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DNMT3A -448A>G polymorphism and cancer risk: a meta-analysis

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ABSTRACT. Cancer is a major public health problem worldwide that involves complex processes and factors. For instance, methylation is important in tumorigenesis. DNA (cytosine-5)-methyltransferase 3A (DNMT3A) is the main *de novo* methyltransferase implicated in this process. In *DNMT3A*, the -448A>G polymorphism is associated with cancer; however, the results of various studies have been conflicting. To clarify the role of *DNMT3A* polymorphisms in cancer, we conducted a meta-analysis of 2014 cases and 3089 control subjects. Odds ratios with 95% confidence intervals were estimated to evaluate the association between the *DNMT3A* -448A>G polymorphism and cancer risk. The results showed that DNMT3A may be a protective factor against all cancer types and colorectal cancer groups. Further studies should be conducted including different ethnicities and large population sizes to generate a comprehensive conclusion.

Key words: Cancer; DNA (cytosine-5)-methyltransferase 3A; Meta-analysis; Single nucleotide polymorphism

INTRODUCTION

Cancer is a major public health concern worldwide. It is estimated that in the United States, there will be 1,665,540 new cancer cases and 585,720 cancer-related deaths in 2014, indicating that 1 of 4 deaths is due to cancer (Siegel et al., 2014). Cancer is a complex disease; for instance, inactivation of a suppressor gene can result in tumorigenesis. Methylation is important for gene silencing (Bird, 2001); the hypermethylation of CpG islands can result in the transcriptional silencing of the corresponding genes, which has been observed in many types of cancer (Ting et al., 2006).

DNA methylation is one of the major epigenetic modifications in mammalian cells (Turek-Plewa and Jagodzinski, 2005). This process is mediated by DNA methyltransferases (DNMTs). In mammals, DNMTs are present in 3 forms: DNMT1, DNMT3A/3B, and DNMT3L (Bestor, 2000). DNMTs can be further divided into 2 groups based on their functional activities: *de novo* methylation and methylation maintenance. DNMT1 was the first discovered methyltransferase that functions as a maintenance methyltransferase in cells (Bestor et al., 1988; Liu et al., 1998). DNMT3A and DNMT3B are the main *de novo* methyltransferases and methylates cytosine to m^5C from unmethylated DNA (Turek-Plewa and Jagodzinski, 2005). DNMT3L does not exhibit catalytic activities, but can enhance *de novo* methyltransferase activity by increasing the binding ability of DNMT3A/DNMT3B to DNA (Chedin et al., 2002; Gowher et al., 2005). In addition, the 2 groups can interact with each other and activate HDAC1, a histone deacetylase that can change the chromatin conformation (Turek-Plewa and Jagodzinski, 2005).

Single nucleotide polymorphisms (SNPs) in many diseases, including cancer, have been extensively investigated as potential markers for predicting susceptibility and guiding individualized treatment programs. A total of 13 SNPs related to *DNMT3A* have been identified; furthermore, the frequencies of 5 SNPs (rs2289195, rs7590760, rs13401241, rs749131, and rs1550117) have been widely investigated (Piotrowski et al., 2014). It was reported that SNP rs1550117 (A>G) was associated with *DNMT3A* promoter activity (Fan et al., 2010). Studies have also investigated the association between *DNMT3A* polymorphisms and cancer risk (Fan et al., 2010; Sun et al., 2012; Yang et al., 2012; Zhao et al., 2012; Mostowska et al., 2013; Shivarov et al., 2013; Cao et al., 2013; Xu et al., 2013; Zhao et al., 2013). However, the heterogeneity of data collection and statistical results remain inconclusive because of inadequate sample sizes. To eliminate this inconsistency, we conducted a meta-analysis of all eligible case-control studies published to date and estimated the cancer risk of *DNMT3A* rs1550117.

MATERIAL AND METHODS

Publication search

To identify all potentially eligible studies, we performed a systematic computerized search of PubMed, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure (CNKI) Data using the following terms: “DNMT3A”; “rs1550117”; “polymorphism”; and “cancer”. Our last retrieval was conducted on April 1, 2014. We also screened the references of the retrieved articles and review articles. Studies were considered eligible if all of the following criteria were satisfied: a) evaluated the association between *DNMT3A* polymorphism and cancer risk; b) case-control study; and c) full-text study and sufficient data to estimate

the odds ratios (OR) with 95% confidence interval (CI) and a P value. The main exclusion criteria were as follows: a) no control population; b) no available genotype frequency; and c) duplication of a previous publication. Two types of cancer described in the same study were considered as 2 independent studies (Fan et al., 2010).

Data extraction

All articles were independently reviewed by 2 investigators. Agreement was reached by discussing the findings when conflicting results were obtained. If a consensus could not be reached, another reviewer was consulted and final decisions were made based on votes. The following information was obtained from each publication: first author, year of publication, country of origin, type of cancer, ethnicity, genotyping method, source of control groups, number of cases and controls, and genotype distribution.

Statistical analysis

We evaluated the Hardy-Weinberg equilibrium of each study describing control subjects by performing a chi-square test at a significance level of $P < 0.05$. We then calculated the strength of association between the *DNMT3A* -448A>G polymorphism and cancer risk using crude OR with 95%CI. The *Z* test was performed to estimate the significance of the pooled ORs, and $P < 0.05$ was considered to be statistically significant. Heterogeneity between studies was evaluated using the chi-square-based I^2 test and the P value of the *Q* test. $P > 0.05$ indicated a lack of heterogeneity, $I^2 < 25\%$ indicated low heterogeneity, I^2 of 25-75% indicated moderate heterogeneity, and $I^2 > 75\%$ indicated high heterogeneity (Higgins et al., 2003). If $I^2 < 50\%$ and $P > 0.05$, pooled ORs were calculated using a fixed-effect model. Otherwise, a random-effect model was used. The association between *DNMT3A* polymorphisms and cancer was investigated using the following methods: allele contrast model (allele G *vs* allele A), heterozygote comparison (GA *vs* AA), homozygote comparison (GG *vs* AA), dominant genetic model (GG/GA *vs* AA), and recessive genetic model (GG *vs* GA/AA). Subgroup analyses were conducted for each cancer type (if any cancer type was described in only 1 study, this type was combined with other cancer groups) and ethnicity. Furthermore, sensitivity analyses were performed by sequentially removing each eligible study. Publication bias was determined using a funnel plot and the Egger test. All P values were two-sided, and statistical analyses were conducted using the STATA software version 12.0 (StataCorp, College Station, TX, USA).

RESULTS

Study characteristics

A total of 129 potentially relevant publications were found in the initial search. After applying additional filters, we included 9 case-control studies in 8 publications that satisfied our inclusion criteria. Figure 1 presents the detailed process of selecting and excluding studies. In one publication, 2 types of cancers were described; as such, each cancer type was considered as a separate study in this meta-analysis (Fan et al., 2010).

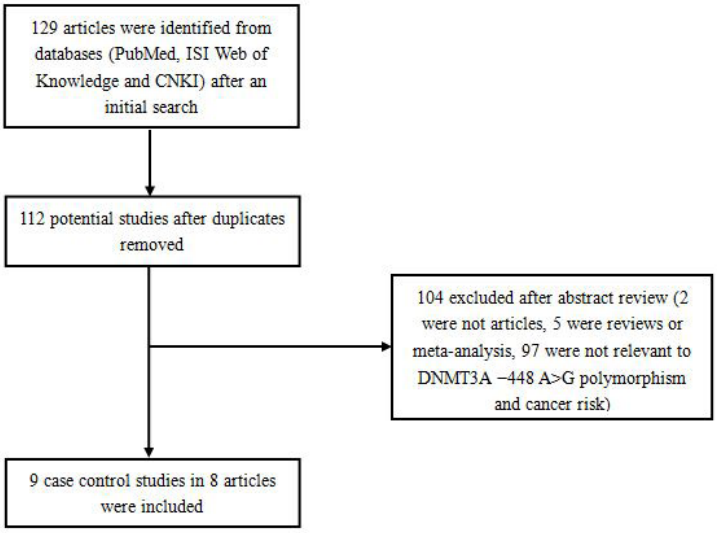

Figure 1. Flow chart of study identification.

Overall, 9 studies, including a total of 2014 cancer cases and 3089 control subjects, were reviewed in this meta-analysis. The characteristics of the included studies are summarized in Table 1. Among these studies, 3 focused on gastric cancer and 2 described colorectal cancer; esophagus, breast, ovarian, and hepatocellular cancers were described in individual studies. Eight studies focused on Asian subjects and 1 study described European subjects. Among the 9 articles, 8 used hospitals as base controls of the cases. In addition, the classic polymerase chain reaction-restriction fragment length polymorphism assay was the most commonly used method.

Table 1. Main characteristics of included studies in this meta-analysis.

Author	Year	Country	Ethnicity	Cancer type	Design	N (case/control)	Genotype distribution of cases/controls			Genotyping methods	HWE (P)
							GG	AG	AA		
Fan	2010	China	Asian	Gastric	HB	208/346	102/218	75/118	31/10	PCR-RFLP	0.20
Fan	2010	China	Asian	Esophageal	HB	96/241	61/149	28/86	7/6	PCR-RFLP	0.11
Sun	2012	China	Asian	Breast	HB	407/468	250/282	130/166	27/20	PCR	0.47
Zhao	2012	China	Asian	Colorectal	HB	258/280	150/178	80/93	28/9	PCR-RFLP	0.45
Mostowska	2013	Poland	European	Ovarian	PB	159/180	135/151	23/29	1/0	PCR-RFLP	0.24
Cao	2013	China	Asian	Gastric	HB	447/961	289/640	142/288	16/33	PCR-RFLP	0.93
Yang	2012	China	Asian	Gastric	HB	242/294	157/191	74/93	11/10	MassARRAY	0.75
Zhao	2013	China	Asian	Hepatocellular	HB	108/225	60/128	44/85	4/12	PCR-RFLP	0.66
Xu	2013	China	Asian	Colorectal	HB	89/94	53/64	32/27	4/3	MassARRAY	0.94

HB = hospital-based; PB = population-based; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; HWE = Hardy-Weinberg equilibrium.

Quantitative synthesis

In the overall comparison, the *DNMT3A* -448A>G polymorphism was significantly

associated with cancer risk when all eligible studies were pooled in the meta-analysis. Table 2 shows that the *DNMT3A* -448A>G polymorphism was associated with a reduced cancer risk in 4 genetic models (OR = 0.833; 95%CI = 0.706-0.984; P = 0.032, $P_{heterogeneity}$ = 0.012 for G-allele *vs* A-allele; OR = 0.504; 95%CI = 0.303-0.838; P = 0.008, $P_{heterogeneity}$ = 0.007 for GG *vs* AA; OR = 0.527; 95%CI = 0.327-0.850; P = 0.009, $P_{heterogeneity}$ = 0.022 for GA *vs* AA; OR = 0.512; 95%CI = 0.313-0.839; P = 0.008, $P_{heterogeneity}$ = 0.009 for GG/AG *vs* AA), but this polymorphism was not associated with a recessive genetic model (OR = 0.889; 95%CI = 0.790-1.002; P = 0.053, $P_{heterogeneity}$ = 0.230 for GG *vs* GA/AA, Figure 2). In the subgroup analyses based on tumor sites, colorectal cancer exhibited similar results (OR = 0.701; 95%CI = 0.546-0.900; P = 0.005, $P_{heterogeneity}$ = 0.838 for G-allele *vs* A-allele; OR = 0.317; 95%CI = 0.159-0.631; P = 0.001, $P_{heterogeneity}$ = 0.346 for GG *vs* AA; OR = 0.348; 95%CI = 0.171-0.707; P = 0.004, $P_{heterogeneity}$ = 0.198 for GA *vs* AA; OR = 0.326; 95%CI = 0.165-0.643; P = 0.001, $P_{heterogeneity}$ = 0.279 for GG/AG *vs* AA; OR = 0.768; 95%CI = 0.569-1.038; P = 0.086, $P_{heterogeneity}$ = 0.689 for GG *vs* GA/AA). No significant association was found between the *DNMT3A* -448A>G polymorphism and gastric cancer risk in any of the genetic models (OR = 0.772; 95%CI = 0.519-1.147; P = 0.200, $P_{heterogeneity}$ = 0.001 for G-allele *vs* A-allele; OR = 0.473; 95%CI = 0.149-1.506; P = 0.205, $P_{heterogeneity}$ = 0.001 for GG *vs* AA; OR = 0.536; 95%CI = 0.197-1.459; P = 0.223, $P_{heterogeneity}$ = 0.006 for GA *vs* AA; OR = 0.495; 95%CI = 0.165-1.483; P = 0.209, $P_{heterogeneity}$ = 0.001 for GG/AG *vs* AA; OR = 0.810; 95%CI = 0.588-1.116; P = 0.197, $P_{heterogeneity}$ = 0.041 for GG *vs* GA/AA). In subgroup analysis by ethnicity, only the Asian group was examined because only 1 study was conducted in Europeans. Furthermore, the results were the same as for the overall comparison (data not shown).

Sensitivity analysis

Sensitivity analysis was conducted to determine the effect of an individual dataset on the final results by sequentially removing each study. The significance of the pooled ORs was similar in the heterozygote comparison, homozygote comparison, and dominant genetic models in the overall comparison (Figure 3).

Heterogeneity analysis

Significant heterogeneity was observed in overall comparisons and specific subgroup analyses (Table 2). However, heterogeneity was eliminated after 1 study (Fan et al., 2010) was removed in the overall comparison (I^2 = 0.0%, $P_{heterogeneity}$ = 0.642 for the G-allele *vs* the A-allele; I^2 = 24.3%, $P_{heterogeneity}$ = 0.235 for GG *vs* AA; I^2 = 35.7%, $P_{heterogeneity}$ = 0.144 for GA *vs* AA; I^2 = 30.9%, $P_{heterogeneity}$ = 0.182 for GG/AG *vs* AA; I^2 = 0.0%, $P_{heterogeneity}$ = 0.869 for GG *vs* GA/AA), and in subgroup analysis (I^2 = 0.0%, $P_{heterogeneity}$ = 0.877 for G-allele *vs* A-allele; I^2 = 0.0%, $P_{heterogeneity}$ = 0.688 for GG *vs* AA; I^2 = 0.0%, $P_{heterogeneity}$ = 0.546 for GA *vs* AA; I^2 = 0.0%, $P_{heterogeneity}$ = 0.634 for GG/AG *vs* AA; I^2 = 0.0%, $P_{heterogeneity}$ = 0.706 for GG *vs* GA/AA). These findings suggest that the study was the primary source of heterogeneity in the overall comparison. In addition, the significance of the pooled ORs and 95%CI remained unchanged in the heterozygote comparison, homozygote comparison, and dominant genetic model in the overall analysis and genetic models of gastric subgroups.

Table 2. Stratified analyses of the DNMT3A -448A>G polymorphism on cancer risk.

Genetic comparison	Cancer type	N (case/control)	OR (95%CI)	P	Test of heterogeneity		Model
					P value	I^2	
G-allele *vs* A-allele	Total	2014/3089	0.833 (0.706-0.984)	0.032	0.012	59.3%	R
	Gastric	897/1601	0.772 (0.519-1.147)	0.200	0.001	85.8%	R
	Colorectal	347/374	0.701 (0.546-0.900)	0.005	0.838	N/A	F
	Others	770/1114	0.970 (0.821-1.147)	0.722	0.982	N/A	F
GG *vs* AA	Total	2014/3089	0.504 (0.303-0.838)	0.008	0.007	62.3%	R
	Gastric	897/1601	0.473 (0.149-1.506)	0.205	0.001	86.3%	R
	Colorectal	347/374	0.317 (0.159-0.631)	0.001	0.346	N/A	F
	Others	770/1114	0.665 (0.416-1.063)	0.088	0.386	1.2%	F
GA *vs* AA	Total	2014/3089	0.527 (0.327-0.850)	0.009	0.022	55.2%	R
	Gastric	897/1601	0.536 (0.197-1.459)	0.223	0.006	80.6%	R
	Colorectal	347/374	0.348 (0.171-0.707)	0.004	0.198	39.8%	F
	Others	770/1114	0.609 (0.377-0.984)	0.043	0.225	31.2%	F
GG/AG *vs* AA	Total	2014/3089	0.512 (0.313-0.839)	0.008	0.009	61.0%	R
	Gastric	897/1601	0.495 (0.165-1.483)	0.209	0.001	85.1%	R
	Colorectal	347/374	0.326 (0.165-0.643)	0.001	0.279	14.6%	F
	Others	770/1114	0.646 (0.407-1.025)	0.064	0.305	17.3%	F
GG *vs* GA/AA	Total	2014/3089	0.889 (0.790-1.002)	0.053	0.230	24.0%	F
	Gastric	897/1601	0.810 (0.588-1.116)	0.197	0.041	68.6%	R
	Colorectal	347/374	0.768 (0.569-1.038)	0.086	0.689	N/A	F
	Others	770/1114	1.038 (0.851-1.267)	0.714	0.978	N/A	F

R = random-effect model; F = fixed-effect model; OR = odds ratio; 95%CI: 95% confidence interval.

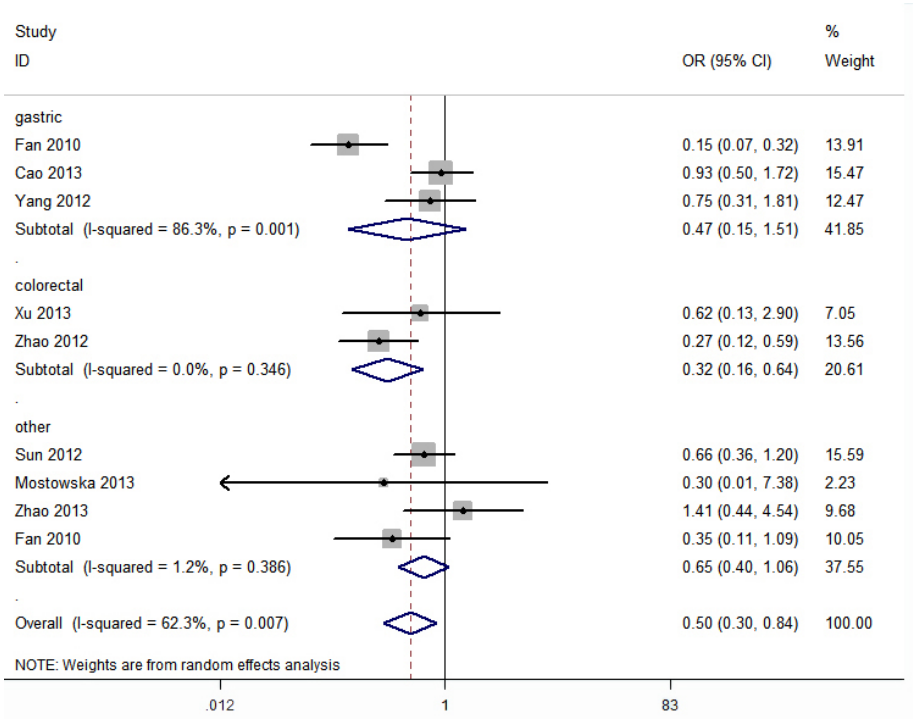

Figure 2. Forest plot for the *DNMT3A* -448A>G polymorphism and cancer susceptibility in the GG *vs* AA comparison.

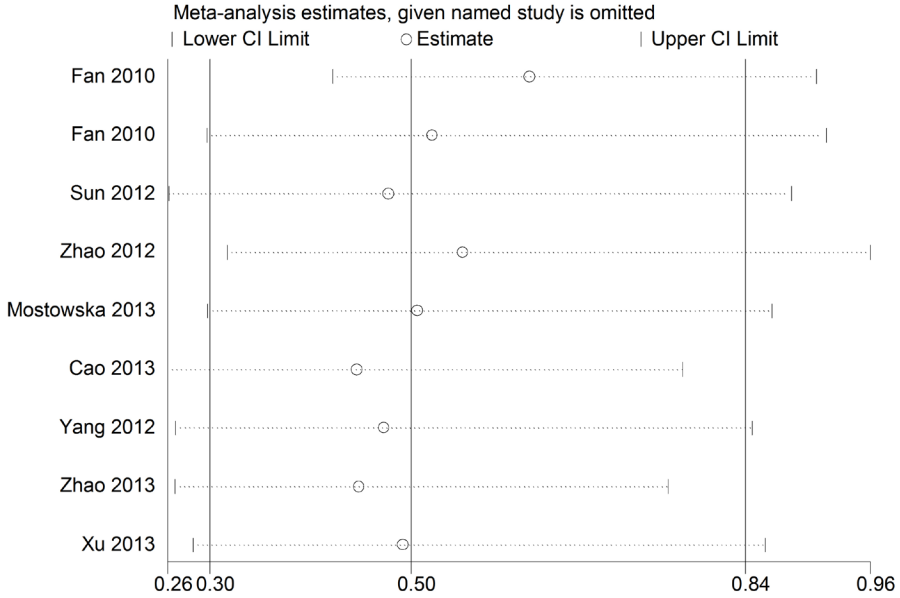

Figure 3. Sensitivity analysis of the influence of GG *vs* AA in overall cancer risk (random-effect model).

Publication bias

Publication bias in the studies involving each gene was detected using Begg's funnel plot and the Egger test. The shape of the funnel plot was symmetrical in all genetic models. Moreover, no statistical significance was detected in the Egger test (P = 0.940, G-allele *vs* A-allele; P = 0.876 for GG *vs* AA; P = 0.898 for GA *vs* AA; P = 0.907 for GG/AG *vs* AA; P = 0.831 for GG *vs* GA/AA; Figure 4).

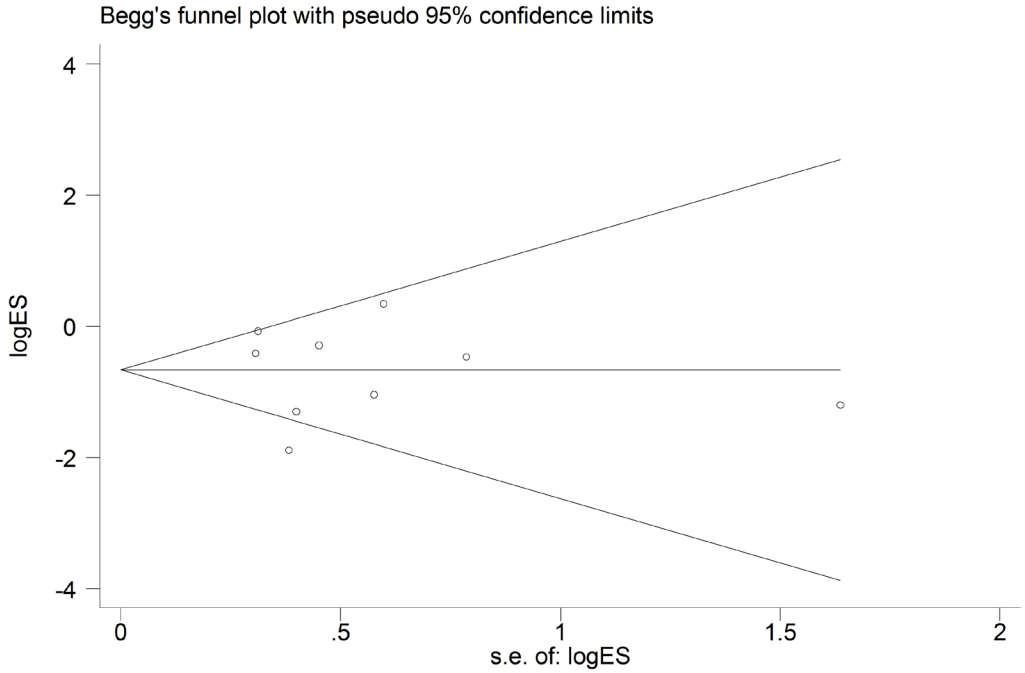

Figure 4. Begg's funnel plot of GG *vs* AA in overall cancer risk.

DISCUSSION

This is the first meta-analysis to detect the association between *DNMT3A* -448A>G polymorphisms and cancer risk. In this meta-analysis, the association between *DNMT3A* -448A>G polymorphism and cancer was observed in the overall comparison and in specific subgroup analyses based on ethnicity and cancer sites. The A>G polymorphism was shown to decrease the risk of cancer in the overall analysis and the colorectal cancer subgroup. This finding indicated that the *DNMT3A* -448A>G polymorphism may exhibit protective functions in cancer. However, no association was detected in the gastric cancer subgroup. The following specific factors may contribute to this discrepancy. The *DNMT3A* -448A>G polymorphism may have different effects in different types of cancer; different genetic backgrounds, living habits, and environmental factors such as tobacco use and alcohol consumption may be related to tumorigenesis, but these factors cannot be observed, and publication bias and time lag bias may be present.

DNMT3A and DNMT3B belong to the same family. Meta-analyses examining the relationship between *DNMT3B* polymorphisms and cancer risk have already been performed (Zhu et al., 2012; Fang et al., 2012; Meng et al., 2014). For instance, a previous study showed that the *DNMT3B* -579G>T polymorphism significantly decreased cancer risk (Zhu et al., 2012). However, no significant association was found between the -149C>T polymorphism in *DNMT3B* and colorectal cancer susceptibility (Fang et al., 2012; Meng et al., 2014). In our meta-analysis, the *DNMT3A* -448A>G polymorphism decreased the risk of colorectal cancer. This result indicates that genes with the same function may be exhibited differently in the same disease.

The following heterogeneities between studies were found in this meta-analysis. Ethnicity is one of the most important factors affecting heterogeneity; additionally, in the same country, genetic backgrounds and environmental factors differ among individuals. Tumor sites and characteristics also contribute to heterogeneity. One cancer type may exhibit different etiologies, organ origins, and histological subtypes, such as *Helicobacter pylori* infection, which is a key factor contributing to gastric cancer (Cao et al., 2013). In this meta-analysis, the main source of heterogeneity may have originated from the study of Fan et al. (2010), who examined gastric cancer.

There were some limitations to this meta-analysis. A small sample size in the studies may have resulted in low statistical power. In addition, studies with negative results are rarely published, particularly studies with small sample sizes (Ioannidis, 1998). Hence, further detailed and large-scale studies are necessary. Our study mainly focused on the Asian population; whether these results can be generalized and applied to other populations remains unclear. Original data, such as diet, alcohol consumption, and smoking status, are insufficient for conducting further evaluation. Publication bias originating from limited studies published in English or Chinese should be considered.

In conclusion, our meta-analysis results showed that the -448A>G polymorphism in the *DNMT3A* promoter region may function as a protective factor against cancer risk. Further studies including different ethnicities and with a large population size should be conducted to reach a comprehensive conclusion.

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Conflicts of interest

The authors declare no conflict of interest.

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