RESEARCH ARTICLE

DNMT3B -149 C>T and -579 G>T Polymorphisms and Risk of Gastric and Colorectal Cancer: a Meta-analysis

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Abstract

Background: Numerous studies have investigated associations of DNA methyltransferase (DNMT) -149 C>T and -579 G>T polymorphisms with gastric cancer (GC) and colorectal cancer (CRC) susceptibility; however, the findings are inconsistent prompting the present meta-analysis. Materials and Methods: Related studies were identified from PubMed, Google scholar, and SID until 10 October 2015. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the associations. Results: Eleven studies were included based on the search criteria for CRC and GC related to the DNMT3B 149 C>T (3,353 cases and 4,936 controls) and DNMT3B 579 G>T (1,387 cases and 2,064 controls) polymorphisms. There was no significant association overall between DNMT3B -149 and 579 polymorphisms and the risk of cancer. In the stratified analysis by cancer type, DNMT3B 579G>T polymorphism was associated with the risk of CRC and GC. While the DNMT3B -149C/T polymorphism was related with a significantly increased risk of CRC in two tested models, dominant (GG+GT *vs.* TT: OR 0.51, 95 % CI 0.38-0.69; P = 0.00, Pheterogeneity=0.69, I^2= 0 %) and heterozygote (GT *vs.* TT: OR 0.50, 95 % CI 0.37-0.69; P=0.00, Pheterogeneity=0.41, I^2= 0 %), no evidence of any association with GC risk was observed as in the pooled analyses. Conclusions: More studies are needed to assess associations of DNMT3B -149C/T and DNMT3B 579G>T polymorphisms with cancer in different ethnicities with large population sizes to generate comprehensive conclusions.

Keywords: DNA methyltransferases - CRC - gastric cancer - polymorphism

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Introduction

DNA methylation is a major epigenetic modulation and is important in transcription regulation and chromatin structure remodeling (Pavlopoulou et al., 2010). In mammals, DNA methylation consists of the covalent postreplicative addition of a methyl group to carbon 5 of the cytosine in a CpG dinucleotide, which is catalyzed by DNA methyltransferases (DNMTs) (Hermann et al., 2004). DNA methyltransferases are the key enzymes for genome methylation, including three activated forms DNMT1, DNMT3A and DNMT3B in human, which each plays a different functional role (Jin et al., 2013). DNMT3A and DNMT3B are the main de novo methyltransferases and methylates cytosine to m5C from unmethylated DNA (Jin et al., 2013., Hermann et al., 2004). DNMT 3A and DNMT3B are required for the establishment and maintenance of genomic methylation patterns and proper murine development (He et al., 2013).

Aberrant DNA methylation could result in genome-wide hypomethylation and regional hypermethylation, which is identified as a possible mechanism of inactivation of tumor suppressor genes (Vizoso et al., 2015).

Common polymorphisms are known in the promoter region of DNMT3B, e.g. a –149 C>T substitution (rs2424913) and a -579 G>T substitution (rs1569686) (Zhang et al., 2015). DNMT3B promoter polymorphisms have been reported to be associated with the risk of malignant solid tumors, such as colorectal cancer, lung cancer, and breast cancer, especially cancer, as T-allele carriers, especially heterozygous genotype, have been shown to have a significant increase in risk of developing lung, head and neck carcinoma (Zhang et al., 2015; Zhu et al., 2015). However, the results remain controversial, depending on the varied ethnicity, tumor types, and study designs.

Recently, a variety of molecular epidemiological studies have been conducted to examine the association

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between -149 C>T (rs2424913) and -579 G>T (rs1569686), and cancer susceptibility (Zhang et al., 2015; Zhu et al., 2015), but the results remain inconclusive. Here, we performed a meta-analysis to derive a more precise evaluation of the association between -149 C>T and -579 G>T polymorphism and colorectal cancer (CRC) and gastric cancer risk.

Materials and Methods

Identification and eligibility of relevant studies

Two authors independently conducted a systematic literature search in the PubMed, Elsevier, and Google scholar databases to identify studies about the relationship between DNMT3B or polymorphisms and CRC and gastric cancer risk (up to December 20, 2015). The search terms and keywords used were as follows: "DNA methyltransferases 3B" or "DNMT3B", "polymorphism" or "variant", "–149 C>T" or "rs2424913", and "-579 G>T" or "rs1569686", "colorectal cancer" or "CRC", and "gastric cancer". The search was limited to English language papers. A manual search for references cited in the eligible articles was also performed to look for additional studies. Studies included in our meta-analysis have to meet the following criteria: (1) use a case–control design and (2) sufficient data for examining an odds ratio (OR) with 95% confidence interval (CI). Major reason for exclusion of studies was no control population.

Data extraction

Two investigators independently extracted data according to the inclusion and exclusion criteria and reached a consensus on all the items. The following data were collected from studies: first author, year of publication, ethnicity, and numbers of genotyped cases and controls. Different ethnic descents were categorized as Caucasian and Asian.

Statistical analysis

The strength of association of DNMT3B -149 and -579 polymorphisms with cancer risk was assessed by odds ratios (ORs) with 95% confidence intervals (CIs) under the heterozygote model (149: CT *vs*. TT; 579: GT*vs*.TT), homozygote model (149: CC *vs*. TT; 579: GG *vs*.TT), recessive model (149: CC *vs*. CT+TT; 579: GG *vs*. GT+TT) and dominant model (149: CC+CT *vs*. TT;

Table 1. Meta-analysis of the total 11 case–control studies assessing the association between DNMT3B 149C>T polymorphism and CRC and Gastric cancer risk

Author	Year	Country	Tumor type	Case/Control	Cases					HWE
					Genotypes			Alleles		
					CC	CT	TT	C	T	
Hu	2010	China	Gastric cancer	259/262	0	2	257	2	516	
Wang	2005	China	Gastric cancer	212/294	0	7	205	7	417	
Aung	2005	Japan	Gastric cancer	152/247	0	0	152	0	304	
alhossaini	2015	Iran	Colorectal cancer	108/185	26	52	30	104	112	
Bao	2011	China	Colorectal cancer	544/533	0	6	538	6	1082	
Karpinski	2010	Poland	Colorectal cancer	186/140	56	91	39	203	169	
de Vogel	2009	Netherlands	Colorectal cancer	659/1736	240	348	115	828	578	
Iacopetta	2009	Australia	Colorectal cancer	828/949	247	414	167	908	748	
Fan	2008	China	Colorectal cancer	137/308	0	2	135	2	272	
Reeves	2008	Australia	Colorectal cancer	194/210	57	91	46	205	183	
Jones	2006	USA	Colorectal cancer	74/72	12	45	17	69	79	
Author	Year	Country	Tumor type	Case/Control	Control					
					Genotypes			Alleles		
					CC	CT	TT	C	T	
Hu	2010	China	Gastric cancer	259/262	0	3	259	3	521	0.92
Wang	2005	China	Gastric cancer	212/294	0	15	279	15	573	0.65
Aung	2005	Japan	Gastric cancer	152/247	0	0	247	0	494	0.65
alhossaini	2015	Iran	Colorectal cancer	108/185	65	99	21	229	141	0.06
Bao	2011	China	Colorectal cancer	544/533	0	12	521	12	1054	0.79
Karpinski	2010	Poland	Colorectal cancer	186/140	45	67	28	157	123	0.73
de Vogel	2009	Netherlands	Colorectal cancer	659/1736	597	895	318	2089	1531	0.57
Iacopetta	2009	Australia	Colorectal cancer	828/949	274	463	212	1011	887	0.53
Fan	2008	China	Colorectal cancer	137/308	0	4	304	4	612	0.9
Reeves	2008	Australia	Colorectal cancer	194/210	63	97	50	223	197	0.29
Jones	2006	USA	Colorectal cancer	74/72	28	27	17	83	61	0.04

579: GG+GT *vs*. TT). The statistical significance of the summary OR was determined with the Z-test. The Z-test was used to determine the significance of combined ORs. The heterogeneity between included studies was evaluated by the Q-test. If P > 0.05, indicating that there exists no significant heterogeneity, the fixed-effects model (Mantel-Haenszel) was selected to combine the data, otherwise, the random-effects model (DerSimonian-Laird) was applied. Subgroup analyses were performed according to the cancer type (CRC or gastric) and ethnicity (Asians and Caucasians). Sensitivity analysis was performed to assess the stability of results. Funnel plots were drawn to estimate the potential publication bias, in which the standard error (SE) of log (OR) of each study was plotted against its log (OR). The funnel plot asymmetry was assessed with Egger's test [28]. Publication bias was assessed with Egger test; P<0.05 was considered statistically significant. Hardy–Weinberg equilibrium (HWE) in the control group was tested using the χ^2-test for goodness of fit. All the tests were two-sided and P<0.05 was considered as statistically significant. All statistical tests for this meta-analysis were performed with CMA.

Results

Study characteristics

Eleven studies were included based on the search criteria for CRC and GC susceptibility related to the DNMT3B 149C>T and DNMT3B 579G>T polymorphisms. Study characteristics were summarized in Tables 1 and 2. There were eleven case–control studies with 3,353 cases and 4,936 controls concerning DNMT3B 149C>T polymorphism (Aung et al., 2005; Wang et al., 2005; Jones et al., 2008; Reeves et al., 2008; Fan et al., 2008; Iacopetta et al., 2009; de Vogel et al., 2009; Hu et al., 2010; Karpinski et al., 2010; Bao et al., 2011; and alhossaini et al., 2015) and four case–control studies with 1,387 cases and 2,064 controls concerning DNMT3B 579G>T polymorphism (Fan et al., 2008; Hu et al., 2010; Bao et al., 2011; Wang et al., 2015). The number of cases included in the studies varied from 74 to 828, and the number of controls varied from 72 to 1736. For the DNMT3B 149C>T polymorphism, there were eight studies of Asian population and three studies of Caucasian population. For the DNMT3B 579G>T polymorphism, all studies were of Asian population. The genotype distributions among the controls of all studies followed Hardy–Weinberg equilibrium except for one study for the DNMT3B 149C>T (Jones et al., 2008).

Quantitative synthesis

DNMT3B 149C>T: When all the eligible studies were pooled into the meta-analysis of DNMT3A polymorphism, there was no significant association between DNMT3B −149C>T polymorphism and cancer risk (for CC+CT *vs*. TT: OR 0.62, 95 % CI 0.37-1.04; P=0.07, $P_{heterogeneity}$=0.00, I^2=89%; CC *vs*. CT+TT: OR 0.87, 95 % CI 0.68-1.11; P=0.26, $P_{heterogeneity}$=0.01, I^2=64%; CT *vs*. TT: OR 0.92, 95 % CI 0.73-1.17; P=0.52, $P_{heterogeneity}$=0.08, I^2=40%; CC *vs*. TT: OR 0.74, 95 % CI 0.49-1.12; P=0.15, $P_{heterogeneity}$=0.00, I^2=78%; C *vs*. T: OR 0.894, 95 % CI 0.75-1.05; P=0.18, $P_{heterogeneity}$=0.01, I^2=57%; Figure 1), Gastric cancer (CC+CT *vs*. TT: OR 0.64, 95 % CI 0.28-1.45; P=0.28, $P_{heterogeneity}$=0.95, I^2=0 %; CT *vs*. TT: OR OR 0.64, 95 % CI 0.28-1.45; P=0.28, $P_{heterogeneity}$=0.95, I^2=0 %; C *vs*. T: OR 0.64, 95 % CI 0.28-1.45; P=0.28, $P_{heterogeneity}$=0.96, I^2=0 %; Figure 1) and Colorectal cancer (CC+CT *vs*. TT: OR 0.61, 95 % CI 0.34-1.10; P=0.10, $P_{heterogeneity}$=0.00, I^2=91%;

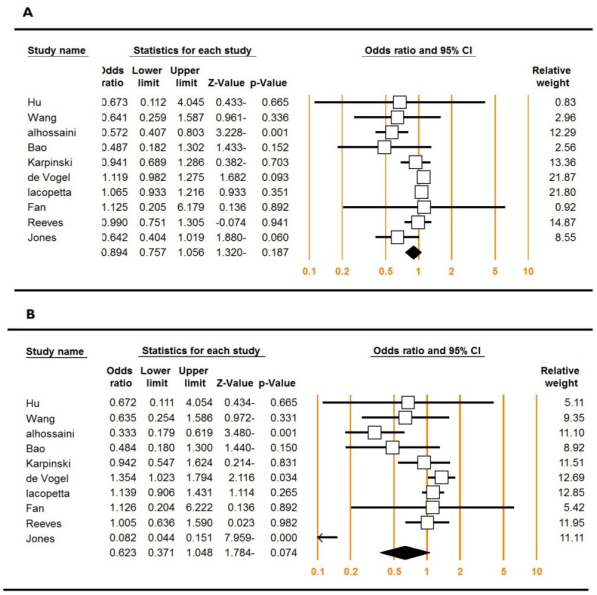

Figure 1. Forest Plots for the Meta-Analysis of the Association between DNMT3B-149C>T Polymorphism and Cancer Risk. (A: C vs. T and B: CC+CT vs. TT)

Table 2. Meta-analysis of the total 4 case-control studies assessing the association between DNMT3B 579G>T polymorphism and CRC and Gastric cancer risk

Author	Year	Country	Tumor type	Case/Control	Cases					HWE
					Genotypes			Alleles		
					GG	GT	TT	G	T	
Wang	2015	China	Gastric Cancer	447/961	5	82	360	92	802	
Hu	2010	China	Gastric cancer	259/262	2	27	230	31	487	
Bao	2011	China	Colorectal cancer	544/533	4	50	490	58	1030	
Fan	2008	China	Colorectal cancer	137/308	0	18	119	18	256	
Author	Year	Country	Tumor type	Case/Control	Control					
					Genotypes			Alleles		
					GG	GT	TT	G	T	
Wang	2015	China	Gastric Cancer	447/961	10	150	801	170	1752	32
Hu	2010	China	Gastric cancer	259/262	4	55	203	63	461	0.9
Bao	2011	China	Colorectal cancer	544/533	2	95	436	99	967	0.18
Fan	2008	China	Colorectal cancer	137/308	6	59	243	71	545	0.28

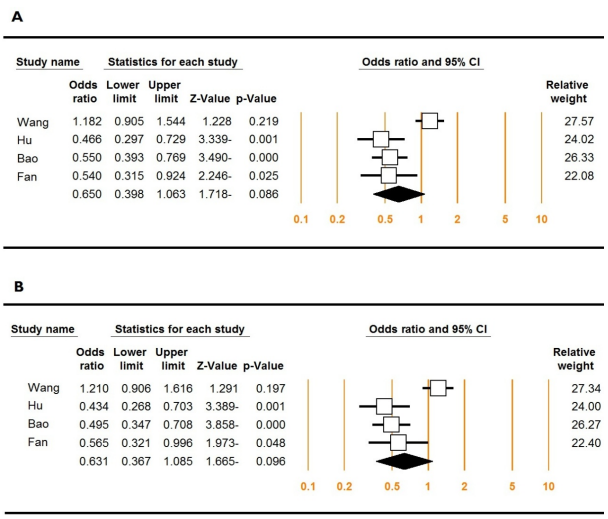

Figure 2. Forest Plots for the Meta-Analysis of the Association between DNMT3B-579G>T Polymorphism and Cancer Risk. (A: C vs. T and B: CC+CT vs. TT)

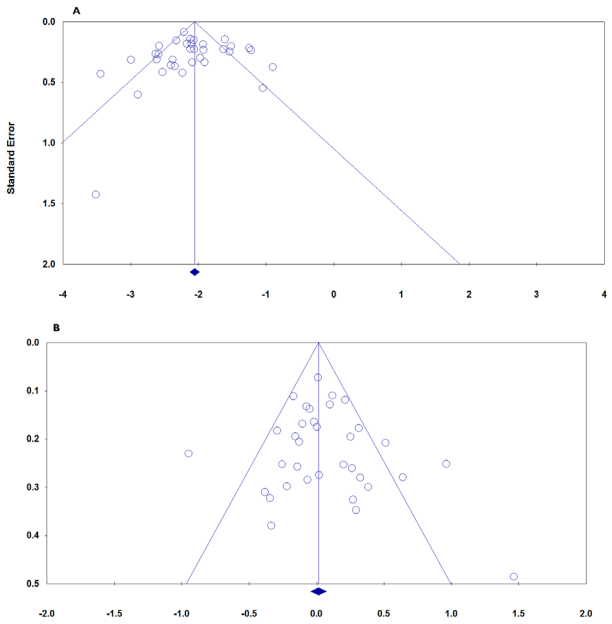

Figure 3. Funnel Plots for the Meta-Analysis of the Association with Cancer Risk. (A: C vs. T and B: CC+CT vs. TT)

CC *vs*. CT+TT: OR 0.87, 95 % CI 0.68-1.11; P=0.26, $P_{heterogeneity}$=0.01, I^2=64%; CT *vs*. TT: OR 0.94, 95 % CI 0.73-1.122; P=0.67, $P_{heterogeneity}$=0.05, I^2=49%; CC *vs*. TT: OR 0.74, 95 % CI 0.49-1.12; P=0.15, $P_{heterogeneity}$=0.00, I^2=78%; C *vs*. T: OR 0.90, 95 % CI 0.75-1.07; P=0.24, $P_{heterogeneity}$=0.006, I^2=64%; Table 1, Figure 1).

DNMT3B 579G>T: We did not find that the DNMT3B 579G>T polymorphism was associated with risk of cancer (G *vs*. T: OR 0.65, 95 % CI 0.39-1.06; P=0.08, $P_{heterogeneity}$=0.00, I^2=54%; GG+GT *vs*. TT: OR 0.63, 95 % CI 0.36-1.08; P=0.09, $P_{heterogeneity}$=0.00, I^2=86 %; GG *vs*. GT+TT: OR 0.91, 95 % CI 0.42-1.97; P=0.81, $P_{heterogeneity}$=0.44, I^2=0 %; GT*vs*.TT: OR 0.73, 95 % CI 0.44-1.19; P=0.21, $P_{heterogeneity}$=0.001, I^2=81 %; GG*vs*.TT: OR 0.86, 95 % CI 0.39-1.87; P=0.71, $P_{heterogeneity}$=0.44, I^2=0 % ; Figure 2), Gastric cancer (G *vs*. T: OR 0.75, 95 % CI 0.30-1.88; P=0.54, $P_{heterogeneity}$=0.00, I^2=91% GG+GT *vs*. TT: OR 0.73, 95 % CI 0.27-2.01; P=0.55, $P_{heterogeneity}$=0.00, I^2=92 % GG *vs*. GT+TT: OR 0.86, 95 % CI 0.34-2.15; P=0.75, $P_{heterogeneity}$=0.45, I^2=0 %; GT*vs*.TT: OR 1.01, 95 % CI 0.65-1.57; P=0.95, $P_{heterogeneity}$=0.12, I^2=57 % GG*vs*.TT: OR 0.85, 95% CI 0.34-2.12; P=0.71, $P_{heterogeneity}$=0.37, I^2=0%). In addition, we did not detect the association between DNMT3B 579G>T polymorphism and CRC risk (G *vs*. T: OR 0.54, 95 % CI 0.41-0.72; P=0.54, $P_{heterogeneity}$=0.95, I^2=0 % (Fixed) GG *vs*. GT+TT: OR 0.76, 95 % CI 0.07-7.95; P=0.82, $P_{heterogeneity}$=0.15, I^2=51 % , GG *vs*. TT: OR 0.68, 95 % CI 0.07-6.27; P=0.73, $P_{heterogeneity}$=0.17, I^2=46 %) except dominant (GG+GT *vs*. TT: OR 0.51, 95 % CI 0.38-0.69; P=0.00, $P_{heterogeneity}$=0.69, I^2=0 %) and heterozygote model (GT*vs*.TT: OR 0.50, 95 % CI 0.37-0.69; P=0.00, $P_{heterogeneity}$=0.41, I^2=0 %).

Publication Bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Figure 3). The Egger's test also showed that All the P values were more than 0.05 (data not shown). Thus, no evident publication bias was found in present study. Sensitivity analysis was conducted by deleting each study in turn from the pooled analysis to examine the influence of the removed data set to the overall ORs. Exclusion of each study did not influence the result in specific genotype comparison for GST polymorphism, suggesting that the results of synthetic analysis were robust.

Discussion

The DNMT3B promoter region polymorphisms role in promoter function and gene expression is still debated both polymorphisms have been extensively investigated in cancer genetic association studies (Naghibalhossaini et al., 2015). In the present meta-analysis we evaluated two functional DNMT3B promoter polymorphisms, namely -149 C>T and - 579 G>T in CRC and gastric cancer risk.

The present meta-analysis included eleven case–control studies with 3,353 cases and 4,936 controls concerning DNMT3B-149C>T polymorphism and four case–control studies with 1,387 cases and 2,064 controls concerning DNMT3B-579G>T polymorphism. When stratified by different types of cancer, we have not found an association between DNMT3B -149C/T polymorphism and CRC and gastric cancer. In addition, there is not an association between DNMT3B-579G>T polymorphism and gastric cancer. However, the DNMT3B-579G>T was associated with CRC risk under dominant and heterozygote models.

Recent meta-analysis based on nine studies showed no significant elevated risk of colorectal cancer, gastric cancer and other cancers with DNMT3B -149C/T polymorphism (Zhu et al., 2015). By including one (Zhong et al., 2013), or two more studies (Wang et al., 2013), we have confirmed that DNMT3B -149C/T polymorphism was not associated with CRC and gastric cancer risk. It seems this probability may be that different types of cancer may have different mechanism of carcinogenesis (Zhu et al.,

2015). In a meta-analysis Xia et al., demonstrated that the DNMT3B-579G>T polymorphism was significantly associated with a subtly decreased cancer risk under heterozygote and dominant genetics models (GT vs TT: OR=0.78, 95%CI: 0.70-0.87, P<0.01; GT + GG vs TT: OR=0.81, 95%CI: 0.68-0.97, P=0.02), especially in colorectal cancer subgroup (Xia et al., 2015). Similarly, in this meta-analysis, we confirmed that DNMT3B-579G>T polymorphism was associated with CRC under two genetic models. Recently, Zhu et al in a meta-analysis of the literature suggests a decreased cancer risk in carriers of the -579 G allele (Zhu et al., 2015).

Many studies revealed the relation between DNMT3B gene polymorphisms and susceptibility of cancers. However, the main findings from the different studies did not reach the same conclusion (Xia et al., 2015; Zhu et al., 2015). It seems this inconsistency may result from the small sample size and the different experimental methods. It should be noted that the distribution of the control group for DNMT3B in Jones's report deviated from Hardy-Weinberg Equilibrium, which may have been due to genotyping errors or selection bias in the control and/or population stratification (Jones et al., 2006). Therefore, as recommended (Attia et al., 2003), we conducted the meta-analysis again with this study removed. Although excluding this study did not affect the result of the association between DNMT3B polymorphism and cancer risk, suggesting a high stability of the meta-analysis results with little effect of this particular study.

There was a moderate heterogeneity for total analysis. To detect the origin of heterogeneity, we carried out subgroup analysis and used random-effects model to pool the results whenever significant heterogeneity was present. In the subgroup analysis by cancer type, strong heterogeneity was found in CRC but not in gastric. This indicated that the heterogeneity might derive form case–control studies those focusing on CRC. In addition, other factors such as differences in gender, age, sample size, and genotyping method might also contribute the heterogeneity.

Meta-analysis has advantages compared to individual studies, however, some potential limitations in our study should be considered. First, methodologies were not uniformly defined. The genotyping methods used were different among these studies, which might have affected the results. This discrepancy between genotyping methods highlights the need for implementing rigorous quality control procedures in future studies. Second, only published studies were included in this meta-analysis. Unpublished data, ongoing studies and articles published in languages other than English and Chinese were not sought, especially those with negative findings, which may have biased our results, although no obvious publication bias was apparent. Third, this meta-analysis was limited by the number of cases and controls as well as small sample sizes, especially in the subgroup analysis by ethnicity. Thus, additional studies are needed to evaluate the effect of these functional polymorphisms on CRC and gastric cancer in different races. Fourth, our results were based on unadjusted estimates; a more precise analysis of the various groups should be conducted according to other factors, such as age and sex. Finally, the existing literature lacks information about potential gene-gene or gene-environment interactions. Given that the role of several environmental factors in the pathogenesis of colorectal and gastric cancer is established, further research should be performed in this direction.

In summary, more studies, more accurate genotype data and larger sample size of different ethnic populations are needed to detect DNMT3B -149C/T and DNMT3B 579G>T polymorphism and its association with cancer in different ethnicities and large population sizes to generate a comprehensive conclusion. Moreover, the interactions between gene–gene, gene–environment, and different SNP loci in the same gene should also be evaluated.

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