LEPTIN rs2167270 G > A (G19A) polymorphism may decrease the risk of cancer: A case-control study and meta-analysis involving 19,989 subjects

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Abstract
Accumulating evidence has suggested that leptin (LEP) is very important for the development of cancer. Recently, a number of case-control studies about the relationship of the rs2167270 G > A (G19A) variants in the LEP gene with the risk of cancer have yielded inconsistent results. In this study, we have carried out a case-control study [1063 esophagogastric junction adenocarcinoma (EGJA) cases and 1677 controls] in a Chinese population. Furthermore, we carried out a pooled-analysis of 13 studies involving 8059 cancer patients and 11,930 controls to assess whether the LEP G19A locus was associated with overall cancer susceptibility. Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were harnessed to evaluate the potential association. In our case-control study, we found an association between the carriers of LEP 19A allele and EGJA risk. In addition, the results of meta-analysis also suggested significant associations with cancer risk (A vs G: OR = 0.92, 95% CI = 0.88–0.97, P = 0.001; AA vs GG: OR = 0.83, 95% CI = 0.74–0.93, P = 0.001, GA/AA vs GG: OR = 0.93, 95% CI = 0.88–0.99, P = 0.023 and AA vs GG/GA: OR = 0.83, 95% CI = 0.74–0.92, P < 0.001). Upon conducting a stratified analysis, we found that LEP 19A allele might decrease the susceptibility of non-Hodgkin lymphoma (NHL) and colorectal cancer (CRC). In a stratified-by-ethnicity analysis, significant associations were also found in Asians, Caucasians, and mixed populations. We can conclude that the LEP G19A polymorphism constitutes a decreased risk of cancer.

KEYWORDS
leptin, meta-analysis, polymorphism, risk

INTRODUCTION

Cancer is a major public health burden worldwide and has been the leading cause of death in China since 2010. Aging and unhealthy lifestyle (e.g. smoking, alcohol consumption, physical inactivity, and high fat, sugar and calorie diets) may contribute to the global burden of cancer. However, the carcinogenic effect is very complicated and remains unknown. Some studies reported that obesity, overweight,
and type 2 diabetes may contribute to an individual's cancer susceptibility.5,7

Leptin (LEP), a hormone of energy expenditure, may contribute to control energy expenditure and balance by suppressing hunger. LEP, a 16 kDa glycol-protein, is predominantly made (>95%) by fat cells.8 LEP interacts with LEP-receptor in the hypothalamus. A number of studies focused on the role of LEP in energy homeostasis and obesity. In addition, some investigations have demonstrated that LEP is associated with insulin signaling, inflammatory, and immune response.9,10 Recently, several researchers reported that serum LEP levels might influence the development and progression of cancer.11,12

It is found that the LEP rs2167270 G > A (G19A) locus is correlated with LEP levels and may also give a fascinating insight into the potential correlations with the development of cancer.13,14 In a previous pooled study, it was found that individuals carrying a LEP 19A allele might have a lower tendency for cancer risk.15 However, most of the eligible studies focused on Caucasians. The potential relationship of this single-nucleotide polymorphism (SNP) with cancer risk for Asians is unclear. Of late, several case-control studies investigating the association between LEP G19A polymorphism and cancer risk have been performed in Asians with relatively large samples.16,17 Thus, it may be meaningful to obtain data from additional studies to get a more meaningful assessment of genetic effects.

In this study, to acquire an understanding of the relationship between LEP polymorphism and risk of cancer, we first studied LEP G19A polymorphism with the susceptibility of developing esophagogastric junction adenocarcinoma (EGJA). And then, we performed a meta-analysis to estimate the relationship of this polymorphism with overall cancer risk.

2 | MATERIALS AND METHODS

2.1 | Case-control study

A total of 1063 unrelated EGJA cases were diagnosed and selected at Fujian Medical University Union Hospital, Fujian Medical University Cancer Hospital and Affiliated People’s Hospital of Jiangsu University. In addition, 1677 noncancer subjects were included in a control group. Both groups belonged to the Chinese Han populations from eastern China. The patients included 759 males and 304 females; the average age was 64.19 ± 8.63 years. Of them, 625 patients had lymph node metastases. There were 305 stage I/II and 758 stage III/IV EGJA patients included in the case group.17 The disease stage was assessed according to AJCC criteria (version 7.0). The control group was composed of 1194 males and 483 females with the mean age of 63.91 ± 10.22 years. Information regarding smoking and drinking has been described in our previous study.17,18 Each participant signed a written informed consent. This study was approved by the review boards of the Jiangsu University as well as the Fujian Medical University. The genomic DNA was carefully extracted from peripheral venous blood of participants by using DNA Kit (Promega, Madison, Wisconsin). The LEP G19A polymorphism was detected by SNPscan genotyping assay (Genesky Biotechnologies Inc., Shanghai, China) according to conditions described by Chen et al.17

2.2 | Meta-analysis

We performed an extensive literature search in PubMed and EMBASE databases, covering all medical publications until 24 August 2018, with the following key words: LEP gene (e.g., ‘LEP’ or ‘leptin’), cancer (e.g., ‘carcinoma,’ ‘cancer,’ ‘maligancy’ or ‘neoplasms’), and polymorphism (e.g., ‘polymorphism,’ ‘SNP’ or ‘variation’). In addition, we also carried out a manual search of the listed references of the included publications and related reviews.

The criteria of literature selection were as follows: (a) investigation designed as a case–control study; (b) focusing on the association of LEP G19A polymorphism with risk of cancer; (c) genotypes data listing in the publications. The major exclusion criteria of studies were as follows: (a) reviews; (b) duplicated reports; (c) not case-control study designs; (c) lack of data for genotype frequencies.

Two authors (J. Yang and Z. Zhong) extracted data from the included publications independently. The following information was collected: (a) first author; (b) publication year; (c) number of cases and controls; (d) country; (e) ethnicity; (f) source of controls; (g) cancer type; (h) genotyping method; and (i) genotype frequency. Ethnicities were defined as mixed, Asians, and Caucasians. For the source of controls, the publications were categorized as hospital-based and population-based studies.

In this study, we analyzed Hardy-Weinberg equilibrium (HWE) using a goodness-of-fit test using an online software (https://ihg.gsff.de/cgi-bin/hw/hwa1.pl). The strength of the correlation between LEP G19A locus and cancer risk was determined by calculating crude odds ratios (ORs) with their 95% confidence intervals (95% CIs). The following four models were calculated: homozygote comparison (AA vs GG), dominant model (AA/GA vs GG), recessive model (AA vs GG/GA), and allele model (A vs G). If $I^2 > 50\%$ or $\beta < 0.1$, it suggested that there was significant heterogeneity. Considering the heterogeneity among the included studies, a different model was used to pool the data. When no significant heterogeneity was identified, the Mantel-Haenszel method (fixed effects model) was used19; otherwise, the Der
Simonian and Laird method (random model) was utilized. Sensitivity analysis was also carried out, which deletes an individual investigation and, in turn, recalculates the remainders. The source of heterogeneity among variables (e.g. cancer type, ethnicity) was explored by subgroup analysis. Begg’s funnel plot and Egger’s regression method were harnessed to examine the publication bias among the included studies. And \( P < 0.1 \) was defined as representative of significant bias. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of the enrolled literatures. If scores \( \geq 6 \) stars, the publication was considered as related high-quality. In this study, all \( P \) values for statistics were calculated with two-sided. STATA 12.0 software (Stata Corp, College Station, Texas) was used to analyze the data.

3 | RESULTS

3.1 | Case-control study

A total of 2740 participants (involving 1063 EGJA patients and 1677 cancer-free controls) were included in this case-control study. Table 1 summarizes the primary information and our data for \( \text{LEP G19A} \) polymorphism.

Table 2 shows the genotype distributions of \( \text{LEP G19A} \) polymorphism. In the analysis of \( \text{LEP G19A} \) polymorphism, differences in the distribution of \( \text{LEP G19A} \) genotypes between EGJA patients and controls were found [GA vs GG: crude OR = 0.79, 95% CI = 0.67–0.93, \( P = 0.006 \); AA vs GG: crude OR = 0.57, 95% CI = 0.37–0.88, \( P = 0.012 \); AA vs GG/GA: crude OR = 0.58, 95% CI = 0.37–0.93, \( P = 0.004 \) and AA vs GG/GA: crude OR = 0.63, 95% CI = 0.41–0.97, \( P = 0.038 \)]. The results of multivariate linear regression analysis also showed that \( \text{LEP G19A} \) polymorphism was correlated with a decreased risk of EGJA (GA vs GG: adjusted OR = 0.79, 95% CI = 0.67–0.93, \( P = 0.005 \); AA vs GG: adjusted OR = 0.58, 95% CI = 0.37–0.90, \( P = 0.015 \); AA vs GG/GA: adjusted OR = 0.64, 95% CI = 0.41–0.99, \( P = 0.046 \)).

3.2 | Meta-analysis

We have summarized the meta-analysis process in Figure 1. Finally, a total of 13 case-control studies with 8059 cases and 11930 controls were included in our analysis (Table 3). There were four case-control studies and our investigation, conducted in Asian population, six case-control studies focused on Caucasian population, and two case-control studies performed in mixed population. Tables 3 and 4 show the characteristics and genotyping data of the included studies, respectively. Table 5 demonstrate the process of quality assessment in this meta-analysis.

### Table 1: Primary information for \( \text{LEP G19A} \) polymorphism

| Genotyped SNPs | MAF\(^a\) for Chinese in database | MAF in our controls (\( N = 1677 \)) | \( P \) value for HWE\(^b\) test in our controls | Genotyping method | Genotyping value, % |
|----------------|----------------------------------|-------------------------------------|-----------------------------------------------|-----------------|---------------------|
| \( \text{LEP G19A} \) | 0.175 | 0.224 | 0.129 | SNPscan | 99.09 |

\(^a\)MAF: minor allele frequency.

### Table 2: Logistic regression analyses of association between \( \text{LEP G19A} \) polymorphism and risk of EGJA

| Genotypes | Cases (\( n = 1063 \)) | Controls (\( n = 1677 \)) | Crude OR (95% CI) | \( P \) | Adjusted OR\(^a\) (95% CI) | \( P \) |
|-----------|-----------------------|--------------------------|-------------------|-----|-----------------------------|-----|
| GG        | 678 65.13             | 998 59.62                | 1.00              | 1.00|
| GA        | 334 32.08             | 603 36.02                | 0.79 (0.67-0.93)  | 0.006| 0.79 (0.67-0.93)            | 0.005|
| AA        | 29 2.79               | 73 4.36                  | 0.57 (0.37-0.88)  | 0.012| 0.58 (0.37-0.90)            | 0.015|
| GA + AA   | 363 34.87             | 676 40.38                | 0.79 (0.67-0.93)  | 0.004| 0.79 (0.67-0.93)            | 0.004|
| GG + GA   | 1012 97.21            | 1601 95.64               | 1.00              | 1.00|
| AA        | 29 2.79               | 73 4.36                  | 0.63 (0.41-0.97)  | 0.038| 0.64 (0.41-0.99)            | 0.046|
| A allele  | 392 18.83             | 749 22.37                |                   |     |                             |     |

\(^a\)Adjusted for age, sex, smoking status, alcohol use and BMI status.
As demonstrated in Table 6, we identified a significant association of the G19A polymorphism in the LEP 5′-UTR region with a decreased risk of overall cancer in four genetic models (A vs G: OR = 0.92, 95% CI = 0.88–0.97, P = 0.001; AA vs GG: OR = 0.83, 95% CI = 0.74–0.93, P = 0.001, GA/AA vs GG: OR = 0.90, 95% CI = 0.83–0.96, P = 0.003).

When we excluded these studies, we also found that LEP G19A polymorphism decreased the risk of overall cancer (A vs G: OR = 0.92, 95% CI = 0.87–0.97, P = 0.002; AA vs GG: OR = 0.87, 95% CI = 0.75–0.99, P = 0.041 and GA/AA vs GG: OR = 0.90, 95% CI = 0.83–0.96, P = 0.003).

In this study, two studies were inconsistent with HWE.24,30 When we excluded these studies, we also found that LEP G19A polymorphism decreased the risk of overall cancer (A vs G: OR = 0.92, 95% CI = 0.87–0.97, P = 0.002; AA vs GG: OR = 0.87, 95% CI = 0.75–0.99, P = 0.041 and GA/AA vs GG: OR = 0.90, 95% CI = 0.83–0.96, P = 0.003).

In an analysis stratified by cancer type was conducted, we found that individuals carrying LEP 19 A allele might have a lower susceptibility of NHL in three models (A vs G: OR = 0.89, 95% CI = 0.80–0.99, P = 0.025; AA vs GG: OR = 0.74, 95% CI = 0.59–0.94, P = 0.012 and AA vs GA/GG: OR = 0.76, 95% CI = 0.61–0.94, P = 0.013). In addition, we also found that the G19A polymorphism in LEP gene was correlated with a decreased susceptibility of CRC in homozygote comparison (OR = 0.80, 95% CI: 0.66–0.97, P = 0.023) and recessive model (OR = 0.75, 95% CI: 0.63–0.90, P = 0.002).

In an analysis stratified by ethnicities, significant associations were found also in Asians (GA/AA vs GG: OR = 0.87, 95% CI = 0.79–0.96, P = 0.005), Caucasians for three models (A vs G: OR = 0.92, 95% CI = 0.85–1.00, P = 0.040; AA vs GG: OR = 0.82, 95% CI = 0.70–0.97, P = 0.048 and AA vs GG/GA: OR = 0.83, 95% CI = 0.71–0.97, P = 0.017), and mixed population (AA vs GG: OR = 0.82, 95% CI: 0.68–1.00, P = 0.048 and AA vs GG/GA: OR = 0.78, 95% CI: 0.65–0.93, P = 0.007).

**FIGURE 1** Flow diagram of the meta-analysis

As demonstrated in Table 6, we identified a significant association of the G19A polymorphism in the LEP 5′-UTR region with a decreased risk of overall cancer in four genetic models (A vs G: OR = 0.92, 95% CI = 0.88–0.97, P = 0.001; AA vs GG: OR = 0.83, 95% CI = 0.74–0.93, P = 0.001, GA/AA vs GG: OR = 0.90, 95% CI = 0.83–0.96, P = 0.003).

**TABLE 3** Characteristics of the studies in meta-analysis

| References     | Publication year | Country | Ethnicity | Cancer type                | Sample size (case/control) | Source of control | Genotype method |
|----------------|------------------|---------|-----------|---------------------------|---------------------------|-----------------|-----------------|
| Skibola et al 24 | 2004             | USA     | Caucasians| Non-Hodgkin lymphoma      | 376/805                   | PB              | TaqMan          |
| Willett et al 25 | 2005             | UK      | Caucasians| Non-Hodgkin lymphoma      | 699/914                   | PB              | TaqMan          |
| Doecke et al 26  | 2008             | Australia| Caucasians| Esophageal cancer         | 774/1352                  | PB              | Sequenom iPLEX  |
| Slattery et al 30 | 2008             | USA     | Mixed     | Colorectal cancer         | 1565/1965                 | Mixed           | TaqMan          |
| Tsilidis et al 31 | 2009             | USA     | Mixed     | Colorectal cancer         | 208/381                   | PB              | TaqMan          |
| Wang et al 27    | 2009             | USA     | Caucasians| Prostate cancer           | 258/258                   | PB              | TaqMan          |
| Moore et al 28   | 2009             | Finland | Caucasians| Prostate cancer           | 1053/1053                 | PB              | TaqMan          |
| Partida-Perez et al 29 | 2010         | Mexico  | Caucasians| Colorectal cancer         | 68/102                    | HB              | PCR-RFLP        |
| Zhang et al 22   | 2012             | China   | Asians    | Non-Hodgkin lymphoma      | 514/557                   | HB              | TaqMan          |
| Kim et al 23     | 2012             | Korea   | Asians    | Breast cancer             | 390/447                   | HB              | MassARRAY       |
| Qiu et al 16     | 2017             | China   | Asians    | Esophageal cancer         | 507/1496                  | HB              | SNPscan         |
| Zhang et al 17   | 2018             | China   | Asians    | Hepatocellular carcinoma | 584/923                   | HB              | SNPscan         |
| Our study        | 2018             | China   | Asians    | Esophagogastric junction adenocarcinoma | 1063/1677           | HB              | SNPscan         |

Abbreviations: HB, hospital-based; PB, population-based.
We checked publication bias by using Begg’s funnel plot and Egger’s test. The statistical results showed that there was no significant bias in this meta-analysis (A vs G: Begg’s test $P = 1.00$, Egger’s test $P = 0.825$; AA vs GG: Begg’s test $P = 0.951$, Egger’s test $P = 0.975$; GA/AA vs GG: Begg’s test $P = 0.428$, Egger’s test $P = 0.981$; AA vs GA/GG: Begg’s test $P = 0.760$, Egger’s test $P = 0.847$; Figure 3). One-way sensitivity analysis was harnessed to confirm the stability of our findings. And we found that the corresponding results were not materially altered (Figure 4).

We assessed the quality score of the eligible studies by using the Newcastle-Ottawa Quality Assessment Scale.32 The results are shown in Table 5. When the related low-quality studies (<6.0) were excluded, the findings were not substantially changed (Table 6).

### 4 | DISCUSSION

In this case-control study, we found that LEP G19A polymorphism decreased the risk of EGJA. To the best of our knowledge, the first pooled-analysis that carried out an extensive evaluation of the G19A polymorphism in the LEP 5'-UTR region with the risk of overall cancer was conducted in 2014.15 In our meta-analysis, 13 publications involving 8059 cases and 11 930 controls were included. Compared with the previous study, more new studies performed in Asian population were recruited.16,17 Although some studies suggested that LEP G19A polymorphism could increase the risk of cancer,17 the pooled ORs of our study confirmed that G19A polymorphism in the LEP gene was correlated with a decreased risk of overall cancer. It is worth noting that this potential association was also observed in Caucasians, Asians, mixed populations, and NHL and CRC subgroups.

In the past few decades, some case-control studies have been designed to explore the potential relationship between G19A polymorphism in the LEP gene and the risk of cancer.16,17,22-31 Skibola et al24 found that LEP G19A polymorphism decreased the risk of NHL in Caucasians. Another study also identified similar findings regarding CRC in mixed populations.30 A previous meta-analysis indicated that a tendency to decrease risk was noted between LEP G19A polymorphism and cancer.15 However, for Asian population, only two case-control studies with small sample sizes were included in this pooled analysis.22,23 The association of LEP G19A polymorphism with cancer risk in Asians was unclear. Recently, several studies investigated the relationship between LEP G19A polymorphism and cancer risk in Asians.16,17 And they found no association between this SNP and cancer risk. Recently, Zhang et al17 reported that LEP G19A variants might increase the risk of HCC.
| References     | Year | Adequate case definition | Representativeness of the cases | Selection of the controls | Definition of Controls | Comparability of the cases and controls | Ascertainment of exposure | Same ascertainment method for cases and controls | Nonresponse rate | Total Stars |
|----------------|------|--------------------------|--------------------------------|---------------------------|------------------------|----------------------------------------|---------------------------|---------------------------------------------|-----------------|-------------|
| Skibola et al  | 2004 | ★                        | ★                              | ★                         | ★                      | ★                                     | ★                         | ...                                         | ...             | 7           |
| Willett et al  | 2005 | ★                        | ★                              | ★                         | ★                      | ★                                     | ★                         | ...                                         | ...             | 7           |
| Doecke et al   | 2008 | ★                        | ★                              | ★                         | ★                      | ★                                     | ★                         | ...                                         | ...             | 4           |
| Slattery et al | 2008 | ★                        | ★                              | ...                       | ★                      | ★                                     | ★                         | ...                                         | ...             | 6           |
| Tsilidis et al | 2009 | ★                        | ★                              | ★                         | ★                      | ★                                     | ★                         | ...                                         | ...             | 7           |
| Wang et al     | 2009 | ★                        | ★                              | ★                         | ★                      | ★                                     | ★                         | ...                                         | ...             | 7           |
| Moore et al    | 2009 | ★                        | ★                              | ★                         | ...                    | ★                                     | ★                         | ...                                         | ...             | 3           |
| Partida-Perez et al | 2010 | ★                        | ★                              | ...                       | ★                      | ★                                     | ★                         | ...                                         | ...             | 4           |
| Zhang et al    | 2012 | ★                        | ★                              | ...                       | ★                      | ★                                     | ★                         | ...                                         | ...             | 6           |
| Kim et al      | 2012 | ★                        | ★                              | ...                       | ★                      | ★                                     | ★                         | ...                                         | ...             | 6           |
| Qiu et al      | 2017 | ★                        | ★                              | ...                       | ★                      | ★                                     | ★                         | ...                                         | ...             | 6           |
| Zhang et al    | 2018 | ★                        | ★                              | ...                       | ★                      | ★                                     | ★                         | ...                                         | ...             | 6           |
| Our study      | 2018 | ★                        | ★                              | ...                       | ★                      | ★                                     | ★                         | ...                                         | ...             | 6           |

* means meet the standard
| Table 6 | Results of the meta-analysis from different comparative genetic models |
|---------|-------------------------------------------------|
|         | A vs G                                           | AA vs GG                          | AA + AG vs GG                   | AA vs AG + GG                   |
|         | No. of studies | OR (95% CI) | P | I² | P (Q-test) | OR (95% CI) | P | I² | P (Q-test) | OR (95% CI) | P | I² | P (Q-test) |
| Total   | 13         | 0.92 (0.88-0.97) | 0.001 | 26.1% | 0.018 | 0.83 (0.74-0.93) | 0.001 | 25.9% | 0.183 | 0.93 (0.88-0.99) | 0.023 | 26.8% | 0.174 | 0.83 (0.74-0.92) | <0.001 | 32.3% | 0.124 |
| HWE     | 11         | 0.92 (0.87-0.97) | 0.002 | 33.6 | 0.130 | 0.87 (0.75-0.99) | 0.041 | 28.7 | 0.172 | 0.90 (0.83-0.96) | 0.003 | 14.9% | 0.302 | 0.89 (0.78-1.01) | 0.080 | 24.7% | 0.209 |
| Ethnicity |          |          |      |     |          |          |      |     |          |          |      |     |          |          |      |     |          |
| Caucasians | 6        | 0.92 (0.85-1.00) | 0.040 | 20.3% | 0.281 | 0.82 (0.70-0.97) | 0.022 | 27.7% | 0.227 | 0.94 (0.84-1.04) | 0.237 | 4.6% | 0.387 | 0.83 (0.71-0.97) | 0.017 | 38.3% | 0.151 |
| Mixed    | 2         | 0.95 (0.87-1.05) | 0.317 | 0.0% | 0.791 | 0.82 (0.68-1.00) | 0.048 | 0.0% | 0.756 | 1.04 (0.91-1.18) | 0.588 | 0.0% | 0.30 | 0.78 (0.65-0.93) | 0.007 | 0.0% | 0.362 |
| Asians   | 5         | 0.90 (0.80-1.02) | 0.105 | 55.0% | 0.064 | 0.87 (0.61-1.25) | 0.452 | 55.8% | 0.060 | 0.87 (0.79-0.96) | 0.005 | 29.7% | 0.223 | 0.91 (0.65-1.27) | 0.571 | 48.8% | 0.099 |
| Cancer type |          |          |      |     |          |          |      |     |          |          |      |     |          |          |      |     |          |
| NHL      | 3         | 0.89 (0.80-0.99) | 0.025 | 0.0% | 0.819 | 0.74 (0.59-0.94) | 0.012 | 0.0% | 0.521 | 0.91 (0.79-1.04) | 0.161 | 0.0% | 0.875 | 0.76 (0.61-0.94) | 0.013 | 0.0% | 0.372 |
| EC       | 2         | 0.98 (0.80-1.20) | 0.834 | 57.7% | 0.124 | 0.97 (0.70-1.35) | 0.849 | 0.0% | 0.335 | 1.00 (0.74-1.35) | 0.999 | 67.1% | 0.081 | 0.94 (0.68-1.28) | 0.681 | 0.0% | 0.581 |
| CRC      | 3         | 0.94 (0.86-1.03) | 0.205 | 0.0% | 0.478 | 0.80 (0.66-0.97) | 0.023 | 0.0% | 0.381 | 1.03 (0.91-1.17) | 0.620 | 0.0% | 0.593 | 0.75 (0.63-0.90) | 0.002 | 45.6% | 0.159 |
| PC       | 2         | 0.93 (0.83-1.06) | 0.275 | 29.7% | 0.233 | 0.91 (0.70-1.18) | 0.485 | 0.0% | 0.389 | 0.90 (0.76-1.06) | 0.204 | 43.9% | 0.182 | 0.96 (0.75-1.22) | 0.740 | 0.0% | 0.672 |
| Others   | 3         | 0.90 (0.72-1.12) | 0.341 | 76.9% | 0.013 | 0.87 (0.45-1.68) | 0.679 | 77.4% | 0.012 | 0.87 (0.71-1.07) | 0.194 | 63.5% | 0.064 | 0.91 (0.50-1.67) | 0.756 | 73.9% | 0.022 |
| Quality scores |     |       |       |      |      |       |       |      |      |       |       |      |      |       |       |      |      |
| ≥6.0    | 10        | 0.92 (0.87-0.97) | 0.001 | 25.8% | 0.206 | 0.82 (0.72-0.93) | 0.001 | 27.3% | 0.192 | 0.93 (0.87-0.99) | 0.033 | 28.0% | 0.187 | 0.81 (0.72-0.91) | <0.001 | 28.8% | 0.180 |
| <6.0    | 3         | 0.94 (0.84-1.05) | 0.280 | 49.2% | 0.139 | 0.89 (0.70-1.13) | 0.327 | 41.9% | 0.179 | 0.94 (0.81-1.09) | 0.429 | 26.8% | 0.174 | 0.83 (0.56-1.23) | 0.359 | 55.2% | 0.107 |

Abbreviations: CRC, colorectal cancer; EC, esophageal cancer; HWE, Hardy-Weinberg equilibrium; NHL, non-Hodgkin lymphoma; PC, prostate cancer. Bold values are statistically significant (P < 0.05).
observed results were more controversial. In the current study, we conducted a case-control study to identify the correlation between LEP G19A variants and the development of EGJA. We first found that LEP G19A polymorphism decreased the risk of EGJA in Asians. To estimate the relationship of LEP G19A polymorphism with cancer risk more extensively, we conducted an updated meta-analysis. It was found that LEP G19A polymorphism may have a lower risk of overall cancer. LEP G19A polymorphism, a SNP in the 5′-untranslated region, could not be translated into amino acid peptides. However, this SNP may influence the RNA translation, stability, and transcription, and then alter the expression of LEP protein. A recent study indicated that LEP 19A allele is correlated with lower levels of LEP. A meta-analysis found that the decreased serum LEP levels were a protective factor to breast cancer risk. It is conceivable that the reduced levels of serum LEP associated with LEP 19A allele may attenuate the risk of cancer. In this meta-analysis, we confirmed this phenomenon. Furthermore, we identified a significant association in Caucasians and Asians for the first time.

The results of the heterogeneity analysis are shown in Table 6. We found that there was no evident heterogeneity across studies. Publication bias was evaluated by Begg’s funnel plots and Egger’s linear regression test. The results showed that no significant bias was observed. In this meta-analysis, we assessed quality of the included studies. We...
found that the related low-quality studies did not influence the findings of overall evaluation. These findings indicated that our conclusions were credible and stable.

Some limitations of the present pooled-analysis should be acknowledged, even though it was powered by involving the latest literatures as well as our case-control study. First, when the data were extracted and pooled, it was found that significantly heterogeneities existed among certain subgroups. Thus, these observed results should be explained with caution in these subgroups. Second, for the lack of critical data (eg such as age, sex, BMI, and environmental factors), gene-environment interaction could not be carried out. Third, in this study, only LEP G19A polymorphism was studied; the interaction of gene-gene was not evaluated. Fourth, in this study, a functional study focusing on the LEP G19A polymorphism was not conducted. Finally, because the eligible studies were limited, our analysis may be underpowered in some subgroups.

In conclusion, it is highlighted that the G19A polymorphism in the LEP 5′-UTR region is associated with a decreased risk of EGJA. In addition, the subsequent meta-analysis also indicates that this SNP decreases the risk of overall cancer. To confirm or refute our findings, large scale case-control studies are needed.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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