Association between two interleukin-2 gene polymorphisms and cancer susceptibility: a meta-analysis

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Background: Several epidemiological studies have illustrated that polymorphisms in interleukin-2 (IL-2) were associated with diverse cancer types. However, recently published statistics were inconsistent and inconclusive. Therefore, the current meta-analysis was performed to elaborate the effects of IL-2 polymorphisms (rs2069762 and rs2069763) on cancer susceptibility.

Material and methods: A total of 5,601 cancer cases and 7,809 controls from 21 published case–control studies were enrolled in our meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association between IL-2 polymorphisms and cancer susceptibility.

Results: Our study demonstrated an increased susceptibility to cancer in rs2069762 (G vs T: OR = 1.268, 95% CI = 1.113–1.445; GG vs TT: OR = 1.801, 95% CI = 1.289–2.516; GT vs TT: OR = 1.250, 95% CI = 1.061–1.473; GG + GT vs TT: OR = 1.329, 95% CI = 1.118–1.579; GG vs GT + TT: OR = 1.536, 95% CI = 1.162–2.030). In the subgroup analysis, increased susceptibility to cancer was identified in the hospital-based group and P_{HWE} < 0.05 (P-value of the Hardy–Weinberg equilibrium [HWE] group). In addition, a positive association with cancer susceptibility was observed among both Chinese and non-Chinese. However, no relationship was detected between the rs2069763 polymorphism of IL-2 and cancer susceptibility.

Conclusion: To conclude, rs2069762 polymorphism of IL-2 contributed to an increased susceptibility to cancer, whereas no association was identified between rs2069763 polymorphism and cancer susceptibility. Further detailed studies are warranted to confirm our findings.

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

Introduction

Based on available epidemiological statistics, cancer has been one of the most common causes of morbidity and mortality around the world.1 In the People’s Republic of China, the overall cancer incidence rate and death rate were 235 and 114.3 (per 100,000 population) in 2013, respectively.2 In the US, cancer is the second most common cause of death, and a total of 1,658,370 new cancer cases and 589,430 cancer deaths were expected to occur in 2015.3 Cancer is a heterogeneous disease due to the involvement of complicated risk factors. There is an increase in the evidence that implies that predisposition to cancer is related to cytokines,4 such as interleukin (IL).3 Studies suggested that accumulation of genetic variants may be implicated in carcinogenesis.5 Therefore, it would be of great importance to identify candidates for prevention and treatment of cancer.

IL-2 is an immunoregulatory cytokine produced by T helper type 1 cells when they are stimulated by mitogens, antigens, or major histocompatibility complexes...
on antigen-presenting cells. It is involved in the chemical activity of T-cell-assisted immune responses and the enhancement of natural killer cell cytolytic process as a growth factor. Medical scientists currently report that polymorphisms of IL-2 gene have been associated with susceptibility to a range of inflammation malfunctions and cancer, including gastric atrophy, rheumatoid arthritis, head and neck cancer, gastric cancer (GC), nasopharyngeal carcinoma, non-Hodgkin lymphoma, myelogenous leukemia, hepatocellular carcinoma (HCC), esophageal squamous cell carcinoma, breast cancer, and bladder cancer. Clinical studies had revealed that both specific and nonspecific antitumor immune responses can be augmented by transfecting IL-2 gene into tumor cells.

Human IL-2 gene is encoded on chromosome 4q26 with well-characterized single-nucleotide polymorphisms, among which one (−330T/G, rs2069762) has been identified in the promoter region and another (+114T/G, rs2069763) at position 114 from the initiation codon in the first exon. Studies on IL-2 gene polymorphisms demonstrated that they play significant roles in regulating the rate of inducible expression and secretion of IL-2. The association between single-nucleotide polymorphisms of IL-2 gene and susceptibility to inflammation-based cancers, such as HCC and GC, has been reported in previously published case–control studies. However, the findings were inconsistent and inconclusive because of the limited sample size. A quantitative synthesis to accumulate all currently available statistics from various studies may uncover evidence on the relationship between genetic polymorphisms and cancer susceptibility.

Although a meta-analysis of IL-2 rs2069762 polymorphism and cancer risk has already been published recently, there existed some drawbacks in that study. First, only one polymorphism of IL-2 was identified, although other polymorphisms may also contribute to cancer susceptibility. Second, only ten publications were enrolled and one of them was ineligible. The cases and controls of these studies were limited (3,060 cases and 3,435 controls). Third, it drew a conclusion that Hardy–Weinberg equilibrium (HWE) status did not affect the relationship of IL-2 rs2069762 polymorphism and cancer susceptibility, which may not be reliable. Fourth, we found that there existed publication bias among included publications after careful calculation. To avoid the abovementioned limitations, we conducted the present meta-analysis aiming to further evaluate the association of IL-2 rs2069763 and rs2069762 polymorphisms with overall cancer susceptibility in 12 publications with 1,556 cases/2,405 controls and 4,054 cases/5,405 controls, respectively.

Materials and methods

Search strategy

We conducted a comprehensive collection research by retrieving PubMed, Web of Science, and Google Scholar databases. The keywords of retrieve were (“IL-2” OR “interleukin-2”) AND (“polymorphism” OR “variant” OR “mutation”) in combination with (“cancer” OR “tumor” OR “carcinoma” OR “leukemia”) without language restriction. The research design was limited to humans. All eligible studies were inspected carefully.

Inclusion and exclusion criteria

Only those articles satisfying the following criteria were included: 1) studies that assessed the association between IL-2 polymorphisms and cancer susceptibility; 2) studies that were case–control or cohort in design; and 3) studies from which detailed genotype frequencies of cases and controls could be obtained directly or calculated from the available data. We excluded studies when they were 1) not case–control study, such as reviews, case reports, and comments; 2) articles without sufficient data of IL-2 genotype; and 3) duplicate data.

Quality assessment

The quality of the enrolled studies was examined independently by Xiuxiu Tan and Junjie Huang referring to the Newcastle–Ottawa scale, which evaluates the quality of nonrandomized studies by the selection of participants, comparability of groups, and exposure assessment. Disagreement was settled as described previously.

Data extraction

The details of each satisfied study were carefully filtered by three independent investigators (Meng Zhang, Xiuxiu Tan, and Junjie Huang). Any disagreements were resolved by discussion until a consensus was reached. The name of first author, the year of publication, ethnicity, source of control, genotyping method, the number of cases and controls, and the P-value of HWE in control groups were collected from each study.

Statistical analysis

The STATA 12.0 software program (Stata Corp, College Station, TX, USA) was used to perform this meta-analysis. The odds ratio (OR) and 95% confidence interval (CI) were
calculated to assess the association between *IL-2* gene polymorphisms and cancer susceptibility. Five different ORs were used to compute: allele contrast model (G vs T), dominant model (GG + GT vs TT), recessive model (GG vs GT + TT), heterozygote comparison (GT vs TT), and homozygote comparison (GG vs TT) (TT, homozygotes for the common allele; GT, heterozygotes; GG, homozygotes). We adopted chi-square test-based *Q* statistic test to assess the heterogeneity within the case–control studies. When the *Q*-test (*P* > 0.1) shows homogeneity across studies, we should choose the fixed effects model; otherwise, the random effects model should be selected. In addition, the effect of heterogeneity was quantified by the *I* value (*I*<25%: no heterogeneity; *I*=25%–50%: moderate heterogeneity; *I*=50%–75%: high heterogeneity; and *I>*75%: extreme high heterogeneity). We also measured the HWE of control groups. We applied stratification analyses on cancer type and ethnicity. Sensibility analysis was performed to assess the stability of the results by deleting one single case–control study each time from enrolled pooled data. In the end, the potential publication bias was evaluated by Begg’s funnel plot and Egger’s regression test. *P*<0.05 was considered as statistically significant.

**Result**

**Included studies’ identification and characteristics**

As shown in Figure 1, the literature research identified a total of 354 related publications. After reading the title and abstract, we reserved 18 articles concerning the association between *IL-2* polymorphisms and cancer susceptibility. Additional six publications were excluded since there were no data for *IL-2* polymorphisms or were duplicates or were about other *IL* polymorphisms. Finally, a total of 12 publications were enrolled. For *IL-2* rs2069763 polymorphism, a total of five publications with six case–control studies comprising 1,556 cases and 2,405 controls were enrolled, while 12 publications with 15 case–control studies comprising 4,045 cases and 5,404 controls were included for rs2069762 polymorphism.

As shown in Table 1, for the six studies of *IL-2* rs2069763 polymorphism, three were hospital-based designs and the others were population-based designs. In addition, three studies conformed to HWE while others did not. As for *IL-2* rs2069762 polymorphism, four studies were population-based and eleven were hospital based. Six conformed to HWE while others did not. When sorted by cancer type, there were two HCC studies, five GC studies, and eight other studies. In terms of the ethnic populations in these studies, nine were from the People’s Republic of China and six were non-Chinese.

**Results of pooled meta-analysis**

Tables 2 and 3 presented the results of meta-analysis, it demonstrated that no significant association between *IL-2* rs2069763 and cancer susceptibility was identified (Table 2, homozygous: OR = 1.039, 95% CI = 0.862–1.252; heterozygous: OR = 1.046, 95% CI = 0.888–1.232; recessive: 1.046, 95% CI = 0.888–1.232; homozygote comparison (GT vs TT), recessive model (GG vs GT + TT), heterozygote comparison (GT vs TT), and homozygote comparison (GG vs TT) (TT, homozygotes for the common allele; GT, heterozygotes; GG, homozygotes). We adopted chi-square test-based *Q* statistic test to assess the heterogeneity within the case–control studies. When the *Q*-test (*P* > 0.1) shows homogeneity across studies, we should choose the fixed effects model; otherwise, the random effects model should be selected. In addition, the effect of heterogeneity was quantified by the *I* value (*I*<25%: no heterogeneity; *I*=25%–50%: moderate heterogeneity; *I*=50%–75%: high heterogeneity; and *I>*75%: extreme high heterogeneity). We also measured the HWE of control groups. We applied stratification analyses on cancer type and ethnicity. Sensibility analysis was performed to assess the stability of the results by deleting one single case–control study each time from enrolled pooled data. In the end, the potential publication bias was evaluated by Begg’s funnel plot and Egger’s regression test. *P*<0.05 was considered as statistically significant.

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Table 1 Characteristics of eligible studies in this meta-analysis

| SNP    | Reference | Year | Ethnicity | Genotyping method | Source of control | Cancer type          | Case     | Control |
|--------|-----------|------|-----------|-------------------|-------------------|----------------------|----------|---------|
|         |           |      |           |                   |                   |                      |          |         |
| rs2069763 | Peng et al | 2014 | Chinese   | PCR-RFLP          | HB                | HCC                  | 21 56 30 | 78 117 92 | 0.002  N |
|         | Wei et al  | 2010 | Chinese   | PCR-RFLP          | NP                | HCC                  | 40 93 47 | 57 99 44  | 0.935  Y  |
|         | Song et al | 2012 | Chinese   | PCR-RFLP          | HB                | NHL                  | 128 220 90 | 138 240 104 | 0.985  Y  |
|         | Savage et al | 2004 | Chinese   | PCR              | PB                | GCC                  | 14 35 33 | 80 148 149 | 0.002  N  |
|         | Savage et al | 2004 | Chinese   | PCR              | PB                | ESCC                 | 26 41 44 | 80 148 149 | 0.002  N  |
|         | Hu et al  | 2013 | Chinese   | PCR              | HB                | Breast cancer        | 187 320 131 | 197 342 143 | 0.809  Y  |
| rs2069762 | Bei et al | 2014 | Chinese   | PCR              | HB                | HCC                  | 292 333 95 | 311 373 100 | 0.469  Y  |
|         | Peng et al | 2014 | Chinese   | PCR-RFLP         | HB                | HCC                  | 47 54 6  | 101 158 28  | 0.003  N  |
|         | Wei et al  | 2010 | Chinese   | PCR-RFLP         | NP                | HCC                  | 46 106 28 | 81 102 17  | 0.054  Y  |
|         | Song et al | 2012 | Korean    | GOPA             | HB                | CL                   | 7 11 5   | 87 54 7    | 0.706  Y  |
|         | Song et al | 2012 | Chinese   | PCR-RFLP         | NLH               |                      | 136 246 56 | 193 250 39 | 0       N     |
|         | Amirzargar et al | 2005 | Iranian   | PCR-SSP          | PB                | CML                  | 4 24 2   | 16 23 1    | 0.032  N  |
|         | Berkovic et al | 2010 | Caucasian | PCR              | PET               |                      | 21 17 8  | 83 63 4    | 0.047  N  |
|         | Berkovic et al | 2010 | Caucasian | PCR              | HB                | GI-NET               | 25 24 6  | 83 63 4    | 0.047  N  |
|         | Berkovic et al | 2010 | Caucasian | PCR              | PB                | GI-NET               | 25 24 6  | 83 63 4    | 0.047  N  |
|         | Savage et al | 2004 | Chinese   | PCR              | PB                | GCC                  | 20 47 16 | 109 174 96 | 0.116  Y  |
|         | Savage et al | 2004 | Chinese   | PCR              | PB                | ESCC                 | 33 43 35 | 109 174 96 | 0.116  Y  |
|         | Hu et al  | 2013 | Chinese   | PCR              | HB                | Breast cancer        | 192 357 89 | 275 351 56 | 0       N     |
|         | Shin et al | 2008 | Korean    | PCR              | PB                | Gastric cancer       | 79 35 8  | 72 16 12   | 0       N     |
|         | Shen et al | 2012 | Chinese   | PCR              | PB                | Bladder cancer       | 109 205 51 | 157 200 33 | 0.005  N  |
|         | Wu et al  | 2009 | Chinese   | PCR              | PB                | Gastric cancer       | 491 441 94 | 516 480 87 | 0.091  Y  |

Notes: $P_{HWE}>0.05$, polymorphisms conformed to HWE in the control group and $P_{HWE}\leq0.05$, polymorphisms did not conform to HWE in the control group.

Abbreviations: SNP, single-nucleotide polymorphism; HWE, Hardy–Weinberg equilibrium; Y, $P_{HWE}>0.05$; N, $P_{HWE}\leq0.05$; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HB, hospital based; HCC, hepatocellular carcinoma; NP, nasopharyngeal; NHL, non-Hodgkin lymphoma; PCR, polymerase chain reaction; PB, population based; GCC, gastric cancer; ESCC, esophageal squamous cell carcinoma; Tag, Tag algorithm; CL, childhood lymphoma; PCR-SSP, polymerase chain reaction–sequence-specific primers; CML, chronic myelogenous leukemia; GEP-NET, gastroenteropancreatic neuroendocrine tumor; PET, pancreatic endocrine tumor; GI-NET, gastrointestinal neuroendocrine tumor; GOPA, GoldenGate™ oligonucleotide pool assay.

Specifically, the analysis indicated that non-Chinese population suffered more risk from this polymorphism (G vs T: OR=1.162–2.030). In the subgroup meta-analysis by ethnicity, the rs2069762 polymorphism was observed with positive association with cancer susceptibility among both Chinese and non-Chinese. Specifically, the analysis indicated that non-Chinese population suffered more risk from this polymorphism (G vs T: OR=1.165–2.097; GG vs TT: OR=1.302–2.079; Figure 2; GT vs TT: OR=1.250, 95% CI=1.061–1.473; GG+GT vs TT: OR=1.329, 95% CI=1.118–1.579; GG vs GT + TT: OR=1.536, 95% CI=1.162–2.030).

Result of subgroup

Tables 2 and 3 also show the outcomes of subgroup analysis. The data in Table 2 suggested that rs2069763 polymorphism of IL-2 has no significant association with cancer susceptibility in the subgroups sorted by either source of controls or $P_{HWE}$. However, as for rs2069762 polymorphism (Table 3), it demonstrated an increased susceptibility to cancer in the hospital-based studies (G vs T: OR=1.1268, 95% CI=1.113–1.445; GG vs TT: OR=1.801, 95% CI=1.289–2.516, Figure 2; GT vs TT: OR=1.250, 95% CI=1.061–1.473; GG+GT vs TT: OR=1.329, 95% CI=1.118–1.579; GG vs GT + TT: OR=1.536, 95% CI=1.162–2.030) and the $P_{HWE}<0.5$ group (G vs T: OR=1.341, 95% CI=1.151–1.561 and GG vs TT: OR=1.218–9.161, Figure 4; GT vs TT: OR=1.438, 95% CI=1.058–1.954, Figure 5; GT vs TT: OR=1.180, 95% CI=0.982–1.418; GG + GT vs TT: OR=1.223, 95% CI=1.003–1.490; and GG vs GT + TT: OR=1.302, 95% CI=1.040–1.629). However, no relationship was identified between the rs2069762 polymorphism of IL-2 and cancer susceptibility within a certain type of cancer.
Table 2 Results of meta-analysis for rs2069763 polymorphism in IL-2 and cancer susceptibility

| Variables (rs2069763) | Case/control | OR (95% CI) | P-value* | P (%) | OR (95% CI) | P-value* | P (%) | OR (95% CI) | P-value* | P (%) |
|-----------------------|--------------|-------------|----------|-------|-------------|----------|-------|-------------|----------|-------|
| Total                 | 1.556/2.405  | G vs T     | 0.983 (0.895–1.079) | 0.748 | 0.0 | 1.039 (0.862–1.252) | 0.701 | 0.0 | 1.046 (0.888–1.232) | 0.803 | 0.0 |
| Source of control     |              |             |          |       |             |          |       |             |          |       |
| HB                    | 1.363/1.651  | 0.984 (0.888–1.090) | 0.511 | 0.0 | 1.039 (0.844–1.278) | 0.484 | 0.0 | 1.060 (0.881–1.275) | 0.551 | 0.0 |
| PB                    | 193/754      | 0.980 (0.780–1.231) | 0.538 | 0.0 | 1.040 (0.677–1.598) | 0.460 | 0.0 | 0.995 (0.697–1.420) | 0.723 | 0.0 |
| HWE                   |              |             |          |       |             |          |       |             |          |       |
| Y                     | 1.256/1.364  | 0.990 (0.888–1.104) | 0.336 | 8.3 | 0.981 (0.788–1.222) | 0.334 | 8.9 | 1.010 (0.829–1.232) | 0.803 | 0.0 |
| N                     | 300/1.041    | 0.963 (0.801–1.159) | 0.800 | 0.0 | 0.916 (0.642–1.308) | 0.704 | 0.0 | 1.128 (0.842–1.511) | 0.453 | 0.0 |
| Total                 | 1.556/2.405  | GG vs GT vs TT | 1.060 (0.912–1.230) | 0.440 | 0.0 | 0.972 (0.835–1.133) | 0.962 | 0.0 |
| Source of control     |              |             |          |       |             |          |       |             |          |       |
| HB                    | 1.363/1.651  | 1.064 (0.905–1.250) | 0.277 | 22.2 | 0.963 (0.807–1.148) | 0.820 | 0.0 |
| PB                    | 193/754      | 1.036 (0.701–1.532) | 0.334 | 0.0 | 1.002 (0.737–1.363) | 0.838 | 0.0 |
| HWE                   |              |             |          |       |             |          |       |             |          |       |
| Y                     | 1.256/1.364  | 1.024 (0.864–1.214) | 0.377 | 0.0 | 0.993 (0.822–1.199) | 0.962 | 0.0 |
| N                     | 300/1.041    | 1.188 (0.866–1.632) | 0.321 | 12.0 | 0.935 (0.722–1.212) | 0.708 | 0.0 |

Notes: P: 0–25, means no heterogeneity; 25–50, means modest heterogeneity; and >50, means high heterogeneity; Y: polymorphisms conformed to HWE in the control group; N: polymorphisms did not conform to in the control group. P-value of Q-test for heterogeneity test. *Statistically significant (P < 0.05). Five different ORs were used to compute: allele contrast model (G vs T), dominant model (GG + GT vs TT), recessive model (GG vs GT + TT), heterozygote comparison (GT vs TT), and homozygote comparison (GG vs TT). (TT, heterozygotes for the common allele; GT, heterozygotes; GG, homozygotes).

Abbreviations: OR, odds ratio; HB, hospital based; PB, population based; HWE, Hardy–Weinberg equilibrium; Y: P<0.05; N: P<0.05.

Table 3 Results of meta-analysis for rs2069762 polymorphism in IL-2 and cancer susceptibility

| Variables (rs2069762) | Case/control | OR (95% CI) | P-value* | P (%) | OR (95% CI) | P-value* | P (%) | OR (95% CI) | P-value* | P (%) |
|-----------------------|--------------|-------------|----------|-------|-------------|----------|-------|-------------|----------|-------|
| Total                 | 4.045/5.404  | G vs T     | 1.268 (1.113–1.445)* | 0.000 | 70.6 | 1.801 (1.289–2.516)* | 0.000 | 74.9 | 1.250 (1.061–1.473)* | 0.002 | 58.7 |
| Cancer type           |              |             |          |       |             |          |       |             |          |       |
| GC                    | 1.387/1.862  | 1.169 (0.948–1.442) | 0.087 | 50.8 | 1.549 (0.783–3.064) | 0.005 | 72.9 | 1.193 (0.923–1.541) | 0.191 | 34.6 |
| HCC                   | 827/1.071    | 0.899 (0.694–1.165) | 0.138 | 54.5 | 0.778 (0.375–1.612) | 0.123 | 58.0 | 0.908 (0.745–1.105) | 0.323 | 0.0 |
| Source of control     |              |             |          |       |             |          |       |             |          |       |
| HB                    | 3.456/4.216  | 1.286 (1.095–1.511)* | 0.000 | 76.0 | 1.950 (1.279–2.971)* | 0.000 | 79.7 | 1.220 (1.017–1.464)* | 0.005 | 60.0 |
| PB                    | 589/1.188    | 1.232 (0.998–1.537) | 0.145 | 44.5 | 1.493 (0.872–2.556) | 0.092 | 53.4 | 1.383 (0.896–2.136) | 0.063 | 58.9 |
| HWE                   |              |             |          |       |             |          |       |             |          |       |
| Y                     | 2.143/2.973  | 1.172 (0.971–1.415) | 0.003 | 71.6 | 1.410 (0.953–2.085) | 0.007 | 68.5 | 1.144 (0.897–1.459) | 0.122 | 42.5 |
| N                     | 1.902/2.431  | 1.341 (1.151–1.561)* | 0.030 | 53.0 | 2.156 (1.326–3.507)* | 0.001 | 70.1 | 1.337 (1.109–1.613)* | 0.127 | 36.4 |
| Ethnicity             |              |             |          |       |             |          |       |             |          |       |
| Chinese               | 3.668/4.666  | 1.162 (1.013–1.332)* | 0.000 | 74.2 | 1.438 (1.058–1.954)* | 0.000 | 72.1 | 1.180 (0.982–1.418) | 0.002 | 67.7 |
| Non-Chinese           | 377/738      | 1.652 (1.302–2.097)* | 0.254 | 23.9 | 4.264 (1.506–12.069)* | 0.003 | 72.3 | 1.525 (1.089–2.316)* | 0.278 | 20.7 |
| Total                 | 4.045/5.404  | GG + GT vs TT | 1.329 (1.118–1.579)* | 0.000 | 66.4 | 1.536 (1.162–2.030)* | 0.000 | 68.8 |

(Continued)
Sensitivity analysis and publication bias

We executed a sensitivity analysis to assess the influence of separate study on the pooled ORs by excluding one single study each time and a negative result was achieved (Figure 6). We detected publication bias through Begg’s funnel plot and Egger’s test. As shown in Figure 7, significant publications bias was revealed for rs2069762 (Egger’s test $P=0.005$), while no obvious bias was identified for rs2069763 (Egger’s test $P=0.146$). Therefore, trim and fill method was conducted for rs2069762 to further evaluate the publication bias. As shown in Figure 8, four theoretical studies were added and no significant difference was obtained ($P<0.05$), proving the stability of our results. The quality of enrolled studies is presented in Table 4.

Discussion

The association between IL-2 gene polymorphisms and susceptibility to various cancers are widely discussed these days. Unfortunately, the results are inconsistent and inconclusive. A recent meta-analysis concerning the association between rs2069762 polymorphism of IL-2 and cancer susceptibility was published, and their results suggested that IL-2 rs2069762 polymorphism was significantly associated with cancer risk. However, several limitations should be noted for this study. First, the investigators only enrolled ten publications for rs2069762 polymorphism, including ten case–controls comprising of 3,060 cases and 3,435 controls.34 However, one unqualified publication was enrolled,35 which adopted samples instead of blood tissues, distinguishing it from other enrolled studies and potentially contributing to bias. In the present work, we excluded this publication and added another three publications. We detected a total of 12 publications, including 15 case–controls comprising of 4,045 cases and 5,404 controls. Second, we also enrolled another IL-2 polymorphism (rs2069763), with five publications containing six case–control studies comprising of 1,556 cases and 2,405 controls, which broadened the scope of analysis. Third, the subgroup analysis sorted by $P_{\text{HWE}}$ in previous meta-analysis showed that $P_{\text{HWE}}$ status did not affect the correlation between IL-2-330T/G polymorphism and cancer susceptibility. Nevertheless, in our study, a significant association was found between $P_{\text{HWE}}<0.05$ group and cancer susceptibility, while no association was identified between $P_{\text{HWE}}\geq0.05$ group and cancer susceptibility. Our work demonstrated that the $P_{\text{HWE}}$ status had a great effect on the pooled ORs. Although no publication bias was found in the previous study, when we excluded the ineligible study from the pooled data and assessed again, significant publication bias was uncovered.35

### Table 3 (Continued)

| Variables (rs2069762) | Case/control | OR (95% CI) | $P$-value* | OR (95% CI) | $P$-value* |
|-----------------------|--------------|-------------|------------|-------------|------------|
| Cancer type           |              |             |            |             |            |
| GC                    | 1.879/1071   | 1.310 (1.074–1.599) | 0.140   | 2.070 (0.936–1.557) | 0.000   |
| HCC                   | 1.565/1071   | 1.310 (1.074–1.599) | 0.140   | 2.070 (0.936–1.557) | 0.000   |
| Sources of control    |              |             |            |             |            |
| GC                    | 1.879/1071   | 1.310 (1.074–1.599) | 0.140   | 2.070 (0.936–1.557) | 0.000   |
| HCC                   | 1.565/1071   | 1.310 (1.074–1.599) | 0.140   | 2.070 (0.936–1.557) | 0.000   |
| Ethnicity             |              |             |            |             |            |
| Chinese               | 1.231/1071   | 1.310 (1.074–1.599) | 0.140   | 2.070 (0.936–1.557) | 0.000   |
| Non-Chinese           | 1.902/1071   | 1.310 (1.074–1.599) | 0.140   | 2.070 (0.936–1.557) | 0.000   |

Notes: $F<0.25$, means highly heterogeneity; $>0.50$, means high homogeneity; $>0.80$, means very high homogeneity; $>0.85$, means very high homogeneity. Five different ORs were used to compute: allele contrast model (G vs T), dominant model (GG + Gg vs TT), recessive model (gg vs gT + TT), heterozygote comparison (gT vs TT), and homozygote comparison (gg vs TT) (TT, homozygotes for the common allele; gT, heterozygotes; gg, homozygotes).

Abbreviations: OR, odds ratio; GC, gastric cancer; HCC, hepatocellular carcinoma; HWE, Hardy–Weinberg equilibrium; Y, polymorphisms conformed to HWE in the control group; n, polymorphisms did not conform to HWE in the control group.

OncoTargets and Therapy 2016:9
Figure 2 OR estimates with the corresponding 95% CI for the association of IL-2 rs2069762 polymorphism with overall cancer risk (GG vs TT); the sizes of the squares represent the weighting of included studies.

Note: Weights are from random effect analysis.

Abbreviations: OR, odds ratio; IL-2, interleukin-2.

Figure 3 OR estimates with the corresponding 95% CI for the association of IL-2 rs2069762 polymorphism with overall cancer risk (GG + GT vs TT) in the subgroups sorted by the source of control; the sizes of the squares represent the weighting of included studies.

Note: Weights are from random effect analysis.

Abbreviations: OR, odds ratio; IL-2, interleukin-2; HB, hospital-based; PB, population-based.
Figure 4 OR estimates with the corresponding 95% CI for the association of IL-2 rs2069762 polymorphism with overall cancer risk (GG vs TT) in the subgroups of PhWe<0.05; the sizes of the squares represent the weighting of included studies.

Note: Weights are from random effect analysis.

Abbreviations: OR, odds ratio; IL-2, interleukin-2; Y, PhWe>0.05; N, PhWe<0.05.

Figure 5 OR estimates with the corresponding 95% CI for the association of IL-2 rs2069762 polymorphism with overall cancer risk (GG vs TT) in the subgroups sorted by ethnic lines; the sizes of the squares represent the weighting of included studies.

Note: Weights are from random effect analysis.

Abbreviations: OR, odds ratio; IL-2, interleukin-2.
Although we have conducted a comprehensive retrieve and revised the disadvantages of the previous study, there are still several limitations that should be noted. First, since cancer is considered a multifactorial disease with interactions between multiple environmental exposures and individual genetic backgrounds, we failed to analyze the gene–gene and gene–environment effects in this study due to insufficient data. Second, most of the included studies were conducted in

Figure 6 Sensibility analysis in studies of the association between the IL-2 rs2069762 polymorphism and cancer susceptibility assessed by deleting one single case–control study at each time from inclusion pooled.

**Abbreviation:** IL-2, interleukin-2.

Figure 7 Publication bias in studies of the association between the IL-2 rs2069762 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test.

**Abbreviations:** Log(OR), the natural logarithm of the odds ratio; IL-2, interleukin-2; SE, standard error.

Figure 8 Publication bias in studies of the association between the IL-2 rs2069762 polymorphism and cancer susceptibility after the trim and fill method was assessed by Begg's funnel plot and Egger's test.

**Abbreviation:** SE, standard error.
| Author          | Ethnicity | Adequacy of case definition | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases/controls | Ascertainment of exposure | Same method of ascertainment | Nonresponse rate |
|-----------------|-----------|-----------------------------|--------------------------------|-----------------------|------------------------|-----------------------------|--------------------------|-------------------------------|------------------|
| Peng et al 12   | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Wei et al 10    | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Song et al 8    | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Savage et al 11 | Chinese   | *                           | *                              | *                     | NA                     | **                         | *                        |                               |                  |
| Hu et al 29     | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Bei et al 9     | Chinese   | *                           | *                              | NA                    | NA                     | **                         | *                        |                               |                  |
| Peng et al 12   | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Wei et al 10    | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Nan et al       | Korean    | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Song et al 29   | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Amirzargar et al 13 | Iranian | *                           | *                              | *                     | NA                     | **                         | *                        |                               |                  |
| Berković et al 10 | Caucasian | *                           | *                              | NA                    | NA                     | **                         | *                        |                               |                  |
| Savage et al 11 | Chinese   | *                           | *                              | *                     | NA                     | **                         | *                        |                               |                  |
| Hu et al 29     | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Shin et al 17   | Korean    | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |
| Shen et al 7    | Chinese   | *                           | *                              | *                     | *                      | **                         | *                        |                               |                  |
| Wu et al 10     | Chinese   | *                           | *                              | NA                    | *                      | **                         | *                        |                               |                  |

Notes: This table identifies “high”-quality choices with a “star.” A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability.

Abbreviation: NA, not applicable.
the Asian and Caucasian populations, thus, the conclusions may barely adapt to these populations. Further studies within different ethnic groups, such as Africans and Latinos, are warranted. Last but not least, the limited number of studies included in the meta-analysis may result in low statistical power to obtain an ideal precision of the pooled estimates.

Conclusion
In conclusion, our meta-analysis suggested that there is no association between rs2069763 polymorphism of IL-2 and cancer susceptibility, whereas an increased susceptibility to cancer was uncovered for rs2069762 polymorphism. Further well-designed studies are still warranted to further exclude the influence of $P_{\text{HWE}}$ < 0.05 and hospital-based groups on cancer susceptibility.

Disclosure
The authors report no conflicts of interest in this work.

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