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Original Article

Association between the CD28 IVS3 +17T>C (rs3116496) polymorphism and cancer susceptibility: a meta-analysis involving 8,843 subjects

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Abstract: The possible association between *CD28* IVS3 +17T>C (rs3116496) polymorphism and cancer susceptibility has been widely investigated. However, the results are conflicting. To verify the association more precisely, we performed a meta-analysis of 11 publications involving a total of 8,843 subjects. In this meta-analysis, 11 publications were included by searching PubMed and EMBASE databases up to May 23, 2014. The cancer susceptibility associated with the *CD28* IVS3 +17T>C polymorphism was evaluated by odds ratios (ORs) with 95% confidence intervals (95% CIs). Heterogeneity, sensitivity and publication bias analyses were also assessed. The result suggested that the *CD28* IVS3 +17T>C polymorphism is not associated with cancer susceptibility in overall cancer. In a stratified analysis by ethnicity, the association of *CD28* IVS3 +17T>C polymorphism with cancer susceptibility was significant in Asians. In a stratified analysis by the origin of cancer cells and system of cancer, *CD28* IVS3 +17T>C polymorphism was not associated with cancer susceptibility. In summary, this meta-analysis demonstrated that the *CD28* IVS3 +17T>C polymorphism may be a cancer susceptibility factor in Asians.

Keywords: Cancer, polymorphism, *CD28*, cancer susceptibility, meta-analysis

Introduction

Cancer is a critical public health problem and one of the leading causes of death worldwide [1]. Accumulating evidence suggests that cancer results from complex mutual effect between genetic and environmental factors [2-4]. The immune reaction acts as an important natural barrier to cancer development and progression. All the principal antitumor responses are cell-mediated, such as by natural killer (NK) cells and T lymphocytes. Thus, genetic mutations of important immunological genes that regulate the function of T lymphocytes and NK cells may alter cancer susceptibility [5].

Effective activation of T cell results from the interaction between multiple costimulatory receptors and their ligands on an antigen presenting cell [6]. CD28, one of the best characterized costimulatory molecules, is expressed by the most T cells. CD28 competes with CTLA-4 for B7 binding, thus enhancing T-cell proliferation, which is inhibited by the CTLA-4-B7 interaction. In the last decade, several molecular epidemiological studies demonstrated an association between *CD28* IVS3 +17T>C (rs3116496) polymorphism and cancer susceptibility. In the previous studies, it was reported that the *CD28* IVS3 +17 TT genotype was associated with a low penetrance risk of cervical cancer and breast cancer in a Chinese Han population [7, 8]. However, an individual investigation may have limited power to achieve a conclusive and reliable result. To further explore the role of the *CD28* IVS3 +17T>C polymorphism in tumorigenesis, we conducted a comprehensive meta-analysis of all eligible publica-

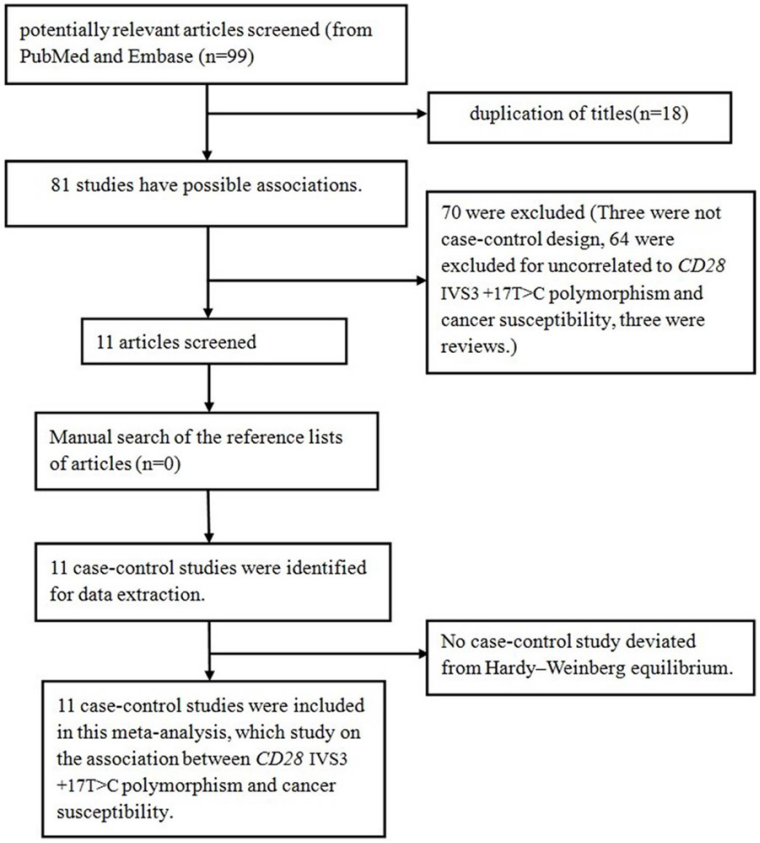

Figure 1. Flow diagram of articles selection process for CD28 IVS3 +17T>C polymorphism and cancer risk meta-analysis.

tions. To the best of our knowledge, this study is the first meta-analysis considering the *CD28* IVS3 +17T>C polymorphism and its association with cancer susceptibility.

Materials and methods

Search strategy

PubMed and EMBASE databases (the last search was updated in May 23, 2014) were searched simultaneously with combination of the following terms: 'CD28', 'polymorphism' or 'SNP' or 'variant', and 'cancer' or 'malignance' or 'carcinoma' or 'Neoplasm' or 'tumor'. The search was limited to human studies and no language restrictions. All bibliographies in reviews and the retrieved articles were checked to identify additional publications.

Inclusion and exclusion criteria

For inclusion, recruited publications had to meet the major selection criteria: (1) evaluating the *CD28* IVS3 +17T>C polymorphism and cancer susceptibility, (2) using a case-control study design, (3) containing complete data on genotype or allele frequency in case groups and control groups. Accordingly, reports without usable data, not case-control study, reviews and duplicated data were excluded.

Data extraction

For each recruited publications the following data was collected independently by two authors (S. Zhang and Y. Wang): (1) the name of first author, (2) cancer type, (3) published year, (4) country of origin, (5) ethnicity, (6) case number and control number, (7) allele and genotype frequency, (8) genotyping method and (9) evidence of Hardy-Weinberg equilibrium (HWE) in controls. When come to conflicting evaluations, disagreements were discussed until reaching conformity on items among all reviewers.

Statistical analysis

The HWE in controls was determined using an internet-based HWE calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The crude odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated to estimate the strength of association between *CD28* IVS3 +17T>C polymorphism and cancer susceptibility. A $P < 0.05$ (two-tailed) was considered as statistically significant. A Chi-square-based I^2 test was used to detect for heterogeneity and an $I^2 < 25\%$ indicates low heterogeneity, $25\% \leq I^2 \leq 50\%$ indicates moderate heterogeneity, and $I^2 > 50\%$ indicates large heterogeneity [9]. When $I^2 > 50\%$ or $P < 0.10$ (two-sided), the random-effects model (the DerSimonian-Laird method) [10] was utilized to analyze the data, otherwise the fixed-effects model (the Mantel-Haenszel method) was used [11]. Sub-group analyses were carried out according to ethnicity, system of cancer, the origin of cancer cells, sample size, and publication year to explore the source of heterogeneity among variables. Galbraith

Table 1. Characteristics of the individual studies included in the meta-analysis

study	year	country	ethnicity	cancer type	No. of cases/ controls	Genotype Method
Chen et al.	2012	China	Asians	breast cancer	565/605	PCR-RFLP
Karabon et al.	2011	Poland	Caucasians	lung cancer	208/326	single-nucleotide primer-extension methods
Chen et al.	2011	China	Asians	cervical cancer	619/985	PCR-RFLP
Ivansson et al.	2010	Sweden	Caucasians	cervical cancer	1306/811	Taqman
Pawlak et al.	2010	Poland	Caucasians	cervical cancer	147/225	single-nucleotide primer-extension methods
Bouwhuis et al.	2010	German	Caucasians	melanoma	763/734	Taqman
Karabon et al.	2009	Poland	Caucasians	myeloma	150/238	SNapShot
Dilmec et al.	2008	Turkey	Caucasians	colorectal cancer	56/162	PCR-RFLP
Suwalska et al.	2008	Poland	Caucasians	leukemia	173/336	single-nucleotide primer-extension methods
Cheng et al.	2006	China	Asians	lymphoma	62/250	PCR-RFLP
Wlodarska-Polinska et al.	2006	Poland	Caucasians	cervical cancer	50/72	SNapShot

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Distribution of *CD28* IVS3 +17T>C polymorphisms genotype and allele among multiple cancer patients and controls

Study	Year	Case			Control			Case		Control		HWE
		TT	TC	CC	TT	TC	CC	C	T	C	T	
Chen et al.	2012	450	109	6	520	81	4	121	1009	89	1121	0.664536
Karabon et al.	2011	153	51	4	230	89	5	59	357	99	549	0.271397
Chen et al.	2011	492	120	7	853	123	9	134	1104	141	1829	0.057968
Ivansson et al.	2010	916	343	42	538	253	19	427	2175	291	1329	0.088850
Pawlak et al.	2010	100	31	1	172	49	2	33	231	53	393	0.462421
Bouwhuis et al.	2010	487	254	22	475	231	24	298	1228	279	1181	0.524521
Karabon et al.	2009	75	21	2	179	55	4	25	171	63	413	0.923949
Dilmec et al.	2008	32	19	5	106	50	6	29	83	62	262	0.972498
Suwalska et al.	2008	112	56	4	256	74	5	64	280	84	586	0.894690
Cheng et al.	2006	52	9	1	192	57	1	11	113	59	441	0.131639
Wlodarska-Polinska et al.	2006	39	9	2	52	18	2	13	87	22	122	0.771165

HWE: Hardy-Weinberg equilibrium.

radial plot was used to detect the major source of heterogeneity. Publication bias of the literature was assessed by Begg's funnel plot and Egger's test. Nonparametric "trim-and-fill" method and one-way sensitivity analysis were both used to confirm the stability of our findings. In addition, for the results of publication bias test, statistical significance was defined as $P < 0.1$ (two-sided). All statistical analyses in meta-analysis were carried out using STATA version 12.0 software (Stata Corporation, College Station, TX).

Results

Characteristics

The detailed selecting and excluding process was shown in **Figure 1**. In total, there were 11 eligible studies [7, 8, 12-20] recruited in this meta-analysis, involving 4099 cancer cases and 4744 controls. Among them, four investigated cervical cancer [7, 13, 14, 20], one investigated lung cancer [12], one investigated colorectal cancer [16], one investigated breast cancer [8], one investigated melanoma [15], one investigated myeloma [19], one investigated leukemia [17] and one study investigated lymphoma [18]. As for subjects, eight were Caucasians [12-17, 19, 20] and three were Asians [7, 8, 18]. Characteristics of these studies are presented in **Table 1**. The distribution of the *CD28* IVS3 +17T>C polymorphism and allele among cases and controls is showed in **Table 2**.

Quantitative synthesis

A total of 8,843 subjects (4099 cancer cases and 4744 controls) from 11 studies were

Table 3. Summary of results of the meta-analysis from different comparative genetic models in the subgroup analysis

	No. (cases/controls)	C vs. T			CC vs. TT			CC+TC vs. TT			CC vs. TC+TT		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	4099/4744	1.14 (0.96-1.35)	0.127	0.002	1.27 (0.93-1.73)	0.134	0.945	1.13 (0.92-1.39)	0.245	<0.001	1.26 (0.93-1.72)	0.135	0.950
Ethnicity													
Asians	1246/1840	1.38 (1.02-1.86)	0.039	0.106	1.58 (0.74-3.34)	0.236	0.789	1.37 (0.94-2.00)	0.101	0.054	1.47 (0.69-3.11)	0.315	0.723
Caucasians	2853/2904	1.01 (0.91-1.12)	0.866	0.128	1.21 (0.86-1.70)	0.265	0.867	1.04 (0.86-1.25)	0.718	0.062	1.23 (0.88-1.72)	0.234	0.876
The origin of cancer cells													
epithelial tumor	2951/3186	1.16 (0.92-1.48)	0.208	0.001	1.41 (0.95-2.09)	0.086	0.958	1.15 (0.86-1.53)	0.356	<0.001	1.43 (0.97-2.11)	0.070	0.977
non-epithelial tumor	1148/1558	1.09 (0.83-1.45)	0.525	0.092	1.06 (0.63-1.75)	0.836	0.626	1.10 (0.78-1.54)	0.599	0.057	1.02 (0.62-1.69)	0.940	0.644
System of cancer													
Reproductive cancer	2122/2093	1.09 (0.77-1.56)	0.624	0.003	1.29 (0.81-2.04)	0.277	0.990	1.07 (0.69-1.66)	0.769	<0.001	1.34 (0.85-2.11)	0.214	0.980
Hematopoietic malignancy	385/824	1.10 (0.69-1.76)	0.684	0.069	1.71 (0.64-4.54)	0.282	0.790	1.07 (0.59-1.93)	0.823	0.032	1.60 (0.60-4.24)	0.344	0.767
Other system cancer	1592/1827	1.17 (0.92-1.49)	0.195	0.059	1.17 (0.74-1.85)	0.512	0.396	1.18 (0.91-1.52)	0.220	0.082	1.14 (0.72-1.79)	0.587	0.433
Sample sizes													
≥ 1000	3253/3135	1.20 (0.91-1.57)	0.192	<0.001	1.17 (0.82-1.67)	0.399	0.712	1.21 (0.87-1.68)	0.249	<0.001	1.17 (0.82-1.67)	0.381	0.663
< 1000	846/1069	1.11 (0.93-1.32)	0.254	0.181	1.64 (0.89-3.01)	0.114	0.947	1.08 (0.89-1.32)	0.421	0.116	1.60 (0.87-2.93)	0.129	0.960
Publication year													
> 2009	3608/3686	1.13 (0.92-1.40)	0.241	0.001	1.16 (0.83-1.63)	0.390	0.920	1.14 (0.88-1.47)	0.315	<0.001	1.17 (0.83-1.64)	0.367	0.893
≤ 2009	491/1058	1.21 (0.97-1.51)	0.094	0.139	1.92 (0.94-3.94)	0.075	0.916	1.09 (0.74-1.62)	0.658	0.075	1.84 (0.90-3.74)	0.095	0.923

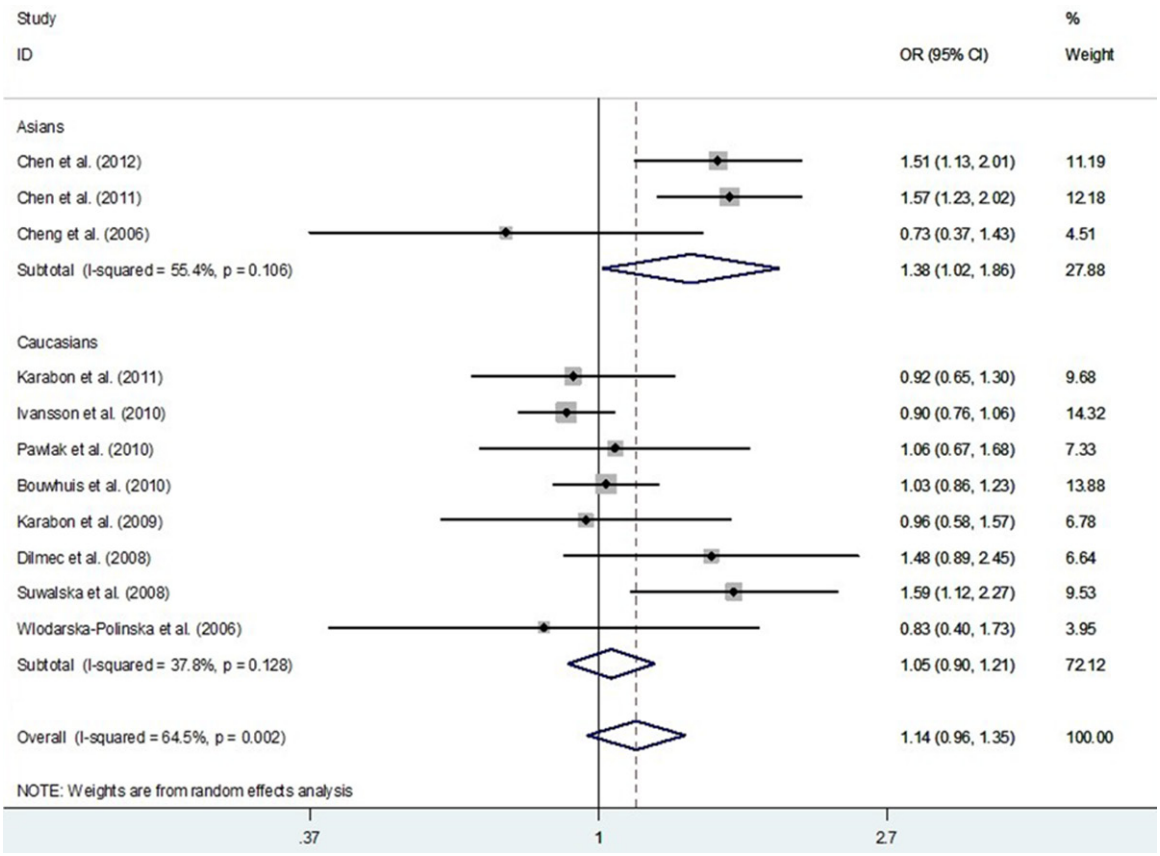

Figure 2. Meta-analysis with a random-effects model for the association between *CD28* IVS3 +17T>C polymorphism and cancer risk (C vs. T compare genetic model).

included to analyze the association of *CD28* IVS3 +17T>C polymorphism with cancer susceptibility. After combining these studies, there was null association of *CD28* IVS3 +17T>C polymorphism with overall cancer susceptibility (**Table 3**; **Figures 2** and **3**). In a stratified analysis by the origin of cancer cells and system of cancer, the association of *CD28* IVS3 +17T>C polymorphism was also non-significant. While in a stratified analysis by ethnicity, a significant increase in cancer risk was detected among Asians in allele genetic models: C vs. T (OR, 1.38; 95% CI, 1.02-1.86; *P* = 0.039), but not Caucasians (**Table 3**).

Tests for publication bias, sensitivity analyses, and heterogeneity

In our study, Begg's funnel plot and Egger's test were used to estimate the publication bias. The results showed that there was no evidence of publication bias (C vs. T: Begg's test *P* = 0.755, Egger's test *P* = 0.676; CC vs. TT: Begg's test *P* = 0.876, Egger's test *P* = 0.138; CC+TC vs. TT: Begg's test *P* = 0.533, Egger's test *P* = 0.852; CC vs. TC+TT: Begg's test *P* = 1.000, Egger's test *P* = 0.179) (**Figure 4**).

We performed one-way sensitivity analysis to assess the influence of an individual study on the pooled OR by omitting one study in turn and the results suggested that our findings were stable (**Figure 5**) (data not shown). We also performed nonparametric "trim-and-fill" method as the other sensitivity analysis method. The adjusted ORs and CIs were not materially altered, suggesting that our findings were robust (CC+TC vs. TT: adjusted pooled OR = 1.13, 95% CI: 0.92-1.39, *P* = 0.245; CC vs. TC+TT: adjusted pooled OR = 1.17, 95% CI: 0.88-1.56, *P* = 0.288; CC vs. TT: adjusted pooled OR = 1.13, 95% CI: 0.85-1.50, *P* = 0.393; C vs. T: adjusted pooled OR = 1.14, 95% CI: 0.96-1.35, *P* = 0.127) (**Figure 6**).

As shown in **Table 3**, the significant heterogeneity was detected in current meta-analysis. Thus, we evaluated the sources of heterogeneity by

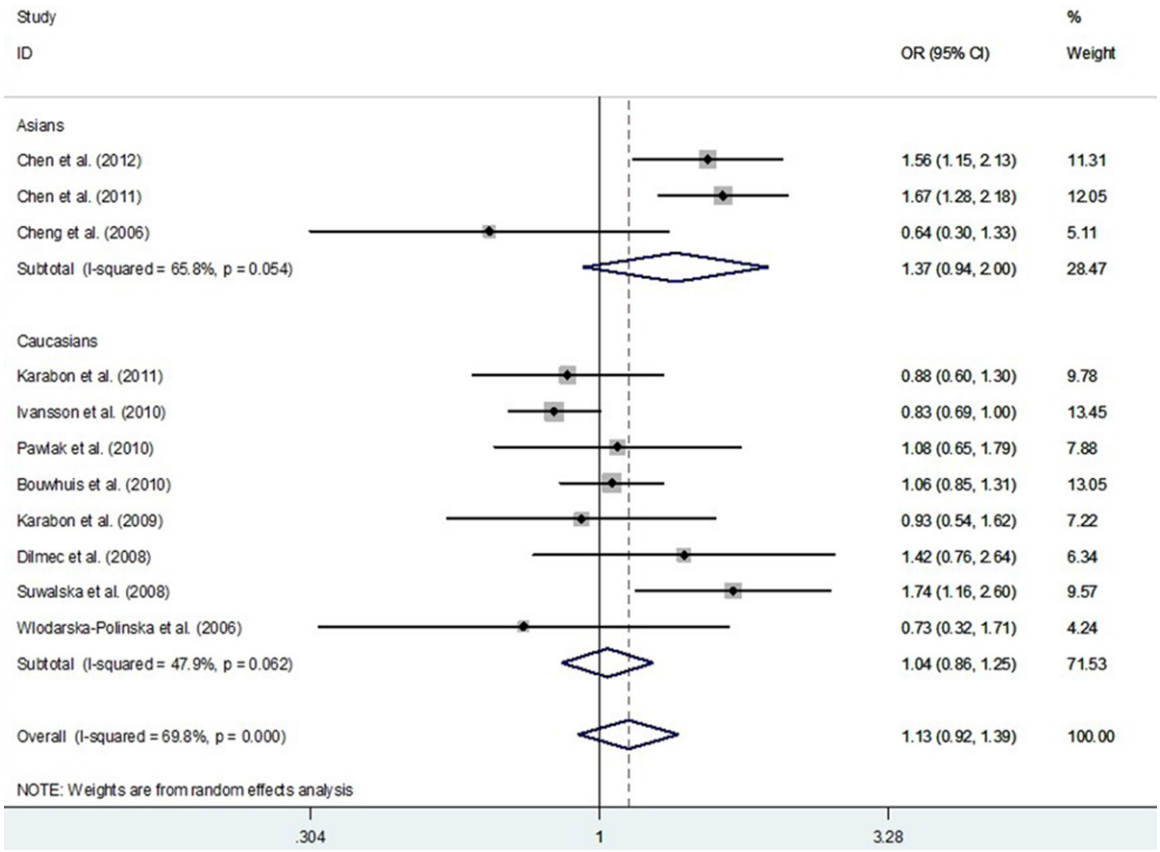

Figure 3. Meta-analysis with a random-effects model for the association between *CD28* IVS3 +17T>C polymorphism and cancer risk (CC+TC *vs*. TT compare genetic model).

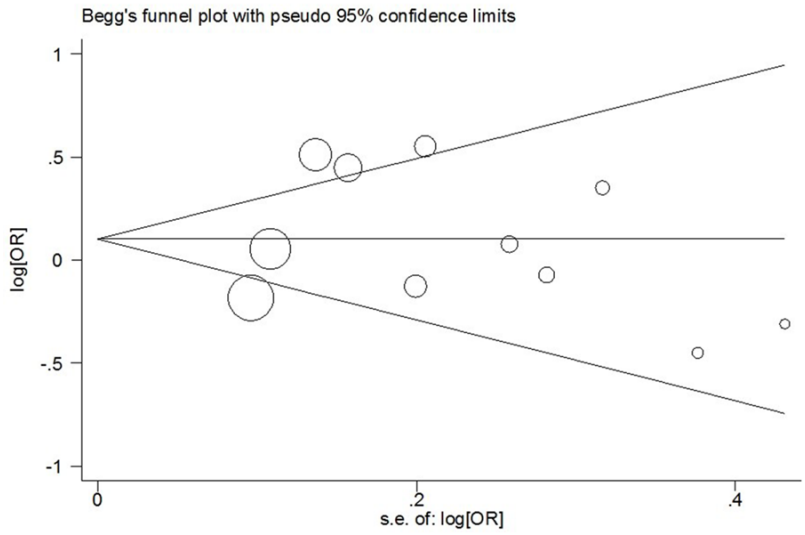

Figure 4. Begg's funnel plot of meta-analysis of between the *CD28* IVS3 +17T>C polymorphism and the risk of cancer in the dominant model.

the origin of cancer cells, system of cancer and ethnicity (**Table 3**). The results suggested that epithelial cancer and reproductive cancer subgroups might contribute to the major sources of heterogeneity. As shown in **Table 3**, heterogeneity was significant in the dominant model. We performed Galbraith radial plot to analyze the heterogeneity (**Figure 7**) and the result showed four outliers, which might contribute to the major source of heterogeneity. We conducted further stratified meta-analyses and the results suggested an association of studies designed in large sample size (≥ 1000 subjects) and publication year after 2009 with more prominent heterogeneity (**Table 3**).

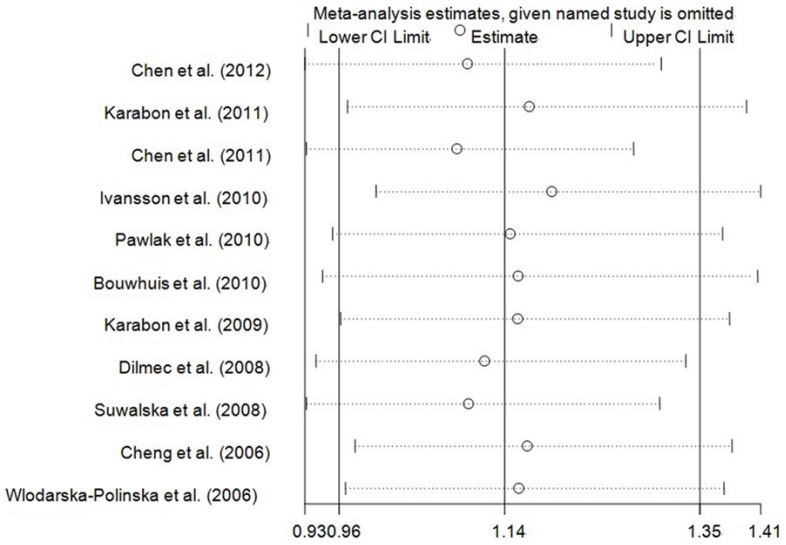

Figure 5. Sensitivity analysis of the influence of C *vs*. T compare genetic model in overall cancer meta-analysis (random-effects estimates).

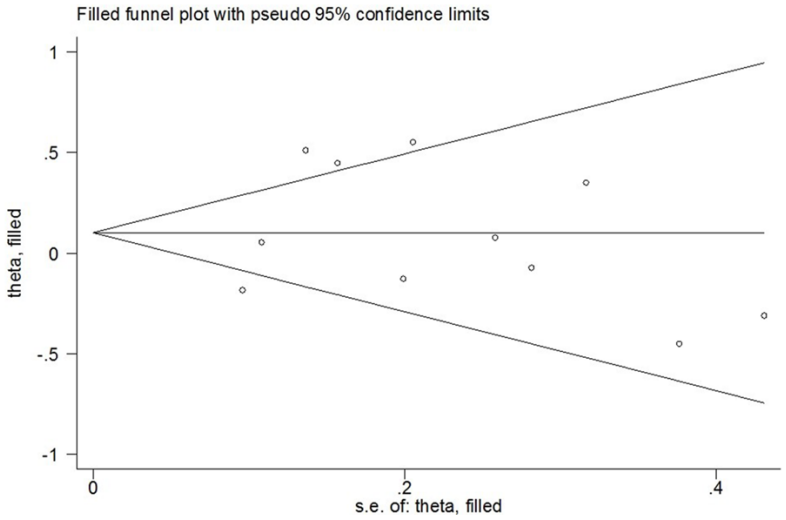

Figure 6. Filled funnel plot of meta-analysis of between the *CD28* IVS3 +17T>C polymorphism and the risk of cancer in the dominant model.

Discussion

The possible association of *CD28* IVS3 +17T>C polymorphism with cancer susceptibility has been widely studied; however, the results are conflicting. To more precisely determine this relationship, a meta-analysis was carried out. The results demonstrated that the *CD28* IVS3 +17T>C polymorphism was not associated with overall cancer susceptibility. In a stratified analysis by the origin of the cancer cells and the cancer system, the association was also non-significant. Meanwhile, in a stratified analysis by ethnicity, a significant increase in cancer susceptibility was detected in the allele model among Asians, but not Caucasians (**Table 3**).

Recently, with the growing interest in the association between mutations of important immunological genes and cancer susceptibility, studies have examined the hypothesis whether *CD28* IVS3 +17T>C polymorphism is relevant to cancer susceptibility; however, their findings were inconclusive and ambiguous. An individual study might be underpowered; therefore, the present study performed a meta-analysis to consider the association of the variant with cancer susceptibility in several cancer systems, the origin of the cancer cells and different ethnicities. One individual study has reported a borderline negative signal of *CD28* IVS3 +17T>C polymorphism with cervical cancer [13]; another three studies reported a positive signal with breast cancer, cervical cancer and leukemia [7, 8, 17]. However, as presented in **Table 3**, the results among 8,843 subjects showed non-significance in overall cancer susceptibility, even in different cancer systems and the origin of the cancer cells. In the stratified analysis by ethnicity, increased susceptibility conferred by the allele model was observed for Asian populations. We also observed borderline evidence of an association between *CD28* IVS3 +17T>C polymorphism and an increased risk of epithelial cancer in the recessive genetic model and homozygote comparison. Considering only 11 publications were included and some of them were designed as small sample sizes (< 1000), our results should be interpret-

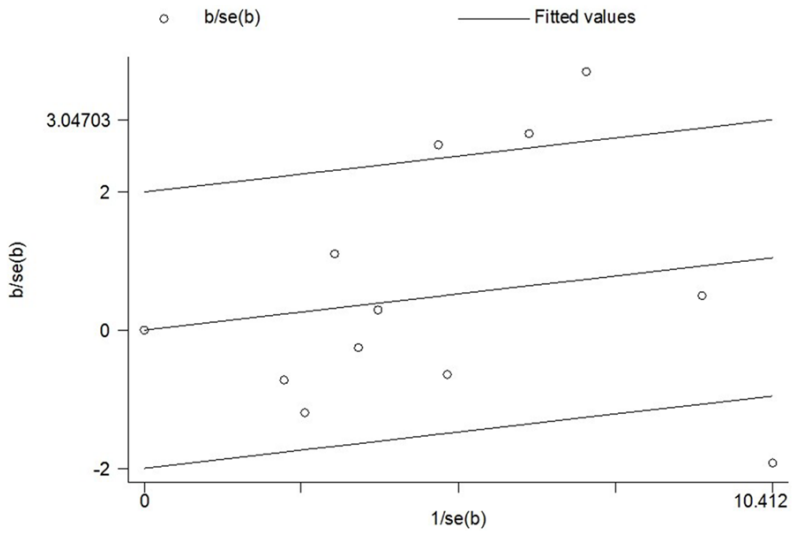

Figure 7. Galbraith radial plot of meta-analysis (CC+TC *vs*. TT compare genetic model).

ed with caution. In the future, more extensive studies with large sample sizes, more types of cancer systems and origins of cancer cells are needed to confirm or refute our findings.

In the current meta-analysis, significant heterogeneity among recruited publications was detected (**Table 3** and **Figure 3**). In general, the sources of heterogeneity included ethnicity, the cancer system, the origin of the cancer cells, sample size and publication year. We performed stratified analyses according to ethnicity, the cancer system and the origin of the cancer cells. In some subgroups, heterogeneity was significantly reduced, suggesting the different influences of these factors, even in the same polymorphism. Further subgroup analyses were conducted based on other factors, such as sample size and publication year (**Table 3**). The pooled subgroup analysis of a subset of large sample size (≥ 1000 subjects) design and publication year after 2009 suggested an association with more noteworthy heterogeneity. According to the Galbraith radial plot (**Figure 7**) and the forest plot (**Figure 3**), four major outliers were detected [7, 8, 13, 17]. Reviewing these publications, they involved certain deficiencies, for example, one was a small sample size design [17] and the cervical cancer cases of the other study were selected from families with at least two affected women [13]. Begg's funnel plots and Egger's tests were used to explore publication bias and no significant publication bias was observed in the meta-analysis. Nonparametric "trim-and-fill" method and one-way sensitivity analysis were both used to conduct sensitivity analyses (**Figures 5** and **6**) and the results suggested that our findings were robust.

Although considerable efforts were made to detect the possible association between *CD28* IVS3 +17T>C polymorphism and cancer susceptibility, there are certain limitations inherited from this meta-analysis that should be acknowledged. Large heterogeneity was detected in the allele genetic model and dominant genetic model, which means these results should be interpreted with caution. Additionally, only 11 published investigations were included in our work; therefore, unpublished studies, if any, might inevitably be missed and lead to bias. Finally, we only focused on IVS3 +17T>C polymorphism in *CD28*, and did not explore other susceptibility genes or polymorphisms.

In summary, despite its limitations, this meta-analysis suggests the *CD28* IVS3 +17T>C polymorphism represents a low risk factor for Asian populations. In the future, further extensive studies with larger sample sizes and more types of cancer should be performed to confirm the influence of *CD28* IVS3 +17T>C polymorphism on cancer susceptibility.

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Disclosure of conflict of interest

None.

Abbreviations

CI, confidence interval; OR, odds ratio; HWE, Hardy-Weinberg equilibrium; NK, natural killer.

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