ORIGINAL RESEARCH

IL-2 -330T/G polymorphism and cancer risk: a meta-analysis

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Purpose: Some studies have investigated the association of *IL-2* -330T/G (rs2069762) polymorphism with cancer risk, but the previous results were conflicting and had relatively low statistical power. Thus, we performed a meta-analysis to derive a more precise estimation of the association between *IL-2* -330T/G polymorphism and cancer risk.

Methods: A literature search was performed systematically using electronic databases. The odds ratio (OR) with 95% confidence interval (CI) was used to estimate the pooled effect.

Results: A total of ten studies including 3,060 cases and 3,435 controls were involved in this meta-analysis. The results indicated that *IL-2* -330T/G polymorphism was significantly associated with cancer risk ([OR =2.03, 95% CI =1.40–2.95] for GG vs TT; [OR =1.37, 95% CI =1.11–1.69] for GT vs TT; [OR =1.46, 95% CI =1.18–1.81] for [GG + GT] vs TT; [OR =1.66, 95% CI =1.24–2.23] for GG vs [GT + TT]; and [OR =1.35, 95% CI =1.16–1.57] for G vs T). In the subgroup analysis according to cancer type, significant association was found in lymphoma ([OR =1.46, 95% CI =1.11–1.91] for GT vs TT; [OR =1.58, 95% CI =1.22–2.05] for [GG + GT] vs TT; [OR =1.84, 95% CI =1.22–2.77] for GG vs [GT + TT]) and other cancers, but not in gastric cancer. In the subgroup analysis by ethnicity, the significant risk was found among Asians, but not among Europeans.

Conclusion: This meta-analysis suggests that *IL-2* -330T/G polymorphism has an increased risk of cancer in Asians. However, further detailed studies are still required to confirm our findings.

Keywords: IL-2, polymorphism, cancer, risk, meta-analysis

Introduction

Cancer is a major public health problem and one of the leading causes of death around the world. According to the estimation of GLOBOCAN, approximately 12.7 million new cases and 7.6 million deaths of cancer had occurred in 2008.[1] Although the pathogenesis of cancer is complex and has not been fully understood, recent studies suggest that genetic factors play critical roles in the pathogenic process of cancer, such as variants in Interleukin-2 (IL-2) gene.

IL-2 is an important immunoregulatory cytokine produced primarily by activated CD4^{+} T-cells, naïve CD8^{+} T-cells and dendritic cells.[2] It has been reported that IL-2 can stimulate proliferation and differentiation of natural killer cells,[3] and promote production of natural killer-derived cytokines such as TNFα, IFNγ and GM-CSF. IL-2-induced proliferation occurs via pro-proliferative signals through the proto-oncogenes c-Fos and c-Myc, in combination with anti-apoptotic signals through Bcl-2 family members.[4] In addition, it can also enhance activation-induced cell death in T-lymphocytes and eliminate self-reactive cells.[5] The role of IL-2 in B cells has also been identified, mostly pertaining to antibody secretion. In IgM-expressing B cells, IL-2 and IL-5 act synergistically to upregulate expression of heavy and

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light chain genes as well as inducing de novo synthesis of the immunoglobulin J chain gene.[6] The latter is required for oligomerization of the IgM pentamer, and represents a tightly controlled stage in B cell activation.[7] Thus, IL-2 has broad essential biological actions, and its dysfunction may have an negative influence on the development of cancer. Human IL-2 gene is located on chromosome 4q26, and in the promoter region, single nucleotide polymorphism -330T/G (rs2069762) has been reported to affect IL-2 production.[8] Some studies have investigated the potential association of *IL-2* -330T/G polymorphism and cancer risk.[9–18] However, the previous results were conflicting and had relatively low statistical power. Considering the important role of IL-2 in tumorigenesis, we performed a meta-analysis on all eligible studies to estimate the overall cancer risk associated with the *IL-2* -330T/G polymorphism.

Methods

Literature search strategy

A literature search of the PubMed, Embase, Chinese National Knowledge Infrastructure and Wang Fang databases was carried out (updated up to March 30, 2015) using the following MeSH terms: "polymorphism or variant", "cancer or tumor" and "IL-2 or Interleukin-2". We also manually searched the reference lists of all eligible studies and review articles in order to obtain additional usable data that can be included in the current meta-analysis. All articles were written in English or in Chinese.

Inclusion and exclusion criteria

We selected eligible studies according to the following criteria: a) case–control studies; b) investigating the association between the *IL-2* -330T/G polymorphism and cancer risk; and c) detailed genotype data for estimating of odds ratio (OR) and 95% confidence interval (CI). Exclusion criteria were the following: a) insufficient information on the distribution of *IL-2* -330T/G genotypes; b) case-only studies; and c) duplicated publications. If multiple studies had overlapping or duplicate data, only those with complete data were included.

Quality assessment of eligible studies

Two investigators independently assessed the quality of eligible studies according to the modified STROBE quality checklist. Forty assessment items that related to quality appraisal were used in this meta-analysis with scores ranging from 0 to 40. On the basis of their scores, these eligible studies were classified into three levels: low quality (0–19), moderate quality (20–29), and high quality (30–40). Disagreements were resolved through discussion.

Data extraction

Two independent investigators extracted the data in standardized data-collection forms. The following data were collected from each study: first author name, year of publication, cancer type, country, ethnicity, and genotype distribution of cases and controls. Disputes were settled by discussion.

Statistical analysis

The Hardy–Weinberg equilibrium (HWE) was utilized to compare the observed genotype frequencies with expected genotype frequencies in controls. Crude ORs with 95% CIs were calculated to evaluate the strength of the association between *IL-2* -330T/G polymorphism and cancer risk. The pooled ORs were performed for additive model (G vs T), dominant model ([GG + GT] vs TT), recessive model (GG vs [GT + TT]) and codominant model (GG vs TT, GT vs TT). Subgroup analysis by cancer type, ethnicity and P_{HWE} was also performed to further assess if the *IL-2* -330T/G polymorphism was associated with cancer susceptibility in each subgroup. A statistical test for heterogeneity was performed based on the Q statistic. If $P_H < 0.05$ for Q-test suggested significant heterogeneity, then the random-effects model was conducted to calculate the pooled OR; otherwise, the fixed-effects model was selected. Sensitivity analysis was performed by omitting each study in turn to assess the quality and consistency of the results. Begg's funnel plot and the Egger's test were used to evaluate possible publication bias of literatures. All statistical tests were performed by using STATA 12.0 software (Stata Corporation, College Station, TX, USA). All the P-values < 0.05 were considered statistically significant.

Results

The flow chart of article selection was presented in Figure 1. A total of 94 literatures were identified through PubMed, Embase, Chinese National Knowledge Infrastructure, and Wang Fang databases. After reviewing the titles and abstracts of the potential available articles, 76 records were excluded mainly because they were of no relevance, were in vitro experiments or were reviews. From the remaining 18 articles, we eliminated five publications due to their nonrelation with *IL-2* -330T/G polymorphism, and three publications due to their insufficient genotype data. Finally, ten articles, including ten studies with 3,060 cases and 3,435 controls, were included in this meta-analysis.

The main characteristics of eligible studies are listed in Table 1. All quality scores of eligible studies were more than 20 (moderate-high quality). The types of cancers studied
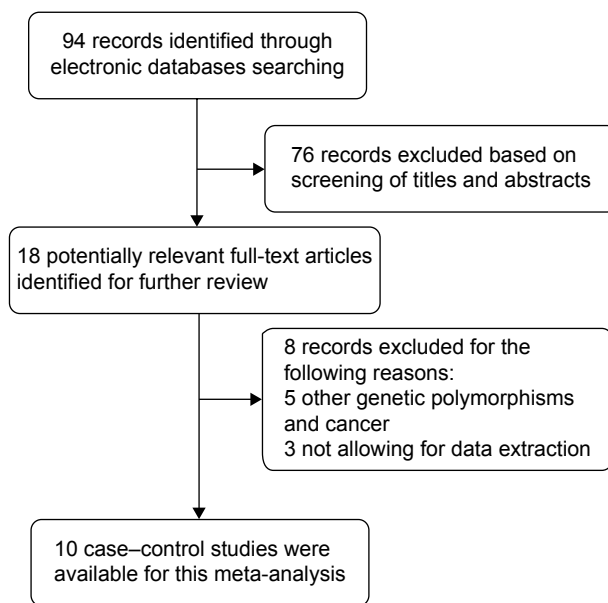
Figure 1 The flow chart of article selection.

included breast cancer,[9] lymphoma,[10,11] bladder cancer,[12] nasopharyngeal carcinoma,[13] gastroenteropancreatic neuroendocrine tumors,[14] gastric cancer,[15,16] chronic myelogenous leukemia,[17] and cutaneous malignant melanoma.[18] In addition, the populations of the studies included Asians and Europeans. After calculating P_{HWE} in controls, we found that four studies were in agreement with HWE ($P_{HWE} \geq 0.05$), and six studies are a deviation from the HWE ($P_{HWE} < 0.05$). Data concerning different cancer types, different populations, and different P_{HWE} status were treated as separate studies in the subgroup analysis.

The evaluations of the association of *IL-2* -330T/G polymorphism with cancer risk are shown in Table 2 and Figure 2. Overall, *IL-2* -330T/G polymorphism was significantly associated with overall cancer risk ([OR =2.03, 95% CI =1.40–2.95] for GG vs TT; [OR =1.37, 95% CI =1.11–1.69] for GT vs TT; [OR =1.46, 95% CI =1.18–1.81] for [GG + GT] vs TT; [OR =1.66, 95% CI =1.24–2.23] for GG vs [GT + TT]; and [OR =1.35, 95% CI =1.16–1.57] for G vs T). In the stratified analysis by cancer types, we found that *IL-2* -330 T/G polymorphism was significantly associated with the risk of lymphoma ([OR =1.46, 95% CI =1.11–1.91] for GT vs TT; [OR =1.58 95% CI =1.22–2.05] for [GG + GT] vs TT; [OR =1.84, 95% CI =1.22–2.77] for GG vs [GT + TT]) and other cancer ([OR =2.34, 95% CI =1.81–3.02] for GG vs TT; [OR =1.41 95% CI =1.21–1.65] for GT vs TT; [OR =1.53 95% CI =1.32–1.78] for [GG + GT] vs TT; [OR =1.88, 95% CI =1.49–2.39] for GG vs [GT + TT]; [OR =1.41, 95% CI =1.27–1.56] for G vs T), but not of gastric

cancer. In addition, subgroup analyses were performed by ethnicity. Significantly increased cancer risks were found among Asians ([OR =1.97, 95% CI =1.33–2.93] for GG vs TT; [OR =1.49, 95% CI =1.18–1.87] for GT vs TT; [OR = 1.56, 95% CI =1.22–1.98] for [GG + GT] vs TT; [OR =1.58, 95% CI =1.18–2.11] for GG vs [GT + TT]; and [OR =1.37, 95% CI =1.16–1.61] for G vs T), but not among Europeans. Stratified analyses by P_{HWE} showed that *IL-2* -330T/G polymorphism was associated with cancer risk in both $P_{HWE} < 0.05$ ([OR =2.13, 95% CI =1.69–2.70] for GG vs TT; [OR =1.47, 95% CI =1.27–1.70] for GT vs TT; [OR =1.56, 95% CI=1.35–1.79] for [GG+GT] vs TT; [OR=1.73, 95% CI=1.39–2.15 for GG vs [GT + TT]; and [OR =1.39, 95% CI =1.26–1.54] for G vs T) and $P_{HWE} \geq 0.05$ ([OR =1.34, 95% CI =1.04–1.73] for GG vs [GT + TT]).

As shown in Figure 3, sensitivity analysis indicated that current results were stable and credible. Publication bias was assessed by Begg's funnel plot and Egger's test. The shape of the Begg's funnel plots seemed symmetrical in all genetic models, suggesting the absence of publication bias (Figure 4). Then, the Egger's test was performed to provide statistical evidence of funnel plots symmetry. The results also indicated a lack of publication bias of the current meta-analysis (P=0.14 for GG vs TT; P=0.08 for GT vs TT; P=0.07 for [GG + GT] vs TT; P=0.17 for GG vs [GT + TT]; and P=0.11 for G vs T).

Discussion
Some studies showed that *IL-2* -330T/G polymorphism was associated with the risk of cancer, including nasopharyngeal carcinoma, gastric cardia cancer, lymphoma, non-Hodgkin lymphoma, bladder cancer, breast cancer, and gastroenteropancreatic neuroendocrine tumor.[9–15] However, other studies indicated that *IL-2* -330T/G polymorphism was not associated with cancer risk, such as gastric cancer and cutaneous malignant melanoma.[16,18] Meta-analysis has been recognized as an important way to detect the effect of selected genetic polymorphisms on disease risk precisely.[19] To the best of our knowledge, the current study was the first meta-analysis providing comprehensive insights into the association of *IL-2* -330T/G polymorphism with cancer risk. Our results indicated that *IL-2* -330T/G polymorphism might contribute to the development of cancer. Subgroup analysis by cancer type demonstrated an increased risk of lymphoma strongly associated with *IL-2* -330T/G polymorphism. Conversely, the relationship of gastric cancer with *IL-2* -330T/G polymorphism turned out to be non-significant. In addition, we conducted stratified

**Table I** Characteristics of eligible studies in this meta-analysis

First author	Year	Country	Ethnicity	Cancer type	Score	P_{HWE}	Cases (n)			Controls (n)			OR (95% CI) from eligible studies
							GG	TG	TT	GG	TG	TT	
Hu et al[9]	2013	People's Republic of China	Asian	Breast cancer	26	0.000	89	357	192	56	351	275	GT vs TT, OR =1.46, 95% CI =1.15–1.84; GG vs TT, OR =2.28, 95% CI =1.55–3.33; (GG + GT) vs TT, OR =1.57, 95% CI =1.25–1.97; GG vs (GT + TT), OR =1.81, 95% CI =1.27–2.58; G vs T, OR =1.41, 95% CI =1.20–1.65
Song et al[10]	2012	Korea	Asian	Lymphoma	27	0.706	5	11	7	7	54	87	GT vs TT, OR =2.53, 95% CI =0.93–6.93; GG vs TT, OR =8.88, 95% CI = 2.23–35.36; (GG + TG) vs TT, OR =3.26, 95% CI =1.27–8.40; GG vs (GT + TT), OR =5.60, 95% CI =1.61–19.49; G vs T, OR =2.82, 95% CI =1.48–5.34
Song et al[11]	2012	People's Republic of China	Asian	Lymphoma	26	0.001	56	246	136	39	250	193	GT vs TT, OR =1.40, 95% CI =1.05–1.85; GG vs TT, OR =2.04, 95% CI = 1.28–3.24; (GG + TG) vs TT, OR =1.48, 95% CI =1.13–1.95; GG vs (GT + TT), OR =1.67, 95% CI =1.08–2.56; G vs T, OR =1.34, 95% CI =1.11–1.62
Shen et al[12]	2012	People's Republic of China	Asian	Bladder cancer	28	0.005	51	205	109	33	200	157	GT vs TT, OR =1.48, 95% CI =1.08–2.02; GG vs TT, OR =2.23, 95% CI = 1.35–3.68; (GG + TG) vs TT, OR =1.58, 95% CI =1.17–2.14; GG vs (GT + TT), OR =1.76, 95% CI =1.11–2.79; G vs T, OR =1.40, 95% CI =1.14–1.73
Wei et al[13]	2010	People's Republic of China	Asian	NPC	29	0.054	28	106	46	17	102	81	GT vs TT, OR =1.83, 95% CI =1.16–2.88; GG vs TT, OR =2.90, 95% CI = 1.44–5.86; (GG + TG) vs TT, OR =1.98, 95% CI =1.28–3.07; GG vs (GT + TT), OR =1.98, 95% CI =1.05–3.76; G vs T, OR =1.59, 95% CI =1.18–2.13
Berković et al[14]	2010	Croatia	European	GEP-NETs	30	0.047	14	41	46	4	63	83	GT vs TT, OR =1.17, 95% CI =0.69–2.00; GG vs TT, OR =6.32, 95% CI = 1.96–20.31; (GG + TG) vs TT, OR =1.48, 95% CI =0.89–2.46; GG vs (GT + TT), OR =5.87, 95% CI =1.87–18.41; G vs T, OR =1.67, 95% CI =1.13–2.48
Wu et al[15]	2009	People's Republic of China	Asian	Gastric cancer	32	0.091	94	441	491	87	480	516	GT vs TT, OR =0.97, 95% CI =0.81–1.15; GG vs TT, OR =0.99, 95% CI =0.84–1.18; GG vs (GT + TT), OR =1.14, 95% CI = 0.83–1.56; (GG + TG) vs TT, OR =1.15, 95% CI =0.85–1.57; G vs T, OR =1.02, 95% CI =0.90–1.17
Shin et al[16]	2008	Korea	Asian	Gastric cancer	31	0.000	8	35	79	12	16	72	GT vs TT, OR =1.99, 95% CI =1.02–3.90; GG vs TT, OR =0.61, 95% CI = 0.24–1.57; (GG + TG) vs TT, OR =1.40, 95% CI =0.79–2.48; GG vs (GT + TT), OR =0.51, 95% CI =0.20–1.31; G vs T, OR =1.06, 95% CI =0.66–1.68
Amirzargar et al[17]	2005	Iran	Asian	CML	30	0.030	2	24	4	1	23	16	GT vs TT, OR =4.17, 95% CI =1.21–14.36; GG vs TT, OR =8, 95% CI = 0.57–111.96; (GG + TG) vs TT, OR =4.33, 95% CI =1.27–14.80; GG vs (GT + TT), OR =2.79, 95% CI =0.24–32.25; G vs T, OR =1.92, 95% CI =0.96–3.85
Howell et al[18]	2003	UK	European	CMM	27	0.640	14	44	79	13	61	86	GT vs TT, OR =0.79, 95% CI =0.48–1.29; GG vs TT, OR =1.17, 95% CI = 0.52–2.65; (GG + TG) vs TT, OR =0.85, 95% CI =0.54–1.35; GG vs (GT + TT), OR =1.29, 95% CI =0.58–2.84; G vs T, OR =0.95, 95% CI =0.66–1.37

Abbreviations: CI, confidence interval; CML, chronic myelogenous leukemia; CMM, cutaneous malignant melanoma; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; HWE, Hardy–Weinberg equilibrium; NPC, nasopharyngeal carcinoma; OR, odds ratio.

Table 2 Meta-analysis of the associations between *IL-2* -330T/G polymorphism and cancer risk in all models

Variables	GG vs TT		GT vs TT		(GG + GT) vs TT		GG vs (GT + TT)		G vs T	
	OR (95% CI)	P_H	OR (95% CI)	P_H	OR (95% CI)	P_H	OR (95% CI)	P_H	OR (95% CI)	P_H
Total	2.03 (1.40–2.95)	<0.01	1.37 (1.11–1.69)	<0.01	1.46 (1.18–1.81)	<0.01	1.66 (1.24–2.23)	<0.01	1.35 (1.16–1.57)	<0.01
Cancer type										
Lymphoma	3.66 (0.89–15.12)	0.05	1.46 (1.11–1.91)	0.27	1.58 (1.22–2.05)	0.12	1.84 (1.22–2.77)	0.07	1.82 (0.89–3.73)	0.03
Gastric cancer	1.06 (0.79–1.44)	0.22	1.29 (0.64–2.58)	0.04	1.02 (0.87–1.20)	0.26	1.07 (0.80–1.42)	0.11	1.02 (0.90–1.16)	0.89
Other cancer	2.34 (1.81–3.02)	0.24	1.41 (1.21–1.65)	0.07	1.53 (1.32–1.78)	0.06	1.88 (1.49–2.39)	0.42	1.41 (1.27–1.56)	0.26
Ethnicity										
Asian	1.97 (1.33–2.93)	<0.01	1.49 (1.18–1.87)	<0.01	1.56 (1.22–1.98)	<0.01	1.58 (1.18–2.11)	0.04	1.37 (1.16–1.61)	<0.01
European	2.58 (0.49–13.43)	0.02	0.94 (0.66–1.36)	0.28	1.09 (0.78–1.54)	0.11	2.60 (0.59–11.49)	0.03	1.26 (0.73–2.18)	0.04
HWE										
≥0.05	2.03 (0.97–4.22)	0.01	1.22 (0.80–1.87)	0.01	1.36 (0.85–2.17)	0.00	1.34 (1.04–1.73)	0.06	1.33 (0.94–1.90)	0.05
<0.05	2.13 (1.69–2.70)	0.05	1.47 (1.27–1.70)	0.50	1.56 (1.35–1.79)	0.70	1.73 (1.39–2.15)	0.05	1.39 (1.26–1.54)	0.67

Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.
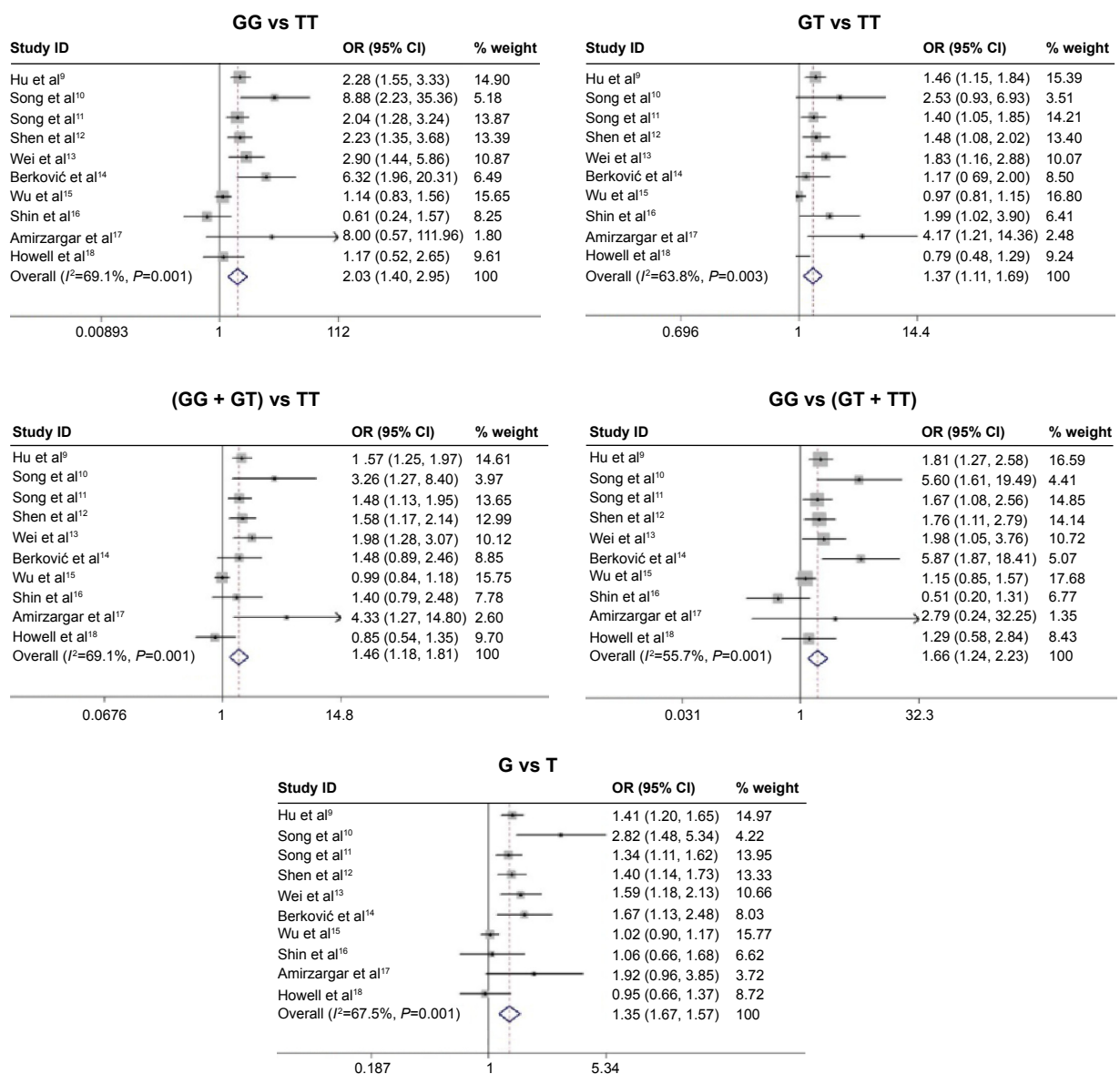
Figure 2 Forest plots representing the pooled results of ORs for the association between *IL-2* -330T/G polymorphism and overall cancer risk.
Note: Weights are from random effect analysis.
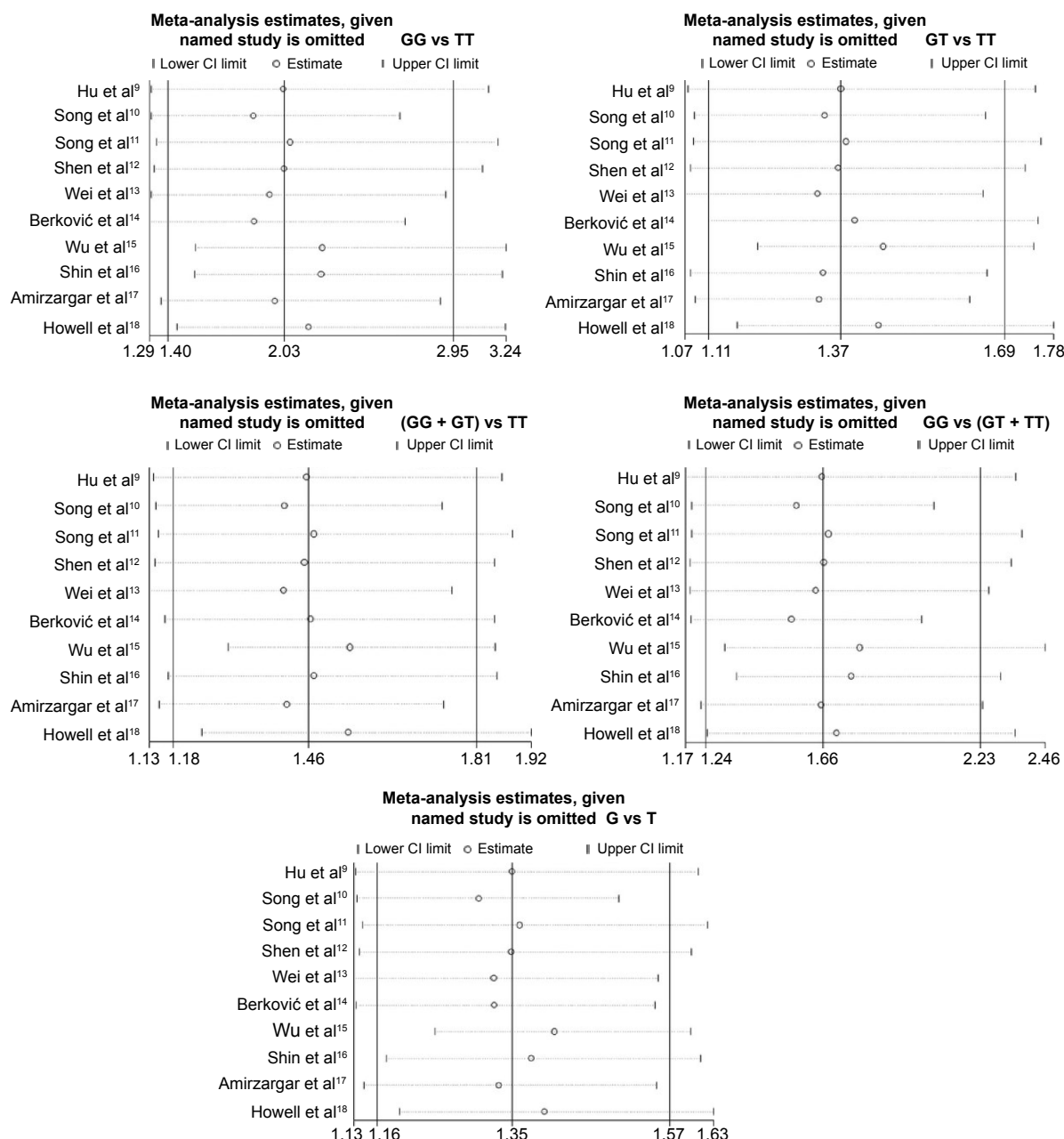**Abbreviations:** CI, confidence interval; OR, odds ratio.

Figure 3 The sensitivity analysis results of *IL-2* -330T/G polymorphism with overall cancer risk.
Abbreviation: CI, confidence interval.

analyses based on ethnicity and found a significant association in Asian, but not in European populations. This might reflect the fact that the development of cancer was associated with different genetic background in different ethnicities. Stratified analyses by P_{HWE} showed significant association in both $P_{HWE} < 0.05$ and $P_{HWE} \geq 0.05$, indicating that P_{HWE} status did not affect the relationship of *IL-2* -330T/G polymorphism with cancer risk.

Despite our great efforts to examine the association between *IL-2* -330T/G polymorphism and cancer risk, some

limitations should be considered. First, lack of the original data of included studies limited our precise evaluation of the association, which might cause information bias. Second, the included studies for subgroup analyses were limited. For example, there were only two studies included in the analysis of European population, which might limit our precise evaluation of risk factor. Third, our analysis did not consider the possibility of gene-environment interactions or the possibility of linkage disequilibrium between gene polymorphisms.
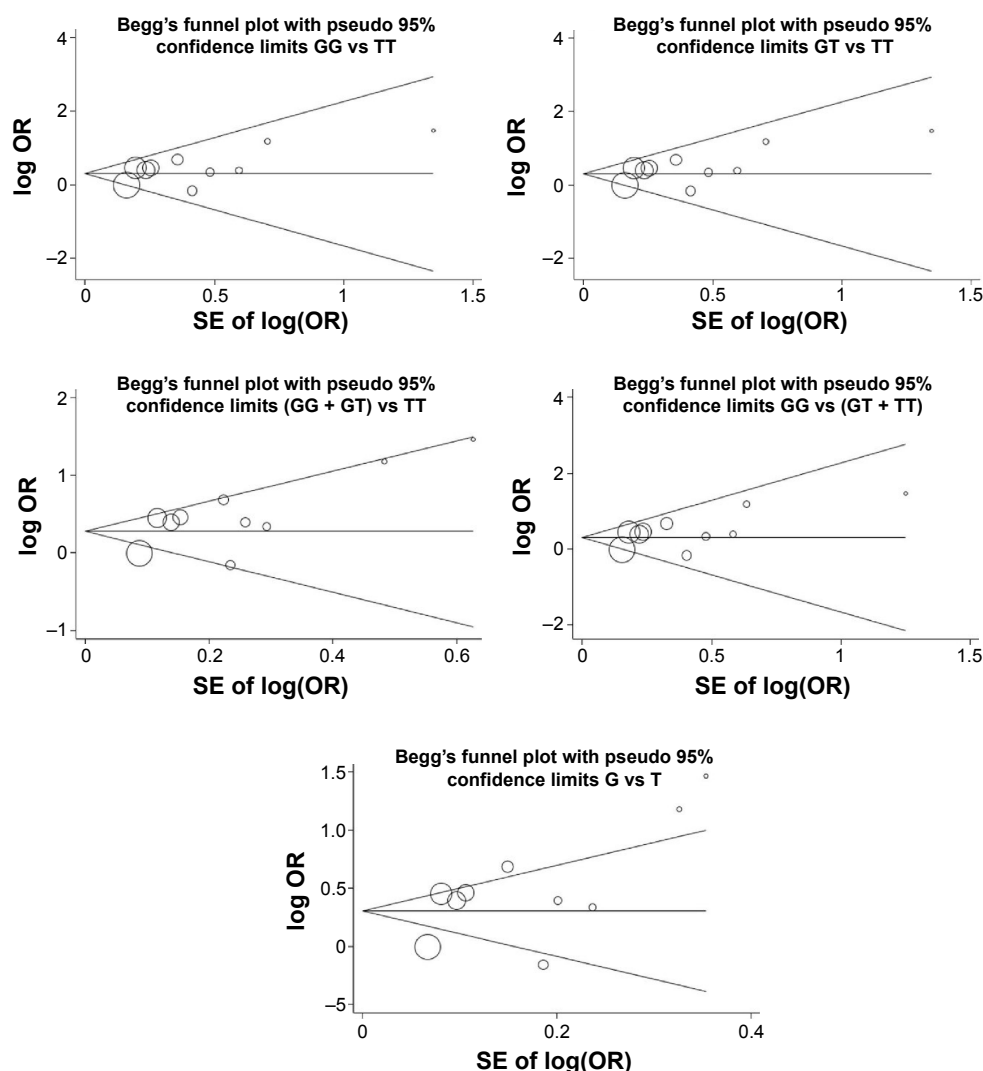
Figure 4 Begg's funnel plots of *IL-2* -330T/G polymorphism with overall cancer risk.
Abbreviations: OR, odds ratio; SE, standard error.

Conclusion

Our meta-analysis suggested that *IL-2* -330T/G polymorphism was a potentially risk factor for the development of cancer in Asian populations. However, due to the limitations mentioned above, further detailed studies are still required to confirm our findings.

Disclosure

The authors report no conflicts of interest in this work.

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