Association between the cytotoxic T-lymphocyte antigen 4 -318C/T polymorphism and malignant tumor risk

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Abstract. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) polymorphic loci -318 cytosine/thymine (-318C/T) has been previously implicated in malignant tumor susceptibility. However, there were no precise conclusions about the correlation, the results from published studies were inconclusive. The aim of the current meta-analysis was to investigate the associations between CTLA-4 -318C/T polymorphisms and risk of malignant tumors in Asian population. We conducted a search in PubMed, Embase, the Chinese Journals Full-Text Database, Chinese Biomedical Database, and the Wanfang database. All studies were published up to September 30, 2015. Two reviewers analysed the data independently. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association. In total, 20 case-controlled studies with 3,539 cases and 4,690 controls were included in the final meta-analysis. The overall estimation demonstrated a significant association between CTLA-4 -318C/T polymorphism and malignant tumor risk in the Asian populations (TT+TC vs. CC: OR, 1.28; 95% CI, 1.07-1.53. TT vs. TC+CC: OR, 1.43; 95% CI, 1.03-1.99; TT vs. CC: OR, 1.51; 95% CI, 1.09-2.10. TC vs. CC: OR, 1.26; 95% CI, 1.06-1.50. T vs. C: OR, 1.25, 95% CI, 1.05-1.47). In the subgroup analysis by countries, we found that the dominant model (TT+TC vs. CC) revealed an increased risk of developing malignant tumors in the Chinese study population (OR, 1.41; 95% CI, 1.13-1.76), but no association was demonstrated in the other countries. The current meta-analysis suggests that CTLA-4 -318C/T polymorphism is significantly associated with the risk of malignance tumors in Asian populations, especially in those from China. Further studies for additional Asian countries are required to further evaluate the association.

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Introduction

Malignant tumors are a complex disease relating to an interaction effect between polygenic inheritance and environmental factors (1). Tumorigenesis and the development of malignant tumors are poorly understood, and further research is required concerning their key underlying factors and molecular abnormalities. In recent years, the response of the immune system to malignant tumors has been the focus of investigation (2). Studies on the role of T lymphocytes and natural killer cells in mediating an antitumor response have been increasing in recent years (3). For this reason, genetic polymorphisms of the genes involved the mediate response of T lymphocytes have been investigated for a possible association with the risk of developing a range of malignant tumors (4,5). One of these genes, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), located on chromosome 2q33, is a member of the immunoglobulin superfamily and has an important role in the regulation of T-lymphocyte activation and proliferation (6). CTLA-4 polymorphisms have been demonstrated to be associated with increased susceptibility to various malignant tumors in a number of different ethnic populations. Previous studies have been performed to determine whether the -318 cytosine/thymine (-318C/T) polymorphism was involved in the etiology of various malignant tumors in Asian population (7-26). However, the results from these studies remain inconclusive and conflicting. The present study aimed to achieve a more precise assessment of the association between CTLA-4 -318C/T polymorphism and malignant tumor risk in an Asian population by performing a meta-analysis on 20 eligible case-control studies to estimate the CTLA-4 -318C/T polymorphism and malignant tumor.

Materials and methods

Literature search. The PubMed, Embase, Chinese Journals Full-Text Database, Chinese Biomedical Database, and Wanfang databases were searched for all articles published up to September 30, 2015. The literature search used a number of keywords including, 'genetic polymorphism', 'cancer OR carcinoma', and 'cytotoxic T-lymphocyte antigen-4

Table I. Characteristics of case-controlled studies included in the meta-analysis.

First author	Year	Country	Cancer type	Genotyping method	Sample size Cases/controls	Refs.
Cheng	2006	China	Lymphoma	PCR-RFLP	62/250	(7)
Erfani	2006	Iran	Breast cancer	PCR-ARMS	283/241	(8)
Wang	2007	China	Breast cancer	PCR-RFLP	117/148	(9)
Su	2007	China	Cervical cancer	PCR-RFLP	144/378	(10)
Hadinia	2007	Iran	Gastrointestinal cancer	PCR-ARMS	155/190	(11)
Li	2010	China	Gastrointestinal cancer	PCR-RFLP	121/236	(12)
Khaghanzadeh	2009	Iran	Lung cancer	PCR-ARMS	126/122	(13)
Rahimifar	2010	Iran	Cervical cancer	PCR-ARMS	54/110	(14)
Liu	2011	China	Bone sarcoma	PCR-RFLP	267/282	(15)
Jiang	2011	China	Cervical cancer	PCR-RFLP, sequenom	100/100	(16)
Yang	2012	China	Bone sarcoma	PCR-RFLP	223/302	(17)
Gokhale	2013	India	Cervical cancer	PCR-RFLP	100/101	(18)
Feng	2013	China	Bone sarcoma	PCR-RFLP	308/362	(19)
Bharti	2013	India	Oral carcinoma	PCR-RFLP	120/180	(20)
Liu	2013	China	Lymphoma	PCR-RFLP	291/300	(21)
Jaiswal	2014	India	Bladder cancer	PCR-ARMS	200/200	(22)
Xiong	2014	China	Cervical cancer	RT-PCR	365/421	(23)
Hui	2014	China	Leukemia	RT-PCR	86/112	(24)
Cheng	2015	China	Lymphoma	PCR-LDR	125/300	(25)
Wang	2015	China	Cervical cancer	RT-PCR	292/355	(26)

All studies fit the Hardy-Weinberg equilibrium and had study populations of Asian ethnicity. PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; PCR-ARMS, PCR-amplification-refractory mutation system; RT-PCR, reverse transcription PCR; PCR-LDR, PCR-ligase detection reaction.

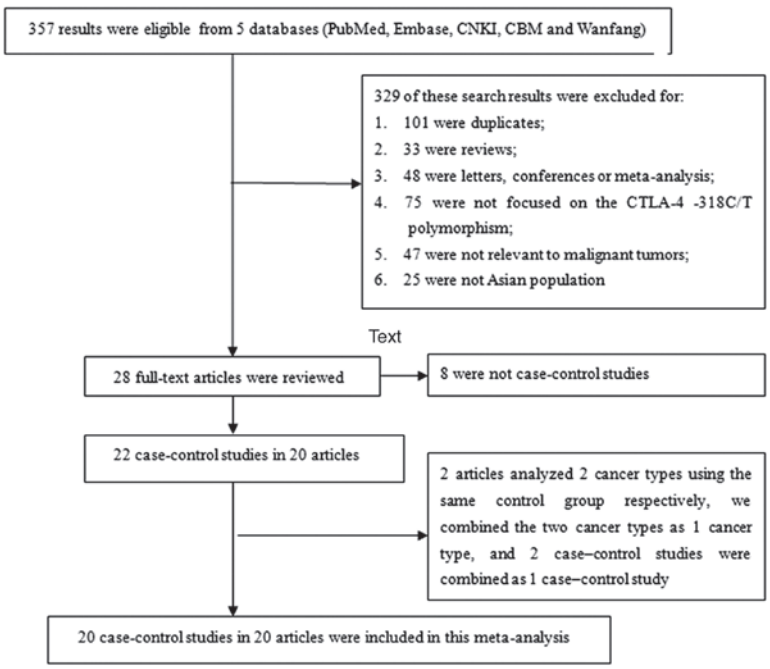

Figure 1. Flow diagram of the study selection process.

OR CTLA-4'. No language restrictions were applied. All of the eligible studies included in the meta-analysis had to meet the following inclusion criteria: i) Evaluation of the CTLA-4 -318C/T polymorphism and malignant tumor risk;

Table II. Distributions of genotypes and alleles in cytotoxic T-lymphocyte antigen 4 -318C/T polymorphisms.

	Case					Control					
First author	CC	TC	TT	C	T	CC	TC	TT	C	T	Refs.
Cheng	59	3	0	121	3	209	40	1	458	42	(7)
Erfani	244	38	1	526	40	206	31	4	443	39	(8)
Wang	84	33	0	201	33	129	19	0	277	19	(9)
Su	105	38	1	248	40	306	67	5	679	77	(10)
Hadinia	129	24	1	282	26	159	24	4	342	32	(11)
Li	99	17	5	215	27	206	27	3	439	33	(12)
Khaghanzadeh	107	17	2	231	21	105	16	1	226	18	(13)
Rahimifar	51	3	0	105	3	89	20	1	198	22	(14)
Liu	175	77	15	427	107	195	80	7	470	94	(15)
Jiang	75	24	1	174	26	92	8	0	192	8	(16)
Yang	149	65	9	363	83	210	85	7	505	99	(17)
Gokhale	93	7	0	193	7	94	7	0	195	7	(18)
Feng	213	89	6	515	101	249	102	11	600	124	(19)
Bharti	112	8	0	232	8	170	10	0	350	10	(20)
Liu	222	64	5	508	74	222	73	5	517	83	(21)
Jaiswal	106	89	5	301	99	112	81	7	305	95	(22)
Xiong	232	127	6	591	139	316	104	1	736	106	(23)
Hui	48	31	7	127	45	84	25	3	193	31	(24)
Cheng	88	36	1	212	38	222	73	5	517	83	(25)
Wang	183	97	12	463	121	266	85	4	617	93	(26)

ii) independent case-control study in design; iii) available data (distribution of alleles and genotypes for cases and controls) estimating an odds ratio (OR) with a 95% confidence interval (95% CI) of CTLA-4 -318C/T gene polymorphisms in both cases and controls; iv) the studies on Asian population; and v) genotype distributions in the controls conformed to the Hardy-Weinberg equilibrium (HWE). The following exclusive criteria were used: i) Repeat or overlapping publications; ii) abstracts, reviews or letters; and iii) studies in which genotype frequencies were not reported.

Data extraction. To enhance credibility and reduce bias in the study, all data were abstracted by two of the authors independently, who complied with the rigorous selection criteria and reached a consensus on all items. The following information was extracted from each study: First author, year of publication, ethnicity and country of origin, type of malignant tumor, sample size, and HWE evidence in controls (Table I).

Statistical analysis. The ORs with corresponding 95% CIs were calculated for the strength of correlations between CTLA-4 -318C/T gene polymorphisms and malignant tumor risks in an Asian population. The significance of the pooled OR was determined by using a Z-test, and $P<0.05$ was considered to indicate a statistically significant difference. In order to assess the association between CTLA-4 -318C/T polymorphism and malignant tumor risk, five genetic models were used to evaluate the pooled ORs of the polymorphism, as follows: Dominant model (TT+TC vs. CC), recessive model (TT vs. TC+CC), homozygous model (TT vs. CC), heterozygous model (TC vs. CC), and allele model (T vs. C) for -318C/T. The OR was calculated by using different effect models according to the result of heterogeneity test. The statistical heterogeneity of studies was checked by using the Chi-square-based Q statistic: When $P\geq0.05$, the fixed-effects model (Mantel-Haenszel method) was used to analyze the data, whereas the random-effects model (the DerSimonian and Laird method) was used if $P<0.05$ (27). In addition, the I^2 test was used, and was considered statistically significant at an I^2 value ≥50%, and the random-effects model was performed. An I^2 value <50% indicates lack of heterogeneity, and therefore the fixed-effects model was used. Through an initial screen of the results, the majority of the included populations were identified as originating from China, hence a subgroup meta-analyses was also performed. The subgroup meta-analyses were conducted by comparing the China population with the population from the rest of Asia for the -318C/T polymorphism. We checked publication bias by visual inspection of asymmetry in funnel plots. In addition, Egger's test was investigated to further evaluate the symmetry of the funnel plot and $P<0.05$ was considered to indicate a statistically significant difference. All statistical tests were performed using STATA version 11.2 (Stata Corp., College Station, TX, USA).

Results

Study selection and characteristics. A total of 357 results were preliminarily identified to meet the inclusion criteria of the present study. Through an initial screening of titles, key words and abstracts, 329 of these search results were excluded

Table III. Summary of total pooled results from different comparative genetic models.

Genetic models	OR (95% CI)	P-value[a]	Test of heterogeneity		
			I^2 (%)[b]	P-value	Model
TT+TC vs. CC	1.28 (1.07-1.53)	0.008	59.4	0.0004	Random
TT vs. TC+CC	1.43 (1.03-1.99)	0.032	20.9	0.211	Fixed
TT vs. CC	1.51 (1.09-2.10)	0.014	27.4	0.142	Fixed
TC vs. CC	1.26 (1.06-1.50)	0.008	53.6	0.002	Random
T vs. C	1.25 (1.05-1.47)	0.010	62.3	0.0004	Random

[a]Test for overall effect. [b]Index of heterogeneity. OR, odds ratio; CI, confidence interval.

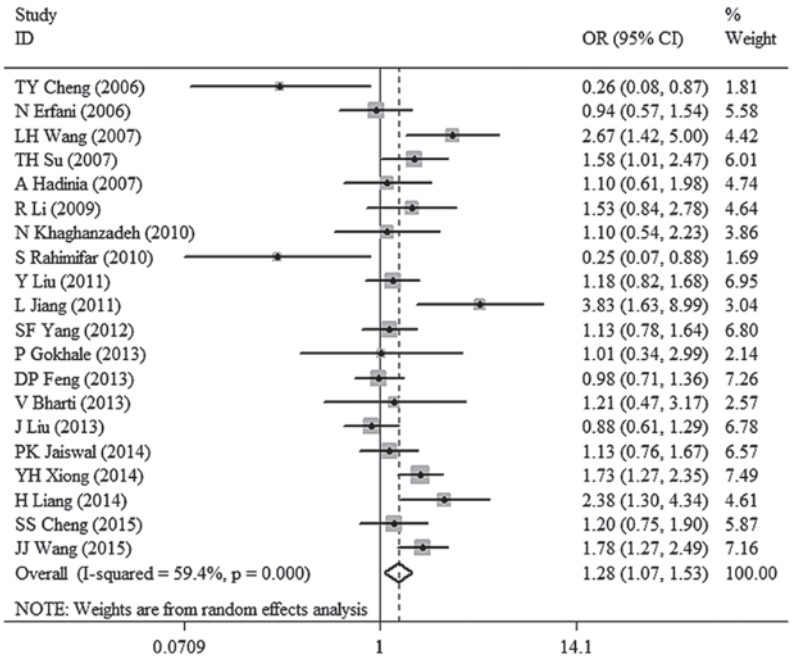

Figure 2. Association between malignant tumor risk in an Asian population and CTLA-4 -318C/T polymorphism under dominant model (TT+TC vs. CC). CTLA-4, cytotoxic T-lymphocyte antigen 4; OR, odds ratio; CI, confidence interval.

(101 were duplicates; 33 were reviews; 48 were letters, conferences or meta-analysis; 75 were not focused on the CTLA-4 -318C/T polymorphism; 47 were not relevant to malignant tumors, and 25 were not researching an Asian population). A total of 28 full-text studies were then reviewed and an additional 8 studies were excluded for not being a case-control study. Thus, 20 articles with a total of 3,539 cases and 4,690 controls were included in the final data extraction (7-26). There were two articles that analyzed two cancer types (colorectal cancer and gastric cancer) using the same control group (11,12). We combined the two cancer types into one (gastrointestinal cancer), and therefore, the two case-controlled studies were combined. Finally, there were 20 case-controlled studies included in the meta-analysis, Fig. 1 shows the detailed procedure for screening eligible studies. The publication years ranged from 2006 to 2015. Among the 20 case-controlled studies, 13 evaluated the relevant correlation in a Chinese population (7,9,10,12,15-17,19,21,23-26), 4 studies in an Iranian population (8,11,13,14), and 3 researched an Indian population (18,20,22). All enrolled studies showed that the genotypes in the healthy control group did not deviate from the HWE, (all P>0.05). The characteristics of each study are listed in Table I, and the distributions of genotypes and alleles in CTLA-4 -318C/T polymorphisms are listed in Table II.

Quantitative synthesis. The summary of results from the meta-analysis of the association between CTLA-4 -318C/T polymorphisms and malignant tumor in Asian populations is shown in Table III. The heterogeneity of the dominant model (TT+TC vs. CC), heterozygous model (TC vs. CC) and allele model (T vs. C) were performed for the 20 case-controlled studies and there was statistical heterogeneity among these models (Table III). However, the heterogeneity of the recessive model (TT vs. TC+CC) and homozygous model (TT vs. CC) were performed for 17 case-control studies (there were three case-control studies excluded by the STATA software automatically for lack of homozygote genotype TT both in cases and controls) and there was no statistical heterogeneity in

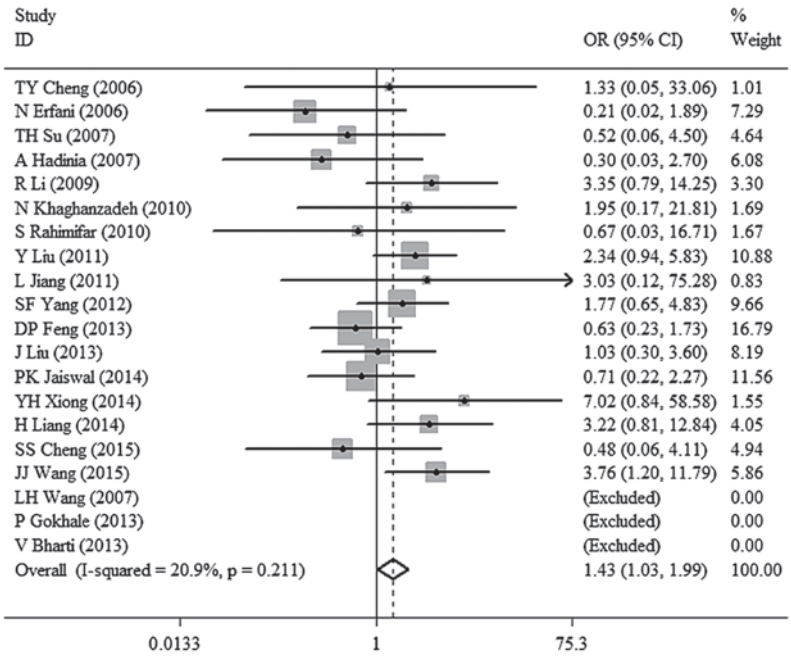

Figure 3. Association between malignant tumor risk in an Asian population and CTLA-4 -318C/T polymorphism under recessive model (TT vs. TC+CC). CTLA-4, cytotoxic T-lymphocyte antigen 4; OR, odds ratio; CI, confidence interval.

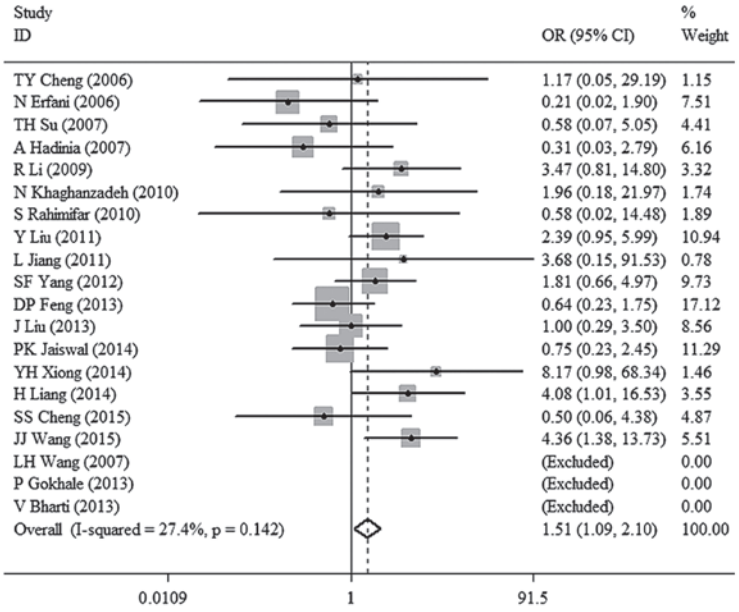

Figure 4. Association between malignant tumor risk in Asian population and CTLA-4 -318C/T polymorphism under homozygous model (TT vs. CC). CTLA-4, cytotoxic T-lymphocyte antigen 4; OR, odds ratio; CI, confidence interval.

the two models (Table III). Data from the meta-analysis for TT+TC vs. CC was as follows: χ^2, 46.84; df=19; P=0.0004 and I^2=59.4%. A random-effects model was used to analyze the data. A significant association between CTLA-4 -318C/T polymorphism and malignant tumor risk (OR, 1.28; 95% CI, 1.07-1.53; P=0.008) was observed in dominant model (Fig. 2). The results also revealed an association between CTLA-4 -318C/T polymorphism and malignant tumor risk in the Asian population under other models [TT vs. TC+CC: OR, 1.43; 95% CI, 1.03-1.99; P=0.032 (Fig. 3). TT vs. CC: OR, 1.51; 95% CI, 1.09-2.10; P=0.014 (Fig. 4). TC vs. CC: OR, 1.26; 95% CI, 1.06-1.50; P=0.008 (Fig. 5). T vs. C: OR, 1.25; 95% CI, 1.05-1.47; P=0.010 (Fig. 6)]. In the subgroup analysis, a significant association between CTLA-4 -318C/T polymorphism and malignant tumor risk in the Chinese population was identified (OR, 1.41; 95% CI, 1.13-1.76; P=0.002 for TT+TC vs. CC; Fig. 7). In addition, there was no association between CTLA-4 -318C/T polymorphism and malignant tumor risk in the populations of other countries (Fig. 7).

Publication bias. No publication bias was detected in either the Begg's funnel plot (data not shown) or Egger's test for

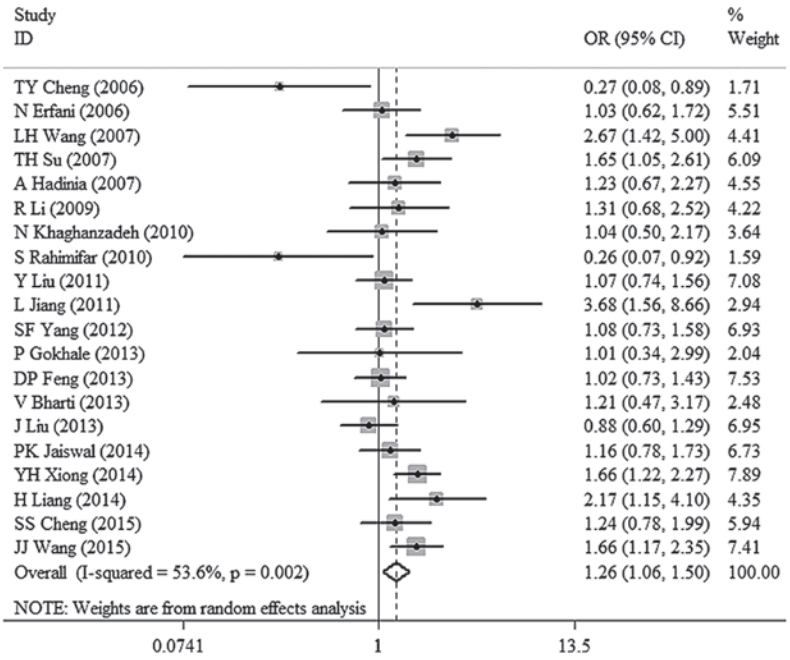

Figure 5. Association between malignant tumor risk in an Asian population and CTLA-4 -318C/T polymorphism under heterozygous model (TC vs. CC). CTLA-4, cytotoxic T-lymphocyte antigen 4; OR, odds ratio; CI, confidence interval.

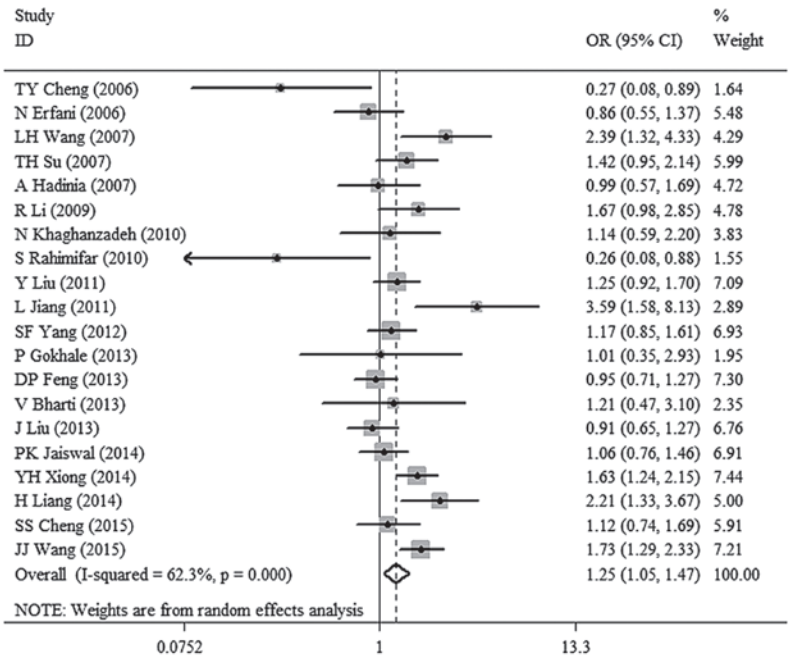

Figure 6. Association between malignant tumor risk in an Asian population and CTLA-4 -318C/T polymorphism under allele model (T vs. C). CTLA-4, cytotoxic T-lymphocyte antigen 4; OR, odds ratio; CI, confidence interval.

TT+TC vs. CC (t=-0.64; P>|=0.533). The relative symmetrical distribution for the Begg's funnel plot (data not shown) or Egger's test (t=-0.58; P>|=0.570) indicated there was no publication bias for allele model (T vs. C).

Discussion

In recent years, an increasing number of studies have revealed the effect of gene polymorphisms in tumorigenesis or the susceptibility to malignant tumors. Tumor immunity is increasing as a focus in malignant tumors research. CTLA-4, an important mediator in T cell proliferation and activation, is important in cancer immunosurveillance (28). Previous studies demonstrated that variants of CTLA-4 -318C/T may increase susceptibility to malignant tumors in Asian populations (7,14,29). However, negative results have been reported in a previous study (16). To date, no meta-analysis has been conducted to comprehensively evaluate the association between the CTLA-4 -318C/T polymorphism and malignant tumor risk in Asian populations. Thus, the current study

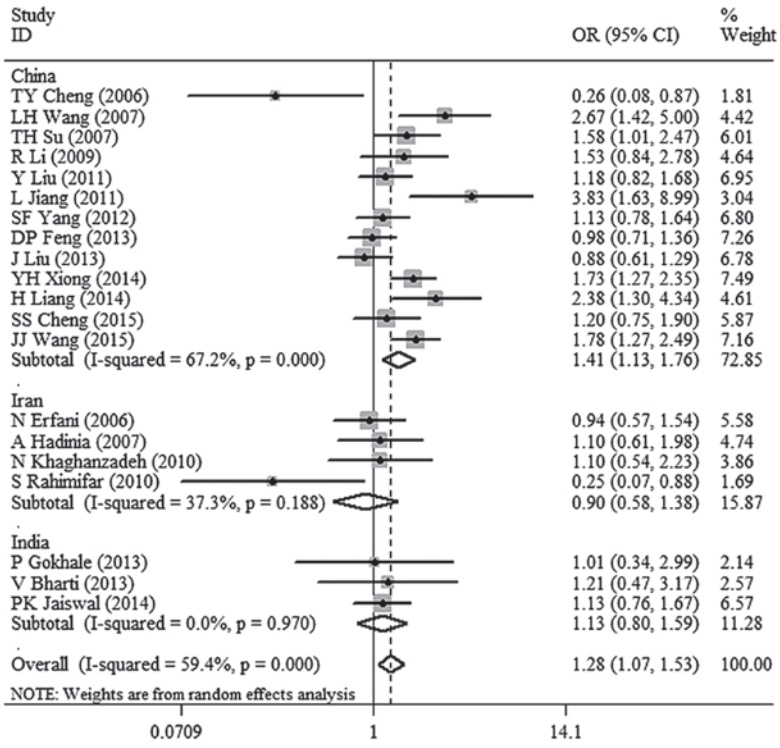

Figure 7. Association between malignant tumor risk in an Asian population and CTLA-4 -318C/T polymorphism under dominant model (TT+TC vs. CC is illustrated in a subgroup analysis by country. CTLA-4, cytotoxic T-lymphocyte antigen 4; OR, odds ratio; CI, confidence interval.

performed a meta-analysis to explore the exact associations between the CTLA-4 -318C/T polymorphism and malignant tumor risk in an Asian population.

The results of our meta-analysis indicated that CTLA-4 -318C/T polymorphism was significantly association with the risk of developing a malignant tumor. The TT+TC genotype and the TC heterozygote carriers exhibited higher malignant tumor incident risks when compared to the CC genotype carriers (TT+TC vs. CC: OR, 1.28; 95% CI, 1.07-1.53; P=0.008. TC vs. CC: OR, 1.26; 95% CI, 1.06-1.50; P=0.008). When the comparisons were conducted between the TT and CC homozygotes or between the T and C alleles, there remained a significant effect from the TT homozygote or the T allele on the risk of malignant tumor, respectively (TT vs. CC: OR, 1.51; 95% CI, 1.09-2.10; P=0.014. T vs. C: OR, 1.25; 95% CI, 1.05-1.47; P=0.010). The analysis reveals that CTLA-4 -318C/T genetic variants may be an important factor in the development and progression of malignant tumors in Asian populations, and individuals with the variant T allele have a ~25% higher risk of developing malignant tumors. In the subgroup analysis, we found that the dominant models (TT+TC vs. CC) had significantly increased the risk of malignant tumor in China (OR, 1.41; 95% CI, 1.13-1.76). In addition, there were no such correlation in Iran and India, indicating that country differences may be a potential factor of heterogeneity for this correlation.

However, the results from current meta-analysis must be interpreted with caution, as some limitations should be considered. First, for the Iran and India study populations, only 5 and 3 case-control studies were included in each, respectively. Second, only published studies in the selected databases were included, and some unpublished studies with null results were ignored. Third, the studies included in the meta-analysis were lacking in original information concerning environmental and lifestyle factors, which prevented us from further performing subgroup analysis according to these variables. All of these limitations may have limited power to reveal a credible association and distort the results. Hence, we addressed the heterogeneity and publication bias through rigorously selecting case-control studies, using a statistical approach to analyze the inconsistent data of selected studies, contributing to a more reliable association between the CTL-4 -318C/T polymorphism and malignant tumor risk in Asian populations. Significant publication bias was not detected for the gene polymorphisms, indicating the reliability of the results from this meta-analysis.

In conclusion, the results from the meta-analysis suggest that the CTL-4 -318 C/T polymorphisms, may be a risk factor for the development of malignant tumors in Asian populations. However, this result should be interpreted with caution, because the eligible studies are only from 3 Asian countries, and the studies contained no more than five individuals, except for those originating from China. A subgroup analysis was performed by country, and the dominant model (TT+TC vs. CC) revealed a significantly increased risk of malignant tumors in the Chinese population (OR, 1.41; 95% CI, 1.13-1.76; P=0.002). However, the analysis did not reveal any association between CTL-4 -318 C/T polymorphisms and the risk of malignant tumor in the Iranian and Indian populations. The fact that there were not sufficient numbers of studies from other Asian nations may distort our conclusion. More intensive studies based on individuals from additional countries in Asia are required to further reveal the precise association between CTL-4 -318C/T polymorphisms and malignant tumor risk in Asian populations.

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