Original Article
Lack of association between *interleukin-2 (IL-2)* gene rs2069762 polymorphism and cancer risk: a meta-analysis

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Abstract: Interleukin-2 (IL-2) is an important member of the cytokines that play critical roles in carcinogenesis. Many studies have investigated the association between *IL-2* rs2069762 polymorphism and cancer risk; however, the results remain controversial. The aim of this study is to assess the correlation between *IL-2* rs2069762 polymorphism and cancer risk. All eligible case-control studies accorded with criteria published up to March 30, 2015 were identified by searching Embase and PubMed databases. Association between *IL-2* rs2069762 polymorphism and cancer risk was assessed by crude odds ratios (ORs) with 95% confidence intervals (CIs), respectively. Ten case-control studies from nine publications with 3095 cases and 4480 controls were included. Overall, *IL-2* rs2069762 polymorphism was not associated with cancer risk in five genetic models (G vs. T: OR = 1.07, 95% CI = 0.95-1.21, P = 0.278; GG vs. TT: OR = 1.16, 95% CI = 0.86-1.57, P = 0.317; GG + TG vs. TT: OR = 1.09, 95% CI = 0.93-1.28, P = 0.273; GG vs. TT + TG: OR = 1.11, 95% CI = 0.85-1.44, P = 0.451; TG vs. TT: OR = 1.08, 95% CI = 0.92-1.28, P = 0.339, respectively). Similar results were also obtained after stratified by ethnicity and cancer type. This meta-analysis indicates that *IL-2* rs2069762 T>G polymorphism is not associated with cancer risk. And the same conclusion is drawn after stratified by cancer type and ethnicity.

Keywords: *IL-2*, polymorphism, cancer susceptibility, meta-analysis

Introduction

Cancer is one of the leading causes of death in economically both developed and developing countries; the burden of cancer is estimated to grow worldwide on account of the aging and growth of the population, particularly in developing countries [1]. According to 2012 global cancer statistics, approximately 14.1 million new cases and 8.2 million deaths of cancer occurred in 2012 worldwide [1]. Cancer is attributed to many factors. Inflammation has been considered as a driving factor in pathogenesis of many cancers [2, 3]. Chronic inflammation may lead to oxidative stress and help to bring about tumor promotion and progression [4]. Cytokines production generated by immune/inflammatory cells is one of the major

tumor-promoting mechanisms [5]. Cytokines are soluble glycoproteins or proteins that are necessary to the function of immunocytes and play vital roles in the inflammatory response [4].

As a potent immunoregulatory cytokine participating in cell-mediated immune response, interleukin-2 (IL-2) is generated by T cells when they are stimulated by mitogens, or interplay with major histocompatibility complexes in antigen-presenting cells and act as one of the T-cell growth factors [6]. IL-2 participates in the regulation of functional activities and proliferation of T cell and natural killer (NK) cell [6]. It also increases NK cell cytolytic activity and promotes immunoglobulin production by B cells [7, 8]. Moreover, IL-2 regulates the expansion and apoptosis of activated T cells and is involved in
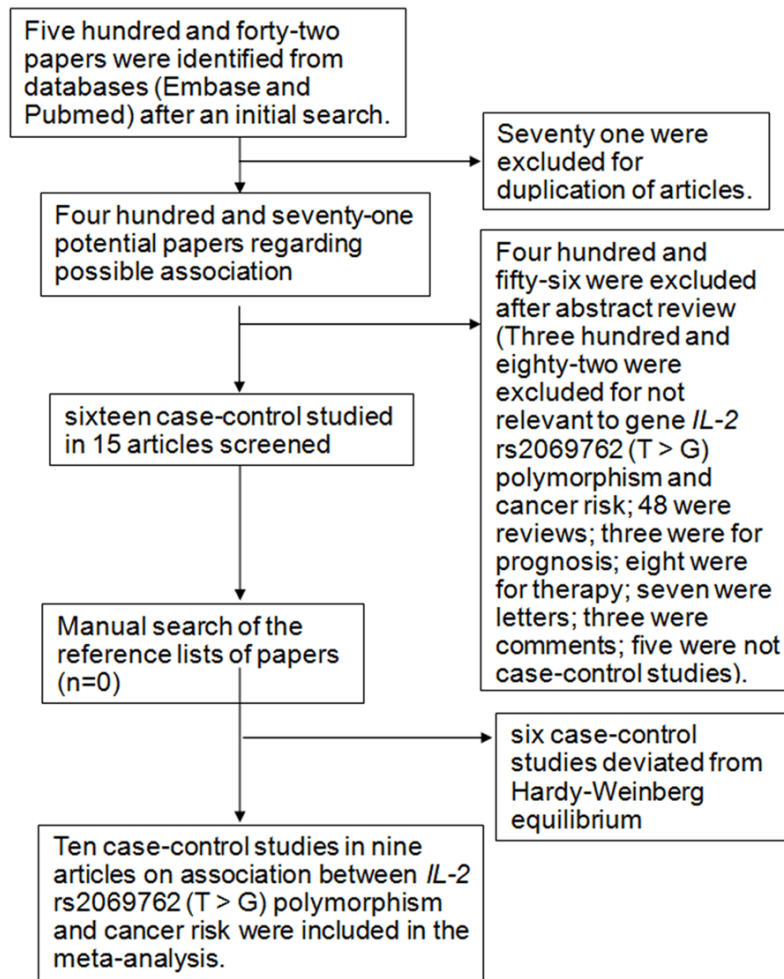
Five hundred and forty-two papers were identified from databases (Embase and Pubmed) after an initial search.

Seventy one were excluded for duplication of articles.

Four hundred and seventy-one potential papers regarding possible association

Four hundred and fifty-six were excluded after abstract review (Three hundred and eighty-two were excluded for not relevant to gene *IL-2* rs2069762 (T > G) polymorphism and cancer risk; 48 were reviews; three were for prognosis; eight were for therapy; seven were letters; three were comments; five were not case-control studies).

sixteen case-control studied in 15 articles screened

Manual search of the reference lists of papers (n=0)

six case-control studies deviated from Hardy-Weinberg equilibrium

Ten case-control studies in nine articles on association between *IL-2* rs2069762 (T > G) polymorphism and cancer risk were included in the meta-analysis.

Figure 1. Flow diagram of articles selection procedures for *IL-2* rs2069762 polymorphism and cancer risk meta-analysis.

the regulatory T cells development [9]. In regard to its correlation to cancer, IL-2 has been estimated to play a crucial role in antitumor immunity [10]. Many clinical studies have indicated that *IL-2* gene transfected into cancer cells can enhance both nonspecific and specific antitumor immune responses [11]. What's more, recombinant IL-2 has been proved to be a promising agent for activation of immune response against different cancers [12]. These results indicated that the *IL-2* gene could be a candidate for cancer gene treatment or therapy.

The *IL-2* gene is located in chromosome 4q26-q27 in humans, which includes five exons and five introns. *IL-2* genetic polymorphisms may influence IL-2 production or protein expression and thus might modulate cancer risk. *IL-2* rs2069762 (-330 T>G) polymorphism in the

promoter region of *IL-2* gene lies near an important transcription factor which is nuclear factor of activated T cells. Thus, this site may affect the activity of transcription factors and then influence the transcription and translation standards of *IL-2* [13]. This single nucleotide polymorphism (SNP) acts as a desired marker for genetic study since it has two common alleles. Recently, it was estimated that *IL-2* polymorphisms have been related to the susceptibility to several cancers, such as bladder cancer [14], nasopharyngeal carcinoma [15], head and neck cancer [16] and Non-Hodgkin Lymphoma [17]. In this study, we aimed to estimate more precisely the association between *IL-2* rs2069762 T>G polymorphism and cancer risk by combining all related publications up to date.

Materials and methods

Identification of eligible studies

We searched relative articles and reviews up to March 30, 2015 in two electronic databases, Embase and PubMed, using key words 'IL-2 or interleukin-2', 'polymorphism or SNP', and 'cancer or carcinoma or malignance'. Only English papers were adopted in our study. References of relative studies and reviews were manually retrieved for additional studies. Studies included in our meta-analysis conformed to the following criteria: (1) evaluation of the *IL-2* polymorphism and cancer risk, (2) case-control study and (3) control genotype distributions according with Hardy-Weinberg equilibrium (HWE). Excluded criteria were: (1) overlapping data, (2) not case-control studies and (3) review publications, comments and letters.

Data extraction

According to the standard criteria, data from the published studies were extracted indepen-

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

Study	Year	Vountry	Ethnicity	Cancer type	No. of cases/control	Souce of control	Genotype method
Peng et al.	2014	China	Asians	Hepatocellular Carcinoma	107/105	hospital based	PCR-RFLP
Bei et al.	2014	China	Asians	Hepatocellular Carcinoma	720/784	hospital based	TaqMan
Song et al.	2012	Korea	Asians	Lymphoma	40/254	hospital based	OPA
Wei et al.	2010	China	Asians	Nasal Pharyngeal Cancer	180/200	hospital based	PCR-RFLP
Ko et al.	2009	Korea	Asians	Gastric cancer	84/336	population based	Snapshot
Wu et al.	2009	China	Asians	Gastric cancer	1045/1100	population based	PCR-RFLP
Savage et al.	2004	China	Asians	Esophageal cancer	130/454	hospital based	Snapshot
Savage et al.	2004	China	Asians	Gastric cancer	91/454	hospital based	Snapshot
Howell et al.	2003	Britain	Caucasians	Melanoma	169/261	hospital based	PCR-ARMS
Rizzato1 et al.	2011	Hungary	Caucasians	Skin cancer	529/532	hospital based	KASPar SNP genotyping

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; OPA: GoldenGate™ oligonucleotide pool assay; PCR-ARMS: Amplification Refractory Mutation System-Polymerase Chain Reaction.

Table 2. Distribution of *IL-2* rs2069762 polymorphism genotype and allele among cancer patients and controls

Study	Year	Case			Control			Case		Control		HWE
		TT	TG	GG	TT	TG	GG	G	T	G	T	
Peng et al.	2014	47	54	6	42	54	9	66	148	72	138	YES
Bei et al.	2014	292	333	95	311	373	100	523	917	573	995	YES
Song et al.	2012	7	11	5	87	54	7	21	25	68	228	YES
Wei et al.	2010	46	106	28	81	102	17	162	198	136	264	YES
Ko et al.	2009	34	44	3	156	132	43	50	112	218	444	YES
Wu et al.	2009	491	441	94	516	480	87	629	1423	654	1512	YES
Savage et al.	2004	33	43	35	109	174	96	113	109	366	392	YES
Savage et al.	2004	20	47	16	109	174	96	79	87	366	392	YES
Howell et al.	2003	79	44	14	86	61	13	72	202	87	233	YES
Rizzato et al.	2011	215	223	58	221	221	60	339	653	341	663	YES

dently by three authors (Y. Wang, Y. Shu and H. Jiang) to populate the requisite information. For each study, the following details were collected: publication data, the first author's surname, country of origin, year of publication, cancer type, ethnicity of subjects, sample size, source of controls, genotype frequency in controls and cases and HWE in controls. In regard to conflicting evaluations, they were solved among all authors by further discussion.

Statistical analysis

We tested HWE of genotype frequencies in control populations using the X^2 test. The strength of the association between *IL-2* rs2069762 T>G polymorphism and cancer risk was measured by Odds ratios (ORs) with 95% confidence intervals (CIs) in allele model (G vs. T), homozygous model (GG vs. TT), dominant model (GG + TG vs. TT), recessive model (GG vs. TG + TT), and additive model (TG vs. TT). Z test was used to examine the statistical significance of the pooled ORs. I^2 test and Q-test were used to quantify the effect of heterogeneity. The random effects model (DerSimonian Laird method) was used when a significant Q-test ($P<0.1$) or $I^2>50\%$, otherwise, the fixed effects model (Mantel-Haenszel method) was carried out [18]. To identify the source of heterogeneity, we performed subgroup analysis by ethnicity, cancer type, source of controls and number of cases. Sensitivity was examined by omitting each study in turn to estimate the stability of results. The publication bias was evaluated by Begger's funnel plots and Egger's linear regression test ($P<0.1$) [19]. Between-study heterogeneities and variations were estimated by Galbraith radial plot, and $P<0.05$ was considered to be statistically significant [20]. All P values were two-sided and statistical analyses were calculated by Stata Version 12.0 software (Stata Corp, College Station, TX).

Table 3. Synthesis of results of the meta-analysis from different comparative gene models in the total and subgroup analysis

|	No. of study	G vs. T			GG vs. TT			GG + TG vs. TT			GG vs. TG + TT			TG vs. 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)	OR (95% CI)	P	P (Q-test)
Total	10	1.07 (0.95-1.21)	0.278	0.019	1.16 (0.86-1.57)	0.317	0.009	1.09 (0.93-1.28)	0.273	0.047	1.11 (0.85-1.44)	0.451	0.016	1.08 (0.92-1.28)	0.339	0.060
Ethnicity																
Asians	8	1.10 (0.94-1.29)	0.226	0.007	1.21 (0.82-1.78)	0.343	0.003	1.16 (0.94-1.42)	0.170	0.023	1.11 (0.79-1.56)	0.531	0.006	1.15 (0.93-1.42)	0.198	0.035
Caucasians	2	1.00 (0.85-1.18)	0.980	0.789	1.03 (0.71-1.48)	0.886	0.722	0.99 (0.79-1.23)	0.893	0.486	1.03 (0.73-1.45)	0.874	0.537	0.97 (0.77-1.23)	0.829	0.330
Cancer type																
Hepatocellular carci	2	0.97 (0.85-1.12)	0.704	0.505	0.97 (0.71-1.32)	0.848	0.371	0.95 (0.78-1.15)	0.594	0.676	1.00 (0.75-1.34)	0.991	0.383	0.94 (0.77-1.16)	0.572	0.840
Gastric cancer	3	1.00 (0.89-1.13)	0.943	0.827	1.00 (0.76-1.32)	0.992	0.135	1.03 (0.89-1.21)	0.669	0.532	0.72 (0.37-1.42)	0.348	0.027	1.20 (0.85-1.68)	0.305	0.116
Other cancer	5	1.26 (0.96-1.66)	0.094	0.004	1.70 (0.96-3.01)	0.069	0.007	1.26 (0.87-1.83)	0.220	0.009	1.49 (0.98-2.26)	0.060	0.059	1.15 (0.81-1.63)	0.446	0.029
Source of Control																
Hospital based	8	1.11 (0.94-1.31)	0.218	0.008	1.27 (0.89-1.82)	0.185	0.012	1.13 (0.90-1.41)	0.288	0.023	1.18 (0.88-1.57)	0.271	0.044	1.09 (0.88-1.34)	0.440	0.062
Population based	2	1.01 (0.89-1.14)	0.892	0.560	0.70 (0.21-2.35)	0.558	0.049	1.02 (0.86-1.19)	0.853	0.413	0.61 (0.14-2.66)	0.511	0.016	1.14 (0.74-1.76)	0.551	0.092
Number of cases																
<500	7	1.15 (0.90-1.46)	0.260	0.007	1.28 (0.70-2.32)	0.423	0.002	1.24 (0.91-1.67)	0.172	0.030	1.13 (0.67-1.92)	0.639	0.003	1.23 (0.90-1.67)	0.194	0.045
≥500	3	1.01 (0.92-1.10)	0.852	0.953	1.05 (0.86-1.28)	0.603	0.838	0.99 (0.88-1.11)	0.870	0.927	1.07 (0.88-1.28)	0.507	0.781	0.98 (0.86-1.10)	0.694	0.873
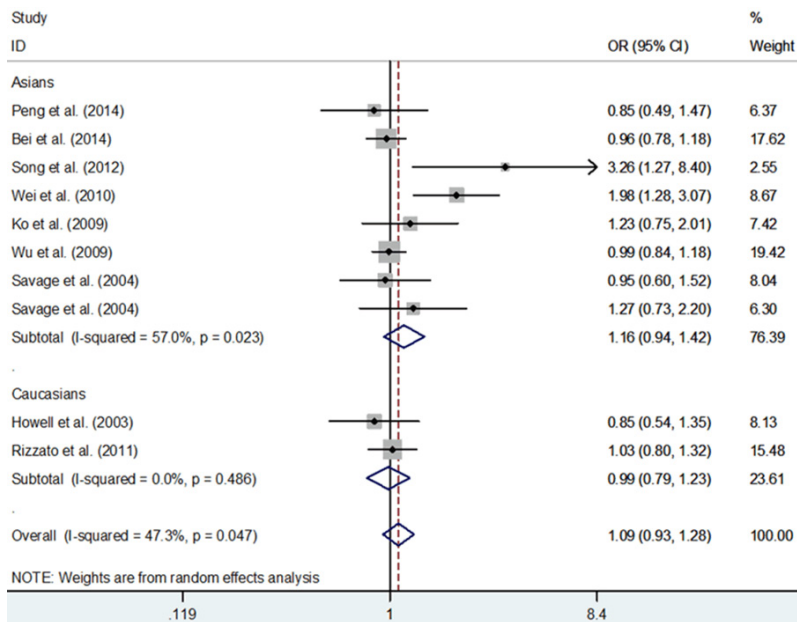
Figure 2. Meta-analysis with a random-effects model for the association between *IL-2* rs2069762 polymorphism and cancer risk (GG + TG vs. TT).

Results

Characteristics of studies

After searching based on the eligible criteria, initially a total of 542 potentially relevant publications were yielded. The detailed study extraction processing was shown in **Figure 1**. In the article reported by Savage et al., esophageal cancer and gastric cancer were separately studied, thus each of them was regarded as an individual study. Finally, a total of 10 case-control studies from 9 articles were included in our meta-analysis.

A total of 3095 cases and 4480 controls were involved in our meta-analysis (**Table 1**). Among these studies, three discussed the association between the *IL-2* rs2069762 T>G polymorphism and gastric cancer, two discussed the association between the *IL-2* rs2069762 T>G polymorphism and hepatocellular carcinoma, and five discussed the association between the *IL-2* rs2069762 T>G polymorphism and other cancers (lymphoma, nasal pharyngeal cancer, esophageal cancer, melanoma, skin cancer). According to ethnicity, two studies discussed Caucasians and 8 studies discussed Asians. According to control source, eight studies were hospital-based and two were population-based. According to the number of cases, they were

<500 in seven studies and ≥500 in three studies. The distribution of *IL-2* rs2069762 T>G polymorphism and allele among controls and patients is listed in **Table 2**.

Quantitative synthesis

Overall, we found no evidence of association between *IL-2* rs2069762 T>G polymorphism and cancer risk (G vs. T: OR = 1.07, 95% CI = 0.95-1.21, *P* = 0.278; GG vs. TT: OR = 1.16, 95% CI = 0.86-1.57, *P* = 0.317; GG + TG vs. TT: OR = 1.09, 95% CI = 0.93-1.28, *P* = 0.273; GG vs. TT + TG: OR = 1.11, 95% CI = 0.85-1.44, *P* = 0.451; TG vs. TT: OR = 1.08, 95% CI = 0.92-1.28, *P* = 0.339, **Table 3** and **Figure 2**). In the stratified analyses, there was no significant relationship for different cancer, similarly, there was no significant relationship for Asians nor Caucasians (**Table 3**).

Bias diagnostics

Egger's test and Begg's funnel plot were used to assess the publication bias, and no evidence of bias was found (G vs. T: Begg's test *P* = 0.592, Egger's test *P* = 0.279; GG vs. TT: Begg's test *P* = 1.000, Egger's test *P* = 0.633; GG + TG vs. TT: Begg's test *P* = 0.210, Egger's test *P* = 0.124; GG vs. TT + TG: Begg's test *P* = 1.000, Egger's test *P* = 0.973; TG vs. TT: Begg's test *P* = 0.283, Egger's test *P* = 0.136, **Figure 3**).

Sensitivity analyses

We performed one-way sensitivity analyses by sequential omission of individual study each time. The analysis results indicated that no individual study significantly influenced the pooled ORs (**Figure 4**, data not shown), indicating the statistically robust results.

Test of heterogeneity

The results manifested there were significant heterogeneities among the studies included. Because ethnicity and cancer type could affect
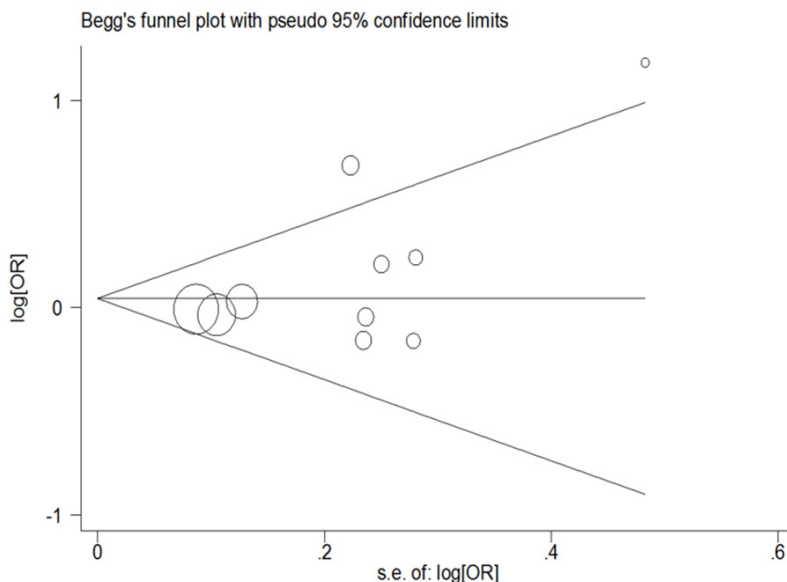
Figure 3. Funnel plot analysis to detect publication bias for the *IL-2* rs2069762 polymorphism in the involved ten data sets (random-effects estimates, GG + TG vs. TT compare genetic model).
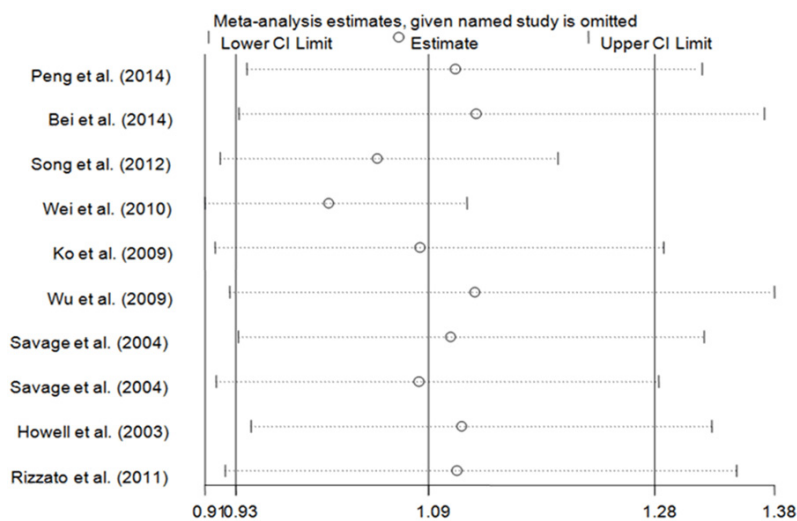

Figure 4. Sensitivity analysis of the effect of GG + TG vs. TT in overall cancer meta-analysis (random-effects assess).

contribute to heterogeneity. Further stratified meta-analysis suggested that more prominent heterogeneity was associated with studies of small number of cases (<500 cases) and hospital-based (**Table 3**).

Discussion

The results showed that *IL-2* rs2069762 T>G polymorphism may not be correlated with cancer risk. Analogous results were found after stratified by cancer type and ethnicity. This is the first meta-analysis including a total of 3095 cases and 4480 controls from 10 case-control studies examining the association of *IL-2* rs2069762 T>G polymorphism with cancer risk.

With the increase of gene association studies, it is even more encouraged to synthesize available data to solve persistent difficulties in obtaining replicable and robust results. Most common gene defects usually make small-to-moderate contributions to malignance risk. So far, many studies had concentrated on the association between *IL-2* rs2069762 T>G polymorphism and cancer risk, but the results were still vague. Several individual studies have provided positive signals of *IL-2* gene rs2069762 T>G polymorphism with cancer, such as hepatocellular carcinoma [22], breast cancer [23], bladder cancer [14], contrastingly, as illustrated in our meta-analysis among 3095 cases and 4480 controls, there was null association, even in different ethnicity and cancer type. In consideration of a modest sum of studies included in our meta-analysis and most of small sample size, there is a suggestion of possible beneficial, reinforcing additional large studies to overthrow or confirm these findings.

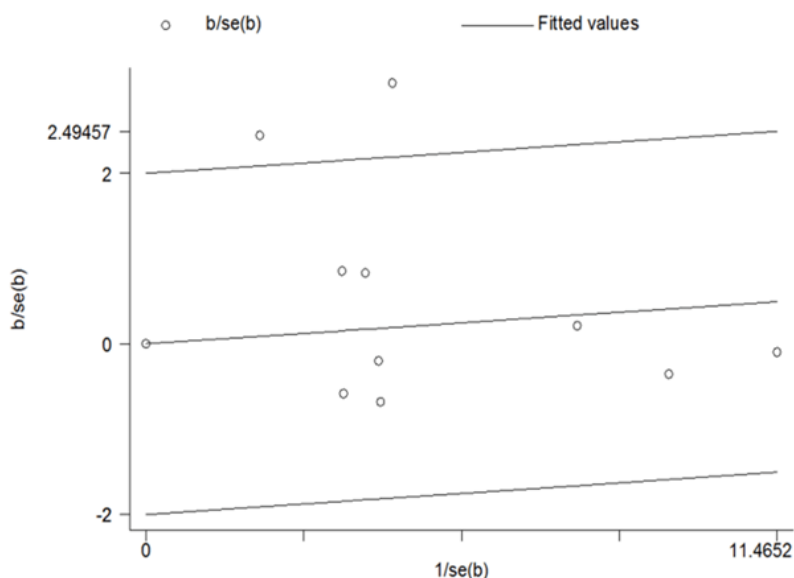the results of meta-analyses, we carried out subgroup analyses by cancer type and ethnicity (**Table 3**). The results suggested that Asian population subgroup and other cancer type may contribute to the heterogeneity. As shown in **Table 3**, heterogeneity was significant in five models comparison. Galbraith radial plot also was used to analyze the heterogeneity in dominant model comparison (**Figure 5**). According to the forest plot, we identified that the studies of Wei et al. [15] and Song et al. [21] might mainly

Figure 5. Meta-analysis heterogeneity by Galbraith radial plot (GG + TG vs. TT compare genetic model).

rs2069762 T>G polymorphism and cancer. Perhaps *IL-2* rs2069762 T>G polymorphism had disparate influence on different type of cancers with different environmental and exposures carcinogenic mechanisms. Also, for some cancer types, there were only several studies and some studies had limited sample sizes. Thus, our study may be underpowered to detect meaningful association. Therefore, more well-designed and large-scale studies are needed to confirm the association.

It is also possible that the latent role of this polymorphism is masked or diluted by other gene-environment or gene-gene interactions. Carcinogenesis is a multifactorial process involving interaction between genetic and environmental factors. In this study, we only summarized one single polymorphism and did not take environmental factors, such as tobacco and alcohol consumption, into account.

In the subgroup analysis of ethnicity, no obvious association was found among Caucasians and Asians, which was consistent with the overall data. Variations on various genes may alter cancer susceptibility among different ethnicities [24, 25]. Thus, Variations of *IL-2* rs2069762 T>G polymorphism may exert different influences on cancer risk among different races. Nevertheless, the results of this study suggested that the polymorphism variations may exert little influence on cancer susceptibility. In this meta-analysis, only two studies about Caucasians were obtained. The insufficient number may give rise to limited statistical power to assess race effect of gene. Therefore, the results should be interpreted carefully. More investigations considering Caucasians are needed to deblur the possible effects of ethnic variations of this SNP on cancer risk.

In the subgroup analysis of cancer type, we also found no association between *IL-2*

In this meta-analysis, we used Galbraith radial plot analysis to test heterogeneity. Heterogeneity between studies for the overall data were evidently found in the five genetic models; therefore, random-effect models were utilized. Then subgroup analysis was carried out to explore the sources of heterogeneity. In the subgroup analyses, evident heterogeneity was also observed in the subgroup analysis on other cancer type, Asians, hospital-based controls and small number of cases. From the forest plot in dominant genetic model, we identified that the studies of Wei et al. [15] and Song et al. [21] as the outliers might mainly contribute to heterogeneity. As regard to publication bias, we did not detect an obvious publication bias in this meta-analysis, indicating the reliability of our results.

Several limitations of this meta-analysis should be addressed. Firstly, among the studied included in this meta-analysis, most of them concerned Asians and only two concerned Caucasians. Data regarding Caucasians were not sufficient. Secondly, subgroup analyses on histological types, age, gender, and other factors (such as smoke and alcohol consumption) were not performed in this study because relevant data were not available in the primary articles. Thirdly, among the included studies, other *IL-2* polymorphisms were studied. However, the number of them was so small that we could not perform the corresponding analysis. More investigations with strict matching criteria and

larger sample size in view of multiple factors are needed to confirm or refute our findings.

In conclusion, this meta-analysis indicates that the *IL-2* rs2069762 T>G polymorphism is not associated with cancer risk. And the same conclusion is drawn after stratified by cancer type and ethnicity. Therefore, for practical reasons, more well-designed and large-scale studies are needed in future to validate or refute the results of this preliminary study.

Acknowledgements

Abbreviations

CI, confidence interval; OR, odds ratio; IL-2, Interleukin-2; HWE, Hardy-Weinberg equilibrium; SNP, single nucleotide polymorphism; NK, natural killer.

Disclosure of conflict of interest

None.

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