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Original Article

Association of *DNMT3B* -283 T > C and -579 G > T polymorphisms with decreased cancer risk: evidence from a meta-analysis

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Abstract: Numerous studies have explored the association of polymorphisms in the *DNA methyltransferase 3b* (*DNMT3B*) gene with the risk of different types of cancer, but yielded controversial results. Therefore, we performed a meta-analysis to derive a more precise estimation of the association between three widely-studied *DNMT3B* polymorphisms and overall cancer susceptibility. Totally, 4 studies with 1234 cases and 1337 controls were eligible for *DNMT3B* -283 T > C (rs6087990), 19 studies with 5332 cases and 7407 controls for *DNMT3B* -149 C > T (rs2424913), and 14 studies with 3933 cases and 4436 controls for *DNMT3B* -579 G > T (rs1569686). Overall, *DNMT3B* -283 T > C was associated with a significantly reduced risk of overall cancer (T vs. C: OR = 0.84, 95% CI = 0.71-0.99, *P* = 0.039). Likewise, the association of *DNMT3B* -579 G > T with a decreased overall cancer risk was also observed (heterozygous: OR = 0.77, 95% CI = 0.65-0.91, *P* = 0.003 and dominant: OR = 0.80, 95% CI = 0.66-0.98, *P* = 0.029); in the subgroup analysis, the protective association was found for lung and colorectal cancer, but not for head and neck cancer. Finally, the pooled analysis showed no significant association between *DNMT3B* -149 C > T and overall cancer susceptibility, but stratification analysis indicated that this polymorphism decreased the risk of developing head and neck cancer (heterozygous: OR = 0.73, 95% CI = 0.59-0.90, *P* = 0.003 and dominant: OR = 0.76, 95% CI = 0.61-0.93, *P* = 0.009). In conclusion, our results suggested that *DNMT3B* -283 T > C and *DNMT3B* -579 G > T but *DNMT3B* -149 C > T might confer protection against overall cancer risk. In the future, large and well-designed case-control studies are needed to validate our findings.

Keywords: *DNMT3B*, polymorphisms, cancer, risk, meta-analysis

Introduction

Cancer is a serious public health problem, with over 12 million new cancer cases diagnosed worldwide each year [1]. Genetic factors play an important role in the development of cancer [2]. DNA methylation, one of the epigenetic markers, can regulate the gene activity and may contribute to the initiation and development of cancer. In human, aberrations of DNA methylation have been found to associate with inactivating of microRNA, which is involved in the maintenance of global gene expression patterns. Moreover, DNA methylation also participates in the modification of histone structure that is commonly disrupted in cancer cells [3-7]. DNA methyltransferases (DNMTs) are the key effectors to establish and maintain proper DNA methylation patterns by converting cytosine residues to 5-methylcytosine (5 mC) within the cytosine-guanine (CpG) dinucleotides [8, 9]. DNMTs family encompasses three active forms, DNMT1, DNMT3A and DNMT3B. DNMT1 has been reported to maintain DNA methylation patterns during replication, whereas DNMT3A and DNMT3B are responsible for *de novo* DNA methylation during embryogenesis and germ cell development [4, 6, 10]. Overexpression of DNMT3B has been found in several different types of tumors, suggesting that DNMT3B plays a critical role in carcinogenesis [11-13].

Human *DNMT3B* gene is located on chromosome 20q11.2 and encodes DNA methyltrans-

ferase 3b (DNMT3B). Single nucleotide polymorphisms (SNPs) in the promoter of *DNMT3B* gene have been reported to be associated with a wide spectrum of cancer, such as colorectal cancer, head and neck cancer, gastric cancer, lung cancer and acute myeloid leukemia [14-18]. Among them, the following three promoter SNPs may be able to alter the promoter activity: *DNMT3B* -149 C > T (rs2424913, in the transcription start site), *DNMT3B* -579 G > T (rs1569686, in the exon 1B transcription start site) and *DNMT3B* -283 T > C (rs6087990, in the exon 1A transcription start site). The three SNPs and their association with cancer risk have been widely studied. However, the individual studies have appeared to either support or negate the association of these SNPs with cancer susceptibility. Therefore, there is an urgent need to determine whether there is a truly association between them.

So far, there were two previously published meta-analyses conducted in 2012 focusing on the association of *DNMT3B* polymorphisms with cancer risk. One of them only involved *DNMT3B* -149 C > T and colorectal cancer, and the other was performed to merely investigate the association between *DNMT3B* -149 C > T and *DNMT3B* -579 G > T and cancer risk [19, 20]. Recently, there have been at least 9 newly published studies, concerning the relationship between these two *DNMT3B* polymorphisms and cancer. In addition, *DNMT3B* -283 T > C polymorphism was not evaluated in the two previous meta-analyses. Hence, we performed an updated meta-analysis to assess the association between the three most frequently reported *DNMT3B* SNPs (-149 C > T, -579 G > T and -283 T > C) and overall cancer risk.

Material and methods

Identification and eligibility of relevant studies

A systematic literature review was performed by searching the PubMed and EMBASE electronic databases before December 31, 2014. The following key words were used for the literature search: "DNMT3B or DNA methyltransferase 3B", "polymorphism or variant" and "cancer or carcinoma or tumor or neoplasm". We also conducted a hand search of reference lists of original and review articles for extra eligible studies.

Inclusion/exclusion criteria

Studies were eligible for inclusion in this meta-analysis if they met the following criteria: 1) case-control studies; 2) focused on the association of *DNMT3B* polymorphisms (-149 C > T, -579 G > T and -283 T > C) and cancer risk; 3) studies with sufficient raw data for estimating odds ratios (ORs) and 95% confidence intervals [21]. Exclusion criteria were as follows: 1) reviews; 2) cancer-only studies; 3) publication with overlapped subjects; 4) genotype distribution of control group was not in Hardy-Weinberg equilibrium (HWE). If studies had partly overlapped subjects, only the latest study or the one with largest sample size was chosen.

Data extraction

Using a standardized form, information from all the publications were independently extracted by two of the authors. We recorded the first author, year of publication, cancer type, genotype methods, ethnicity, and numbers of cases and controls with the different genotypes for each of *DNMT3B* SNPs. In the subgroup analysis by cancer type, if there was only one study regarding a specific type of cancer, we merged the study into "other" group.

Quality assessment

We assessed the quality of each study using the quality assessment criteria [22, 23]. The quality assessment criteria included seven aspects: 1) representativeness of case, 0-2 points; 2) representativeness of control, 0-3 points; 3) ascertainment of cancer case, 0-2 points; 4) control selection, 0-2 points; 5) genotyping examination, 0-2 points; 6) HWE; 0-1 points; and 7) total sample size, 0-3 points. Quality scores ranged from 0 to 15. Studies with scores > 9 were considered as high quality studies; otherwise, studies were considered to have a low quality.

Statistical analysis

We conducted all statistical analysis using STATA software (Version 11.0; Stata Corp LP, College Station, TX). ORs and their corresponding 95% CI were applied to evaluate the strength of association between *DNMT3B* gene polymorphisms and cancer risk. Heterogeneity between studies was tested by Chi square-

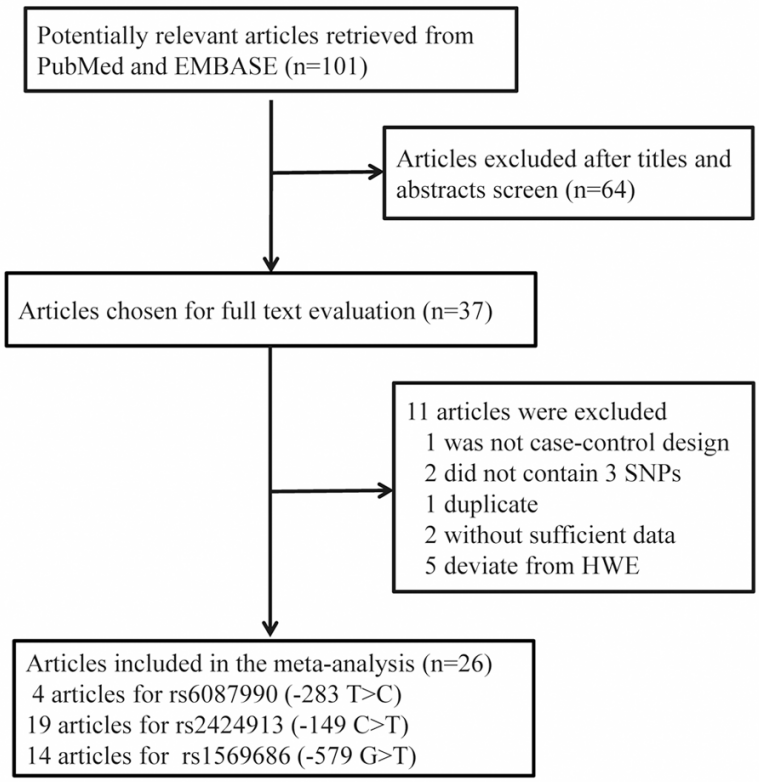

Figure 1. Flow diagram of included studies.

based Q-test. A $P > 0.10$ indicated a lack of observed heterogeneity between studies, and then, the fixed-effects model was used to calculate the pooled ORs [24]. Otherwise, the random-effects model was used [25]. Publication bias was checked using Begger's funnel plots and Egger's linear regression test [26].

Results

Study characteristics

As shown in **Figure 1**, a total of 101 potential relevant articles were found. After initial examination of titles and abstracts, 64 publications were excluded. Of the remaining 37 relevant publications, 11 studies were further removed for the following reasons: one was cancer-only study [27], two did not investigate any of the three *DNMT3B* polymorphisms [28, 29], one reported on the same population as another included study [30], two failed to provide sufficient genotype distribution data [31, 32], and five were deviated from HWE [33-37]. As a result, 26 eligible studies were included in the final meta-analysis, including 4 articles (1234 cases and 1337 controls) for *DNMT3B* -283 T > C [17, 18, 38, 39], 19 articles (5332 cases and 7407 controls) for *DNMT3B* -149 C > T [14-16, 40-55], and 14 articles (3933 cases and 4436 controls) for *DNMT3B* -579 G > T [15-18, 38-42, 48, 49, 56-58]. The genotype distributions in control groups for the *DNMT3B* -149 C > T and *DNMT3B* -579 G > T polymorphism were all in compliance with HWE in all included studies, whereas the genotype distributions of *DNMT3B* -283 T > C was deviated from HWE in one study [18]. Since the distribution of *DNMT3B* -579 G > T followed HWE (HWE = 0.27) in this study [18], we decided to include this one in our final meta-analysis.

As summarized in **Table 1**, all the four studies for *DNMT3B* -283 T > C were conducted among Asians. In term of *DNMT3B* -149 C > T, there were two head and neck cancer, two gastric cancer, three hepatocellular cancer, and seven colorectal cancer studies, as well as five studies on "other" cancer. Eleven studies focused on Caucasians, seven on Asians and one on mixed ethnicity. For *DNMT3B* -579 G > T, there were 2 lung cancer, 2 gastric cancer and 2 head and neck cancer studies identified. Moreover, 8 studies were merged into "other" group. Among these studies, 3 studies were conducted on Caucasians and 11 on Asians. All 4 studies were classified as high quality studies for *DNMT3B* -283 T > C, while 7 and 3 studies were classified as low quality studies for *DNMT3B* -149 C > T and -579 G > T, respectively.

Meta-analysis results

First of all, individuals with rs6087990 (-283 T > C) TT or CT genotype were not significantly association with cancer risk compared with carriers of wild type CC genotype (TT vs. CC: OR = 0.71, 95% CI = 0.45-1.14, $P = 0.161$ and CT vs. CC: OR = 0.87, 95% CI = 0.72-1.06, $P = 0.170$). Similarly, no significantly association were found under the recessive and dominant

Table 1. Characteristics of eligible studies in this meta-analysis

Surname	Year	Ethnicity	Cancer type	Genotype method	Case	Control	HWE	Score
-283 T > C								
Zheng	2013	Asian	Acute myeloid leukemia	HRM	317	406	0.01	12
Chang	2008	Asian	Nasopharyngeal carcinomas	MALDI-TOF	259	250	0.57	11
Chang	2007	Asian	Head and neck cancer	MALDI-TOF	226	249	0.60	10
Lee	2005	Asian	Lung cancer	PCR-RFLP	432	432	0.59	13
-149 C > T								
Succi	2014	Caucasian	Head and neck cancer	Real-Time PCR	237	488	0.12	9
Mostowska	2013	Caucasian	Ovarian cancer	HRM	159	180	0.83	9
Lao	2013	Asian	Hepatocellular carcinoma	PCR-RFLP	108	216	0.84	8
Sotelo	2013	Caucasian	Cervical cancer	PCR-RFLP	70	200	0.17	10
Bao	2011	Asian	Colorectal cancer	PCR-RFLP	544	533	0.79	14
Karpinski	2010	Caucasian	Colorectal cancer	PCR-RFLP	186	140	0.74	9
Hu	2010	Asian	Gastric cancer	PCR-RFLP	259	262	0.93	13
Ezzikouri	2009	Caucasian	Hepatocellular carcinoma	PCR-RFLP	96	222	0.88	10
Iacopetta	2009	Caucasian	Colorectal cancer	PCR-RFLP	828	949	0.54	14
de Vogel	2009	Caucasian	Colorectal cancer	SBE	703	1810	0.58	14
Liu	2008	Caucasian	Head and neck cancer	PCR-RFLP	832	843	0.15	15
Fan	2008	Asian	Colorectal cancer	PCR-RFLP	137	308	0.91	12
Reeves	2008	Caucasian	Colorectal cancer	PCR-RFLP	194	210	0.29	8
Wu	2007	Asian	Hepatocellular carcinoma	PCR-RFLP	100	140	0.97	10
Jones	2006	Mixed	Colorectal cancer	PCR-SSCP	74	72	0.05	9
Wang	2005	Asian	Gastric cancer	PCR-RFLP	212	294	0.65	13
Singal	2005	Caucasian	Prostate cancer	PCR-RFLP	81	42	0.75	5
Li	2005	Asian	Acute leukemia	PCR-RFLP	160	240	0.84	10
Montgomery	2004	Caucasian	Breast cancer	PCR-RFLP	352	258	0.13	10
-579 G > T								
Zheng	2013	Asian	Acute myeloid leukemia	HRM	317	406	0.27	12
Mostowska	2013	Caucasian	Ovarian cancer	HRM	159	180	0.74	9
Lao	2013	Asian	Hepatocellular carcinoma	PCR-RFLP	114	210	0.33	8
Sotelo	2013	Caucasian	Cervical cancer	PCR–RFLP	70	200	0.99	10
Liu	2012	Asian	Lung cancer	PCR–RFLP	181	135	0.22	12
Bao	2011	Asian	Colorectal cancer	PCR-RFLP	544	533	0.18	14
Srivastava	2010	Asian	Gallbladder carcinoma	PCR-RFLP	209	218	0.25	9
Hu	2010	Asian	Gastric cancer	PCR-RFLP	259	262	0.90	13
Liu	2008	Caucasian	Head and neck cancer	PCR-RFLP	832	843	0.79	15
Fan1	2008	Asian	Esophagus carcinoma	PCR-RFLP	194	210	0.40	12
Fan2	2008	Asian	Colorectal cancer	PCR-RFLP	137	308	0.29	10
Chang	2008	Asian	Nasopharyngeal carcinomas	MALDI-TOF	259	250	0.19	11
Chang	2007	Asian	Head and neck cancer	MALDI-TOF	226	249	0.22	10
Lee	2005	Asian	Lung cancer	PCR-RFLP	432	432	0.52	13

HRM, high-resolution melting method; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphisms; SBE, single base extension, SSCP, single-strand conformational polymorphism; HWE, Hardy-Weinberg equilibrium.

model (recessive: OR = 0.71, 95% CI = 0.44-1.12, *P* = 0.140 and dominant: OR = 0.85, 95% CI = 0.70-1.02, *P* = 0.080). Interestingly, comparison of allele frequency revealed that T allele was associated with significantly decreased risk of cancer compared with C allele (T vs. C: OR = 0.84, 95% CI = 0.71-0.99, *P* = 0.039) (**Table 2** and **Figure 2**).

Table 2. Meta-analysis of the association between studied *DNMT3B* polymorphisms and cancer risk

Variables	N (Case/Control)	Homozygous		Heterozygous		Recessive		Dominant		Allele	
		OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}
-283 T > C		TT vs. CC		CT vs. CC		TT vs. (CT + CC)		(CT +TT) vs. CC		T vs. C	
All	4 (1234/1337)	0.71 (0.45-1.14)	0.969	0.87 (0.72-1.06)	0.370	0.71 (0.44-1.12)	0.976	0.85 (0.70-1.02)	0.540	0.84 (0.71-0.99)	0.717
-149 C > T		CC vs. TT		CT vs. TT		CC vs. (CT + TT)		(CT +CC) vs. TT		C vs. T	
All	19 (5332/7407)	1.00 (0.88-1.13)	0.132	1.10 (0.89-1.36)	< 0.001	1.00 (0.91-1.10)	0.258	1.07 (0.88-1.30)	0.001	1.01 (0.91-1.12)	0.015
Cancer type											
Head and neck	2 (1069/1331)	0.80 (0.63-1.01)	0.332	0.73 (0.59-0.90)	0.335	1.00 (0.84-1.20)	0.666	0.76 (0.61-0.93)	0.300	0.91 (0.81-1.02)	0.443
Hepatocellular	3 (304/578)	1.16 (0.55-2.43)	-	1.20 (0.46-3.15)	0.266	0.98 (0.59-1.63)	-	1.18 (0.45-3.04)	0.267	1.06 (0.47-2.38)	0.273
Colorectal	7 (2666/4022)	1.06 (0.90-1.25)	0.370	1.08 (0.93-1.26)	0.685	1.00 (0.88-1.13)	0.047	1.07 (0.93-1.23)	0.799	1.01 (0.91-1.11)	0.325
Gastric	2 (471/556)	-	-	0.64 (0.28-1.45)	0.956	-	-	0.64 (0.28-1.45)	0.956	0.65 (0.29-1.45)	0.962
Other	5 (822/920)	1.19 (0.85-1.67)	0.147	1.65 (0.92-2.97)	0.003	0.99 (0.77-1.28)	0.300	1.59 (0.89-2.82)	0.002	1.23 (0.87-1.75)	0.004
Ethnicity											
Caucasian	11 (3738/5342)	1.01 (0.89-1.14)	0.199	1.08 (0.86-1.34)	0.001	1.02 (0.92-1.12)	0.909	1.06 (0.87-1.30)	0.002	1.02 (0.95-1.09)	0.253
Asian	7 (1520/1993)	4.94 (0.20-122.01)	-	1.06 (0.46-2.47)	0.015	4.52 (0.18-111.74)	-	1.07 (0.45-2.55)	0.011	1.08 (0.45-2.57)	0.009
Mixed	1 (74/72)	0.43 (0.17-1.11)	-	1.67 (0.73-3.80)	-	0.30 (0.14-0.66)	-	1.04 (0.48-2.23)	-	0.64 (0.40-1.02)	-
-579 G > T		GG vs. TT		GT vs. TT		GG vs. (GT + TT)		(GT + GG) vs. TT		G vs. T	
All	14 (3933/4436)	1.16 (0.73-1.87)	0.006	0.77 (0.65-0.91)	0.021	1.26 (0.85-1.87)	0.014	0.80 (0.66-0.98)	< 0.001	0.86 (0.71-1.04)	< 0.001
Cancer type											
Lung	2 (613/567)	0.63 (0.20-2.01)	0.442	0.70 (0.52-0.93)	0.323	0.68 (0.21-2.15)	0.431	0.69 (0.52-0.92)	0.416	0.72 (0.56-0.93)	0.525
Colorectal	2 (681/841)	0.69 (0.06-7.75)	0.139	0.51 (0.37-0.69)	0.410	0.75 (0.07-8.63)	0.136	0.51 (0.38-0.70)	0.698	0.55 (0.41-0.73)	0.953
Head and neck	2 (1058/1092)	0.86 (0.65-1.13)	-	0.82 (0.64-1.04)	0.950	0.99 (0.81-1.21)	-	0.83 (0.66-1.04)	0.898	0.93 (0.82-1.07)	0.595
Other	8 (1581/1936)	1.39 (0.71-2.73)	0.014	0.88 (0.69-1.11)	0.073	1.47 (0.81-2.68)	0.014	0.93 (0.69-1.24)	0.004	0.99 (0.74-1.32)	< 0.001
Ethnicity											
Caucasian	3 (1061/1223)	0.89 (0.70-1.14)	0.813	0.81 (0.65-1.02)	0.925	1.02 (0.85-1.22)	0.803	0.84 (0.70-1.04)	0.906	0.95 (0.84-1.08)	0.783
Asian	11 (2872/3213)	1.19 (0.55-2.59)	0.014	0.76 (0.61-0.94)	0.005	1.25 (0.59-2.64)	0.020	0.78 (0.60-1.02)	< 0.001	0.82 (0.62-1.08)	< 0.001

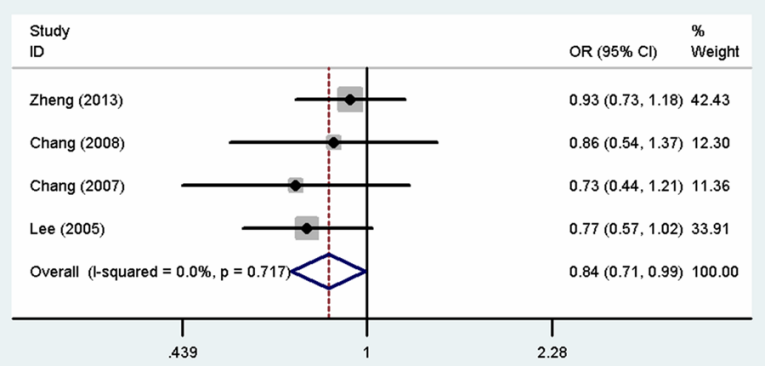

Figure 2. Forest plot for the association between *DNMT3B* -283 T > C polymorphism and overall cancer risk (T vs. C).

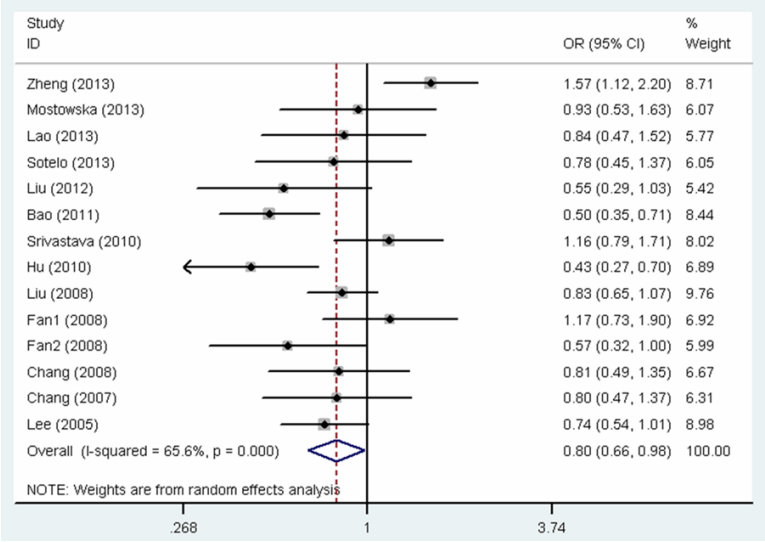

Figure 3. Forest plot for the association between *DNMT3B* -579 G > T polymorphism and overall cancer risk (GT + GG vs. TT).

For rs2424913 (-149 C > T), its null association with risk of overall cancer was found (homozygous: OR = 1.00, 95% CI = 0.88-1.13, *P* = 0.973; heterozygous: OR = 1.10, 95% CI = 0.89-1.36, *P* = 0.392; recessive: OR = 1.00, 95% CI = 0.91-1.10, *P* = 0.963; dominant: OR = 1.07, 95% CI = 0.88-1.30, *P* = 0.513, and comparison of allele frequency: OR = 1.01, 95% CI = 0.91-1.12, *P* = 0.210). In the stratified analysis by ethnicity, we did not detect significant association between *DNMT3B* -149 C > T polymorphism and cancer susceptibility in Asian or in Caucasian populations. While data was stratified by cancer type, this polymorphism was shown to significantly decreased the risk of head and neck cancer (heterozygous: OR = 0.73, 95% CI = 0.59-0.90, *P* = 0.003 and dominant: OR = 0.76, 95% CI = 0.61-0.93, *P* = 0.009), but not the risk of hepatocellular cancer, gastric cancer, colorectal cancer and others (**Table 2**).

For rs1569686 (-579 G > T), interestingly, the *DNMT3B* -579 G > T polymorphism seemed to confer decreased overall cancer risk (heterozygous: OR = 0.77, 95% CI = 0.65-0.91, *P* = 0.003; dominant: OR = 0.80, 95% CI = 0.66-0.98, *P* = 0.029, **Table 2** and **Figure 3**). The protective association remained significant for lung cancer (heterozygous: OR = 0.70, 95% CI = 0.52-0.93, *P* = 0.013; dominant: OR = 0.69, 95% CI = 0.52-0.92, *P* = 0.011 and allele: OR = 0.72, 95% CI = 0.56-0.93, *P* = 0.013), colorectal cancer (heterozygous: OR = 0.51, 95% CI = 0.37-0.69, *P* < 0.001; dominant: OR = 0.51, 95% CI = 0.38-0.70, *P* < 0.001 and comparison of allele frequency: OR = 0.55, 95% CI = 0.41-0.73, *P* < 0.001), and Asians (heterozygous: OR = 0.76, 95% CI = 0.61-0.94, *P* = 0.014).

Heterogeneity and sensitivity analyses

There were substantial between-studies heterogeneities observed for *DNMT3B* -149 C > T while calculating pooled risk estimates under the heterozygous model (*P* < 0.001), dominant model (*P* = 0.001), and comparison of allele frequency (*P* = 0.015), but not homozygous model (*P* = 0.132) and recessive model (*P* = 0.258). The leave-one-out sensitivity analysis showed that six studies changed the pooled ORs. After excluding the six studies [42, 44, 46, 48, 54, 55], the degree of heterogeneity dramatically decreased (homozygous model, *P* = 0.426; recessive model, *P* = 0.163; heterozygous model, *P* = 0.440; dominant model, *P* = 0.577 and comparison of allele frequency, *P* = 0.466), without qualitatively altering the overall estimates (homozygous: OR = 0.92, 95% CI = 0.73-1.17; heterozygous: OR = 0.94, 95% CI = 0.77-

1.15; recessive: OR = 0.91, 95% CI = 0.76-1.10; dominant: OR = 0.92, 95% CI = 0.76-1.11; and comparison of allele frequency: OR = 0.94, 95% CI = 0.83-1.05). For *DNMT3B* -283 T > C, no significant heterogeneity was found (homozygous model, $P = 0.969$; recessive model, $P = 0.976$; heterozygous model, $P = 0.370$; dominant model, $P = 0.540$ and comparison of allele frequency, $P = 0.717$). On the contrary, there is obvious heterogeneity under all the modes of inheritance for *DNMT3B* -579 G > T (homozygous model, $P = 0.006$; recessive model: $P = 0.014$; heterozygous model, $P = 0.021$; dominant model, $P < 0.001$ and comparison of allele frequency, $P < 0.001$). We next performed a leave-one-out sensitivity analysis. After excluding six studies [15, 16, 18, 40, 41, 57], the heterogeneity dramatically disappeared (homozygous model, $P = 0.682$; recessive model, $P = 0.625$; heterozygous model, $P = 0.297$; dominant model, $P = 0.254$ and comparison of allele frequency, $P = 0.079$), without qualitatively altering the overall estimates (homozygous: OR = 0.81, 95% CI = 0.63-1.04; heterozygous: OR = 0.77, 95% CI = 0.67-0.89; recessive: OR = 0.95, 95% CI = 0.79-1.15; dominant: OR = 0.77, 95% CI = 0.67-0.88), except for comparison of allele frequency (OR = 0.85, 95% CI = 0.77-0.94).

Publication bias

There was no obvious asymmetry in Begger's funnel plots and no significant publication bias detected by Egger's linear regression test in the current meta-analysis, *DNMT3B* -283 T > C ($P = 0.546$ for homozygous model; $P = 0.724$ for recessive model; $P = 0.684$ for heterozygous model; $P = 0.611$ for dominant model, and $P = 0.488$ for comparison of allele frequency), *DNMT3B* -149 C > T ($P = 0.535$ for homozygous model; $P = 0.103$ for recessive model; $P = 0.516$ for heterozygous model; $P = 0.668$ for dominant model and $P = 0.879$ for comparison of allele frequency) and *DNMT3B* -579 G > T ($P = 0.860$ for homozygous model; $P = 0.772$ for recessive model; $P = 0.706$ for heterozygous model; $P = 0.505$ for dominant model and $P = 0.274$ for comparison of allele frequency).

Discussion

DNA methyltransferase 3b is necessary for the establishment and maintenance of genomic methylation patterns and facilitate proper embryonic development [59]. It was demonstrated that some polymorphisms in the *DNMT3B* gene could significantly increase the promoter activity in lung cancer in 2002 [35]. Since then, a number of epidemiological studies have assessed the association between *DNMT3B* gene polymorphisms and the risk of different types of cancer, but the findings are inconclusive. In order to resolve this conflict, this meta-analysis with 26 studies was performed to provide an updated, more precise estimation of the associations of three *DNMT3B* polymorphisms (-283 T > C, -149 C > T and -579 G > T) with cancer risk.

To the best of our knowledge, no previous meta-analysis has comprehensively assessed the association between the three *DNMT3B* polymorphisms and overall cancer risk. To data, there were only two meta-analyses investigating the association between *DNMT3B* polymorphisms and cancer risk [19, 20]. Fang et al. attempted to evaluate the association of the *DNMT3B* -149 C > T polymorphism with the risk of colorectal cancer. They pooled together seven eligible studies, comprising 2666 cases and 4022 controls, and failed to provide the evidence of such association [19]. Zhu et al. performed a meta-analyses including 5229 cases/6910 controls from 17 case-control studies for *DNMT3B* -149 C > T and 3513 cases/3714 controls from 11 case-control studies for *DNMT3B* -579 G > T in 2012 [20]. The results indicated that there was no significant association between *DNMT3B* -149 C > T and cancer risk under all genetic model, even in the stratified analysis by cancer type. However, a significant association of *DNMT3B* -579 G > T with decreased cancer risk, particularly for colorectal cancer, were found while using heterozygous model, dominant model and comparison of allele frequency. It was worth noting that Zhu et al. included some publications that were deviated from HWE [20]. In contrast, in the current meta-analysis, we excluded all publications deviate from HWE [34, 35, 37]. Moreover, we included several extra case-control studies about these two polymorphisms that were published since 2012 [14, 18, 40-42, 56]. As results, some findings in the present meta-analysis were different from those in the previous meta-analysis: 1) Unlike the previous meta-analysis, we found that *DNMT3B* -149 C > T was associated with a decreased risk of head

and neck cancer under the heterozygous model and dominant model; 2) We failed to replicate the significant association between *DNMT3B* -579 G > T and overall cancer risk under the comparison of allele frequency; 3) We found a significant association between *DNMT3B* -579 G > T and lung cancer under the heterozygous, dominant, and allele comparison model for the first time. The exclusion of the publication deviated from HWE and the inclusion of several additional eligible studies might reduce the chance of false positive results and increase the statistical power to evaluate the association of interest. Taken together, this meta-analysis provided some new insight into the mechanisms of the development of cancer, especially for head and neck cancer, lung cancer and colorectal cancer.

There were several limitations inherited from the published studies in this meta-analysis. First, the sample size was not large enough to draw a convincing conclusion for *DNMT3B* -283 T > C and the sample size in some subgroup analysis was also relatively small for *DNMT3B* -149 C > T and *DNMT3B* -579 G > T. Second, significant heterogeneities were observed under a few genetic models, thus we chose the random-effects to calculate ORs and 95% CIs. Third, due to lacking other important original data, our conclusions were based on unadjusted estimates of ORs without adjustment for environment factors such as smoking or drinking habits.

In conclusion, our meta-analysis suggests that *DNMT3B* -283 T > C and *DNMT3B* -579 G > T may play a protective role against cancer. Moreover, in the subgroup analysis, *DNMT3B* -579 G > T appeared to contribute to decreased risk of lung cancer and colorectal cancer as well as decreased cancer risk among Asians; meanwhile, *DNMT3B* -149 C > T was associated with a reduced risk of head and neck cancer. Future large-scale case-control designed prospective studies are warranted to confirm our finding in different ethnicities and in different cancer types.

Disclosure of conflict of interest

None.

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