Association Between the CD28 c.17 +3 T>C Polymorphism (rs3116496) and Cancer Risk: An Updated Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Numerous studies have been conducted on whether CD28 rs3116496 polymorphism affected cancer susceptibility, and these findings have been controversial. Thus, the purpose of this study was to assess the relationship between rs3116496 and susceptibility to cancer.

Material/Methods: The research published as of October 25, 2018 were comprehensively searched in PubMed, Embase, Cochrane Library and Chinese Wanfang database, CNKI, CBM. Statistical calculations performed using Stata12.0.

Results: Overall analyses found that rs3116496 was a risk factor for cancer (C versus T, OR=1.14, 95% CI: 1.01–1.29, P_H=0.003), and the heterogeneity was moderate (I^2=53.3%). In subgroup analysis results by cancer types, the analysis showed that rs3116496 was a risk factor for breast cancer and leukemia. In the subgroup analysis by ethnicity, rs3116496 was a risk factor for cancer in the Asian population. After P_{HWE}<0.05 was deleted, the analysis showed that rs3116496 might be related to the increased risk of colorectal cancer.

Conclusions: Our meta-analysis confirmed that rs3116496 was significantly related to cancer risk, especially in an Asian population, and was strongly correlated with the increased risk of breast cancer, leukemia and colorectal cancer.

MeSH Keywords: **Antigens, CD28 • Genes, Neoplasm • Meta-Analysis • Polymorphism, Genetic**

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Background

Noncommunicable diseases now account for most of the world's deaths, and cancer is expected to be the chief cause of death and the single most important obstacle to improving life expectancy in the world in the 21st century [1]. The multifaceted interaction of many gene *loci* and a variety of environmental factors play a crucial role in the occurrence and development of cancer. One of the most important mechanisms in the process of tumorigenesis and the development of cancer is that abnormal activation of T cells leads to impaired immune monitoring function and insufficient anti-tumor response [2,3]. The level of T cell activation depends on the balance between the co-stimulatory and co-inhibitory signals emitted by the co-signaling molecules. Studies by Chechlinska et al. and Li et al. showed that cytotoxic T lymphocyte antigen 4 (CTLA-4) and differentiated cluster 28 (CD28) was one of the immune mediators involved in malignant transformation [4,5]. CD28 is constitutionally expressed on most T cells and is a primary T-cell co-stimulatory molecule that enhances T-cell activation and proliferation [6].

CD28 is an important immunomodulatory protein, encoded by the same chromosome site CTLA-4, with 31% amino acid homology and close interaction [7]. Defects in the CD28 pathway lead to tolerance and incapacity to oncogenic antigens [8,9]. T/C substitution at position +17 of the CD28 gene is located in the third intron (IVS3 +17T/C) [10]. Though there is no evidence showing that the CD28 IVS3 +17T/C (rs3116496) polymorphism has an impact on the expression or the function of the CD28 gene, this SNP is located near the splice acceptor site which suggests a potential effect on CD28 signaling and T-cell activation [11]. It is not clear whether the C allele at rs3116496 contributes to the various cancers by itself, or is a marker simply in linkage disequilibrium with the true susceptible gene [9,12–15]. Thus, the purpose of this study was to assess the relationship between rs3116496 and susceptibility to cancer.

Material and Methods

Search strategies

The research published as of October 25, 2018 was comprehensively searched in PubMed, Embase, the Cochrane Library, Chinese Wanfang database, CNKI and CBM, used the following keywords and Mesh terms: 'neoplasm, cancer, carcinoma, carcinogenesis, tumor, tumour, neoplasia' and 'polymorphism, genetic; polymorphism, variant, mutation, single nucleotide polymorphism, SNP' and 'lung' and 'rs3116496, Tp44, CD28, CD28 molecule'.

Selection criteria

If the following inclusion criteria were met, relevant studies were included: 1) the original case-control study detected the relationship between rs3116496 and cancer risk, and provided the frequency of CD28 rs3116496 mutant genotypes in the case and control group. The exclusion criteria in this study were as follows: 1) eliminated conference abstract or report, review or meta-analysis, and republished articles; 2) studies with insufficient data to extract were also excluded.

Data extraction and quality assessment

Two independent authors performed the initial search, imported EndNote and deleted the duplicate record automatically or manually, screened the titles and abstract, recognized the potentially studies, and retrieved the full text. The same 2 investigators independently determined studies for inclusion. The following data from each selected article were collected: the surname of the first author, publication year, country, ethnicity, cancer types, and genotype methods of CD28 rs3116496 polymorphism.

The quality of qualified case-control studies was estimated by the same 2 investigators, using the Newcastle-Ottawa [16]. The articles were refereed on 3 domains, including selection, comparability and outcomes. A score of 0 to 4, 5 to 7, and 8 to 10 was considered low quality, moderate quality and high-quality studies.

Statistical analysis

We estimated CD28 rs3116496 polymorphisms and cancer risk by 5 genetic models combined the dominance ratio (ORs) and 95% confidence intervals (CI). If $P<0.05$ or 95% CI does not include 1, it was considered statistically significant. The Cochran Q statistic with chi-square (with P_Q) and the Higgins I^2 test was used to determine the heterogeneity among-study variability. When $P_Q<0.05$ or $I^2>50\%$ indicated significant heterogeneity [17], and the data will be analyzed through the random effect model. If the contrary, the fixed effect model was chosen. We assessed publication bias by funnel plots and Egger's ($P<0.05$). Statistical calculations were performed using Stata12.0.

Results

The literature search found 788 documents with 132 studies were excluded after duplicates were removed, and 591 studies were excluded after reviewing the retrieved literature's titles and abstracts. The full text of 65 remaining citations was screened, and finally 19 studies including 11 811
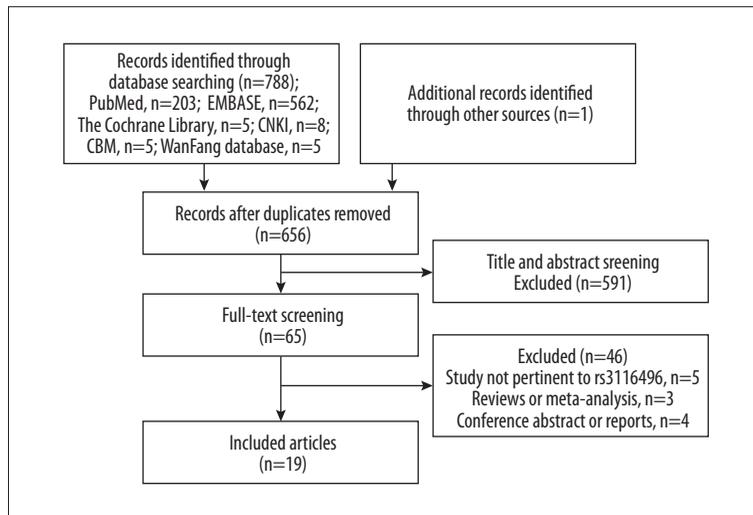
Figure 1. Flow chart of study selection.

patients were included in this meta-analysis [9,12–15,18–31]. The flow chart of the meta-analysis is represented in Figure 1. The basic information and quality evaluation (NOS) results included in the study are shown in Table 1. The included studies looked at cancer patients in Asia (n=6) [9,12,13,21,29,30] and Caucasians (n=13) [14,15,18–20,22–28,31]. In addition, in terms of cancer types, leukemia (n=2) [12,26], breast cancer (n=3) [9,13,15], colorectal cancer (n=3) [20,27,30)], cervical cancer (n=4) [21–23,28], and other cancers (prostate cancer, gastric cancer, renal cell carcinoma, non-small-cell lung cancer, melanoma, myeloma, lymphoma) were included in studies [4,9,14,18,25,29,31].

Meta-analysis results

Rs3116496 was associated with a statistically significant increase in cancer risk in the allele model (OR=1.14, 95% CI: 1.01–1.29, P_H=0.003), heterogeneity was moderate (I^2=53.3%) (Figure 2, Table 2).

Stratified analysis of CD28 rs3116496 polymorphism was done by cancer types (Figure 3, Table 2), rs3116496 was associated increase in cancer risk in the breast cancer and leukemia. For breast cancer, in the allele and dominant model (OR=1.36, 95% CI: 1.12–1.64, I^2=0.0%; OR=1.37, 95% CI: 1.10–1.71, I^2=0.0%). For leukemia, in the allele, dominant, recessive, and homozygote model (OR=1.63, 95% CI: 1.19–2.25, I^2=0.0%; OR=1.65, 95% CI: 1.14–2.37, I^2=0.0%; OR=2.97, 95% CI: 1.05–8.41, I^2=39.1%; OR=3.14, 95% CI: 1.08–9.11, I^2=15.8%) (Figure 3, Table 2).

In the subgroup analysis by ethnicity, rs3116496 was associated increase in cancer risk in the Asian population, according to the genetic model allele, dominant, recessive and homozygote (OR=1.44, 95% CI: 1.20–1.73, I^2=26.7%; OR=1.39, 95% CI: 1.10–1.77, I^2=44.6%; OR=2.12, 95% CI: 1.30–3.47, I^2=0.0%; OR=2.16, 95% CI: 1.32–3.54, I^2=0.0%) (Figure 4, Table 2).

Heterogeneity test

This analysis revealed heterogeneity in the relationship between rs3116496 and total cancer (allele: I^2=53.3%, dominant: I^2=54.2%, heterozygous: I^2=56.2%) (Figure 2A, 2B, 2E). Our subgroup analysis established that race (Figure 4A, 4B, 4E) and cancer type (Figure 3A, 3B, 3E) were major sources of heterogeneity.

Publication bias

The shape of funnel plots (Figure 5) and Egger's test (allele: *P*=0.482; dominant: *P*=0.659; recessive: *P*=0.631; homozygote: *P*=0.560; heterozygote: *P*=0.833) were symmetrical and no publication bias was observed.

Sensitivity analysis

Only 1 of the 19 studies we included had a P_{HWE}<0.05. We reanalyzed the study after deletion and compared the results with those before deletion. There were slight changes in the results. First, except for the allele model, rs3116496 was also associated with significantly increased cancer risk in the recessive model and the pure model (recessive: OR=1.32, 95% CI: 1.03–1.69, P_H=0.752; homozygote: OR=1.33, 95% CI: 1.04–1.71, P_H=0.809). Second, when subgroup analysis was performed according to cancer types, it was found that rs3116496 was related to the increased risk of colorectal cancer in allele model and dominant model, while no changes were observed in other cancers. But no significant changes were found in the subgroup analysis by ethnicity.

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

Author	Year	Country	Ethnicity	Genotyping method	Source of control	Cancer type	Cases/ control	Cases			Control			HWE p-value	NOS
								CC	TC	TT	CC	TC	TT		
Ramzi	2018	Iran	Asians	PCR-RFLP	HB	Leukemia	59/46	10	12	37	1	11	26	0.898	6
Yan	2017	China	Asians	MALDI-TOF MS	HB	Breast cancer	307/305	23	67	217	11	71	223	0.083	9
Karabon	2017	Poland	Caucasians	PCR-RFLP	PB	Prostate cancer	301/301	8	86	207	6	84	211	0.477	7
Arikan	2017	Turkey	Caucasians	PCR-RFLP	PB	Gastric cancer	55/105	4	19	32	11	35	59	0.107	5
Isitmangil	2016	Turkey	Caucasians	PCR-RFLP	HB	Breast cancer	79/76	5	33	41	7	22	47	0.082	6
Tupikowsk	2015	Poland	Caucasians	PCR-RFLP	PB	Renal cell carcinoma	236/518	2	61	173	8	125	381	0.534	7
Wang	2015	China	Asians	PCR-RFLP	HB	Colorectal cancer	240/147	3	48	189	0	18	129	0.429	7
Kucukhuseyin	2015	Turkey	Caucasians	PCR-RFLP	HB	Colorectal cancer	80/115	5	27	48	14	38	63	0.039	7
Chen	2012	China	Asians	PCR-RFLP	PB	Breast cancer	565/605	6	109	450	4	81	520	0.665	8
Karabon	2011	Poland	Caucasians	Multiplex PCR SNaPshot	PB	Non-small-cell lung cancer	208/328	4	51	153	5	89	230	0.271	7
Chen	2011	China	Asians	PCR-RFLP	PB	Cervical cancer	619/985	7	120	492	9	123	853	0.058	8
Ivansson	2010	Sweden	Caucasians	Taqman	PB	Cervical cancer	1306/811	42	343	916	19	253	538	0.089	7
Pawlak	2010	Poland	Caucasians	Multiplex PCR SNaPshot	ND	Cervical cancer	147/225	1	31	100	2	49	172	0.462	6
Bouwhuis	2010	German	Caucasians	Taqman	PB	Melanoma	763/734	22	254	487	24	231	475	0.525	8
Karabon	2009	Poland	Caucasians	Multiplex PCR SNaPshot	ND	Myeloma	150/238	2	21	75	4	55	179	0.924	5
Dilmec	2008	Turkey	Caucasians	PCR-RFLP	HB	Colorectal cancer	56/162	5	19	32	6	50	106	0.972	5
Suwalska	2008	Poland	Caucasians	Multiplex PCR SNaPshot	PB	Leukemia	172/335	4	56	112	5	74	256	0.895	6
Cheng	2006	China	Asians	PCR-RFLP	HB	Lymphoma	62/250	1	9	52	1	57	192	0.132	8
Wlodarska-Polinska	2006	Poland	Caucasians	SNapShot	ND	Cervical cancer	50/72	2	9	39	2	18	52	0.771	5

Multiplex PCR SNaPshot – multiplex polymerase chain reaction SNaPshot method; HB – hospital-based; PB – population-based; ND – no description.
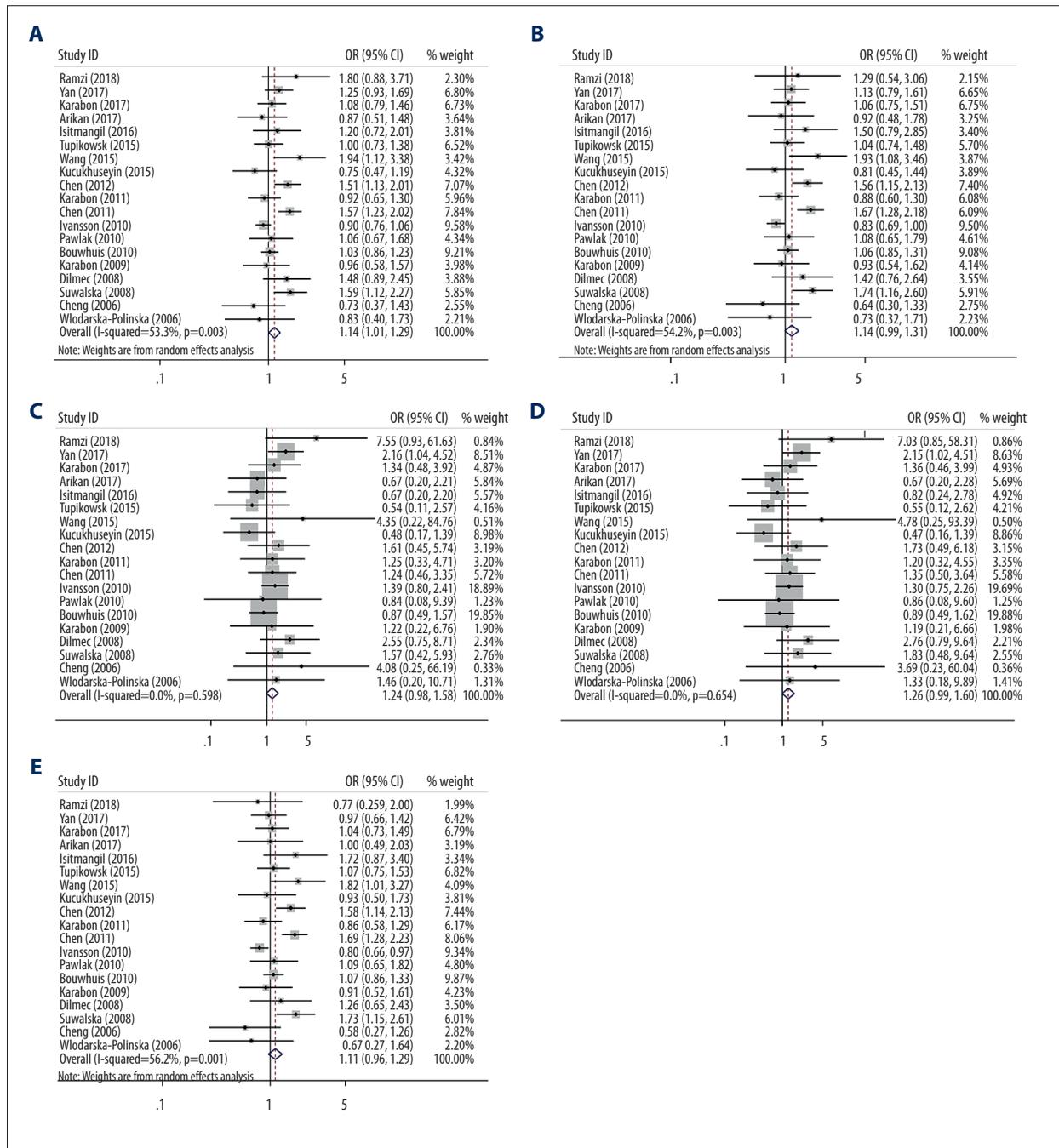
Figure 2. (A–E) Forest plot of CD28 rs3116496 polymorphism for cancer susceptibility under the 5 genetic models.

Discussion

Numerous studies have been conducted on whether CD28 rs3116496 polymorphism affected cancer susceptibility, and these findings have been controversial. Our study showed that CD28 rs3116496 was significantly related to cancer risk. Additionally, the risk of breast cancer, leukemia, and colorectal cancer increased significantly in patients with rs3116496, and we also found that they were more likely to develop cancer

in Asian populations. CD28 may be a tumor suppressor gene, while rs3116496 polymorphism of CD28 gene showed positively correlation with the increased risk of cancer.

The influence of genes on the occurrence and development of cancer leads to the study of genetic polymorphisms with cancer. Tumor-specific T-cell response was beneficial to inhibit tumor development, which was affected by co-stimulatory and co-inhibitory signals [32]. As one of the most characterized

Table 2. Overall and stratified analyses of the association between CD28 rs3116496 polymorphism and cancer risk.

Variables	N	C allele *vs.* T allele			CC +TC *vs.* TT			CC *vs.* TT+TC		
		OR (95% CI)	P	I² %	OR (95% CI)	P	I² %	OR (95% CI)	P	I² %
Total	19	1.14 (1.01– 1.29)	0.039	53.3%	1.14 (0.99– 1.31)	0.072	54.2%	1.24 (0.98– 1.58)	0.074	0.0%
Cancer types										
Breast	3	1.36 (1.12– 1.64)	0.002	0.0%	1.37 (1.10– 1.71)	0.004	0.0%	1.58 (0.91– 2.74)	0.103	26.3%
Leukemia	2	1.63 (1.19– 2.25)	0.003	0.0%	1.65 (1.14– 2.37)	0.007	0.0%	2.97 (1.05– 8.41)	0.041	39.1%
Colorectal	3	1.27 (0.72– 2.24)	0.408	73.4%	1.30 (0.78– 2.17)	0.314	55.2%	1.06 (0.51– 2.18)	0.882	59.6%
Cervical	4	1.09 (0.77– 1.56)	0.624	78.9%	1.07 (0.69– 1.66)	0.769	83.4%	1.34 (0.85– 2.11)	0.214	0.0%
Other	7	0.99 (0.88– 1.12)	0.920	0.0%	1.00 (0.87– 1.15)	0.995	0.0%	0.94 (0.63– 1.41)	0.760	0.0%
Ethnicity										
Asian	6	1.44 (1.20– 1.73)	0.001	26.7%	1.39 (1.10– 1.77)	0.007	44.6%	2.12 (1.30– 3.47)	0.003	0.0%
Caucasian	13	1.02 (0.92– 1.12)	0.769	12.7%	1.03 (0.90– 1.16)	0.694	24.0%	1.04 (0.78– 1.37)	0.800	0.0%

Variables	N	CC *vs.* TT			TC *vs.* TT		
		OR (95% CI)	P	I² %	OR (95% CI)	P	I² %
Total	19	1.26 (0.99–1.60)	0.064	0.0%	1.11 (0.96–1.29)	0.154	56.2%
Cancer types							
Breast	3	1.68 (0.96–2.93)	0.069	0.0%	1.33 (0.93–1.90)	0.116	51.4%
Leukemia	2	3.14 (1.08–9.11)	0.035	15.8%	1.30 (0.61–2.78)	0.502	57.1%
Colorectal	3	1.09 (0.52–2.28)	0.811	62.8%	1.30 (0.88–1.93)	0.184	16.0%
Cervical	4	1.29 (0.81–2.04)	0.277	0.0%	1.04 (0.65–1.68)	0.858	85.1%
Other	7	0.95 (0.63–1.43)	0.802	0.0%	1.00 (0.87–1.16)	0.946	0.0%
Ethnicity							
Asian	6	2.16 (1.32–3.54)	0.002	0.0%	1.26 (0.93–1.71)	0.134	61.8%
Caucasian	13	1.04 (0.79,1.38)	0.767	0.0%	1.03 (0.90–1.18)	0.671	30.0%

N – number of comparison.

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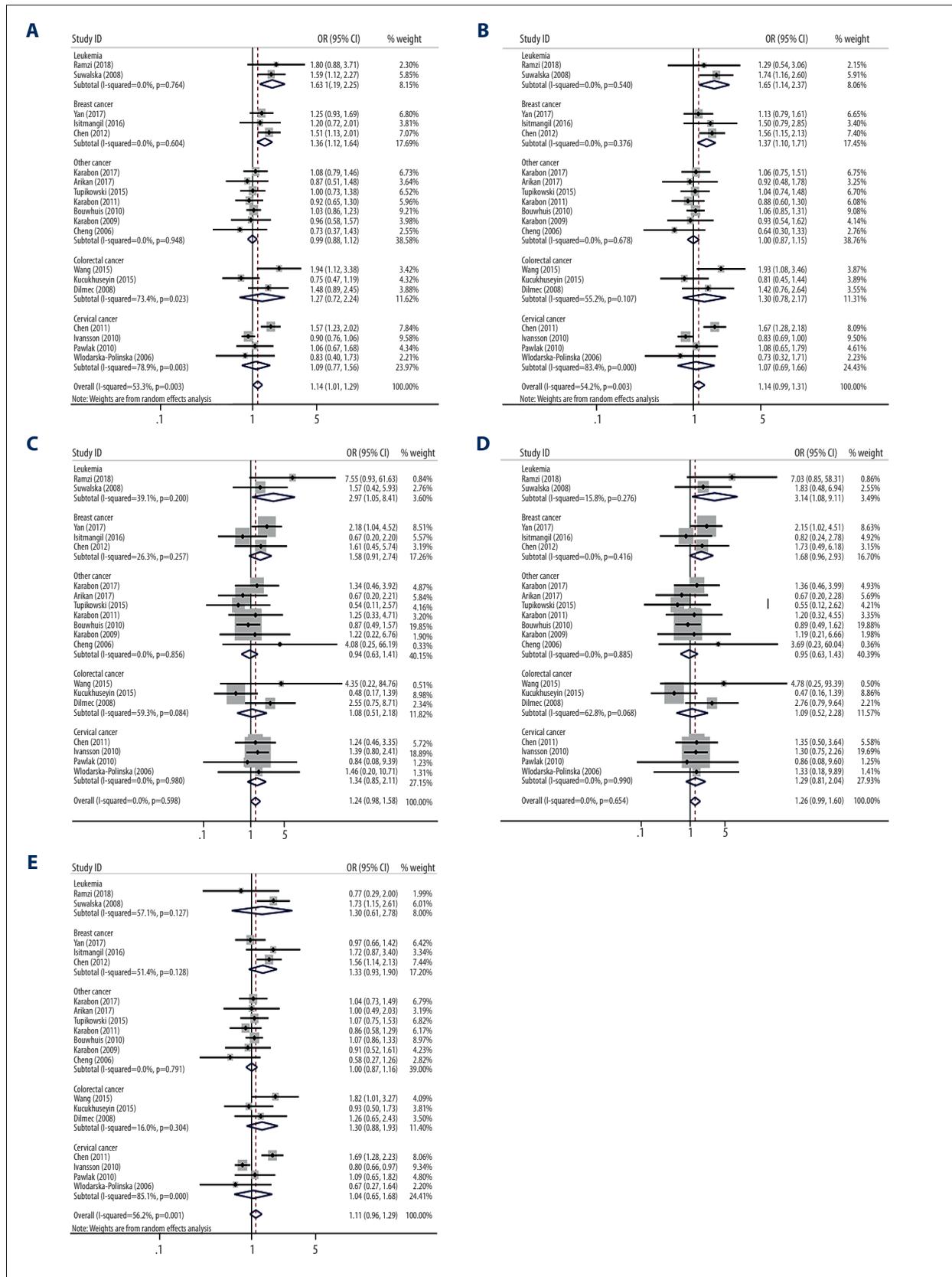
Figure 3. (**A–E**) Forest plot of CD28 rs3116496 polymorphism for cancer susceptibility by cancer types under the 5 genetic models.
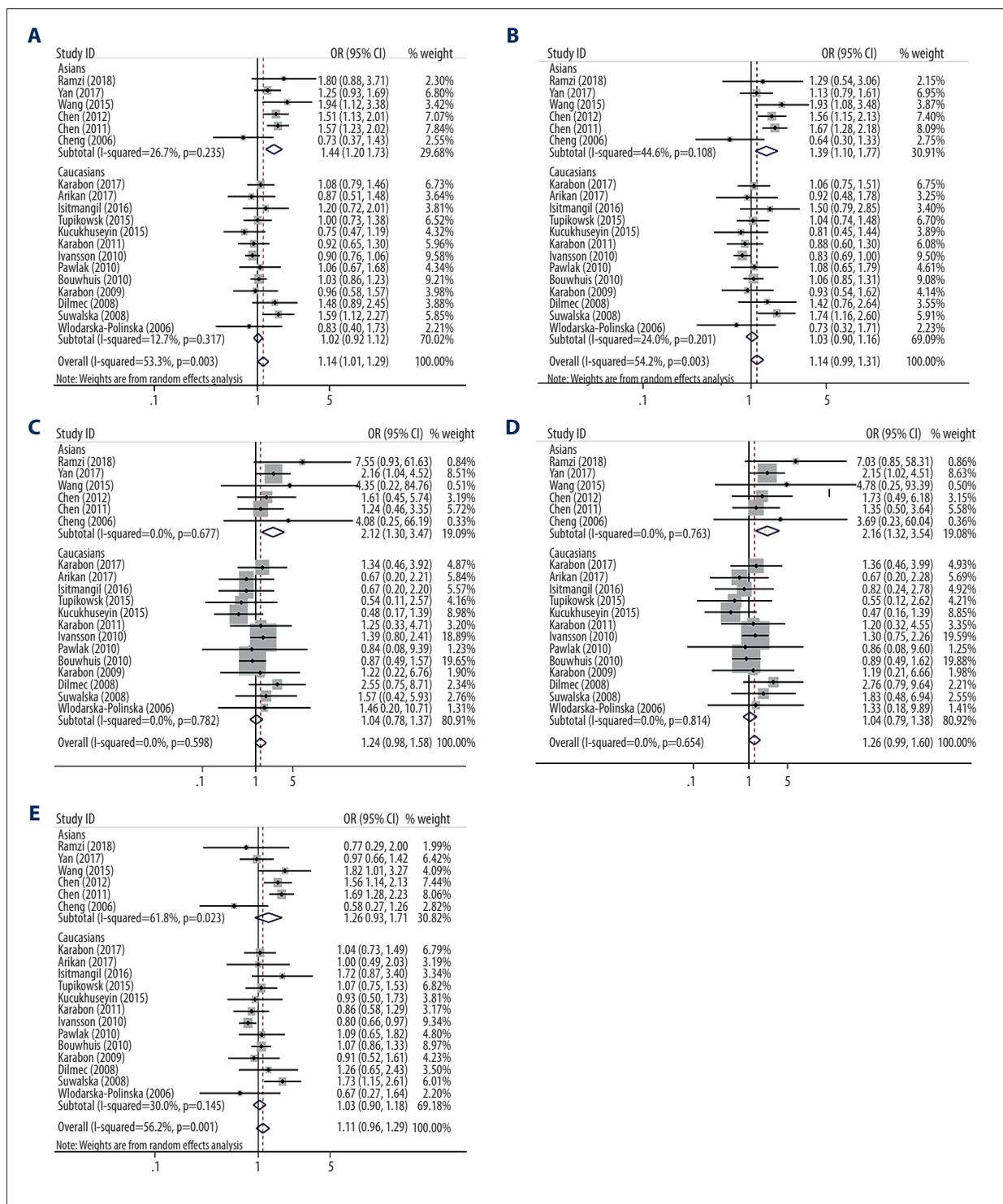
Figure 4. (A–E) Forest plot of CD28 rs3116496 polymorphism for cancer susceptibility by ethnicity under the 5 genetic models.
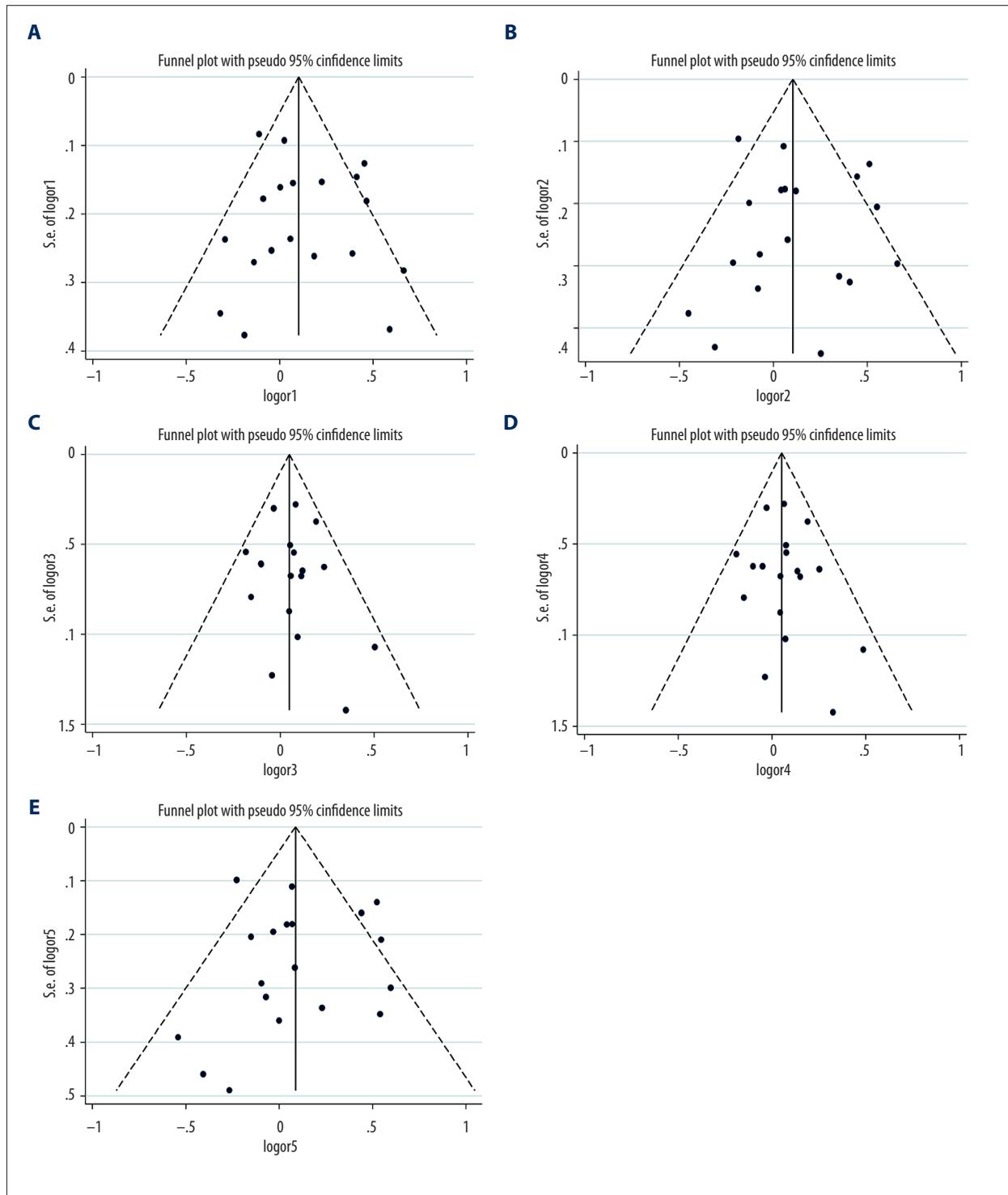
Figure 5. (**A–E**) The funnel plot for the test of publication bias under the 5 genetic models.

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co-stimulatory molecules, CD28 competes with CLTA-4 (co-inhibitory molecules) to bind B7 to enhance T-cell proliferation [33]. Rs3116496 polymorphism may lead to imbalance of expression of various CD28 protein subtypes through abnormal splicing, thus leading to changes in immune function. A report found that sCD28 expression was different in each rs3116496 genotype in patients with rheumatoid arthritis, and the level of sCD28 in TT carriers was higher than that in TC genotype [34]. In addition, sCTLA4 and sCD28 can be used for the diagnosis of breast cancer patients [15]. The high expression of CD28 was found to be associated with the improvement of OS in all BC patients (HR=0.8, 95% CI: 0.64–0.99, *P*=0.041). We hypothesized that CD28 is a tumor suppressor gene, but since these clinical data are from the database, more convincing studies are needed to verify this conclusion [13].

Up to now, 3 meta-analyses regarding the impact of rs3116496 on cancer risk have been performed [33,35,36]. Compared with Cong et al. (2014), Baek et al. (2015) and Zhang et al. (2015) studies, our study had the following differences. First, the inclusion of more studies and larger sample sizes indicated that our estimation of the relationship between CD28 SNP and cancer risk was relatively accurate. Second, stratified analysis based on ethnicity was helpful for a more comprehensive consideration of the relationship between rs3116496 polymorphism

and different populations. Third, most importantly, we found a significant association of rs3116496 with breast and leukemia cancer susceptibility.

There were also several limitations to our meta-analysis. First, other heterogeneity sources such as source of control and the different genotype methods, were not validated. Second, interactions between genes and environment might alter the risk of cancer, and due to the lack of some relevant data, we were unable to evaluate potential gene-environmental interactions.

Conclusions

Our meta-analysis demonstrated that rs3116496 was significantly related to cancer risk, especially in an Asian population. In addition, subgroup analysis showed that rs3116496 was strongly correlated with the increased risk of breast cancer, leukemia, and colorectal cancer. More well-designed studies are needed to elucidate the possible role of this mutation in different cancers.

Conflict of interest

None.

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