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*Original Article*

# Associations between interleukin-17A (G/-197A) polymorphism and cancer susceptibility: a systematic review and meta-analysis of 30 case-control studies

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**Abstract:** Background: A number of previous case-control studies have reported the associations between Interleukin-17 (IL-17) A (G/-197A) polymorphism and risk of cancer. However, the results remained to be not consistent. We performed a meta-analysis to detect the susceptibility that IL-17A (G/-197A) polymorphism contributes to cancer. Method: We conducted a comprehensive research via the electricity databases of PubMed, Embase, Web of Science, CBM and CNKI to identify eligible literatures published up to November, 2015. Totally, 30 case-control studies with 8652 cases and 10699 controls were satisfied our inclusion criterias. A calculating pooled odds ratio (OR) was applied to evaluate the degree of candidate associations. Calculating evidences of these associations were estimated and enhanced by a sensitivity analyses, a test of publication bias and a false-positive report probability (FPRP). Result: In overall analysis, a significant correlation was observed between IL-17A (G/-197A) polymorphism and cancer potential susceptibility. Furthermore, stratified analysis based on subgroups indicated that IL-17A (G/-197A) polymorphism showed a closely relationship with an increased cancer risk in gastric cancer and cervical cancer, but not in colorectal cancer in subgroup of cancer types. And a higher susceptibility was found in Asian population compared with Caucasian population. Conclusion: Our present meta-analysis suggested that a significant relationship exists between IL-17A (G/-197A) polymorphism and cancer potential susceptibility as 30 studies are pooled together.

**Keywords:** Interleukin-17A, cancer susceptibility, gene polymorphism, meta-analysis

## Introduction

It is well established that cancer is one of the most common causes of death in the worldwide. About 14.0 million patients are diagnosed with various types of cancer, and almost half of the cases die of this extremely fatal disease per year [1]. Large numbers of researches have identified that biological and genetic factors play a crucially important role in the morbidity of cancer [2-4], moreover, each type of cancer has their own specific susceptible factors, such as Helicobacter pylori infection for gastric cancer, chronic hepatitis B virus infection for hepatocellular carcinoma, Philadelphia chromosome for chronic myeloid leukemia and so on. Recently, accumulating data have demonstrated that a variety of inflammatory cytokines are involved in the occurrence and development of cancer [5-7], which may provide a novel explanation of tumorigenesis in inflammatory-related malignancy.

IL-17, also named as CTLA-8, is a proinflammatory cytokine family mainly produced by Th-17 cells and neutrophils, which consists of six members as IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. All the members are encoded by homologous genes and have similar biological functions. Significant effects of IL-17 on autoimmune disease, for example, Sjogren's syndrome [8] and rheumatiod [9], were confirmed during the past few decades. In addition, a lot of evidences from recent studies showed that overexpression of IL-17 levels correlated with advanced cancer stage [10, 11]. Furthermore,

IL-17 was identified to be a lead cause in carcinogenesis, which facilitated the proliferation [12], migration and invasion [13], drug resistance of cancer cells [14] to promote tumor progression. However, the concrete mechanism remains poorly understood.

Epidemiological studies have confirmed the important genetic functions of single nucleotide polymorphism (SNP) in cancer susceptibility [15, 16]. Since the first paper focused on the relationship between IL-17A (G/-197A) polymorphism and gastric cancer in 2009 by Tomoyuki shibata [17], many similar publications were conducted to investigate its associations with multitype of cancers. Although each eligible case-control study provided a specific conclusion, however, the results were not consistent. Some literatures indicated a significant positive correlation between IL-17A (G/-197A) polymorphism and the risk of cancer, but various opinions were observed in the other researches. These different findings have suggested one limitation of an individual study. Therefore, we set out to conduct a meta-analysis, as a powerful tools, to explore IL-17A (G/-197A) polymorphism associated with cancer potential susceptibility.

## Materials and methods

### *Search strategy*

We performed a comprehensive search from the databases of PubMed, Embase, Web of Science, Chinese Biomedical Literature Database (CBM) and China National Knowledge Infrastructure (CNKI) up to November 2015. The following search string was used: "[IL-17A (-197G/A) or interleukin-17A (-197G/A)] and [cancer or carcinoma or neoplasm] and [polymorphism or variant or mutation]". Conference papers were manually retrieved from the Third Military Medical University Library.

### *Inclusion criteria*

The eligible studies were included according to the following criteria: (1) The association between IL-17A (-197G/A) gene polymorphism and cancer risk was investigated; (2) Patient groups were diagnosed as cancer; (3) Studies must focus on human and the frequence of genotype was available; (4) Sufficient data to calculate odds ratio (OR) and 95% confidence interval (CI).

### *Exclusion criteria*

The main exclusive criteria were: (1) Studies not concerning IL-17A (-197G/A) gene polymorphism and cancer susceptibility; (2) Non-case-control studies and duplicate publications; (3) Abstracts, case reports and review articles; (4) Insufficient data on the distribution of IL-17A (-197G/A) genotypes.

### *Data extraction*

The first author, year of publication, type of cancer, ethnicity, sources of the control groups, genotyping methods, genotype frequencies of patients and controls, and HWE test results of control group were extracted from all of the available publications by two independent researchers (Yu-xing Jiang and Gao-ming Li). Any disagreements were resolved through consulting with a third researcher, and the consensus was reached through discussions.

### *Statistical analysis*

The odds ratios (OR) and 95% confidence intervals (CI) were used as efficacy indicators in this meta-analysis. $P<0.05$ was considered statistically significant. We used the allele model (A vs. G), dominant model (AA/AG vs. GG), recessive model (AA vs. GG/AG), homozygous comparison (AA vs. GG) and heterozygous model (AG vs. GG) in this study. The statistical significance of the pooled ORs were tested by Z-test, and the significance level was $P<0.05$. HWE was estimated by chi-square test in the control group. Heterogeneity was evaluated by Cochrane Q test and $P<0.10$ was considered significant. Pooled ORs were calculated using a fixed effect model (Mantel-Haenszel method) or random effect model (DerSimonian-Laird method) according to the absence ($P>0.10$ and $I^2<50\%$) or presence ($P<0.10$ or $I^2>50\%$) of heterogeneity. To detect further associations and explore the possible sources of heterogeneity, subgroup analysis was performed based on the cancer type, ethnicity, source of control groups and genotyping method. For evaluating the stability of the results, the sensitivity analyses were conducted. The potential publication bias was analyzed by Begg's funnel plots and Egger's test. Stata 11.0 (Stata Corporation, College

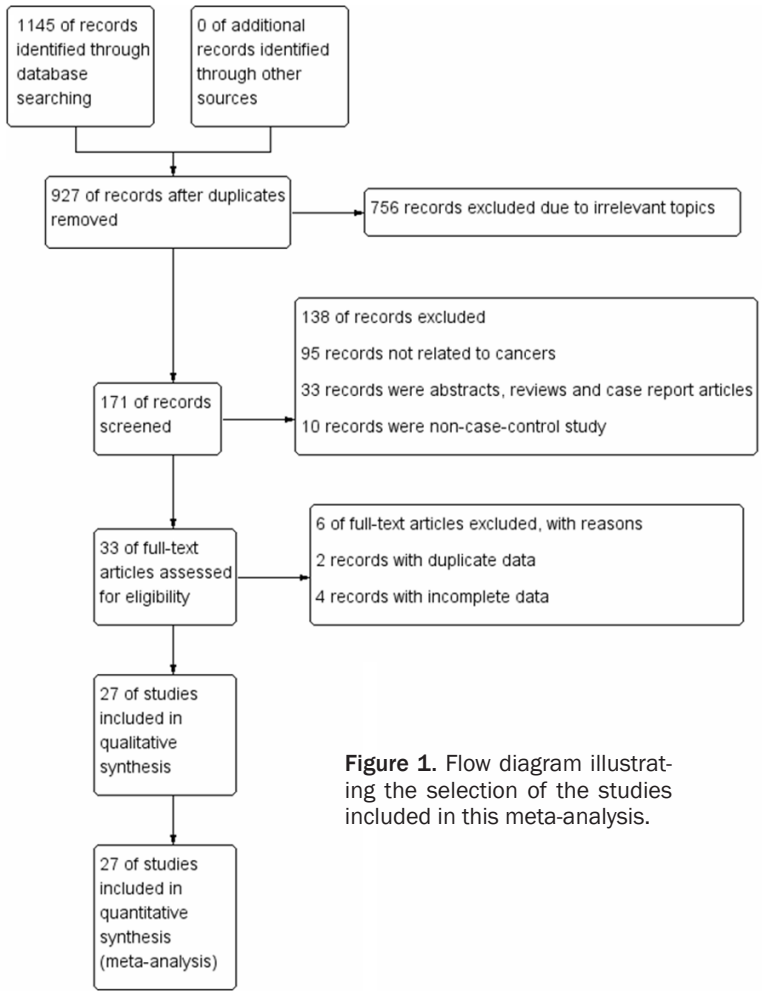


**Figure 1.** Flow diagram illustrating the selection of the studies included in this meta-analysis.

Station, TX, USA) software was used for the meta-analysis.

The method reported by Wacholder et al [18] was applied to estimate the FPRP values of each statistically significant association. A priority probability of 0.001 was set to detect an odds ratio (OR) of the researched genotype of 1.5. FPRP less than 0.2 was considered as a significant association. Excel spreadsheet provided by Wacholder et al. [18] was used to calculate the statistical power and FPRP values.

## Results

*Literature research and meta-analysis databases*

In the primary search, 1145 eligible publications focusing on Interleukin-17A (G/-197A) polymorphism with respect to cancer susceptibility were identified. There were 927 displayed after duplicated removed. Subsequently, 756 were excluded because of their irrelevant topics. 138 were excluded due to the thesis, of them, 95 were not related to malignant tumor, 43 were abstracts, reviews and case report articles, 10 were non-case-control studies. Furthermore, 6 records with overlapped or incomplete data were removed from the presented 33 papers. At last, a total of 27 articles [17, 19-44] with 30 case-control studies were selected for this meta-analysis, including 8652 cases and 10699 controls (**Figure 1**). Among these investigations, 13 were conducted for gastric cancer, 4 for colorectal cancer, 2 for cervical cancer, 2 for ovarian cancer, 2 for hepatocellular carcinoma, and one study for papillary thyroid cancer, esophageal cancer, lung cancer, breast cancer, acute myeloid leukemia, bladder cancer, oral squamous cell carcinoma, respectively. All the cases were confirmed by pathological diagnosis and the whole main characteristics from each paper were summarized in **Table 1**.

*Quantitative data synthesis*

All of the results from this study were presented in **Table 2**. Overall meta-analysis indicated a significant positive association between IL-17A (G/-197A) polymorphism and cancer susceptibility in all genetic models (A vs. G: OR=1.18, 95% CI=1.10-1.26, *P*<0.001; AA/AG vs. GG: OR=1.18, 95% CI=1.08-1.29, *P*=0.002; AA vs. GG/AG: OR=1.34, 95% CI=1.16-1.54, *P*<0.001; AA vs. GG: OR=1.40, 95% CI=1.21-1.62, *P*<0.001; AG vs. GG: OR=1.10, 95% CI=1.00-1.22, *P*=0.001). Furthermore, FPRP values of allele model (FPRP=0.001), recessive model (FPRP=0.001) and homozygous comparison (FPRP=0.038) were less than 0.2 at the prespecified prior probability of 0.001, suggesting that these results were worthy of attention.

**Table 1.** Basic characteristics from included studies selected for this meta-analysis

| Author | Year | Country | Type of carcinoma | Source of controls | Genotyping method | Cases | | | Controls | | | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | AA | AG | GG | AA | AG | GG | |
| Tomoyuki Shibata | 2009 | Japan | Gastric cancer | HB | PCR-SSCP | 69 | 124 | 94 | 49 | 299 | 175 | <0.01 |
| Xiaoqin Wu | 2010 | China | Gastric cancer | PB | PCR-RFLP | 250 | 485 | 210 | 204 | 371 | 193 | 0.35 |
| Chen JJ | 2010 | China | Gastric cancer | PB | TaqMan | 220 | 522 | 300 | 224 | 541 | 325 | 0.97 |
| Tomiyasu Arisawa | 2012 | Japan | Gastric cancer | HB | PCR-SSCP | 84 | 137 | 112 | 72 | 293 | 218 | 0.08 |
| Lihong Wang | 2012 | China | Breast cancer | PB | SNaPshot | 92 | 234 | 165 | 58 | 245 | 198 | 0.17 |
| Yi Quan | 2012 | China | Cervical cancer | PB | TaqMan | 76 | 142 | 93 | 80 | 215 | 168 | 0.43 |
| Ruan Yang | 2012 | China | Ovarian cancer | HB | PCR-RFLP | 20 | 60 | 12 | 12 | 24 | 2 | 0.03 |
| Alireza Rafiei | 2013 | Iran | Gastric cancer | PB | PCR-RFLP | 44 | 61 | 56 | 21 | 72 | 78 | 0.49 |
| Bin Zhou | 2013 | China | Bladdercancer | HB | TaqMan | 68 | 154 | 79 | 78 | 204 | 164 | 0.29 |
| Zhu Qinghai | 2014 | China | Gastric cancer | HB | MassARRAY | 45 | 122 | 126 | 61 | 216 | 273 | 0.07 |
| Xukui Zhang | 2014 | China | Gastric cancer | PB | MassARRAY | 48 | 102 | 110 | 67 | 187 | 258 | <0.01 |
| Inés Omrane | 2014 | Tunis | Colorectal cancer | PB | PCR-RFLP | 3 | 51 | 48 | 6 | 38 | 95 | 0.39 |
| Nan Wang | 2014 | China | Gastric cancer | PB | PCR-RFLP | 91 | 211 | 160 | 58 | 190 | 214 | 0.12 |
| Xue-E Xi | 2014 | China | Hepatocellular carcinoma | PB | PCR-RFLP | 46 | 71 | 38 | 46 | 90 | 35 | 0.46 |
| Wajih Kaabachi | 2014 | Tunis | Lung cancer | PB | PCR-RFLP | 12 | 80 | 147 | 13 | 79 | 166 | 0.37 |
| Jun Yin | 2014 | China | Esophageal cancer | HB | SNPscan Kit | 80 | 180 | 104 | 79 | 174 | 117 | 0.34 |
| Na Li | 2014 | China | Hepatocellular carcinoma | HB | PCR-RFLP | 110 | 197 | 88 | 50 | 85 | 39 | 0.8 |
| Tomasz Wróbel | 2014 | Poland | Acute myeloid leukemia | PB | PCR-RFLP | 14 | 25 | 23 | 20 | 67 | 38 | 0.29 |
| Kutikhin | 2014 | Russia | Gastric cancer | PB | TaqMan | 10 | 26 | 24 | 36 | 165 | 99 | 0.01 |
| Kutikhin | 2014 | Russia | Colorectal cancer | PB | TaqMan | 32 | 104 | 84 | 36 | 165 | 99 | 0.01 |
| Zhengbing Ren | 2014 | China | Gastric cancer | HB | SNPscan Kit | 42 | 126 | 67 | 98 | 218 | 150 | 0.26 |
| Gonzalez | 2014 | Chile | Gastric cancer | HB | TaqMan | 8 | 36 | 103 | 8 | 59 | 105 | 0.94 |
| Kutikhin | 2014 | Russia | Ovarian cancer | PB | TaqMan | 11 | 31 | 33 | 30 | 81 | 57 | 0.9 |
| Kutikhin | 2014 | Russia | Rectal cancer | PB | TaqMan | 17 | 56 | 42 | 36 | 165 | 99 | 0.01 |
| Kazem Nemati | 2015 | Iran | Colorectal cancer | PB | PCR-RFLP | 20 | 82 | 100 | 39 | 50 | 110 | <0.01 |
| Qiongying Lv | 2015 | China | Cervical cancer | HB | PCR-RFLP | 37 | 117 | 110 | 20 | 105 | 139 | 0.98 |
| Yawen Gao | 2015 | China | Gastric cancer | HB | PCR-RFLP | 83 | 250 | 239 | 72 | 241 | 260 | 0.17 |
| Young Chan Lee | 2015 | Korea | Papillary thyroid cancer | HB | PCR | 24 | 42 | 28 | 47 | 137 | 76 | 0.28 |
| Ning Li | 2015 | China | Oral squamous cell carcinoma | HB | TaqMan | 29 | 43 | 49 | 13 | 33 | 55 | 0.03 |
| W.T.Qi | 2015 | China | Gastric cancer | PB | MassARRAY | 42 | 110 | 100 | 25 | 105 | 122 | 0.73 |

Next, to better understand biological functions this genetic factor contributes to cancer potential susceptibility, subgroup was divided based on the data characteristic. In stratified analysis by cancer types, significant elevated cancer risk was observed in gastric cancer (A vs. G: OR=1.22, 95% CI=1.10-1.34, *P*<0.001; AA/AG vs. GG: OR=1.19, 95% CI=1.07-1.33, *P*=0.059; AA vs. GG/AG: OR=1.50, 95% CI=1.19-1.89, *P*<0.001; AA vs. GG: OR=1.57, 95% CI=1.27-1.93, *P*<0.001) and cervical cancer (A vs. G: OR=1.38, 95% CI=1.18-1.62, *P*=0.449; AA/AG vs. GG: OR=1.43, 95% CI=1.14-1.80, *P*=0.514; AA vs. GG/AG: OR=1.66, 95% CI=1.23-2.24, *P*=0.466; AA vs. GG: OR=1.89, 95% CI=1.35-2.64, *P*=0.401; AG vs. GG: OR=1.29, 95% CI=1.01-1.64, *P*=0.508). FPRP values of gastric cancer in allele model (FPRP=0.032) and cervical cancer in allele model (FPRP=0.089) were both less than 0.2, indicating the associations were reliable. However, no significant association was observed in colorectal cancer and the other types of cancer (**Table 2** and **Figure 2**).

When subgroup was classified by ethnicity, there was a remarkable association between IL-17A (G/-197A) polymorphism and Asian populations in all genetic models (A vs. G: OR=1.22, 95% CI=1.14-1.31, *P*=0.001; AA/AG vs. GG: OR=1.24, 95% CI=1.15-1.34, *P*=0.195; AA vs. GG/AG: OR=1.40, 95% CI=1.19-1.64, *P*<0.001; AA vs. GG: OR=1.51, 95% CI=1.29-1.77, *P*<0.001; AG vs. GG: OR=1.15, 95% CI=1.06-1.25, *P*=0.186). FPRP values were less than 0.2 in the allele models (FPRP=0.000), Dominant model (FPRP=0.000), recessive model (FPRP=0.037) and homozygous comparison (FPRP=0.001), suggesting the results were credible and stable. However, no significant variation was showed in Caucasian populations by the results (**Table 2** and **Figure 3**).

**Table 2.** Stratified analyses of the IL-17A (-197G/A) polymorphism with cancer susceptibility

| | | Allele model (A vs. G) | | | Dominant model (AA/AG vs. GG) | | | Recessive model (AA vs. GG/AG) | | | Homozygous comparison (AA vs. GG) | | | Heterozygous comparison (AG vs. GG) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | OR (95% CI) | $P_h$ | FPRP | OR (95% CI) | $P_h$ | FPRP | OR (95% CI) | $P_h$ | FPRP | OR (95% CI) | $P_h$ | FPRP | OR (95% CI) | $P_h$ | FPRP |
| Total | 30 | 1.18 (1.10, 1.26)* | 0.000 | 0.001 | 1.18 (1.08, 1.29)* | 0.002 | 0.214 | 1.34 (1.16, 1.54)* | 0.000 | 0.038 | 1.40 (1.21, 1.62)* | 0.000 | 0.008 | 1.10 (1.00, 1.22)* | 0.001 | 0.986 |
| Type of Cancer | | | | | | | | | | | | | | | | |
| Gastric cancer | 13 | 1.22 (1.10, 1.34)* | 0.000 | 0.032 | 1.19 (1.07, 1.33)* | 0.059 | 0.685 | 1.50 (1.19, 1.89)* | 0.000 | 0.539 | 1.57 (1.27, 1.93)* | 0.000 | 0.053 | 1.09 (0.97, 1.23) | 0.004 | 0.994 |
| Colorectal cancer | 4 | 1.06 (0.83, 1.35) | 0.068 | 0.998 | 1.17 (0.75, 1.84) | 0.004 | 0.998 | 0.87 (0.49, 1.54) | 0.039 | 0.999 | 0.87 (0.62, 1.22) | 0.401 | 0.998 | 1.28 (0.71, 2.31) | 0.000 | 0.998 |
| Cervical cancer | 2 | 1.38 (1.18, 1.62)* | 0.449 | 0.089 | 1.43 (1.14, 1.80)* | 0.514 | 0.779 | 1.66 (1.23, 2.24)* | 0.466 | 0.783 | 1.89 (1.35, 2.64)* | 0.401 | 0.683 | 1.29 (1.01, 1.64)* | 0.508 | 0.977 |
| Others | 11 | 1.11 (0.98, 1.26) | 0.029 | 0.991 | 1.10 (0.92, 1.32) | 0.049 | 0.997 | 1.23 (1.02, 1.49)* | 0.156 | 0.972 | 1.26 (0.98, 1.62) | 0.048 | 0.987 | 1.05 (0.88, 1.25) | 0.117 | 0.998 |
| Ethnicity | | | | | | | | | | | | | | | | |
| Asian | 20 | 1.22 (1.14, 1.31)* | 0.001 | 0.000 | 1.24 (1.15, 1.34)* | 0.195 | 0.000 | 1.40 (1.19, 1.64)* | 0.000 | 0.037 | 1.51 (1.29, 1.77)* | 0.000 | 0.001 | 1.15 (1.06, 1.25)* | 0.186 | 0.504 |
| Caucasian | 9 | 1.08 (0.90, 1.29) | 0.012 | 0.997 | 1.05 (0.81, 1.35) | 0.004 | 0.999 | 1.14 (0.78, 1.66) | 0.007 | 0.998 | 1.07 (0.75, 1.53) | 0.043 | 0.999 | 1.02 (0.75, 1.39) | 0.000 | 0.999 |
| Mixed | 1 | 0.77 (0.52, 1.14) | N/A | 0.996 | 0.67 (0.42, 1.07) | N/A | 0.995 | 1.18 (0.43, 3.23) | N/A | 0.999 | 1.02 (0.37, 2.82) | N/A | 0.999 | 0.62 (0.38, 1.02) | N/A | 0.994 |
| Source of Controls | | | | | | | | | | | | | | | | |
| HB | 13 | 1.19 (1.08, 1.32)* | 0.007 | 0.502 | 1.19 (1.05, 1.35)* | 0.098 | 0.873 | 1.41 (1.10, 1.80)* | 0.000 | 0.894 | 1.51 (1.21, 1.89)* | 0.004 | 0.401 | 1.09 (0.94, 1.26) | 0.040 | 0.996 |
| PB | 17 | 1.16 (1.05, 1.28)* | 0.000 | 0.757 | 1.17 (1.02, 1.33)* | 0.002 | 0.942 | 1.28 (1.07, 1.53)* | 0.001 | 0.874 | 1.32 (1.08, 1.60)* | 0.001 | 0.838 | 1.11 (0.97, 1.28) | 0.002 | 0.993 |
| Genotyping Method | | | | | | | | | | | | | | | | |
| PCR-RFLP | 12 | 1.17 (1.03, 1.33)* | 0.001 | 0.942 | 1.25 (1.07, 1.47)* | 0.022 | 0.876 | 1.16 (0.90, 1.48) | 0.001 | 0.996 | 1.24 (0.94, 1.64) | 0.001 | 0.993 | 1.23 (1.04, 1.46)* | 0.017 | 0.948 |
| Taqman | 9 | 1.08 (0.93, 1.25) | 0.004 | 0.997 | 1.02 (0.82, 1.27) | 0.002 | 0.999 | 1.23 (1.06, 1.43)* | 0.393 | 0.877 | 1.29 (1.02, 1.64)* | 0.093 | 0.977 | 0.95 (0.77, 1.18) | 0.010 | 0.998 |
| MassARRAY | 3 | 1.33 (1.17, 1.52)* | 0.846 | 0.029 | 1.36 (1.14, 1.63)* | 0.923 | 0.505 | 1.55 (1.20, 2.00)* | 0.796 | 0.625 | 1.73 (1.32, 2.26)* | 0.782 | 0.282 | 1.26 (1.04, 1.52)* | 0.976 | 0.942 |
| Other technologies | 6 | 1.23 (1.10, 1.37)* | 0.143 | 0.000 | 1.16 (1.02, 1.32)* | 0.891 | 0.961 | 1.61 (1.07, 2.41)* | 0.000 | 0.983 | 1.63 (1.18, 2.25)* | 0.906 | 0.027 | 1.02 (0.87, 1.20) | 0.236 | 0.999 |

N: number of studies included; OR: odds ratio; CI: confidence interval; $P_h$: *p* value for heterogeneity; FPRP: false positive report probability; *: OR with statistical significance.

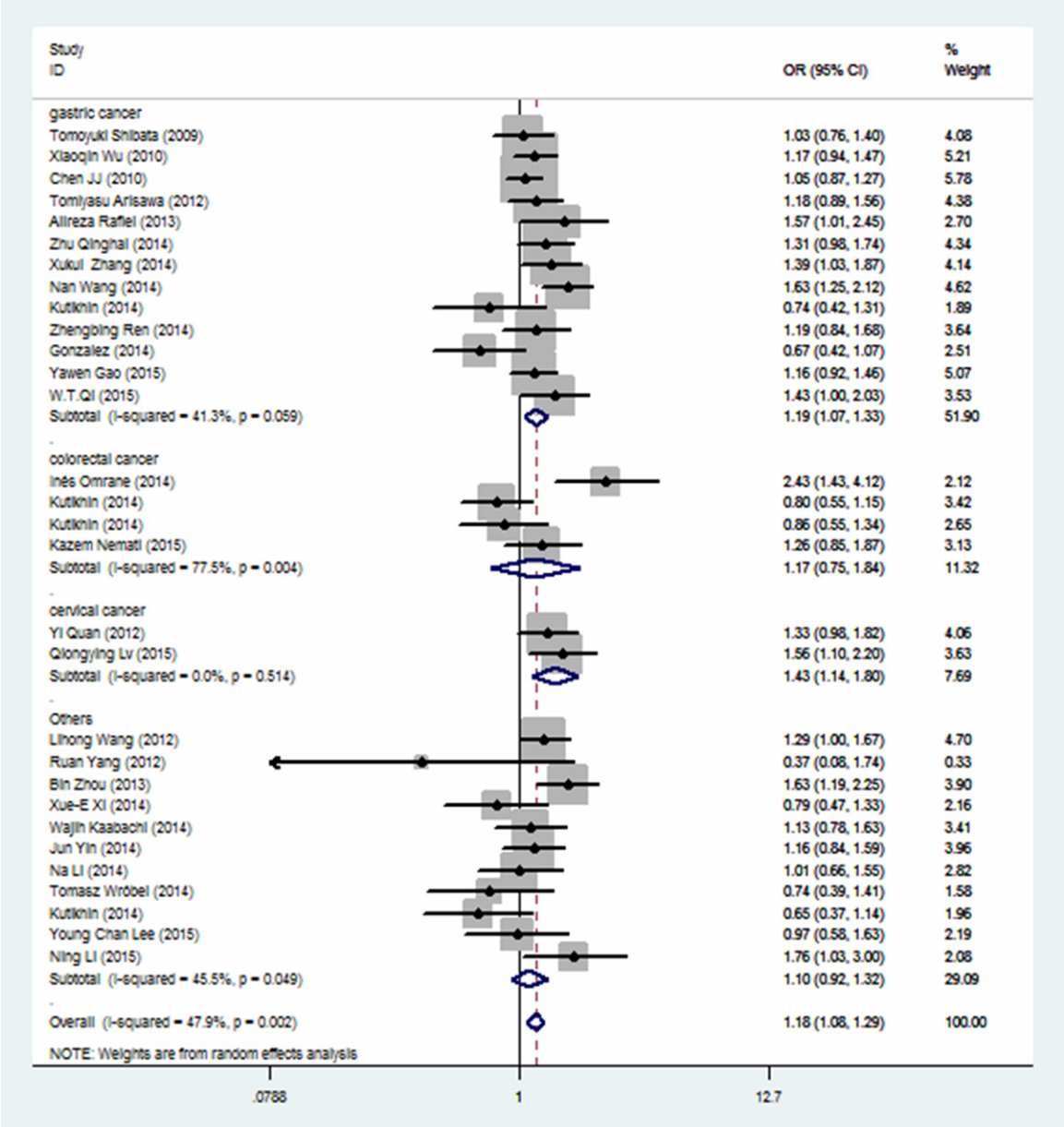


**Figure 2.** Forest plot of cancer susceptibility associated with IL-17A (-197G/A) dominant model (AA/AG vs. GG) in stratified analysis classified by types of cancer. The squares correspond to the study-specific OR and the horizontal lines represent 95% confidence interval (CI) for this estimate. The area of the squares reflects the study specific weight and the diamond indicates the overall effect.

Subsequently, in the classified analysis by the source of control, the results suggested a moderate increased risk of cancer associated with not only population-based controls (PB) (A vs. G: OR=1.16, 95% CI=1.05-1.28, *P*<0.001; AA/AG vs. GG: OR=1.17, 95% CI=1.02-1.33, *P*=0.002; AA vs. GG/AG: OR=1.28, 95% CI=1.07-1.53, *P*=0.001; AA vs. GG: OR=1.32, 95% CI=1.08-1.60, *P*=0.001), but also hospital-based controls (HB) (A vs. G: OR=1.19, 95% CI=1.08-1.32, *P*=0.007; AA/AG vs. GG: OR=1.19, 95% CI=1.05-1.35, *P*=0.098; AA vs. GG/AG: OR=1.41, 95% CI=1.10-1.80, *P*<0.001; AA vs. GG: OR=1.51, 95% CI=1.21-1.89, *P*=0.004) (**Table 2** and **Figure 4**). However, it was not sufficient robust to withstand the FPRP analysis.

At last, according to the genotyping methods, IL-17A (G/-197A) polymorphism genotyped by PCR-RFLP (A vs. G: OR=1.17, 95% CI=1.03-

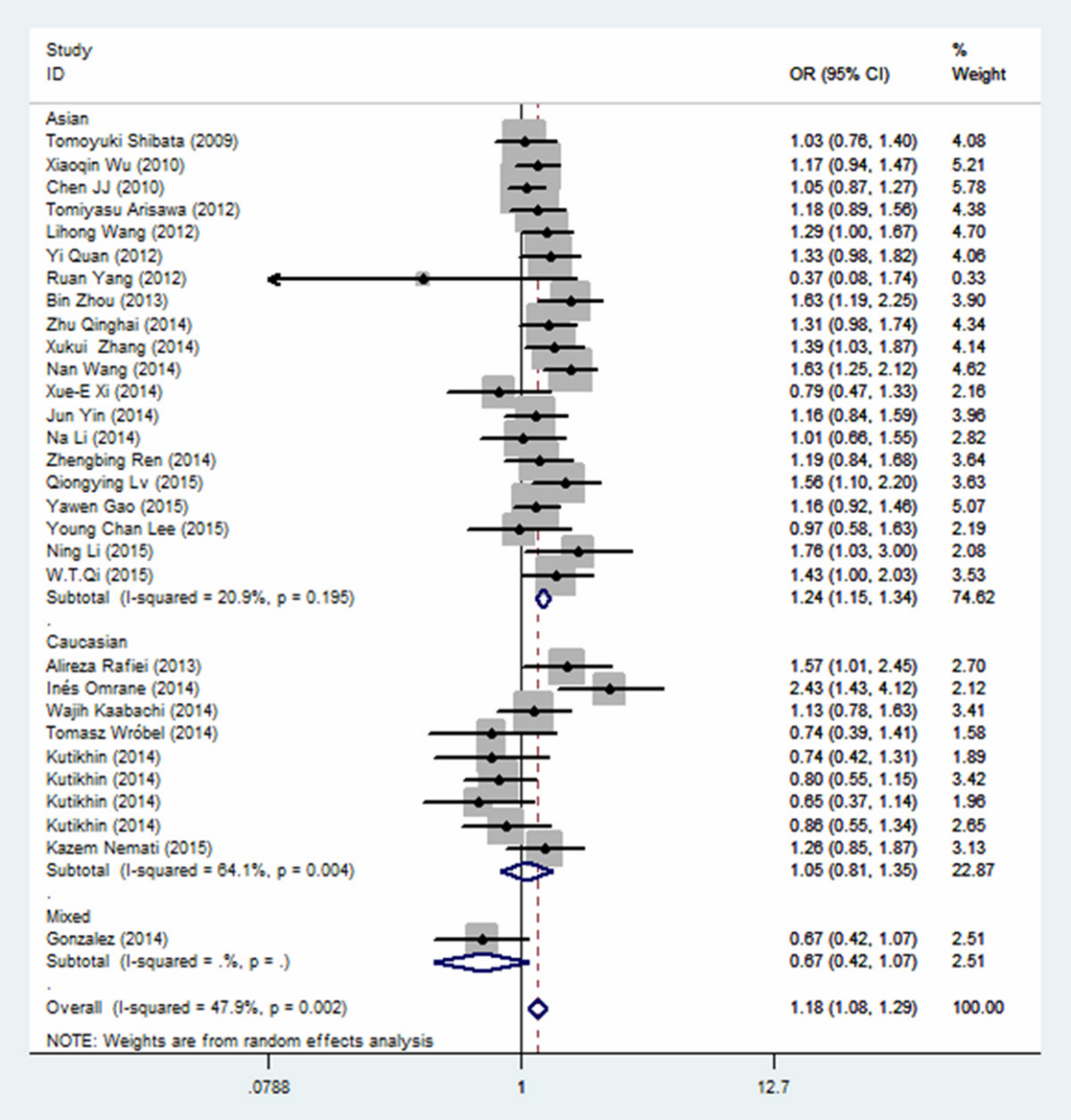


**Figure 3.** Forest plot of cancer susceptibility associated with IL-17A (-197G/A) dominant model (AA/AG vs. GG) in stratified analysis classified by ethnicity. The squares correspond to the study-specific OR and the horizontal lines represent 95% confidence interval (CI) for this estimate. The area of the squares reflects the study specific weight and the diamond indicates the overall effect.

1.33, *P*=0.001; AA/AG vs. GG: OR=1.25, 95% CI=1.07-1.47, *P*=0.022; AG vs. GG: OR=1.23, 95% CI=1.04-1.46, *P*=0.017) and MassARRAY (A vs. G: OR=1.33, 95% CI=1.17-1.52, *P*=0.846; AA/AG vs. GG: OR=1.36, 95% CI=1.14-1.63, *P*=0.923; AA vs. GG/AG: OR=1.55, 95% CI= 1.20-2.00, *P*=0.796; AA vs. GG: OR=1.73, 95% CI=1.32-2.26, *P*=0.782; AG vs. GG: OR=1.26, 95% CI=1.04-1.52, *P*=0.976) and the other methods (A vs. G: OR=1.23, 95% CI=1.10-1.37, *P*=0.143; AA/AG vs. GG: OR=1.16, 95% CI= 1.02-1.32, *P*=0.891; AA vs. GG/AG: OR=1.61, 95% CI=1.07-2.41, *P*<0.001; AA vs. GG: OR=1.63, 95% CI=1.18-2.25, *P*=0.906) were found to be related to an increased cancer risk, FPRP value of MassARRAY in allele model (FPRP=0.029) was less than 0.2, indicating that the results merited attention. In addition, we only detect two discrepancies in the genetic models assessed in Taqman (AA vs. GG/AG:

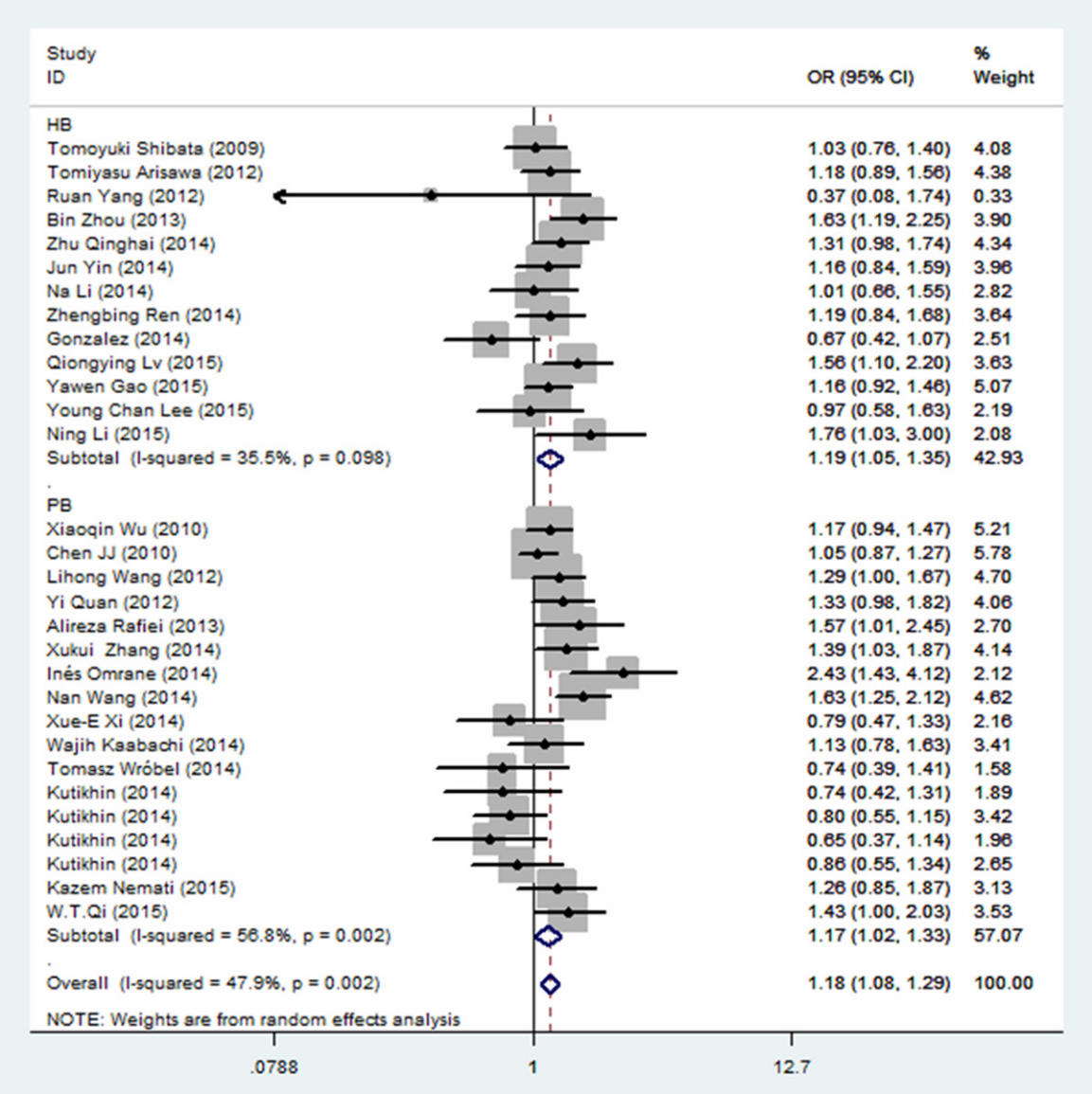


**Figure 4.** Forest plot of cancer susceptibility associated with IL-17A (-197G/A) dominant model (AA/AG vs. GG) in stratified analysis classified source of controls. The squares correspond to the study-specific OR and the horizontal lines represent 95% confidence interval (CI) for this estimate. The area of the squares reflects the study specific weight and the diamond indicates the overall effect.

OR=1.23, 95% CI=1.06-1.43, *P*=0.393; AA vs. GG: OR=1.29, 95% CI=1.02-1.64, *P*<0.001). FPRP value was less than 0.2 in the allele model (FPRP=0.000), indicating that this association was stable.

*Sensitivity analysis and cumulative analyses*

We conducted a sensitive analysis to investigate the influences of each case-control study on the overall analysis. The result suggested that there was no significant alteration in the combined pooled odds radios. In addition, Cumulative analyses, performed year on year, indicated a stable odds radios and confidence intervals. Both of the tests showed robust evidences for this meta-analysis (**Figure 5**).

*Publication bias*

Publication bias of the selected studies was assessed by Begger's funnel plot and Egger's regression method. The funnel plot revealed a obvious trend of approximate symmetry in

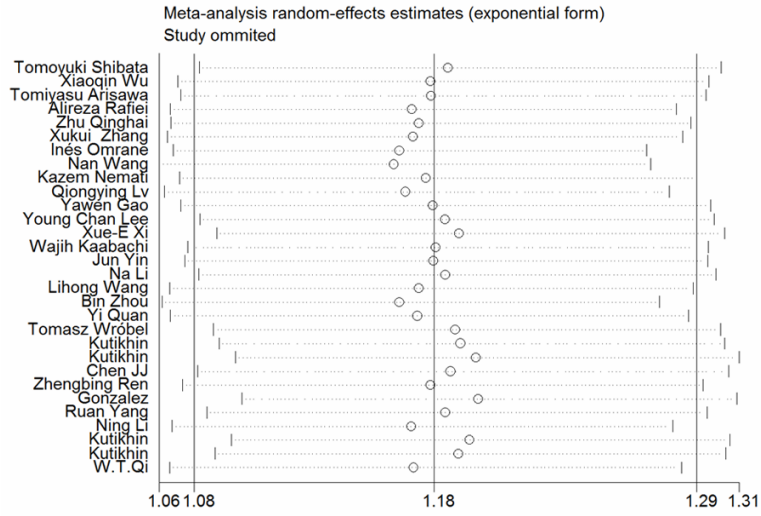


**Figure 5.** Influence analysis of the summary odds radio coefficients on the correlation for IL-17A (-197G/A) polymorphism with cancer susceptibility (according to the dominant model).

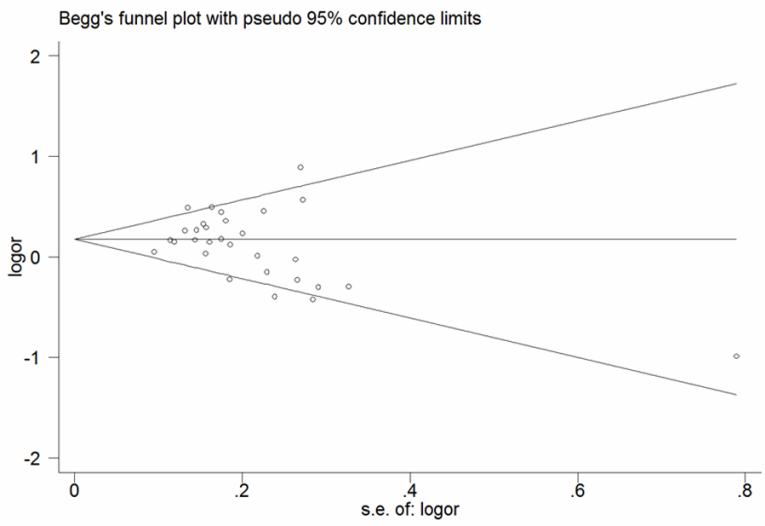


**Figure 6.** Funnel plots of the dominant model (AA/AG vs. GG) of IL-17A (-197G/A) polymorphism to evaluate the publication bias. Each point represents an individual case-control study.

IL-17A (G/-197A) polymorphism. Egger's test was performed to explore the statistical evidence of funnel plot symmetry, and the result showed that no publication bias were found from dominant model in this present meta-analysis ($P$=0.163) (**Figure 6**).

## Discussion

Inflammatory microenvironment was identified to play a significant role in tumor occurrence and development [45-47]. A series of inflammatory cytokines were important components in this specific condition, involving in many pathologic processes to promote malignant tumor progression [48, 49]. About the biological functions of inflammatory chemokine IL-17 in multitype cancers, more controversies rather than consistence existed over the past few decades. But recently, a growing body of evidences have confirmed the positive regulation for carcinoma by IL-17. Results from the study of Prabhala implied that IL-17 was correlated with the proliferation of multiple myeloma cells [50]. he article by Gu found a migration and invasion in lung cancer via epithelial-mesenchymal transition induced by Interluekin-17 [13]. Moreover, Numasaki have showed that IL-17 can increase the availability of tumor angiogenesis [51], similar findings were recorded in the papers of Wakita [52] and Candido [53]. Besides, more and more investigations focused on IL-17A (G/-197A) polymorphism were conducted to explore the tumor genetic mechanism. However, the results remained inconsistent. While more than 20 case-control studies revealed that IL-17A (G/-197A) polymorphism contribute to the susceptibility to many kinds of cancer, dissenting views were observed in other papers. Some scholars believed that no association was existed between this polymorphism and cancer, and some even regarded it as a protective factor for carcinoma.

Because of the conflicting results, several meta-analyses were set out to detect the relationship between this gene mutation and cancer susceptibility [54-56]. However, they extracted all the eligible data before January 20,

2014 and many other individual studies with a series of increasing data were published after that period. To better understand the genetic association and provide a comprehensive conclusion based on a larger sample, we conducted this new meta-analysis.

Our present investigation pooled 30 individual studies in 27 publications together, in a total of 8652 cases and 10699 controls. Overall analysis displayed a significant association between IL-17A (G/-197A) polymorphism and increased susceptibility of cancer in all the five models (A vs. G: OR=1.18, 95% CI=1.10-1.26, *P*<0.001; AA/AG vs. GG: OR=1.18, 95% CI=1.08-1.29, *P*=0.002; AA vs. GG/AG: OR=1.34, 95% CI=1.16-1.54, *P*<0.001; AA vs. GG: OR=1.40, 95% CI=1.21-1.62, *P*<0.001; AG vs. GG: OR=1.10, 95% CI=1.00-1.22, *P*=0.001) with a noteworthy false-positive report probability, which indicated that this mutation may be an important predisposed factor for malignant tumor. Results from sensitive analyses and publication bias enhanced the reliability of this conclusion.

To detect the further relevances, we performed subgroup analyses. At first, stratified analysis was classified by types of carcinoma, we have found a significant correlation in gastric cancer and cervical cancer, but not in colorectal cancer and other types of cancer. Compared with our previous study [57] focused on gastrointestinal malignancy, we elucidated the respective associations. While a high susceptibility in gastric cancer, a few more corresponding reports are needed for colorectal cancer. When subgroup was divided by ethnicity, a certain increased cancer risk was observed in Asian population, not only in digestive system malignancy as reported by one previous meta-analysis [58], but also for cancers of the overall types included by our study. However, we failed to discovered any associations between IL-17A (G/-197A) polymorphism and Caucasian population. With the evidence from FPRP in four of all the models, we assumed that IL-17A (G/-197A) polymorphism was plausible to play an important role in Asian cancer morbidity. Whereas one paper focused on mixed ethnicity was involved in this analysis, we could not obtain an accurate view, due to less credibility of single study. Furthermore, analysis was restricted to the source of controls, moderate increased risk was presented between four models of IL-17A (G/-197A) polymorphism and PB controls. Interestingly, the same association was displayed in HB controls. Inconsistent with the analysis result of a previous system review [55], although HB studies may have some bias because their controls probably contain benign and various disease that may affect the progression of cancers, it was noticeable to consider that whether the HB studies had a combination with incomplete representations. Besides, proper and representative controls need to be screened according to a system of restricted criterias before further studies were set on. In addition, we detected this association by genotyping methods, the results had certain discrepancies observed from these technologies, we conceived it might attribute to the various scientific theories of each methods.

In spite of scientific design and strictly statistical analysis, several limitations are inevitable to be considered in this present work. Firstly, moderate heterogeneity was observed in overall and subgroup analyses. We conducted further work to explore its potential origin in stratified analyses based on types of cancer, ethnicity, the source of controls and genotyping methods, however sources of the heterogeneity still remain unclear. Secondly, as a multi-factorial disease affected by complex interactions, cancer has a strong combination with environmental exposure and life styles, such as smoking, drinking, dieting and geographic areas. But even with a carefully seeking in included literatures, little of these data can be extracted for our meta-analysis. Thirdly, due to constraints of the sample size and cancer types, we failed to retrieve reports for some other common cancers, such as nervous system malignant tumor, integumentary system cancer, pancreatic cancer, neither to investigate the associations between these cancers and IL-17A (G/-197A) polymorphism. Fourthly, only published papers were involved in this meta-analysis, we considered that some relevant important but unpublished researches need to be taken into account. With some crucial biological data, these investigations may give rise to a potential publication bias.

Nonetheless, quite a few strengths are indispensable to be emphasized. Firstly, to our knowledge, this is the latest systematic review to estimate the effect of IL-17A (G/-197A) polymorphism in the linkage along with cancer potential susceptibility. Secondly, we applied

not only *P* value to identify the statistical evidences, but also a false-positive report probability to enhance the stability and reliability of all the results. Furthermore, most of the populations in this study are from geographic areas with a high cancer morbidity and mortality, our findings are likely to provide a crucial reference for further cancer prevention and treatment.

In conclusion, our present meta-analysis suggests that IL-17A (G/-197A) polymorphism may contribute to potential susceptibility to cancer. Moreover, significant relevances with increased cancer risk are discovered in gastric cancer and cervical cancer, Asian population, PB-controls and HB-controls by stratified analysis, which may further confirms its roles of cancer risk factor in these subgroups. Nevertheless, more results from large homogeneous studies are necessary to demonstrate these associations and explore the concrete mechanism.

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## Disclosure of conflict of interest

None.

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