European Journal of Human Genetics (2010) 18, 370–378

www.nature.com/ejhg

ARTICLE

Methionine synthase *A2756G* polymorphism and cancer risk: a meta-analysis

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Polymorphisms in methionine synthase (*MTR*) gene may be involved in carcinogenesis by affecting DNA methylation. However, association studies on *MTR A2756G* polymorphism in cancers have reported conflicting results. Therefore we performed a meta-analysis to better assess the associations. A total of 24 896 cancer patients and 33 862 controls from 52 articles for *MTR A2756G* were investigated. Overall, individuals carrying *MTR* 2756GG genotype had a subtly reduced cancer risk under a recessive genetic model (odds ratio (OR), 0.92; P=0.053; 95% confidence interval (95% CI), 0.84–1.00; I^2=0.0%; $P_{heterogeneity}$=0.61). In the subgroup analyses by ethnicity, 2756GG was associated with a significantly reduced cancer risk in European populations (OR, 0.83; P=0.001; 95% CI, 0.74–0.93; I^2=0.0%; $P_{heterogeneity}$=0.99). However, in Asian populations, a significantly elevated association between 2756GG genotype and cancer risk was observed (OR, 1.33; P=0.012; 95% CI, 1.06–1.65; I^2=0.0%; $P_{heterogeneity}$=0.50). In studies stratified by tumor site, there was a significantly reduced risk of acute lymphoblastic leukemia (ALL) (OR, 0.54; P=0.049; 95% CI, 0.29–1.00; I^2=10.7%; $P_{heterogeneity}$=0.33) and colorectal cancer (OR, 0.63; P=0.004; 95% CI, 0.47–0.87; I^2=0.0%; $P_{heterogeneity}$=0.73) in European populations. Our study indicates that *MTR A2756G* polymorphism is a candidate gene polymorphism for cancer susceptibility regardless of environmental factors. Large-scale, well-designed, and population-based studies are required to further investigate gene–gene and gene–environment interactions on *MTR A2756G* polymorphism and tissue-specific cancer risk in an ethnicity-specific population.
European Journal of Human Genetics (2010) **18,** 370–378; doi:10.1038/ejhg.2009.131; published online 14 October 2009

Keywords: *MTR*; cancer; polymorphism; meta-analysis

INTRODUCTION

DNA methylation is critical for regulating gene expression and gene integrity. Mechanism of carcinogenesis by abnormal DNA methylation is complex. Gene-specific hypermethylation and global DNA hypomethylation are two of the most common patterns observed in many tumors.[1] Methionine synthase is a vitamin B_{12}-dependent enzyme, which catalyzes the remethylation of homocysteine to methionine and the concurrent demethylation of 5-methyltetrahydrofolate to tetrahydrofolate. Methionine synthase has a key role in maintaining adequate intracellular folate, methionine and normal homocysteine concentrations. Methionine is an essential amino acid and precursor of S-adenosylmethionine, which is a universal methyl-group donor involved in methylation reactions including DNA methylation.[2]

A common polymorphism in methionine synthase (*MTR*) gene (2756A→G, rs1805087) was initially thought to be associated with lower enzyme activity than *MTR* 2756AA genotype, causing homocysteine elevation and DNA hypomethylation.[3] However, in subsequent investigations, some studies suggested a modest inverse association between 2756GG polymorphism and homocysteine levels, indicating an increased enzymatic activity of the variant genotype.[4] Moreover, Paz *et al.*[5] found that individuals who carried 2756GG showed a lower frequency of CpG island hypermethylation in tumor suppressor genes.

For now, there are a large number of molecular epidemiological studies conducted to evaluate the role of *MTR* polymorphism in different kinds of neoplasm. However, the association between polymorphism and cancer risk is still controversial. Here, we performed a meta-analysis including subgroup analysis from all eligible studies to assess the association of *MTR A2756G* polymorphism with cancer risk.

MATERIALS AND METHODS

Identification and eligibility of relevant studies

We conducted a computerized literature search of PubMed database (from January 1991 to May 2008) using the following keywords and subject terms: 'methionine synthase' or '*MTR*', 'polymorphism', and 'cancer' or 'carcinoma' or 'neoplasm'. References of retrieved articles were also screened. When a study reported results on different racial descent subpopulations or tumor sites, we treated each subpopulation or tumor as a separate comparison. Studies included in the meta-analysis had to meet all the following criteria: (a) use unrelated individuals, (b) have available genotype frequencies for both patients and control populations, and (c) genotype distribution of the control population must be in Hardy–Weinberg equilibrium.

Data extraction

Two investigators extracted data independently. When it came to conflicting evaluations, an agreement was reached after a discussion. Data were collected on the authors, journal, year of publication, ethnicity and country of study population (mixed or unknown populations were categorized as 'Others' group), study design, demographics, selection and characteristics of cancer patients and controls (gender, age, sample size, type of sample for genotyping and other variables that can be sources of bias), tumor site, methods for genotyping, *MTR* polymorphism genotyping information, interactions between environmental factors or genes.

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Received 18 February 2009; revised 28 May 2009; accepted 26 June 2009; published online 14 October 2009

Statistical analysis

Unadjusted OR corresponding to a 95% CI of each study was first calculated in a 2×2 table.[6] The meta-analysis assessed association between allele G and cancer risk compared with allele A (G vs A), as well as using homozygote comparison (GG vs AA), the recessive genetic model (GG vs AG+AA), the dominant genetic model (AG+GG vs AA) and AG vs AA contrast. Between-study heterogeneity was measured using a *Q*-statistic test[7] and an *I*-square statistic.[8] $P<0.10$ was considered representative of significant statistical heterogeneity because of the low power of the statistic. A fixed-effect model using the Mantel–Haenszel method and a random-effects model using the DerSimonian and Laird method were used to pool the results.[9] The *Z* test was used to assess the significance of the pooled OR and a *P*-value of <0.05 was considered significant.

Subgroup analysis was stratified by the study characteristic of racial descent, study design and tumor site, respectively. Furthermore, meta-regression analysis[10] was performed to investigate three potential sources of heterogeneity including ethnicity (Asian vs European), study design (hospital-based vs population-based) and tumor site (one tumor site vs other tumor sites). Statistical significance was defined as a *P*-value less than 0.10 because of the relatively weak statistical power.

Sensitivity analysis was performed by sequential omission of individual studies and tumor sites under various comparisons in worldwide, Asian and European populations, respectively. We also did cumulative meta-analysis to evaluate the trend of summary ORs (95% CIs) by year of publication.

Publication bias was investigated by funnel plot. Funnel plot asymmetry was assessed by the method of Egger's linear regression test.[11]

Hardy–Weinberg equilibrium was tested by the χ^2-test using a web-based program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl); Analyses were performed using the software Stata version 10.0. All *P*-values were two-sided.

RESULTS

Eligible studies

Based on the search criteria, 102 articles were found. Sixty-one articles reporting *MTR A2756G* polymorphism and cancer risk were identified, but only 52 articles met our inclusion criteria. Overall, a total of 24 896 cancer patients and 33 862 controls available from 52 articles (71 studies) for *MTR A2756G* polymorphism were investigated.

Meta-analysis database

We established a database based on the extracted information from each eligible article (Table 1). Tumors were confirmed by histological or pathogenic analysis in 45 articles (87%). Forty-five articles (87%) matched in age and 46 articles (88%) matched in sex. While genotyping, only 17 articles (33%) randomly repeated a portion of samples, and 11 articles (21%) described use of blindness of the status of DNA samples. Among 52 articles, 20 (38%) investigated the interactions between polymorphisms and environmental factors, whereas 19 (37%) studied the combined effect with other genes.

Quantitative synthesis

There were significant differences in terms of variant 2756G allele frequency between the two major ethnicities (Asian, 15.0%; 95% CI, 12.7–17.3%; European, 19.6%; 95% CI, 18.8–20.5%; $P<0.0001$). Table 2 indicates the associations between *MTR A2756G* polymorphism and cancer risks (ORs). Overall, individuals carrying *MTR* 2756GG genotype had a subtly reduced cancer risk compared with individuals with 2756AA genotype (OR, 0.91; $P=0.049$; 95% CI, 0.83–1.00; $I^2=9.3\%$; $P_{heterogeneity}=0.26$). In different ethnicities, 2756GG was associated with a significantly reduced cancer risk in European populations (OR, 0.83; $P=0.001$; 95% CI, 0.74–0.93; $I^2=0.0\%$; $P_{heterogeneity}=0.99$) (Figure 1). However, in Asian populations, a significantly elevated association between 2756GG genotype and cancer risk was found (OR, 1.33; $P=0.012$; 95% CI, 1.06–1.65; $I^2=0.0\%$; $P_{heterogeneity}=0.50$) (Figure 2). Furthermore, according to different study designs in Asian populations, 2756GG genotype led to a significantly increased cancer risk in hospital-based studies (OR, 1.56; $P=0.001$; 95% CI, 1.21–2.01; $I^2=0.0\%$; $P_{heterogeneity}=0.60$) whereas there was an insignificantly decreased cancer risk in population-based studies (OR, 0.83; $P=0.421$; 95% CI, 0.53–1.31; $I^2=0.0\%$; $P_{heterogeneity}=0.69$). In the subgroup analysis stratified by tumor site, there was a significantly reduced risk of ALL (OR, 0.54; $P=0.049$; 95% CI, 0.29–1.00; $I^2=10.7\%$; $P_{heterogeneity}=0.33$), as well as of colorectal cancer (OR, 0.63; $P=0.004$; 95% CI, 0.47–0.87; $I^2=0.0\%$; $P_{heterogeneity}=0.73$) in European populations (Figure 1). No significant association was found in other tumor sites.

Test of heterogeneity

Q-statistic indicated no significant heterogeneity among the 71 studies about *MTR A2756G* polymorphism. However, meta-regression indicated that both ethnicity (Asian vs European, $P<0.001$) and study design (hospital-based vs population-based, $P=0.071$) significantly contributed to the heterogeneity for *MTR A2756G* polymorphism under the recessive genetic model. Moreover, colorectal adenoma for *MTR* (colorectal adenoma vs other tumors, $P=0.076$) showed significant contribution to the heterogeneity.

Sensitivity analysis and cumulative meta-analysis

The pooled ORs were consistently significant in Asian populations or European populations by omitting one study or one tumor at a time under the recessive genetic model and homozygote comparison, suggesting robustness of our results. In the cumulative meta-analysis, for Asian or European populations, the pooled ORs tended to be stable and the associations tended toward significant associations with accumulation of more data over time (Figures 3 and 4).

Publication bias

Funnel plots and Egger's test were performed to assess publication bias. No publication bias was detected for *MTR A2756G* (GG vs AG+AA, $t=1.14$, $P=0.257$). Figure 5 showed the Begg's funnel plot of the Egger's test.

DISCUSSION

This article investigated the relationship between *MTR A2756G* polymorphism and cancer susceptibility. Overall, 2756GG was associated with a significantly reduced cancer risk in European populations, but an elevated cancer risk in Asian populations under the recessive genetic model and homozygote comparison. Sensitivity analysis indicated robustness of our results.

In this meta-analysis, ethnicity was identified as a potential source of between-study heterogeneity by meta-regression and subgroup analyses for *A2756G* polymorphism. Many factors may contribute to the fact that the same polymorphism has different roles in different ethnic populations. First, cancer is a complex disease and different genetic backgrounds may cause the discrepancy. There were significant differences in terms of variant 2756G allele frequency between the two major ethnicities. Secondly, different populations usually have different linkage disequilibrium patterns. A polymorphism may be in close linkage with another nearby causal variant in one ethnic population but not in another. *MTR A2756G* polymorphism may be in close linkage with different nearby causal variants in different populations. Thirdly, clinical heterogeneity like age, sex ratio, dietary, years from onset and disease severity may also explain the discrepancy. Different

Table 1 Characteristics of eligible studies investigated the association between *MTR A2756G* polymorphism and cancer risk

First author (reference)	*Country (racial descent)*	*Study design*	*Patient (AA/AG/GG)*	*Control (AA/AG/GG)*	*Variant allele frequency*
Malignant lymphoma					
Matsuo[3]	Japan (Asian)	Hospital-based	(63/26/7)	(156/81/6)	(0.19)
Lincz[34]	USA (European)	Population-based	(110/34/5)	(187/99/12)	(0.21)
Gemmati[32]	Italy (European)	Population-based	(129/65/6)	(158/89/10)	(0.21)
Linnebank[41]	Germany (European)	Population-based	(26/5/0)	(83/51/8)	(0.24)
Matsuo[42]	Japan (Asian)	Hospital-based	(172/88/13)	(335/150/15)	(0.18)
Lightfoot[43]	England (European)	Population-based	(382/190/17)	(507/222/26)	(0.18)
Niclot[44]	France (European)	Population-based	(144/24/3)	(149/51/6)	(0.15)
Lee[45]	Australia (mixed)[a]	Population-based	(364/173/22)	(304/180/21)	(0.22)
Lim[46]	USA (mixed)	Population-based	(186/79/7)	(169/62/10)	(0.17)
Kim[47]	Korea (Asian)	Population-based	(442/133/9)	(1282/392/26)	(0.13)
Colorectal cancer					
Ma[2]	USA (mixed)	Prospective study [b]	(145/61/6)	(235/95/16)	(0.18)
	USA (mixed)	Prospective study	(103/37/4)	(82/42/6)	(0.21)
Le Marchand[36]	USA (Asian)	Population-based	(212/91/12)	(259/119/16)	(0.19)
	USA (European)	Population-based	(103/43/2)	(116/50/5)	(0.18)
	USA (Hawaiian)	Population-based	(57/17/2)	(72/14/1)	(0.09)
Matsuo[48]	Japan (Asian)	Hospital-based	(90/47/5)	(156/79/6)	(0.19)
Pufulete[1]	UK (European)	Hospital-based	(19/8/1)	(45/23/8)	(0.26)
Ulvik[49]	Norway (European)	Prospective study	(1457/647/64)	(1402/693/97)	(0.20)
Matsuo[13]	Japan (Asian)	Hospital-based	(165/78/14)	(499/247/25)	(0.19)
Ulrich[27]	USA (mixed)	Population-based	(1015/529/56)	(1264/608/90)	(0.20)
Koushik[50]	USA (mixed)	Prospective study	(222/121/20)	(529/239/36)	(0.19)
Theodoratou[51]	Scotland (mixed)	Population-based	(630/332/37)	(662/318/30)	(0.19)
Breast cancer					
Justenhoven[52]	Germany (European)	Population-based	(366/197/22)	(415/193/27)	(0.19)
Shrubsole[53]	China (Asian)	Population-based	(877/181/8)	(932/195/11)	(0.10)
Yu[54]	Taiwan (Asian)	Prospective study	(85/22/1)	(324/92/2)	(0.12)
Kotsopoulos[55]	Canada (European)	Hospital-based	(635/273/31)	(489/252/34)	(0.21)
Suzuki[56]	Japan (Asian)	Hospital-based	(301/135/19)	(616/269/25)	(0.18)
Bladder cancer					
Kimura[57]	Germany (European)	Hospital-based	(113/48/4)	(102/44/4)	(0.17)
Lin[35]	USA (African)	Hospital-based	(17/4/0)	(11/10/0)	(0.24)
	USA (European)	Hospital-based	(276/117/16)	(267/123/18)	(0.20)
	USA (Mexican-American)	Hospital-based	(6/9/0)	(11/8/0)	(0.21)
Ouerhani[58]	Tunisia (African)	Population-based	(50/58/3)	(86/43/2)	(0.18)
Colorectal adenoma					
Chen[59]	USA (mixed)	Prospective study	(166/85/6)	(456/236/21)	(0.20)
Pufulete[1]	UK (European)	Hospital-based	(18/14/3)	(45/23/8)	(0.26)
Goode[4]	USA (European)	Hospital-based	(328/161/24)	(408/183/18)	(0.18)
Hazra[14]	USA (mixed)	Prospective study	(333/171/25)	(338/177/17)	(0.20)
Lymphoid leukemia					
Gemmati[32]	Italy (European)	Population-based	(88/29/1)	(158/89/10)	(0.21)
Gast[15]	Germany (European)	Population-based	(280/153/13)	(375/151/21)	(0.18)
Petra[16]	Central Europe (European)	Population-based	(51/16/1)	(161/82/15)	(0.22)
Esophageal cancer					
Yang[17]	Japan (Asian)	Hospital-based	(103/56/6)	(322/157/15)	(0.19)
Ott[30]	Germany (European)	Hospital-based	(202/108/8)	(164/73/8)	(0.18)
Gastric cancer					
Zhang[18]	Poland (European)	Population-based	(182/96/15)	(270/123/20)	(0.20)
Ott[30]	Germany (European)	Hospital-based	(174/83/13)	(164/73/8)	(0.18)
Lung cancer					
Shi[19]	USA (European)	Hospital-based	(761/249/25)	(830/293/25)	(0.15)
Hung[31]	Central Europe (European)	Hospital-based	(887/511/62)	(1089/589/98)	(0.22)
Suzuki[20]	Japan (Asian)	Hospital-based	(319/175/21)	(698/291/40)	(0.18)

Table 1 (Continued)

First author (reference)	*Country (racial descent)*	*Study design*	*Patient (AA/AG/GG)*	*Control (AA/AG/GG)*	*Variant allele frequency*
Multiple myeloma					
Lincz[34]	USA (European)	Population-based	(51/25/4)	(187/99/12)	(0.21)
Kim[21]	Korea (Asian)	Population-based	(144/29/0)	(1282/392/26)	(0.13)
Lima[22]	Brazil (mixed)	Hospital-based	(74/42/7)	(144/37/7)	(0.14)
Glioma					
Semmler[23]	Germany (European)	Population-based	(236/85/7)	(228/152/20)	(0.24)
Bethke[29]	Denmark (European)	Population-based	(67/29/3)	(70/25/5)	(0.18)
	England (European)	Population-based	(256/101/13)	(240/115/13)	(0.19)
	England (European)	Population-based	(131/74/6)	(129/75/10)	(0.22)
	Finland (European)	Population-based	(74/49/5)	(82/45/4)	(0.20)
	Sweden (European)	Population-based	(122/67/8)	(133/57/7)	(0.18)
Meningioma					
Bethke[29]	Denmark (European)	Population-based	(73/33/4)	(70/40/3)	(0.20)
	England (European)	Population-based	(113/54/7)	(106/60/8)	(0.22)
	England (European)	Population-based	(77/39/5)	(75/42/6)	(0.22)
	Finland (European)	Population-based	(50/24/3)	(56/17/4)	(0.16)
	Sweden (European)	Population-based	(98/45/6)	(94/51/4)	(0.20)
Semmler[24]	Germany (European)	Hospital-based	(197/81/12)	(184/92/11)	(0.20)
Cervical cancer					
Kang[25]	Korea (Asian)	Hospital-based	(53/10/2)	(58/14/0)	(0.10)
Shekari[26]	India (north indian)	Hospital-based	(181/14/5)	(118/63/14)	(0.23)
Head and neck cancer					
Zhang[28]	USA (European)	Hospital-based	(472/232/17)	(876/327/31)	(0.16)
Suzuki[12]	Japan (Asian)	Hospital-based	(151/75/11)	(496/195/20)	(0.17)
Prostate cancer					
Kimura[33]	Germany (European)	Hospital-based	(87/41/4)	(102/44/4)	(0.17)
Marchal[37]	Spain (European)	Hospital-based	(118/54/9)	(138/55/11)	(0.19)
Other cancer sites					
Wang[38c]	China (Asian)	Hospital-based	(90/8/3)	(298/38/1)	(0.06)
Hung[31d]	Central Europe (European)	Hospital-based	(277/139/20)	(1089/589/98)	(0.22)
Moore[39e]	Central and Eastern Europe (European)	Hospital-based	(545/258/45)	(683/383/68)	(0.23)
Sirachainan[40f]	Thailand (Asian)	Hospital-based	(49/23/1)	(156/48/0)	(0.12)

[a]Mixed ethnicity: Lim[46], Ma[2], Ulrich[27], Koushik[50], Theodoratou[51], Lima[22], mostly Caucasian; Chen[59], Hazra[14], Nurses' Health Study.
[b]Prospective studies, including nested case–control and case–cohort studies.
[c]Pancreatic cancer.
[d]Upper aero-digestive cancer.
[e]Renal cancer.
[f]Brain tumors.

populations may have differences in dietary intake of nutrients, some of which take part in the tumor formation. Last but not least, the difference may arise from chance, such as type I error. Consequently, further research was needed to investigate the reason for the discrepancy in this study.

Although the pooled result was robust in Asian populations, it should still be treated with caution because of different study designs. Among 16 Asian studies, there were 11 hospital-based studies, but only four population-based studies. The genotype distribution in hospital-based studies may not be representative of the general population. Meta-regression indicated that study design significantly contributed to the heterogeneity. Based on different study designs in Asian populations, 2756GG was associated with a significantly increased cancer risk in hospital-based studies, but an insignificantly reduced cancer risk in population-based studies. Therefore, the pooled result in Asian populations may be a spurious finding and larger population-based studies were required to further clarify the association between *MTR A2756G* polymorphism and cancer susceptibility in Asian populations. Furthermore, among 11 hospital-based Asian studies, eight studies were related to the Japanese population, whose participants were all recruited in the framework of the hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). Therefore, the difference between these two study designs may be caused by geographical discrepancy. Meta-analysis of these eight studies showed a significantly elevated association between 2756GG genotype and cancer risk (OR, 1.47; P=0.004; 95% CI, 1.13–1.91; I^2=0.0%; $P_{\text{heterogeneity}}$=0.80). Moreover, minor allele frequency for the Japanese population (0.183) was a little lower than that

Table 2 Summary OR (95% CI) and I^2 for various contrasts of *MTR A2756G* polymorphism and cancer risk

Subgroup	*No.of studies*	*GG vs AG+AA*		*AG+GG vs AA*		*GG vs AA*		*AG vs AA*		*G vs A*	
		OR (95% CI)	*I^2(%)*	*OR (95% CI)*	*I^2(%)*	*OR (95% CI)*	*I^2(%)*	*OR (95% CI)*	*I^2(%)*	*OR (95% CI)*	*I^2(%)*
Racial descent											
Asian	16	1.33 (1.06–1.65)[c]	0.0	1.06 (0.97–1.14)	8.9	1.35 (1.08–1.69)[c]	0.0	1.03 (0.95–1.12)	5.8	1.07 (1.00–1.15)	13.5
Population-based	4	0.83 (0.53–1.31)	0.0	0.92 (0.81–1.05)	28.7	0.82 (0.52–1.28)	0.0	0.93 (0.82–1.07)	5.3	0.92 (0.82–1.04)	39.7
Hospital-based	11	1.56 (1.21–2.01)[c]	0.0	1.16 (1.04–1.28)[c]	0.0	1.61 (1.25–2.09)[c]	0.0	1.11 (1.00–1.24)	0.0	1.17 (1.07–1.28)[c]	0.0
European	40	0.83 (0.74–0.93)[c]	0.0	0.94 (0.87–1.01)	51.0[a]	0.82 (0.73–0.92)[c]	0.0	0.96 (0.89–1.03)	47.0[a]	0.94 (0.88–1.00)[c]	48.3[a]
Population-based	23	0.79 (0.65–0.97)[c]	0.0	0.88 (0.77–1.01)	60.7[a]	0.78 (0.63–0.96)[c]	0.0	0.90 (0.79–1.03)	57.7[a]	0.89 (0.79–0.99)[c]	57.5[a]
Hospital-based	16	0.90 (0.77–1.05)	0.0	0.99 (0.93–1.05)	24.7	0.89 (0.76–1.04)	0.0	1.00 (0.93–1.07)	22.0	0.98 (0.93–1.03)	20.1
Others	15	0.93 (0.77–1.12)	14.4	1.00 (0.81–1.22)	81.7[a]	0.94 (0.72–1.24)	36.8[a]	1.01 (0.82–1.24)	79.8[a]	0.99 (0.83–1.17)	80.8[a]
Study design											
Population-based	33	0.84 (0.72–0.97)[c]	0.0	0.93 (0.85–1.03)	60.0[a]	0.83 (0.72–0.97)[c]	0.0	0.95 (0.86–1.05)	56.7[a]	0.93 (0.86–1.01)	56.7[a]
Hospital-based	31	1.02 (0.89–1.16)	18.3	1.02 (0.92–1.13)	66.1[a]	1.09 (0.91–1.29)	28.7[a]	1.01 (0.91–1.12)	63.2[a]	1.03 (0.94–1.12)	65.9[a]
Prospective studies	7	0.83 (0.66–1.04)	30.7	0.94 (0.86–1.03)	22.9	0.82 (0.65–1.03)	39.0	0.95 (0.87–1.05)	0.0	0.93 (0.86–1.01)	42.5
Tumor site											
Colorectal cancer	12	0.85 (0.72–1.02)	26.8	0.99 (0.92–1.06)	20.1	0.86 (0.72–1.02)	33.3	1.01 (0.94–1.08)	0.0	0.99 (0.90–1.08)	39.1[a]
Asian	3	1.32 (0.83–2.10)	0.0	1.00 (0.82–1.21)	0.0	1.30 (0.81–2.08)	0.0	0.96 (0.79–1.18)	0.0	1.03 (0.87–1.21)	0.0
European	3	0.63 (0.47–0.87)[c]	0.0	0.87 (0.77–0.98)[c]	0.0	0.61 (0.45–0.84)[c]	0.0	0.90 (0.80–1.02)	0.0	0.86 (0.77–0.95)[c]	0.0
Others	6	0.91 (0.72–1.16)	13.2	1.07 (0.98–1.18)	12.4	0.94 (0.74–1.19)	22.0	1.09 (0.99–1.20)	0.0	1.04 (0.96–1.13)	34.0
Malignant lymphoma	10	0.96 (0.73–1.27)	0.0	0.87 (0.73–1.04)	60.3[a]	0.94 (0.71–1.23)	2.2	0.87 (0.73–1.04)	58.0[a]	0.90 (0.78–1.05)	58.9[a]
Asian	3	1.49 (0.93–2.40)	26.3	1.04 (0.88–1.23)	0.0	1.50 (0.93–2.41)	18.1	1.00 (0.84–1.19)	0.0	1.07 (0.92–1.24)	0.0
European	5	0.75 (0.49–1.17)	0.0	0.68 (0.46–1.02)	76.7[a]	0.72 (0.46–1.12)	0.0	0.70 (0.46–1.04)	75.5[a]	0.72 (0.51–1.00)	74.2[a]
Breast cancer	5	0.94 (0.70–1.27)	0.0	0.97 (0.87–1.08)	21.2	0.94 (0.69–1.27)	9.4	0.98 (0.87–1.09)	7.2	0.97 (0.89–1.07)	27.9
Asian	3	1.26 (0.77–2.06)	0.0	1.01 (0.87–1.18)	0.0	1.26 (0.77–2.07)	0.0	1.00 (0.85–1.17)	0.0	1.03 (0.89–1.18)	0.0
Glioma[b]	6	0.74 (0.50–1.11)	0.0	0.91 (0.68–1.23)	69.7[a]	0.71 (0.47–1.07)	7.6	0.93 (0.69–1.24)	65.6[a]	0.91 (0.71–1.16)	68.6[a]
European											
Meningioma[b]	6	1.03 (0.65–1.65)	0.0	0.89 (0.74–1.08)	0.0	0.99 (0.62–1.59)	0.0	0.88 (0.72–1.07)	0.0	0.92 (0.79–1.09)	0.0
European											
ALL[b]	3	0.54 (0.29–1.00)[c]	10.7	0.76 (0.39–1.46)	85.0[a]	0.55 (0.30–1.01)	38.7	0.82 (0.44–1.53)	82.8[a]	0.74 (0.42–1.31)	84.5[a]
European											
Bladder cancer	5	0.96 (0.53–1.71)	0.0	1.12 (0.66–1.90)	73.0[a]	0.98 (0.54–1.75)	0.0	1.12 (0.66–1.90)	71.9[a]	1.09 (0.73–1.62)	65.8[a]
Colorectal adenoma	4	1.31 (0.90–1.90)	0.0	1.06 (0.92–1.23)	0.0	1.33 (0.91–1.95)	0.0	1.04 (0.89–1.21)	0.0	1.08 (0.95–1.22)	0.0
Lung cancer	3	0.88 (0.68–1.13)	0.0	1.06 (0.90–1.25)	59.4[a]	0.90 (0.70–1.16)	0.0	1.08 (0.91–1.29)	61.5[a]	1.02 (0.94–1.11)	52.8
Multiple myeloma	3	1.01 (0.49–2.06)	9.2	1.08 (0.52–2.26)	86.4[a]	1.06 (0.52–2.16)	31.5	1.09 (0.53–2.23)	84.4[a]	1.04 (0.54–2.00)	86.5[a]
Other sites[d]	14	0.97 (0.80–1.19)	15.9	0.99 (0.81–1.21)	78.5[a]	0.96 (0.79–1.18)	33.9	0.98 (0.80–1.19)	76.3[a]	1.01 (0.85–1.19)	78.2[a]
Asian	5	1.91 (1.12–3.23)[c]	9.3	1.22 (1.00–1.50)	0.0	2.01 (1.18–3.42)[c]	4.5	1.16 (0.94–1.43)	0.0	1.24 (1.04–1.48)[c]	0.0
European	8	0.93 (0.74–1.16)	0.0	1.06 (0.92–1.21)	42.9[a]	0.92 (0.74–1.16)	0.0	1.05 (0.95–1.16)	41.1	1.02 (0.94–1.10)	34.3
Overall	71	0.92 (0.84–1.00)	0.0	0.98 (0.92–1.04)	61.0[a]	0.91 (0.83–1.00)[c]	9.3	0.98 (0.92–1.04)	56.9[a]	0.98 (0.93–1.03)	60.4[a]

[a]Random effect estimate.
[b]All were European studies.
[c]Significant results, *P*-value <0.05.
[d]If the tumor site contains less than three independent individual studies, it was categorized into the 'Other sites' group.

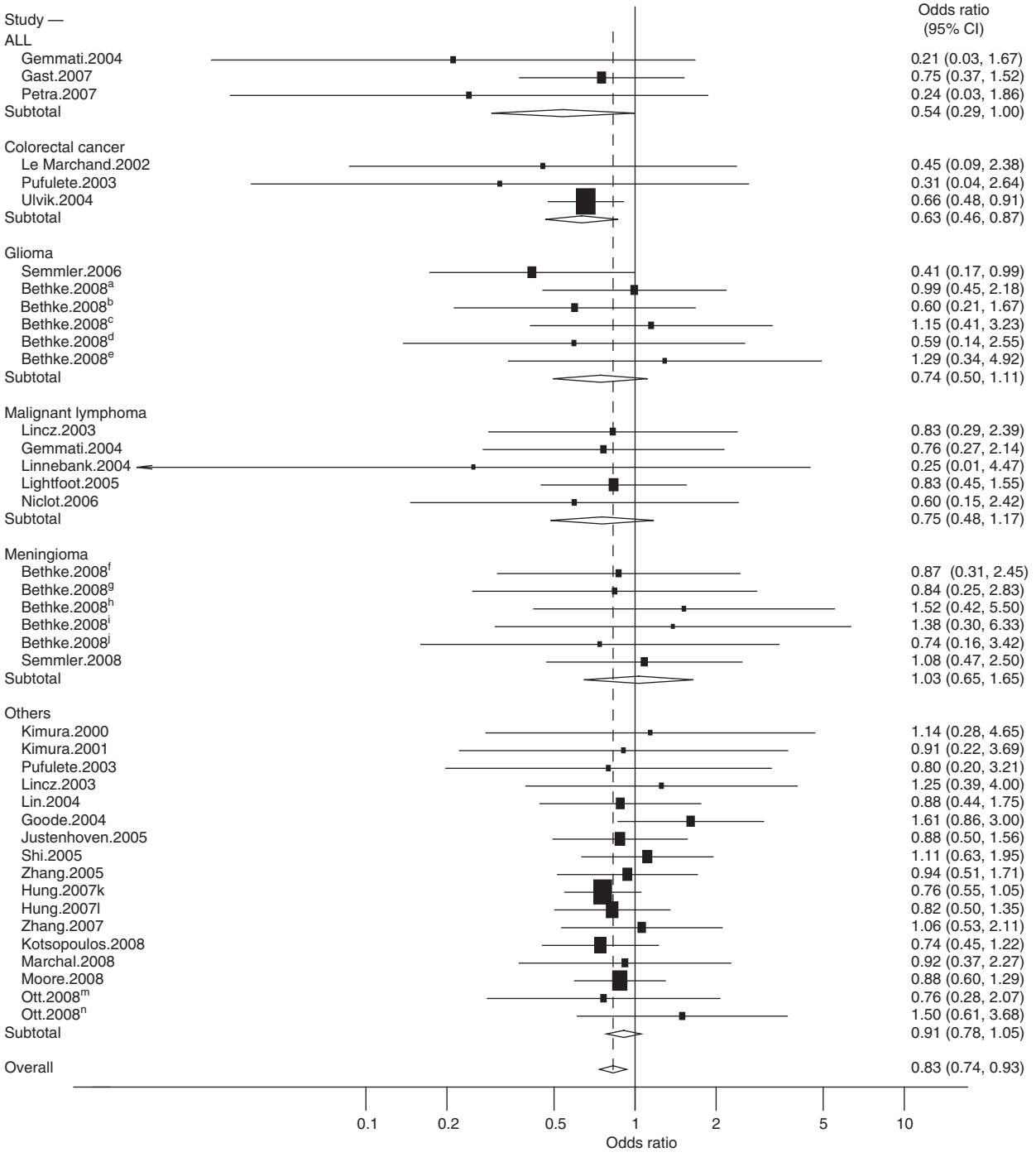

Figure 1 Meta-analysis for methionine synthase (*MTR*) *A2756G* polymorphism and cancer stratified according to different tumor sites in European populations (GG *vs* AG+AA). For each study, the estimate of OR and its 95% CI is plotted with a box (■) and a horizontal line. The size of a box is proportional to the weight that the study has in calculating the summary effect estimate (◇). The center of the diamond indicates the OR and the ends of the diamond correspond to the 95% CI. [a]UK-north, [b]UK-southeast, [c]Sweden, [d]Denmark, [e]Finland, [f]UK-north, [g]UK-southeast, [h]Sweden, [i]Denmark, [j]Finland, [k]lung cancer, [l]upper aero-digestive cancer, [m]esophageal cancer, [n]gastric cancer.

in HapMap data (0.202). Based on this, controls from these eight hospital-based Asian studies may be a little different from the general population, which can contribute to the discrepancy. Interestingly, we found that the G allele frequency in Japanese populations was significantly higher than that in Chinese populations. However, we could not investigate whether *A2756G* polymorphism has different roles in these two groups, because of limited data.

Cancer is an extremely complex disease and the same polymorphism may have different roles in different tumor sites. Meta-regression indicated that colorectal adenoma made significant contributions to the heterogeneity. For colorectal adenoma, only four studies including 1334 patients and 1930 controls were retrieved. Ethnicity and study design of these four studies were inconsistent. Furthermore, controls in one study[4] were not matched by age. Besides, the result of each

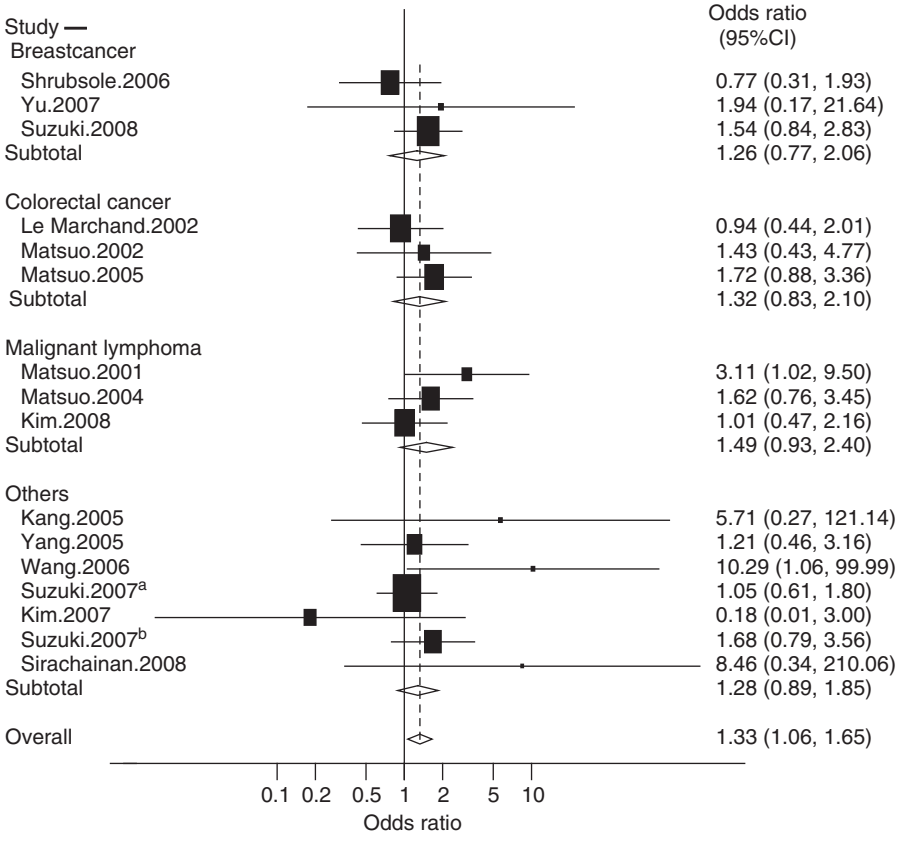

Figure 2 Meta-analysis for *MTR A2756G* polymorphism and cancer stratified according to different tumor sites in Asian populations (GG *vs* AG+AA). [a]Lung cancer, [b]head and neck cancer.

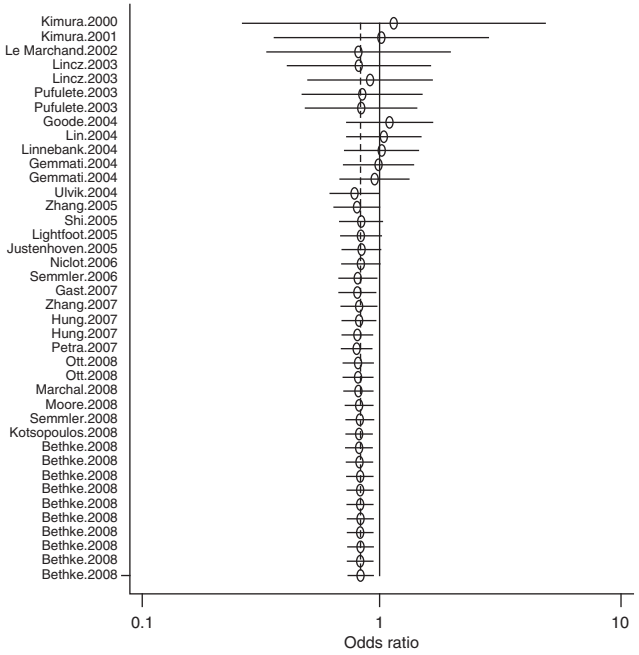

Figure 3 Cumulative meta-analysis for *MTR A2756G* polymorphism and cancer risk in European populations (GG *vs* AG+AA). Horizontal line, the summary of all results as each study is added rather than the results of a single study.

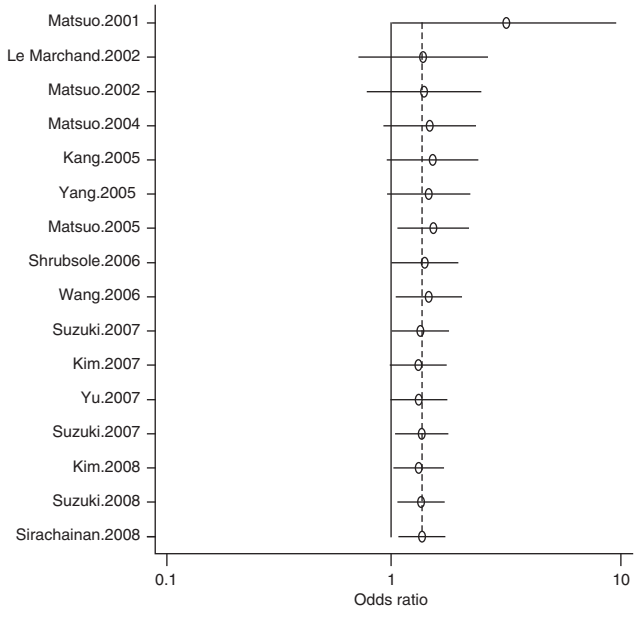

Figure 4 Cumulative meta-analysis for *MTR A2756G* polymorphism and cancer risk in Asian populations (GG *vs* AG+AA).

study might also be influenced by gene–gene and gene–environment interactions. Because these aforementioned factors might contribute to the heterogeneity, more studies were needed to clarify whether *MTR A2756G* polymorphism truly had a different role in colorectal adenoma.

In this meta-analysis, 20 (38%) of 52 recruited articles investigated the interactions between polymorphisms and environmental factors, whereas 19 (37%) studied gene–gene interactions. However, not all of

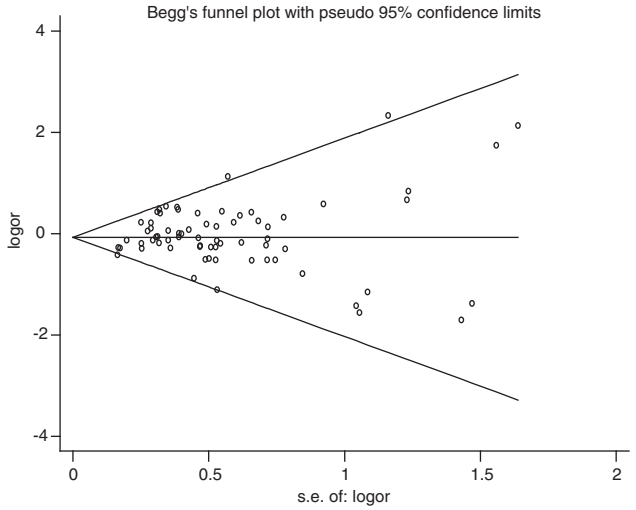

Figure 5 Begg's funnel plot of the Egger's test for publication bias of *MTR A2756G* polymorphism and cancer risk (GG *vs* AG+AA). The horizontal line in the funnel plot indicates the fixed-effects summary estimate, whereas the sloping lines indicate the expected 95% confidence intervals for a given SE.

these articles analyzed the same environmental or genetic factors such as folate intake, vitamin B_{12} intake, vitamin B_6 intake, methionine intake, alcohol consumption, smoke status, *MTHFR*, *TYMS*, *MTRR*, *SHMT1* and *CBS* gene. The results of these articles were conflicting. For example, the interaction between *MTR A2756G* polymorphism and alcohol consumption for cancer risk was significant in four articles[2,4,12,13], but null in others. Owing to lack of original data and difference in study designs, we cannot perform meta-analysis. This inconsistency may be due to chance, because an individual study with a small sample size may not have enough power to detect interactions. Environmental or genetic factors may also have different effects on different cancer types. Moreover, most articles used self-administered questionnaires to evaluate environmental factors. Two main limitations of self-administered questionnaires were recall bias and misclassification bias. Obtained data may not reflect intake as accurately as that from other methods, such as biological markers. Therefore, large-scale, well-designed and population-based studies are required to investigate gene–gene and gene–environment interactions on *MTR A2756G* polymorphism and cancer risk.

Our meta-analysis significantly increased statistical power by pooling data from different studies. Meanwhile, we did not detect any publication bias, which indicated reliability of the pooled results. However, several limitations should be considered in the present meta-analysis. First, because only published studies were retrieved in the meta-analysis, publication bias might be possible, even though the statistical test did not show it. Secondly, we used unadjusted ORs in our meta-analysis. If individual data were available, adjusted ORs could be obtained to conduct a more precise analysis. Thirdly, only a few studies investigated the interactions among gene–gene and gene–environment. Because of limited data and different study designs, the results of interactions were conflicting. Fourthly, multiple testing problems are inevitable since we analyzed different cancer types, ethnicities and study designs, under five different genetic models. *Z*-test *P*-values were adjusted to reduce the type I error induced by multiple tests. Adjusted *P*-values were calculated by $P \times k$ (the number of subgroups). This adjustment did not change the conclusions for Asian populations or European populations, but negated original positive associations for ALL and colorectal cancer in European populations. Finally, study numbers were small in the subgroup analysis stratified by tumor site. Therefore, subgroup analysis may not have sufficient statistical power to identify the association between these polymorphisms and cancer risk.

Despite these limitations, our results still yield interesting conclusions. The *MTR A2756G* polymorphism may be a reduced risk factor for cancer in European populations, especially for ALL and colorectal cancer. However, the positive association for *MTR A2756G* in Asian populations may be spurious, because *MTR A2756G* is associated with an increased risk of cancer in hospital-based studies and a decreased risk of cancer in population-based studies. As the biological role of *MTR A2756G* SNP is not quite clear now, it is difficult to interpret how associations between *MTR A2756G* and cancer risk in European populations may be biologically relevant. Further studies should investigate the biological mechanism and function of *MTR A2756G* polymorphism.

ACKNOWLEDGEMENTS

This research is supported by National Basic Research Program of China (973 Program, 2007CB914304) and New Century Excellent Talents in University (NCET-06-0356).

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