeneity}} = 0.508$), homozygote model (OR, 1.283; $P = 0.002$; 95% CI, 1.096–1.501; $P_{\text{heterogeneity}} = 0.661$), and recessive model comparison (OR, 1.263; $P = 0.003$; 95% CI, 1.085–1.471; $P_{\text{heterogeneity}} = 0.8$). However, cancer risk decreased non-significantly in hospital-based studies under dominant model comparison (OR, 0.484; $P = 0.001$; 95% CI, 0.330–0.709; $P_{\text{heterogeneity}} = 0.001$). In the subgroup analysis stratified by tumor type, the *MTRR* G allele was associated with an increased risk of "other cancers" compared to the A allele (OR, 1.08; $P = 0.000$; 95% CI, 1.035–1.127; $P_{\text{heterogeneity}} = 0.102$). Also for "other cancers", we found that the variant genotypes were associated with a significantly increased cancer risk using all genetic models (homozygote comparison: OR, 1.196, $P = 0.001$, 95% CI: 1.093–1.310, $P_{\text{heterogeneity}} = 0.079$; heterozygote comparison: OR, 1.089, $P = 0.015$, 95% CI: 1.017–1.166, $P_{\text{heterogeneity}} = 0.193$; dominant model: OR, 1.111, $P = 0.001$, 95% CI: 1.042–1.185, $P_{\text{heterogeneity}} = 0.077$; recessive model: OR, 1.108, $P = 0.007$, 95% CI: 1.028–1.194, $P_{\text{heterogeneity}} = 0.199$). No significant association was found for other tumor sites.

Sensitivity analysis and cumulative meta-analysis

Pooled ORs were consistently significant in Asian populations or European populations by omitting one study or one tumor at a time under the homozygote and dominant genetic model comparison, suggesting robustness of our results (data not shown). In the cumulative meta-analysis, the pooled ORs tended to be stable and the associations tended toward significant associations with accumulation of more data over time.

Publication bias

Funnel plots were generated to assess publication bias. The Egger's test was performed to statistically evaluate funnel plot symmetry. The results showed no evidence of publication bias ($P = 0.58$; Fig. 4).

Discussion

Similar to MTR, MTRR is a critical enzyme for the biosynthesis of methionine, which is the precursor for methylation reactions. MTRR is also involved in the regeneration of tetrahydrofolate for nucleotide biosynthesis. Changes in this enzyme may significantly influence DNA synthesis, methylation and repair. The A66G single nucleotide polymorphism at codon 22 is one of the most common polymorphisms in the *MTRR* gene, and the variant MTRR enzyme has a lower affinity for MTR [14], and is inconsistently associated with elevated blood or plasma homocysteine levels [15]. DNA hypomethylation is an early and consistent event in cancer development, marked by an elevation in homocysteine [16]. The *MTRR* variant G

Table 1 Characteristics of eligible studies in the meta-analysis of *MTRR A66G* polymorphism and cancer risk

First author (reference)	Year	Country (racial descent)	Study design	Patient (AA/AG/GG)	Control (AA/AG/GG)	Variant allele frequency	*P* (HWE)
Colorectal cancer							
Koushik [22]	2006	USA (mixed)	Prospective study	(82/159/110)	(163/399/245)	0.55	1
Marchand [8]	2002	USA (Asian)	Population-based	(148/140/26)	(193/170/30)	0.29	0.47
	2002	USA (European)	Population-based	(26/81/40)	(45/86/39)	0.48	1
	2002	USA (Hawaiian)	Population-based	(30/34/12)	(40/38/9)	0.32	1
Theodoratou [23]	2008	Scotland (mixed)	Population-based	(200/456/339)	(198/482/329)	0.56	0.34
Otani [24]	2005	Japan (Asian)	Hospital-based	(58/44/5)	(128/82/14)	0.24	0.86
Matsuo [7]	2002	Japan (Asian)	Hospital-based	(64/55/23)	(112/114/15)	0.3	0.06
Steck [25]	2009	USA (African)	Population-based	(116/99/24)	(169/127/26)	0.28	0.77
	2009	USA (European)	Population-based	(53/155/99)	(109/256/168)	0.56	0.55
Hazra [26]	2007	USA (European)	Hospital-based	(113/258/162)	(111/264/158)	0.54	1
Lymphoid leukemia							
Kim [27]	2008	Korea (Asian)	Population-based	(370/322/75)	(857/718/125)	0.28	0.14
Gemmati [28]	2004	Italy (European)	Population-based	(28/58/23)	(59/122/76)	0.53	0.46
Gast [9]	2007	Germany (European)	Population-based	(109/236/111)	(97/294/158)	0.56	0.06
Petra [29]	2007	Central European (European)	Population-based	(15/36/17)	(47/136/75)	0.55	0.5
Gra [30]	2008	Russia (European)	Population-based	(135/42)[a]	(151/95)[a]	NA	NA
Robert [31]	2009	The Netherlands (European)	Population-based	(59/117/66)	(101/245/153)	0.55	0.86
Breast cancer							
Lissowska [32]	2007	Poland (European)	Population-based	(358/970/663)	(430/1110/753)	0.57	0.57
Shrubsole [33]	2006	China (Asian)	Population-based	(621/393/70)	(687/422/76)	0.24	0.29
Suzuki [34]	2008	Japan (Asian)	Hospital-based	(205/205/42)	(456/366/90)	0.3	0.19
Kotsopoulos [35]	2008	Canada (European)	Hospital-based	(222/448/270)	(179/360/243)	0.54	0.05
Xu [36]	2008	USA (mixed)	Population-based	(279/549/230)	(276/600/223)	0.48	0.05
Sangrajrang [37]	2010	Thailand (Asian)	Hospital-based	(295/218/46)	(229/210/46)	0.31	0.9
Bladder cancer							
Moore [20]	2007	Spain (European)	Hospital-based	(267/531/291)	(232/510/274)	0.52	0.9
Rouissi [38]	2009	Tunisia (North Africa)	Hospital-based	(59/88/38)	(77/85/29)	0.37	0.5
Multiple myeloma							
Kim [39]	2007	Korea (Asian)	Population-based	(91/69/14)	(857/718/125)	0.28	0.13
Lima [40]	2007	Brazil (mixed)	Hospital-based	(32/63/28)	(53/102/33)	0.45	0.23
Malignant lymphoma							
Gemmati [28]	2004	Italy (European)	Population-based	(51/106/43)	(59/122/76)	0.53	0.5
Kim [41]	2007	Korea (Asian)	Population-based	(292/235/57)	(857/718/125)	0.28	0.14
Gastric cancer							
Stolzenberg-Solomon [18]	2003	USA (Asian)	Population-based	(136/137/36)	(186/179/33)	0.31	0.3
Zhang [42]	2007	USA (European)	Population-based	(56/133/106)	(78/188/147)	0.58	0.2
Head and neck cancer							
Suzuki [19]	2007	Japan (Asian)	Hospital-based	(108/100/29)	(332/315/64)	0.31	0.43
Zhang [43]	2005	USA (European)	Hospital-based	(114/376/231)	(276/589/369)	0.54	0.17
Lung cancer							
Suzuki [44]	2007	Japan (Asian)	Hospital-based	(235/226/54)	(484/446/100)	0.31	0.89
Shi [45]	2005	USA (European)	Hospital-based	(162/503/370)	(231/542/375)	0.56	0.19
Meningioma							
Bethke [46]	2008	Denmark (European)	Population-based	(41/47/22)	(40/55/18)	0.4	1
	2008	England (European)	Population-based	(54/83/37)	(74/78/23)	0.35	0.74
	2008	England (European)	Population-based	(41/57/23)	(39/59/25)	0.44	0.85

Table 1 continued

First author (reference)	Year	Country (racial descent)	Study design	Patient (AA/AG/GG)	Control (AA/AG/GG)	Variant allele frequency	*P* (HWE)
	2008	Finland (European)	Population-based	(26/37/14)	(30/33/14)	0.4	0.35
	2008	Sweden (European)	Population-based	(39/84/26)	(53/74/22)	0.4	0.73
Glioma							
Bethke [46]	2008	Denmark (European)	Population-based	(42/50/7)	(40/37/23)	0.42	0.05
	2008	England (European)	Population-based	(115/177/78)	(128/179/62)	0.41	1
	2008	England (European)	Population-based	(69/97/45)	(66/101/47)	0.46	0.08
	2008	Finland (European)	Population-based	(39/69/20)	(43/70/18)	0.4	0.27
	2008	Sweden (European)	Population-based	(68/94/35)	(66/97/34)	0.42	1
Pancreatic cancer							
Suzuki [47]	2008	Japan (Asian)	Hospital-based	(78/67/12)	(374/330/81)	0.31	0.5
Prostate cancer							
Marchal [48]	2007	Spain (European)	Hospital-based	(38/105/39)	(46/111/47)	0.5	0.26
Cervical cancer							
Tong [49]	2010	Korea (Asian)	Hospital-based	(137/17)[a]	(407/23)[a]	NA	NA
Esophagus cancer							
Stolzenberg-Solomon [18]	2003	USA (Asian)	Population-based	(50/63/16)	(186/179/33)	0.31	0.29
Hepatocellular cancer							
Kwak [17]	2008	Korea (Asian)	Population-based	(40/45/9)	(111/78/12)	0.25	0.85

Prospective study: including nested case–control and case-cohort studies

HWE Hardy–Weinberg equilibrium, *MTRR* methionine synthase reductase, *NA* not available

[a] Numbers of the AA + AG and GG genotypes

allele-bearing genotype has been significantly associated with an increased risk of hepatocellular carcinoma [17] and esophageal squamous cell carcinoma [18], however other studies suggested that this *MTRR* polymorphism was less clearly associated with susceptibility to cancer [10, 19, 20]. The lack of concordance across many of these studies reflects limitations in the studies, such as small sample sizes, ethnic differences, and poor research methodology. Meta-analysis is a powerful tool for summarizing the results from different studies with enhanced precision, by producing a single estimate of the major effects. It can overcome the problem of small sample size and inadequate statistical power in genetic studies of complex traits, and it can provide more reliable results than a single case–control study [21].

Our meta-analysis, including 18,661 cases and 27,678 controls from 35 published case–control studies, explored the association between the *MTRR A66G* polymorphism and cancer risk. Overall, we found evidence that the variant genotypes of *MTRR* were associated with a significant increase in overall cancer risk using a G vs. A, or a dominant model comparison. Interestingly, 66GG was associated with a significantly increased cancer risk in Asian, but not in European populations under the recessive genetic model and by homozygote comparison. Many factors may contribute to the finding that the same polymorphism has different impacts in different ethnic populations. This may be due to genetic trait differences, since the *MTRR A66G* polymorphism showed distinct frequencies among different ethnic groups. For example, the G-allele frequency among controls was 0.29 in Asian populations and 0.53 in European populations, suggesting a possible ethnic difference. Nonetheless, different linkage disequilibrium patterns usually exist in different populations. The *MTRR A66G* polymorphism may be in close linkage with different nearby causal variants in one ethnic population but not in others. Other factors such as selection bias and different matching criteria may also play an important role in the discrepancy. Finally, the influence of the genetic variant may be masked by the presence of other, as-yet unidentified causal genes involved in the tumor formation. Different populations may have differences in dietary intake of nutrients, some of which affect cancer development. Thus, further investigations are warranted to validate ethnic differences in the effect of this functional polymorphism on cancer risk, especially in Europeans.

Although the pooled results were robust in Asian populations, they should still be treated with caution because of different study designs. When stratified separately by population-based and hospital-based studies, inverse results were observed in Asian populations, that is, 66GG was associated with increased cancer risk in the population-

Table 2 Summary of comparisons for *MTRR A66G* polymorphism and cancer risk

Contrast	Variables	Comparisons	OR	95% CI	*P* (heterogeneity)[a]	*P*-value	*P* (publication bias)
G vs. A	Overall	39	1.039	1.009–1.078	0.021	0.043	0.58
	Study design						
	Population-based	23	1.033	0.996–1.071	0.056	0.08	0.672
	Hospital-based	15	1.052	1.004–1.101	0.06	0.032	0.748
	Ethnicity						
	Asian	15	1.063	1.011–1.119	0.328	0.018	0.334
	Population-based	8	1.089	1.020–1.163	0.508	0.011	0.134
	Hospital-based	7	1.025	0.946–1.112	0.223	0.544	0.768
	European	17	1.009	0.950–1.073	0.005	0.764	0.253
	Population-based	11	0.981	0.902–1.067	0.02	0.66	0.352
	Hospital-based	6	1.047	0.956–1.148	0.041	0.321	0.726
	Others[b]	7	1.041	0.971–1.116	0.425	0.256	0.027
	Tumor type						
	Colorectal cancer	10	1.057	0.988–1.131	0.698	0.105	0.015
	Lymphoid leukemia	5	0.899	0.762–1.061	0.023	0.208	0.227
	Breast cancer	6	1	0.950–1.053	0.379	0.995	0.433
	Other cancers[c]	18	1.08	1.035–1.127	0.102	0.001	0.739
GG vs. GA	Overall	39	1.035	0.989–1.083	0.151	0.137	0.516
	Study design						
	Population-based	23	1.044	0.977–1.117	0.623	0.202	0.728
	Hospital-based	15	1.02	0.939–1.108	0.232	0.645	0.365
	Ethnicity						
	Asian	15	1.027	0.958–1.101	0.566	0.45	0.445
	Population-based	8	1.239	1.056–1.454	0.887	0.008	0.998
	Hospital-based	7	1.095	0.807–1.486	0.034	0.561	0.715
	European	17	1.065	0.967–1.173	0.043	0.201	0.841
	Population-based	11	0.971	0.891–1.058	0.649	0.501	0.125
	Hospital-based	6	0.996	0.906–1.095	0.87	0.935	0.441
	Others[b]	7	0.961	0.853–1.082	0.51	0.508	0.152
	Tumor type						
	Colorectal cancer	10	1.017	0.908–1.138	0.497	0.777	0.099
	Lymphoid leukemia	5	0.931	0.812–1.069	0.328	0.311	0.36
	Breast cancer	6	1.007	0.927–1.094	0.195	0.87	0.658
	Other cancers[c]	18	1.089	1.017–1.166	0.193	0.015	0.431
GG vs. AA	Overall	39	1.094	1.006–1.191	0.004	0.037	0.485
	Study design						
	Population-based	23	1.081	0.971–1.205	0.033	0.154	0.542
	Hospital-based	15	1.134	0.978–1.317	0.016	0.097	0.76
	Ethnicity						
	Asian	15	1.189	1.055–1.341	0.191	0.005	0.605
	Population-based	8	1.283	1.096–1.501	0.661	0.002	0.343
	Hospital-based	7	1.071	0.888–1.291	0.08	0.475	0.81
	European	17	1.022	0.898–1.164	0.002	0.739	0.301
	Population-based	11	0.96	0.807–1.142	0.016	0.645	0.368
	Hospital-based	6	1.114	0.910–1.364	0.017	0.297	0.848
	Others[b]	7	1.072	0.930–1.235	0.427	0.339	0.024
	Tumor type						
	Colorectal cancer	10	1.113	0.968–1.279	0.221	0.133	0.067
	Lymphoid leukemia	5	0.809	0.553–1.184	0.009	0.275	0.36
	Breast cancer	6	0.996	0.893–1.111	0.794	0.943	0.221
	Other cancers[c]	18	1.196	1.093–1.310	0.079	0.001	0.746

Table 2 continued

Contrast	Variables	Comparisons	OR	95% CI	*P* (heterogeneity)[a]	*P*-value	*P* (publication bias)
GG + GA vs. AA	Overall	39	1.05	0.994–1.109	0.031	0.081	0.588
	Study design						
	Population-based	23	1.039	0.984–1.097	0.218	0.17	0.627
	Hospital-based	15	1.083	0.978–1.199	0.026	0.126	0.771
	Ethnicity						
	Asian	15	1.052	0.985–1.124	0.515	0.129	0.313
	Population-based	8	1.073	0.986–1.167	0.531	0.102	0.086
	Hospital-based	7	0.484	0.330–0.709	0.001	0.001	0.972
	European	17	1.049	0.944–1.165	0.004	0.374	0.596
	Population-based	11	0.726	0.600–0.879	0.001	0.001	0.535
	Hospital-based	6	0.953	0.800–1.135	0.022	0.588	0.908
	Others[b]	7	1.002	0.896–1.121	0.36	0.969	0.098
	Tumor type						
	Colorectal cancer	10	1.051	0.945–1.170	0.571	0.358	0.028
	Lymphoid leukemia	5	0.809	0.553–1.184	0.009	0.275	0.36
	Breast cancer	6	1.017	0.938–1.104	0.276	0.681	0.533
	Other cancers[c]	18	1.111	1.042–1.185	0.077	0.001	0.501
GG vs. GA + AA	Overall	41	1.051	0.983–1.125	0.01	0.144	0.38
	Study design						
	Population-based	24	1.032	0.941–1.131	0.021	0.501	0.87
	Hospital-based	16	1.062	0.983–1.148	0.059	0.126	0.254
	Ethnicity						
	Asian	16	1.197	1.068–1.341	0.106	0.002	0.485
	Population-based	8	1.263	1.085–1.471	0.8	0.003	0.602
	Hospital-based	8	1.18	0.882–1.579	0.016	0.266	0.493
	European	18	0.967	0.889–1.052	0.039	0.435	0.041
	Population-based	12	0.912	0.799–1.041	0.019	0.171	0.116
	Hospital-based	6	1.033	0.945–1.129	0.531	0.478	0.469
	Others[b]	7	1.112	0.992–1.247	0.839	0.068	0.004
	Tumor type						
	Colorectal cancer	10	1.1	0.986–1.228	0.347	0.089	0.159
	Lymphoid leukemia	6	0.807	0.602–1.081	0.004	0.151	0.326
	Breast cancer	6	0.996	0.912–1.087	0.772	0.926	0.369
	Other cancers[c]	19	1.108	1.028–1.194	0.199	0.007	0.199

MTRR methionine synthase reductase, *OR* odds ratio, *CI* confidence interval

[a] If $P_{\text{heterogeneity}} > 0.05$, the fixed-effects model was selected to pool the data. Otherwise, the random-effects model was used

[b] Ethnicities excluded Asian and European populations

[c] If the tumor site contained fewer than three independent individual studies, it was categorized into the "other cancers" group

based studies, and decreased cancer risk in the hospital-based studies. The pooled results in Asian populations may be a spurious finding, and larger population-based studies are required to further clarify the association between the *MTRR A66G* polymorphism and cancer susceptibility in Asian populations. These inconsistent results suggest that selection bias is an important issue for studies of the genetic cause of cancer. Hospital-based studies have a high risk of producing unreliable results because hospital-based controls may not always authentically represent the general population, especially when the genotypes under investigation are expected to affect disease conditions that might be seen in the hospital-based controls. Thus, the use of proper and representative population-based control participants is of great importance in reducing bias in such genotype association studies.

Subgroup analysis by cancer type showed an increased cancer risk for "other cancers" by homozygote or heterozygote comparison, as well as using the dominant and recessive models. However, we failed to find any significant association between the *MTRR A66G* polymorphism and colorectal cancer, breast cancer, or lymphoid leukemia in any comparison models. Although the reason for these discrepancies is not completely understood, many factors

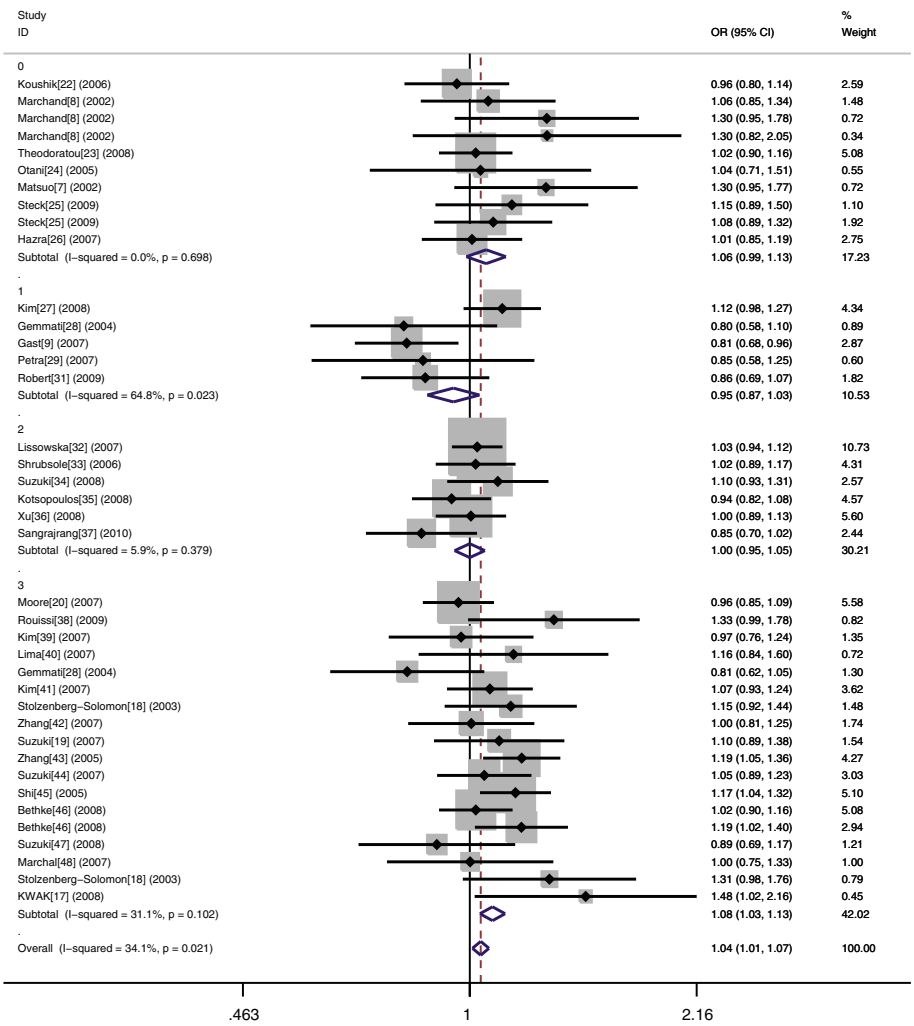

Fig. 1 Forest plot of cancer risk associated with the *MTRR A66G* polymorphism (G vs. A) in overall populations. The *squares* and *horizontal lines* correspond to the study-specific OR and 95% CI. The *area of the squares* reflects the study-specific weight (inverse of the variance). *Diamonds* represent the pooled OR and 95% CI

may be contributing. First, the *MTRR A66G* polymorphism might have a different role in different cancers. Second, studies with small sample sizes may be underpowered for detecting a small but real association. In the "other cancers" groups of our meta-analysis, only one or two studies were available for each specific cancer type, and they had very small case–control numbers, so larger studies are needed to confirm this relationship. Third, the result of each study might be influenced by gene–gene or gene–environment interactions, because environmental factors or other genes may predominate in the development of cancer. Consequently, additional prospective studies are needed to clarify whether the *MTRR A66G* polymorphism truly affects different types of cancer in different ways.

In this meta-analysis, 17 of 35 eligible studies investigated interactions between polymorphisms and environmental factors, and 15 studied gene–gene interactions. The results were conflicting. Not all analyzed the same genetic or environmental factors, which included folate-mediated one-carbon metabolism genes (*MTHFR*, *TYMS*, *MTR*, *SHMT1*, *CBS*), vitamin B_6 intake, vitamin B_{12} intake, folate intake, methionine intake, cigarette consumption, and alcohol status. Environmental or genetic factors may have different effects on different cancer types or ethnicities. The obtained data may not reflect intake as accurately as other methods, such biological markers. Consequently, large-scale, well-designed, population-based studies are required to investigate gene–gene and gene–environment interactions on the *MTRR A66G* polymorphism and cancer risk.

Heterogeneity is a potential problem when interpreting the results of all meta-analysis. Significant between-study heterogeneity existed in homozygote (GG vs. AA), recessive genetic model (GG vs. GA + AA), and dominant genetic model (GG + GA vs. AA) comparisons. After subgroup analyses by ethnicity, the heterogeneity was effectively decreased or removed. The reason might be that differences of genetic backgrounds and the environment existed among different ethnicities.

Some limitations of this meta-analysis should be addressed. First, not having the original data for the reviewed studies limited our evaluation of potential gene–

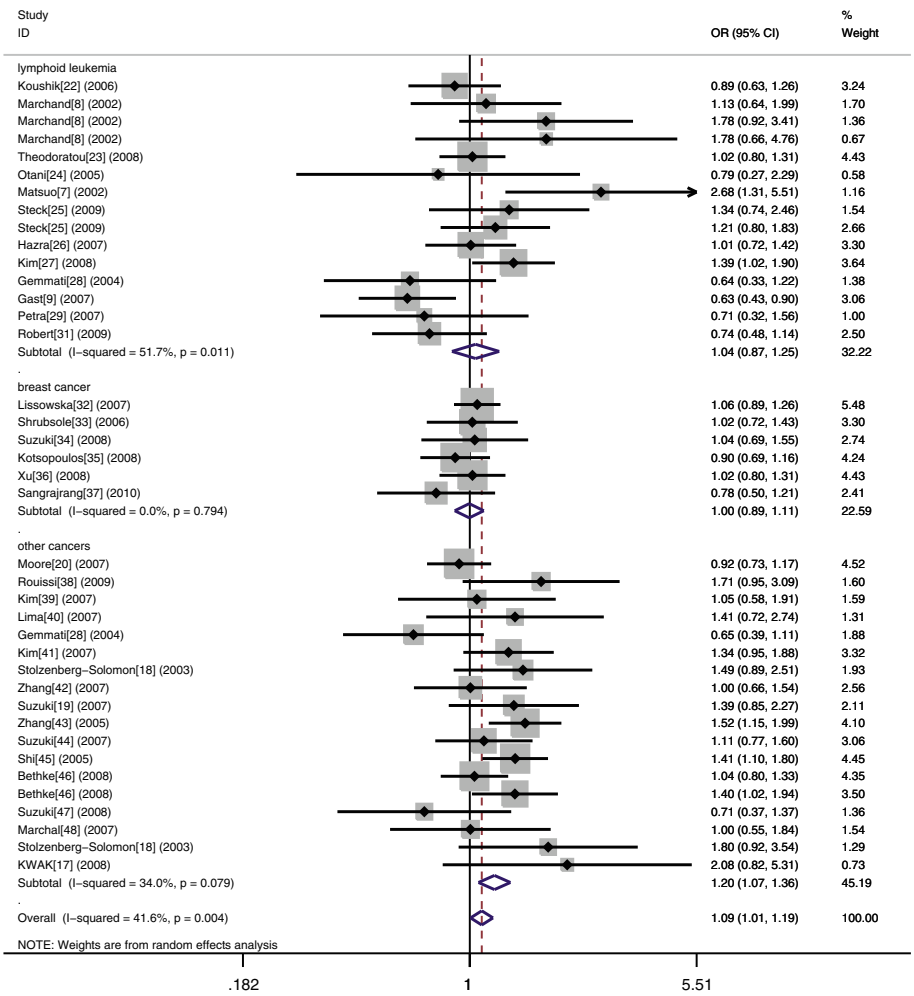

Fig. 2 Forest plot of cancer risk associated with the *MTRR A66G* polymorphism (GG vs. AA) in overall populations. The *squares* and *horizontal lines* correspond to the study-specific OR and 95% CI. The *area of the squares* reflects the study-specific weight (inverse of the variance). The *diamonds* represent the pooled OR and 95% CI

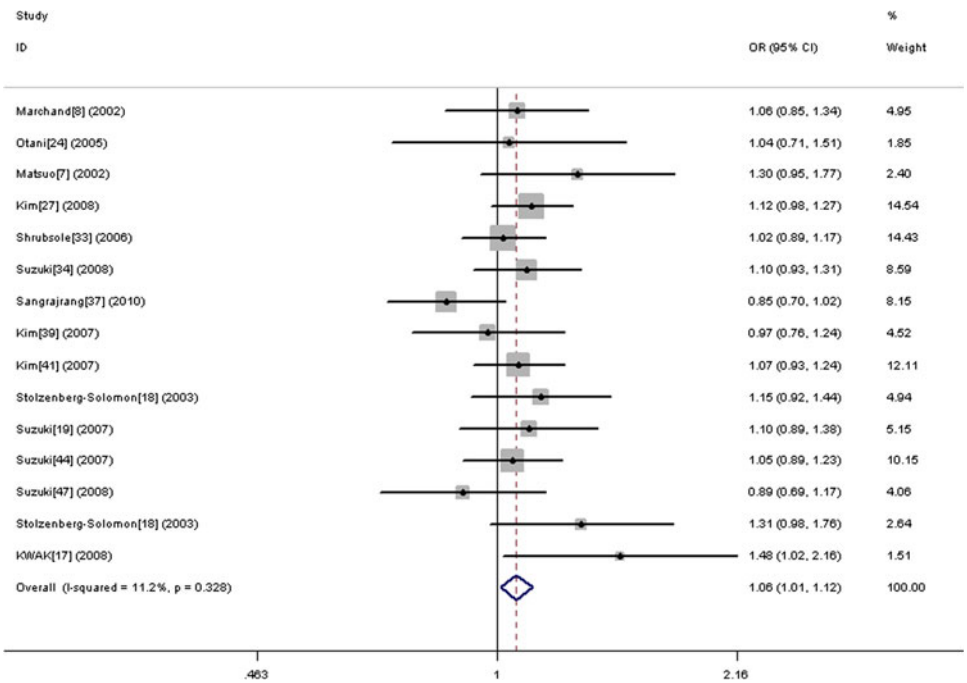

Fig. 3 Forest plot of cancer risk associated with the *MTRR A66G* polymorphism (G vs. A) in Asian populations. The *squares* and *horizontal lines* correspond to the study-specific OR and 95% CI. The *area of the squares* reflects the study-specific weight (inverse of the variance). The *diamonds* represent the pooled OR and 95% CI

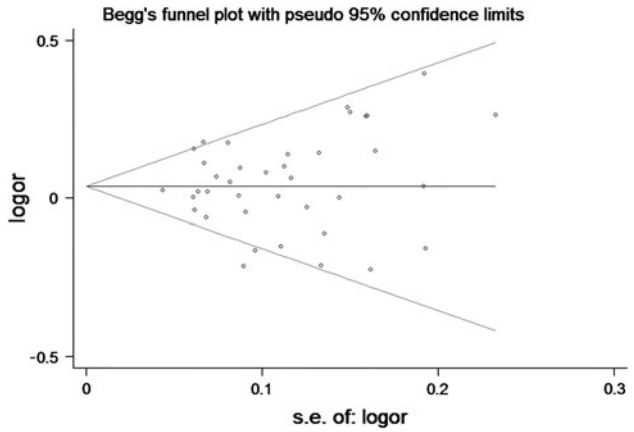

Fig. 4 Begg's funnel plot of the Egger's test for publication bias of *MTRR A66G* polymorphism and cancer risk (G vs. A). The *horizontal line* in the funnel plot indicates the random-effects summary estimate. *Sloping lines* indicate the expected 95% CI for a given SE

gene, gene–environment, or even different polymorphism loci of the same gene, which all may affect cancer risk. Second, because of the data limitation, we did not perform stratification analysis by age, sex, smoking status, drinking status, obesity, or other variables. This might have caused serious confounding bias. Third, although the funnel plot and Egger's test showed no publication bias, selection bias may have occurred because only published studies were retrieved. The number of published studies was not sufficiently large for a comprehensive analysis, particularly for a specific cancer type. Nonetheless, advantages in our meta-analysis should also be acknowledged. First, a substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication bias was detected, indicating that the pooled results should be reliable. Third, the quality of case–control studies included in the meta-analysis was satisfactory based on our selection criteria.

In summary, this meta-analysis identified evidence of an association between the *MTRR A66G* polymorphism and cancer risk, supporting the hypothesis that the *MTRR A66G* may cause an increased risk of cancer, especially in people of Asian descent. As the biological role of *MTRR A66G* SNP is still unclear, predicting the effect of *MTRR A66G* on cancer risk in European populations is difficult. Future studies with large sample sizes and tissue-specific biological characterization are required to investigate the biological mechanism and function of the *MTRR A66G* polymorphism.

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Conflict of interest None.

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