Association of metabolism-related genes polymorphisms with adenocarcinoma of the oesophagogastric junction: Evidence from 2261 subjects

Weifeng Tang | Jun Liu | Zhihui Zhong | Hao Qiu | Mingqiang Kang

1Department of Cardiothoracic Surgery, Affiliated People’s Hospital of Jiangsu University, Zhenjiang, Jiangsu, China
2Department of Medical Oncology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, Fujian, China
3Department of Orthopaedics, The Fuzhou Second Hospital, Affiliated Hospital of Xiamen University, Fuzhou, Fujian, China
4Department of Immunology, Jiangsu University, Zhenjiang, Jiangsu, China
5Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Correspondence
Weifeng Tang, Department of Cardiothoracic Surgery, Affiliated People’s Hospital of Jiangsu University, Zhenjiang, 212000 Jiangsu, China. Email: twf01001@126.com

Mingqiang Kang, Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, 350001 Fujian, China. Email: Mingqiang_Kang@126.com

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Abstract
The etiology of adenocarcinoma of the esophagogastric junction (AEG) remains unclear. It is believed that the increasing of AEG may be correlated with the elevated ratio of obesity and overweight. Thus, metabolism-related genes and variants may play important roles in the occurrence and progress of AEG. The current investigation involved 720 patients with AEG and 1541 healthy controls. We selected transcription factor 7-like 2 (TCF7L2) rs7903146 and rs290481, INS rs689 and INSR rs1799817 single-nucleotide polymorphisms (SNPs), and explored the association of these SNPs with lymph node status and risk of AEG. The polymerase chain reaction was harnessed to identify the genotyping of four polymorphisms. We found that TCF7L2 rs290481 (T > C) and INSR rs1799817 (G > A) polymorphisms were associated with the increased susceptibility of AEG (P = .007 and 0.004 for TCF7L2 rs290481 in TC vs TT and TC/CC vs TT models, and P = .040 for INSR rs1799817 in GA/AA vs GG model). We also conducted a subgroup analysis by different cancer stage. We identified that TCF7L2 rs290481, INS rs689, and INSR rs1799817 SNPs increased the susceptibility of AEG in different cancer stage subgroups. In addition, we found that rs290481 SNP in TCF7L2 gene increased the risk of lymph node metastasis in drinking patients with AEG. However, the association of INSR rs1799817 SNP with a decreased risk of lymph node metastasis in smoking patients with AEG was found. Our findings highlight that TCF7L2 rs290481, INS rs689, and INSR rs1799817 polymorphisms may increase the risk of AEG. In addition, TCF7L2 rs290481 and INSR rs1799817 SNPs may influence the lymph node metastasis in patients with AEG.

KEYWORDS
adenocarcinoma, esophagogastric junction, metabolism, obesity, overweight, polymorphism, risk
Compared to gastric cancer, adenocarcinoma of the esophagogastric junction (AEG) is a special type of carcinoma. AEG involves both distal esophageal and proximal gastric adenocarcinoma. Some evidences demonstrate that AEG is unlike distal gastric adenocarcinoma in tumor evolution, molecular characteristics, and biology behavior.\textsuperscript{1} The incidence of AEG is rapidly increasing in East Asia, Europe, and North America over the last two decades.\textsuperscript{2-4} The occurrence and progress of AEG are unknown. It is assumed that the increasing of AEG may be associated with the elevated ratio of obesity and overweight.\textsuperscript{5} It is estimated that the 5-year survival rate of AEG is only 10 to 15%.\textsuperscript{6} Revealing novel cancer markers are helpful to improve the diagnosis and prognosis of patients with AEG.

The transcription factor 7-like 2 (TCF7L2) is a functional transcription factor, which locates on the long arm of chromosome 10q25.2-q25.3. TCF7L2 is a member of the high mobility group box family.\textsuperscript{7} The TCF7L2 protein might be implicated in regulating Wnt/β-catenin signaling pathway,\textsuperscript{8,9} therefore, it could be associated with the etiology of malignancy. Chen et al\textsuperscript{10} reported that frequent TCF7L2 overexpression was identified in both primary and metastatic gastric cancer. Ishiguro et al\textsuperscript{11} also reported that expression of TCF7L2 in esophageal squamous cell carcinoma might be correlated with a poor prognosis. There are many single-nucleotide polymorphisms (SNPs) in \textit{TCF7L2} gene identified in the past investigations (https://www.ncbi.nlm.nih.gov/snp/?term=TCF7L2). The rs7903146 and rs290481 polymorphisms were two of the most widely explored SNPs in \textit{TCF7L2} gene. Previous studies demonstrated that \textit{TCF7L2} rs7903146 polymorphism conferred the susceptibility to breast cancer.\textsuperscript{12,13} Ling et al\textsuperscript{14} found that \textit{TCF7L2} rs290481 T > C had a tendency of risk to hepatocellular carcinoma (HCC). However, the association of \textit{TCF7L2} SNPs with the risk of AEG remains unknown.

Recently, it is found that both cancer and diabetes have increased the prevalence and many malignancies are attributable to obesity and overweight-related diseases.\textsuperscript{15} Evidence indicated that excess insulin (INS) might favor tumor.\textsuperscript{16} Cancer promotion mechanisms of hyperinsulinemia have been expounded in previous in vitro studies. Insulin receptor (INSR) is overexpressed in most tumor tissues compared to normal tissues.\textsuperscript{17} Cancer cells may be more keen to the role of INS. Approximately 20% of patients with breast cancer have an over 10-fold INSR expression than normal tissue.\textsuperscript{18} A shorter INSR-A isoform (INSR-A) is expressed in cancer cells. However, INSR-B is a dominant form in INS target tissues (e.g., liver, adipose, and muscle etc) and significantly affect metabolic activity. Compared to INSR-B, the INSR-A has an increased mitogenic effect and binds both insulin-like growth factor-2 and INS with high affinity.\textsuperscript{19,20} Previous study has shown that \textit{INS} rs689 was associated with the risk of polycystic ovary syndrome,\textsuperscript{21} and there was a study indicated that \textit{INSR} rs1799817 was related to the occurrence of type 2 diabetes (T2D). Mahmoudi et al\textsuperscript{22} reported that the \textit{INSR} rs1799817 was a risk factor to CRC among women. But, so far, there was no investigation focused on the relationship between \textit{INS} rs689 and \textit{INSR} rs1799817 and AEG risk.

In this study, we selected \textit{TCF7L2} rs7903146 and rs290481, \textit{INS} rs689 and \textit{INSR} rs1799817 and explored the association of these SNPs with AEG.

\section{Materials and Methods}

\subsection{Subjects}

This study involved 720 patients with AEG and 1541 healthy controls. All AEG cases were diagnosed by gastroscope and pathology. The healthy controls matched to patients with AEG by ethnicity, sex, and age. A total of 1541 controls was recruited. The detailed information of the participants was present in our previous study.\textsuperscript{23} Each participant was informed of the study purpose and signed a written informed consent. In this study, a questionnaire was used to collect demographic data (sex and age), smoking, and drinking history. In addition, body mass index (BMI) \geq 24 kg/m² was used as the criterion for overweight and obesity.\textsuperscript{24,25} This study protocol was approved by the ethical committees of Jiangsu University.

\subsection{DNA extraction and stored}

Each individual donated a venous blood sample with ethylenediaminetetraacetic acid anticoagulant, which was stored in a refrigerator at −80°C. The genomic DNA from whole blood was carefully extracted by using a Promega DNA Purification Kit (Promega, Madison).

\subsection{TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 polymorphisms genotype}

\textit{TCF7L2} rs7903146 and rs290481, \textit{INS} rs689 and \textit{INSR} rs1799817 SNPs were genotyped by SNPscan genotyping assay (Genesky Biotechnologies Inc, Shanghai, China). To perform quality control, we randomly selected 90 DNA samples. The genotypes of \textit{TCF7L2} rs7903146 and rs290481, \textit{INS} rs689 and \textit{INSR} rs1799817
were tested by another research assistant. The reproducibility was 100%.

### 2.4 Statistical analysis

SAS software (Version 9.4; SAS Institute Inc, Cary, NC) was used to conduct data analysis. All genotypic distributions were checked whether the distribution of genotype frequencies was in Hardy–Weinberg equilibrium by using an internet-based software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Mean age, weight, height, and BMI were expressed as the mean ± standard deviation (SD). The Student t test was used to compare continuous variables. Statistical significance of genotypes between two groups was assessed by using Fisher’s exact/Chi-square (χ²) test, crude/adjusted odds ratio, and 95% confidence interval (95%). A P < .05 was considered as statistical significance.

### RESULTS

#### 3.1 Baseline characteristics

The selected risk factors and demographics of participants are listed in Table 1. In our study, 720 patients with AEG were enrolled. Among the patients, 532 were males (73.89%) and 188 were females (26.11%). In case group, the mean age and SD was 64.21 ± 8.82 years. There were 424 patients (58.89%) with lymphatic metastasis and 296 patients without lymphatic metastasis (41.11%). The patients with AEG included 211 cases with stage I/II and 509 with stage III/IV disease. Two authors reviewed the clinical data and assessed the disease stage by using the AJCC version 7.0 criteria (2010). For controls, we recruited 1541 cancer-free individuals, 1137 males (73.78%), and 404 females (26.22%). Their age mean ± SD was 64.30 ± 10.19 years. Age and sex were full-matched.

| Variable                  | Overall cases (n = 720) | Overall controls (n = 1541) | P<sup>a</sup> |
|---------------------------|------------------------|-----------------------------|--------------|
| Age, y, M ± SD            | 64.21 ± 8.82           | 64.30 ± 10.19               | .826         |
| Age, y                    |                        |                             | .312         |
| <64, n (%)                | 327 (45.42)            | 735 (47.70)                 |              |
| ≥64, n (%)                | 393 (54.58)            | 806 (52.30)                 |              |
| Sex                       |                        |                             | .958         |
| Male, n (%)               | 532 (73.89)            | 1137 (73.78)                |              |
| Female, n (%)             | 188 (26.11)            | 404 (26.22)                 |              |
| Smoking                   |                        |                             | .015         |
| Never, n (%)              | 525 (72.92)            | 1196 (77.61)                |              |
| Ever, n (%)               | 195 (27.08)            | 345 (22.39)                 |              |
| Drinking                  |                        |                             | .001         |
| Never, n (%)              | 608 (84.44)            | 1377 (89.36)                |              |
| Ever, n (%)               | 112 (15.56)            | 164 (10.64)                 |              |
| Height (cm), M ± SD       | 164.8 (± 7.28)         | 166.2 (± 7.21)              | <.001        |
| Weight (kg), M ± SD       | 61.98 (± 10.35)        | 65.94 (± 9.78)              | <.001        |
| BMI (kg/m²), M ± SD       | 22.77 (± 3.13)         | 23.85 (± 2.96)              | <.001        |
| <24, n (%)                | 476 (66.11)            | 827 (53.67)                 | <.001        |
| ≥24, n (%)                | 244 (33.89)            | 714 (46.33)                 |              |
| Lymph node status         |                        |                             |              |
| Positive, n (%)           | 424 (58.89)            |                            |              |
| Negative, n (%)           | 296 (41.11)            |                            |              |
| AJCC TMN stage            |                        |                             |              |
| I + II, n (%)             | 211 (29.31)            |                            |              |
| III + IV, n (%)           | 509 (70.69)            |                            |              |

Note: Bold values are statistically significant (P < .05). Abbreviations: AJCC, American Joint Committee on Cancer; AEG, esophagogastric junction; BMI, body mass index; M ± SD, mean ± standard deviation. 

<sup>a</sup>Two-sided χ² test and the student t test.
We found that there were significant differences in the distribution of smoking, drinking status, and BMI among the two groups. Table 2 lists the primary information of TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 polymorphisms.

### 3.2 Association of TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 polymorphisms with AEG

Table 3 summaries the genotype distribution of TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 polymorphisms. Compared with the TCF7L2 rs290481 TT genotype, TC and TC/CC genotypes might be associated with the risk of AEG (TC vs TT: crude \( P = .007 \) and TC/CC vs TT: crude \( P = .004 \) [Table 4]). Additionally, compared with the INSR rs1799817 GG genotype, we found that INSR rs1799817 GA/AA genotypes increased the risk of AEG (GA/AA vs GG: crude \( P = .036 \) [Table 4]). After adjustment for BMI, sex, alcohol use and smoking status, the significant association was not altered (Table 4).

We also conducted a subgroup analysis by different cancer stage. We identified that TCF7L2 rs290481, INS rs689 and INSR rs1799817 SNPs increased the susceptibility of AEG in different cancer stage subgroups (TCF7L2 rs290481; TC vs TT genetic model: adjusted \( P = .010 \); TC/CC vs TT genetic model: adjusted \( P = .008 \) for stage I/II subgroup; INS rs689; AA vs TT genetic model: adjusted \( P = .046 \); AA vs TT/TA genetic model: adjusted \( P = .045 \) for stage III/IV subgroup; INSR rs1799817; GA/AA vs GG genetic model: adjusted \( P = .034 \) for stage III/IV subgroup [Table 4]).

However, the association between TCF7L2 rs7903146 SNP and AEG risk was not found (Table 4).

### 3.3 Association of TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 loci with AEG in subgroups

The number of TCF7L2 rs290481 genotype in different subgroups were shown in Table 5. After logistic regression analysis, we found that TCF7L2 rs290481 SNP was associated with the risk of AEG in male, <64 years, \( \geq 64 \) years, never smoking, never drinking, BMI <24 kg/m\(^2\) and BMI \( \geq 24 \) kg/m\(^2\) subgroups (Table 5).

After adjusting alcohol use, smoking status, sex, age, and BMI, the association of INSR rs1799817 SNP with the risk of AEG was found in male, < 64 years, ever smoking and ever drinking subgroups (Table 6).
Association between TCF7L2 rs7903146, rs290481, INS rs689 and INSR rs1799817 loci, and lymph node status in AEG patients

Among the 720 AEG cases, there were 424 patients with lymphatic metastasis and 296 patients without lymphatic metastasis. There was null relationship of TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 SNPs with different lymph node status (Table 7).

Association of TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 loci with the risk of lymph node metastasis in AEG patients in different stratification groups

After adjustment for risk factors, the results indicated that rs290481 SNP in TCF7L2 gene increased the risk of lymph node metastasis in drinking AEG patients (TC vs TT genetic model: adjusted $P = .047$ (Table 8)).

An association of INSR rs1799817 SNP with the risk of lymph node metastasis of patients with AEG was found in some subgroups (ever smoking subgroup: AA vs GG: adjusted $P = .002$; AA vs GG/GA: adjusted $P = .001$ and ever drinking subgroup: AA vs GG/GA: adjusted $P = .030$ [Table 9]).

The correlation between TCF7L2 rs7903146 and INS rs689 polymorphisms and lymph node metastasis in patients with AEG was not found in different stratification groups (data were not shown).

4 | DISCUSSION

It is believed that elevated ratio of obesity and overweight may be associated with an increasing of AEG. TCF7L2, INS, and INSR gene may be implicated in the development of obesity and overweight. Here, we studied the potential relationships of TCF7L2 rs7903146 and rs290481, INS rs689 and INSR rs1799817 polymorphisms with AEG susceptibility. Finally, we found that TCF7L2 rs290481, INS rs689, and INSR rs1799817 polymorphisms might be associated with the increased susceptibility of AEG. In addition, we found that TCF7L2 rs290481 and INSR rs1799817 SNPs might influence the lymph node metastasis in patients with AEG in some subgroups.

TCF7L2 rs290481 (T > C) locus is located in intron 13 (NC_000010.10:g.114923825C>T). Zhu et al. reported that rs290481 polymorphism in TCF7L2 gene increased the susceptibility of T2D and linked to the level of fasting

| Genotype       | Overall cases (n = 720) | Stage I/II patients (n = 211) | Stage III/IV patients (n = 509) | Controls (n = 1541) |
|----------------|------------------------|------------------------------|---------------------------------|---------------------|
|                | n  | %   | n   | %  | n   | %  | n   | %   |
| TCF7L2 rs7903146 C > T |    |      |     |     |     |     |     |     |
| CC             | 666| 94.87| 193 | 93.69| 473 | 95.36| 1448| 94.15|
| CT             | 35 | 4.99 | 12  | 5.83 | 23  | 4.64 | 88  | 5.72 |
| TT             | 1  | 0.14 | 1   | 0.49 | 0   | 0    | 2   | 0.13 |
| T allele       | 37 | 2.64 | 14  | 4.09 | 23  | 2.32 | 92  | 2.99 |
| TCF7L2 rs290481 T > C |    |      |     |     |     |     |     |     |
| TT             | 229| 32.48| 60  | 29.13| 169 | 33.87| 596 | 38.75|
| TC             | 372| 52.77| 116 | 56.31| 256 | 51.30| 697 | 45.32|
| CC             | 104| 14.75| 30  | 14.56| 74  | 14.83| 245 | 15.93|
| C allele       | 580| 41.13| 176 | 42.72| 404 | 40.48| 1187| 38.59|

**TABLE 3** The frequencies of TCF7L2 rs7903146 C > T, rs290481 T > C, INS rs689 T > A, and INSR rs1799817 G > A polymorphisms in different AEG subgroups

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| Genotype       | Overall cases (n = 720) | Stage I/II patients (n = 211) | Stage III/IV patients (n = 509) | Controls (n = 1541) |
|----------------|------------------------|------------------------------|---------------------------------|---------------------|
|                | n  | %   | n   | %  | n   | %  | n   | %   |
| TCF7L2 rs7903146 C > T |    |      |     |     |     |     |     |     |
| CC             | 666| 94.87| 193 | 93.69| 473 | 95.36| 1448| 94.15|
| CT             | 35 | 4.99 | 12  | 5.83 | 23  | 4.64 | 88  | 5.72 |
| TT             | 1  | 0.14 | 1   | 0.49 | 0   | 0    | 2   | 0.13 |
| T allele       | 37 | 2.64 | 14  | 4.09 | 23  | 2.32 | 92  | 2.99 |
| TCF7L2 rs290481 T > C |    |      |     |     |     |     |     |     |
| TT             | 229| 32.48| 60  | 29.13| 169 | 33.87| 596 | 38.75|
| TC             | 372| 52.77| 116 | 56.31| 256 | 51.30| 697 | 45.32|
| CC             | 104| 14.75| 30  | 14.56| 74  | 14.83| 245 | 15.93|
| C allele       | 580| 41.13| 176 | 42.72| 404 | 40.48| 1187| 38.59|

**INS rs689 T > A**

| Genotype       | Overall cases (n = 720) | Stage I/II patients (n = 211) | Stage III/IV patients (n = 509) | Controls (n = 1541) |
|----------------|------------------------|------------------------------|---------------------------------|---------------------|
|                | n  | %   | n   | %  | n   | %  | n   | %   |
| TT             | 638| 90.50| 187 | 90.78| 451 | 90.38| 1411| 91.80|
| TA             | 60 | 8.51 | 18  | 8.74 | 42  | 8.42 | 121 | 7.87 |
| AA             | 7  | 0.99 | 1   | 0.49 | 6   | 1.20 | 5   | 0.33 |
| A allele       | 74 | 5.25 | 20  | 4.85 | 54  | 5.41 | 131 | 4.26 |

**INS rs1799817 G > A**

| Genotype       | Overall cases (n = 720) | Stage I/II patients (n = 211) | Stage III/IV patients (n = 509) | Controls (n = 1541) |
|----------------|------------------------|------------------------------|---------------------------------|---------------------|
|                | n  | %   | n   | %  | n   | %  | n   | %   |
| GG             | 215| 30.50| 67  | 32.52| 148 | 29.66| 538 | 35.00|
| GA             | 359| 50.92| 98  | 47.57| 261 | 52.30| 730 | 47.50|
| AA             | 131| 18.58| 41  | 19.90| 90  | 18.04| 269 | 17.50|
| A allele       | 621| 44.04| 180 | 43.69| 441 | 44.19| 1268| 41.25|

**Abbreviations**: AEG, esophagogastric junction; TCF7L2, transcription factor 7-like 2.
### TABLE 4 Logistic regression analyses of association of TCF7L2 rs7903146 C > T, rs290481 T > C, INSR rs689 T > A, and INSR rs179981 G > A polymorphisms with risk of AEG

| Genotype      | Overall patients (n = 720) vs controls (n = 1541) | Stage I/II patients (n = 211) vs controls (n = 1541) | Stage III/IV patients (n = 509) vs controls (n = 1541) |
|---------------|--------------------------------------------------|---------------------------------------------------|--------------------------------------------------|
|               | Crude OR (95% CI) | Adjusted ORa (95% CI) | P   | Crude OR (95% CI) | Adjusted ORa (95% CI) | P   | Crude OR (95% CI) | Adjusted ORa (95% CI) | P   |
| TCF7L2 rs7903146 C > T |                                  |                                                  |       |                        |                                                  |       |                        |                                                  |       |
| CT vs CC      | 0.84 (0.56–1.26) | .408 | 0.84 (0.56–1.27) | .410 | 1.00 (0.54–1.86) | .998 | 1.00 (0.54–1.87) | .991 | 0.78 (0.49–1.25) | .301 | 0.78 (0.48–1.25) | .298 |
| TT vs CC      | 1.06 (0.10–11.72) | .962 | 1.08 (0.10–12.11) | .951 | 3.67 (0.3340.60) | .290 | 4.14 (0.37–46.69) | .251 | ... | ... | ... |
| CT/TT vs CC   | 0.87 (0.59–1.29) | .491 | 0.87 (0.58–1.30) | .493 | 1.08 (0.59–1.98) | .793 | 1.09 (0.60–2.00) | .773 | 0.78 (0.49–1.25) | .306 | 0.78 (0.49–1.25) | .301 |
| TT vs CC/CT   | 1.10 (0.10–12.11) | .940 | 1.13 (0.10–12.67) | .922 | 3.75 (0.34–41.50) | .282 | 4.30 (0.38–48.78) | .239 | ... | ... | ... |
| TCF7L2 rs290481 T > C |                                   |                                                  |       |                        |                                                  |       |                        |                                                  |       |
| TC vs TT      | 1.31 (1.08–1.59) | .007 | 1.31 (1.08–1.60) | .007 | 1.53 (1.11–2.12) | .009 | 1.53 (1.11–2.12) | .010 | 1.23 (0.99–1.53) | .066 | 1.23 (0.98–1.53) | .074 |
| CC vs TT      | 1.04 (0.79–1.37) | .768 | 1.06 (0.80–1.39) | .699 | 1.13 (0.71–1.78) | .605 | 1.12 (0.71–1.78) | .621 | 1.01 (0.74–1.38) | .946 | 1.04 (0.76–1.42) | .809 |
| TC/CC vs TT   | 1.32 (1.09–1.59) | .004 | 1.32 (1.09–1.60) | .004 | 1.54 (1.12–2.12) | .008 | 1.54 (1.12–2.12) | .008 | 1.24 (1.00–1.53) | .051 | 1.24 (1.00–1.53) | .051 |
| CC vs. TT/TC  | 0.91 (0.71–1.17) | .475 | 0.92 (0.72–1.19) | .536 | 0.90 (0.60–1.36) | .613 | 0.89 (0.59–1.35) | .593 | 0.92 (0.69–1.22) | .557 | 0.94 (0.71–1.26) | .694 |
| INSR rs689 T > A |                                              |                                                  |       |                        |                                                  |       |                        |                                                  |       |
| TA vs TT      | 1.08 (0.78–1.48) | .663 | 1.09 (0.79–1.52) | .589 | 1.10 (0.65–1.84) | .728 | 1.13 (0.67–1.91) | .636 | 1.07 (0.74–1.54) | .735 | 1.09 (0.75–1.59) | .635 |
| AA vs TT      | 3.03 (0.96–9.58) | .059 | 2.85 (0.89–1.13) | .078 | 1.72 (0.21–12.69) | .723 | 1.82 (0.21–15.77) | .587 | 3.68 (1.12–12.13) | .032 | 3.43 (1.02–11.51) | .046 |
| TA/AA vs TT   | 1.18 (0.86–1.62) | .307 | 1.19 (0.87–1.63) | .276 | 1.14 (0.69–1.89) | .617 | 1.19 (0.71–1.98) | .508 | 1.19 (0.84–1.69) | .324 | 1.21 (0.85–1.73) | .284 |
| AA vs. TT/TA  | 3.07 (0.98–7.90) | .056 | 2.88 (0.90–9.21) | .075 | 1.50 (0.17–12.86) | .713 | 1.85 (0.21–16.08) | .575 | 3.73 (1.13–12.27) | .030 | 3.45 (1.03–11.57) | .045 |
| INSR rs179981 G > A |                                              |                                                  |       |                        |                                                  |       |                        |                                                  |       |
| GA vs GG      | 1.16 (0.95–1.42) | .147 | 1.16 (0.95–1.41) | .159 | 1.01 (0.73–1.40) | .949 | 1.02 (0.73–1.41) | .930 | 1.23 (0.98–1.54) | .078 | 1.22 (0.97–1.54) | .085 |
| AA vs GG      | 1.15 (0.89–1.49) | .297 | 1.15 (0.88–1.49) | .310 | 1.15 (0.76–1.73) | .512 | 1.16 (0.77–1.75) | .491 | 1.15 (0.85–1.55) | .364 | 1.14 (0.84–1.54) | .396 |
| GA/AA vs GG   | 1.23 (1.01–1.49) | .056 | 1.23 (1.01–1.49) | .040 | 1.12 (0.82–1.52) | .483 | 1.13 (0.83–1.54) | .453 | 1.28 (1.03–1.59) | .028 | 1.27 (1.02–1.59) | .034 |
| AA vs GG/GA   | 1.08 (0.85–1.36) | .535 | 1.08 (0.85–1.36) | .537 | 1.17 (0.81–1.69) | .398 | 1.18 (0.82–1.71) | .382 | 1.04 (0.80–1.35) | .784 | 1.03 (0.79–1.35) | .820 |

Note: Bold values are statistically significant (P < .05).
Abbreviations: AEG, esophagogastric junction; CI, confidence interval; OR, odds ratio; TCF7L2, transcription factor 7–like 2.

*Adjusted for age, sex, smoking status, alcohol use and BMI status.
### Table 5

Stratified analyses between *TCF7L2* rs290481 T > C polymorphism and AEG risk by sex, age, BMI, smoking status, and alcohol consumption

| Variable                  | TCF7L2 rs290481 T > C (case/control)$^a$ | Adjusted OR $^b$ (95% CI); $P$ |
|---------------------------|-----------------------------------------|---------------------------------|
|                           | TT  | TC  | CC  | TT  | TC  | CC  | TC / CC  | CC vs (TC/TT) |
| Sex                       |     |     |     |     |     |     |          |               |
| Male                      | 165/431 | 287/511 | 72/192 | 1.00 | **1.42 (1.12–1.78); $P = .003$** | 0.95 (0.69–1.32); $P = .757$ | 1.34 (1.07–1.68); $P = .010$ | 0.79 (0.59–1.06); $P = .113$ |
| Female                    | 64/165 | 85/186 | 32/53  | 1.00 | 1.04 (0.71–1.53); $P = .834$ | 1.42 (0.84–2.41); $P = .192$ | 1.25 (0.86–1.80); $P = .241$ | 1.45 (0.89–2.36); $P = .134$ |
| Age                       |     |     |     |     |     |     |          |               |
| <64                       | 103/289 | 168/338 | 46/106 | 1.00 | 1.25 (0.93–1.67); $P = .136$ | 1.16 (0.76–1.76); $P = .490$ | **1.34 (1.01–1.77); $P = .046$** | 1.06 (0.72–1.54); $P = .785$ |
| ≥64                       | 126/307 | 204/359 | 58/139 | 1.00 | **1.35 (1.03–1.76); $P = .030$** | 0.99 (0.68–1.43); $P = .948$ | 1.29 (1.00–1.67); $P = .052$ | 0.85 (0.60–1.18); $P = .327$ |
| Smoking status            |     |     |     |     |     |     |          |               |
| Never                     | 160/458 | 277/542 | 75/194 | 1.00 | **1.37 (1.09–1.72); $P = .008$** | 1.02 (0.74–1.40); $P = .916$ | **1.37 (1.10–1.71); $P = .006$** | 0.87 (0.65–1.17); $P = .356$ |
| Ever                      | 69/138 | 95/155 | 29/51  | 1.00 | 1.16 (0.78–1.71); $P = .471$ | 1.11 (0.64–1.93); $P = .720$ | 1.16 (0.80–1.69); $P = .436$ | 1.03 (0.62–1.72); $P = .911$ |
| Alcohol consumption       |     |     |     |     |     |     |          |               |
| Never                     | 191/537 | 315/614 | 88/224 | 1.00 | **1.35 (1.10–1.67); $P = .005$** | 1.04 (0.77–1.40); $P = .811$ | **1.36 (1.10–1.66); $P = .004$** | 0.89 (0.68–1.17); $P = .413$ |
| Ever                      | 38/59 | 57/83 | 16/21  | 1.00 | 1.07 (0.62–1.84); $P = .814$ | 1.10 (0.50–2.44); $P = .807$ | 1.08 (0.64–1.82); $P = .781$ | 1.06 (0.52–2.20); $P = .868$ |
| BMI (kg/m$^2$)            |     |     |     |     |     |     |          |               |
| <24                       | 152/318 | 244/378 | 68/129 | 1.00 | 1.26 (0.98–1.61); $P = .071$ | 1.04 (0.73–1.47); $P = .848$ | **1.29 (1.01–1.64); $P = .040$** | 0.93 (0.68–1.28); $P = .656$ |
| ≥24                       | 77/278 | 128/319 | 36/116 | 1.00 | **1.41 (1.02–1.95); $P = .038$** | 1.11 (0.71–1.74); $P = .649$ | **1.38 (1.01–1.89); $P = .042$** | 0.93 (0.62–1.39); $P = .711$ |

Note: Bold values are statistically significant ($P < .05$). Abbreviations: AEG, esophagogastric junction; BMI, body mass index; CI, confidence interval; OR, odds ratio; TCF7L2, transcription factor 7-like 2.

$^a$For *TCF7L2* rs290481 T > C, the genotyping was successful in 705 (97.92%) EGJA cases and 1538 (99.81%) controls.

$^b$Adjusted for multiple comparisons (age, sex, smoking status, BMI, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
### Table 6: Stratified analyses between INSR rs1799817 G > A polymorphism and AEG risk by sex, age, BMI, smoking status, and alcohol consumption

| Variable          | INSR rs1799817 G > A (case/control) | Adjusted OR\(^b\) (95\% CI); \(P\) |
|-------------------|-------------------------------------|--------------------------------------|
|                   | GG  | GA  | AA  | GG  | GA  | AA  | GA/AA | AA vs (GA/GG) |
| Sex               |     |     |     |     |     |     |       |               |
| Male              | 154 | 269 | 406 | 101 | 183 | 30  | 1.00   | 1.24 (0.98–1.57); \(P = .075\) |
| Female            | 61  | 90  | 132 | 30  | 86  | 30  | 1.00   | 1.02 (0.62–1.35); \(P = .656\) |
| Age               |     |     |     |     |     |     |       |               |
| <64               | 84  | 171 | 251 | 62  | 128 | 62  | 1.00   | 1.24 (0.91–1.68); \(P = .169\) |
| ≥64               | 131 | 188 | 287 | 69  | 141 | 69  | 1.00   | 1.06 (0.81–1.39); \(P = .690\) |
| Smoking status    |     |     |     |     |     |     |       |               |
| Never             | 159 | 259 | 405 | 94  | 218 | 94  | 1.00   | 1.07 (0.84–1.34); \(P = .597\) |
| Ever              | 56  | 100 | 133 | 37  | 51  | 37  | 1.00   | 1.48 (0.98–2.23); \(P = .060\) |
| Alcohol consumption |     |     |     |     |     |     |       |               |
| Never             | 186 | 298 | 466 | 110 | 243 | 110 | 1.00   | 1.03 (0.83–1.28); \(P = .784\) |
| Ever              | 29  | 61  | 72  | 21  | 26  | 21  | 1.00   | 2.39 (1.35–4.25); \(P = .003\) |
| BMI (kg/m\(^2\))  |     |     |     |     |     |     |       |               |
| <24               | 135 | 243 | 277 | 86  | 147 | 86  | 1.00   | 1.17 (0.91–1.52); \(P = .226\) |
| ≥24               | 80  | 116 | 261 | 45  | 122 | 45  | 1.00   | 1.11 (0.80–1.54); \(P = .522\) |

Note: Bold values are statistically significant \((P < .05)\). Abbreviations: AEG, esophagogastric junction; BMI, body mass index; CI, confidence interval; OR, odds ratio.

\(^a\)For INSR rs1799817 G > A, the genotyping was successful in 705 (97.92\%) EGJA cases and 1537 (99.74\%) controls.

\(^b\)Adjusted for multiple comparisons (age, sex, smoking status, BMI and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
A previous study evaluated the potential association between TCF7L2 rs290481 variants and cancer risk in Chinese patients with T2D. It is observed that TCF7L2 rs290481 polymorphism was positively associated with cancer susceptibility under the additive model.\(^2\) The previous report showed that TCF7L2 rs290481 might influence the risk of HCC.\(^1\) Individuals carrying Crs290487Ars290489 haplotype might have a significantly higher HCC susceptibility than those with Trs290481Grs290489.\(^1\) In this SNP, we found that the rs290481TC and TC/CC genotype of TCF7L2 gene is relevant to increased susceptibility and progress of AEG. In addition, we also found that the potential association was more significant in BMI \(\geq 24\) kg/m\(^2\), which was in line with the findings of those studies mentioned above.\(^1, 26\)

In this study, the relationship between rs1799817 G > A polymorphism in the INS gene and AEG risk was also explored. We found that INS rs1799817 G > A polymorphism might confer the risk to AEG. However, we found INS rs1799817 G > A SNP might improve the progress of AEG. Maybe this polymorphism plays different role in different phases of AEG. Our results were similar to a previous study suggesting a positive association between the INS rs1799817 locus and colorectal cancer in the female.\(^2\) In this study, compared with INS rs1799817 GG genotype, rs1799817 AA/GA genotype increased 1.23-fold risk of AEG. We first investigated the relationship between the INS rs1799817 polymorphism and the risk of AEG. Since the functional consequence of INS rs1799817 G > A polymorphism is a synonymous codon (https://www.ncbi.nlm.nih.gov/snp/?term=rs1799817), indicating that it could not change the primary structure of the INS protein, the potential biological mechanism for this SNP altering the susceptibility for AEG is largely unknown. However, exon 17 of the INS gene encodes the sequence of the tyrosine kinase domain, which plays a vital role in the function of INS protein. Although INS rs1799817 G > A polymorphism is a

| TABLE 7 | Logistic regression analyses of the association between TCF7L2 rs7903146 C > T, rs290481 T > C, INS rs689 T > A, and INSR rs1799817 G > A polymorphisms, and lymph node status in AEG patients |
|----------|----------------------------------------------------------------------------------|
| Genotype | Positive (n = 424) n % | Negative (n = 296) n % | Crude OR (95%CI) P | Adjusted OR * (95%CI) P |
| TCF7L2 rs7903146 C > T | | | | |
| CC | 394 95.17 | 272 94.44 | 1.00 | 1.00 |
| CT | 20 4.83 | 15 5.21 | 0.92 (0.47–1.84) | 0.822 | 0.95 (0.48–1.90) | .887 |
| TT | 0 0.00 | 1 0.35 | ... | ... | ... | ... |
| CT+TT | 20 4.83 | 16 5.56 | 0.86 (0.44–1.70) | .669 | 0.88 (0.45–1.75) | .720 |
| CC+CT | 414 100 | 287 99.65 | 1.00 | 1.00 |
| TT | 0 0.00 | 1 0.35 | ... | ... | ... | ... |
| TCF7L2 rs290481 T > C | | | | |
| TT | 127 30.53 | 102 35.29 | 1.00 | 1.00 |
| TC | 225 54.09 | 147 50.87 | 1.24 (0.89–1.71) | .204 | 1.26 (0.90–1.75) | .178 |
| CC | 64 15.38 | 40 13.84 | 1.29 (0.81–2.06) | .284 | 1.30 (0.81–2.08) | .275 |
| TC+CC | 289 69.47 | 187 64.71 | 1.24 (0.90–1.71) | .184 | 1.25 (0.91–1.72) | .177 |
| TT+TC | 352 84.62 | 249 86.16 | 1.00 | 1.00 |
| CC | 64 15.38 | 40 13.84 | 1.13 (0.74–1.74) | .570 | 1.13 (0.73–1.73) | .587 |
| INS rs689 T > A | | | | |
| TT | 375 90.14 | 263 91.00 | 1.00 | 1.00 |
| TA | 36 8.65 | 24 8.30 | 1.06 (0.62–1.81) | .839 | 1.03 (0.60–1.78) | .915 |
| AA | 5 1.20 | 2 0.69 | 1.76 (0.34–9.15) | .500 | 1.75 (0.33–9.21) | .512 |
| TA+AA | 41 9.86 | 26 9.00 | 1.11 (0.66–1.85) | .702 | 1.08 (0.64–1.81) | .785 |
| TT+TA | 411 98.80 | 287 99.31 | 1.00 | 1.00 |
| AA | 5 1.20 | 2 0.69 | 1.75 (0.34–9.06) | .507 | 1.74 (0.33–9.17) | .515 |
| INSR rs1799817 G > A | | | | |
| GG | 123 29.57 | 92 31.83 | 1.00 | 1.00 |
| GA | 221 53.13 | 138 47.75 | 1.21 (0.86–1.70) | .267 | 1.19 (0.84–1.67) | .325 |
| AA | 72 17.31 | 59 20.42 | 0.92 (0.60–1.42) | .713 | 0.92 (0.59–1.41) | .689 |
| GA+AA | 293 70.43 | 197 68.17 | 1.11 (0.80–1.54) | .520 | 1.08 (0.78–1.51) | .628 |
| GG+GA | 344 82.69 | 230 79.58 | 1.00 | 1.00 |
| AA | 72 17.31 | 59 20.42 | 0.82 (0.56–1.20) | .297 | 0.82 (0.56–1.20) | .301 |

Abbreviations: AEG, esophagogastric junction; CI, confidence interval; OR, odds ratio; TCF7L2, transcription factor 7-like 2.

*Adjusted for age, sex, smoking, alcohol use and BMI status.
TABLE 8  Stratified analyses between TCF7L2 rs290481 T > C polymorphism and lymph node status in AEG patients by sex, age, BMI, smoking status, and alcohol consumption

| Variable                  | TCF7L2 rs290481 T > C (Positive/ Negative)a | Adjusted ORb (95% CI); P     |
|---------------------------|---------------------------------------------|-----------------------------|
|                           | TT  | TC  | CC  | TT  | TC  | CC  | TC/CC | CC vs (TC/TT) |
| Sex                       |     |     |     |     |     |     |       |                |
| Male                      | 88/77 | 173/114 | 42/30 | 1.00 | 1.31 (0.89–1.94); P = .175 | 1.21 (0.69–2.12); P = .506 | 1.29 (0.89–1.88); P = .184 | 1.02 (0.62–1.70); P = .932 |
| Female                    | 39/25 | 52/33  | 22/10 | 1.00 | 1.02 (0.52–2.01); P = .952 | 1.50 (0.60–3.72); P = .387 | 1.14 (0.60–2.14); P = .697 | 1.48 (0.64–3.39); P = .358 |
| Age                       |     |     |     |     |     |     |       |                |
| <64                       | 61/42 | 104/64  | 31/15 | 1.00 | 1.14 (0.68–1.90); P = .616 | 1.45 (0.69–3.04); P = .321 | 1.20 (0.74–1.96); P = .455 | 1.35 (0.69–2.64); P = .388 |
| ≥64                       | 66/60 | 121/83  | 33/25 | 1.00 | 1.33 (0.85–2.10); P = .211 | 1.14 (0.61–2.15); P = .681 | 1.29 (0.84–1.98); P = .249 | 0.96 (0.54–1.69); P = .879 |
| Smoking status            |     |     |     |     |     |     |       |                |
| Never                     | 90/70 | 171/106 | 46/29 | 1.00 | 1.31 (0.88–1.95); P = .190 | 1.27 (0.72–2.24); P = .401 | 1.30 (0.89–1.91); P = .180 | 1.08 (0.65–1.79); P = .773 |
| Ever                      | 37/32 | 54/41  | 18/11 | 1.00 | 1.11 (0.59–2.08); P = .748 | 1.42 (0.58–3.52); P = .444 | 1.17 (0.65–2.13); P = .598 | 1.34 (0.59–3.09); P = .487 |
| Alcohol consumption       |     |     |     |     |     |     |       |                |
| Never                     | 108/83 | 185/130 | 54/34 | 1.00 | 1.10 (0.77–1.59); P = .597 | 1.22 (0.73–2.05); P = .456 | 1.13 (0.79–1.60); P = .501 | 1.15 (0.72–1.83); P = .568 |
| Ever                      | 19/19 | 40/17  | 10/6  | 1.00 | 2.42 (1.01–5.78); P = .047 | 1.84 (0.54–6.24); P = .331 | 2.27 (1.00–5.18); P = .051 | 1.10 (0.36–3.35); P = .872 |
| BMI (kg/m²)               |     |     |     |     |     |     |       |                |
| <24                       | 89/63 | 152/92  | 41/27 | 1.00 | 1.17 (0.77–1.77); P = .472 | 1.06 (0.59–1.91); P = .840 | 1.14 (0.77–1.70); P = .513 | 0.97 (0.57–1.64); P = .902 |
| ≥24                       | 38/39 | 73/55  | 23/13 | 1.00 | 1.42 (0.79–2.53); P = .241 | 1.75 (0.76–4.03); P = .187 | 1.49 (0.86–2.58); P = .161 | 1.43 (0.67–3.07); P = .355 |

Note: Bold values are statistically significant (P < .05). Abbreviations: AEG, esophagogastric junction; BMI, body mass index; CI, confidence interval; OR, odds ratio; TCF7L2, transcription factor 7–like 2.

a For TCF7L2 rs290481 T > C, the genotyping was successful in 705 (97.92%) EGJA cases.

b Adjusted for multiple comparisons (age, sex, smoking status, BMI and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
Table 9  Stratified analyses between INSR rs1799817 G> A polymorphism and lymph node status in AEG patients by sex, age, BMI, smoking status and alcohol consumption

| Variable          | INSR rs1799817 G > A (Positive/Negative) | Adjusted OR b (95% CI); P |  |
|-------------------|----------------------------------------|--------------------------|---|
|                   | GG          | GA           | AA           | GG          | GA           | AA           | GA/AA        | AA vs (GA/GG) | |
| Sex               |             |              |              |             |              |              |              |               |               |
| Male              | 88/66       | 160/109      | 55/46        | 1.00        | 1.04 (0.69–1.56); P = .850 | 0.86 (0.52–1.43); P = .566 | 0.99 (0.67–1.45); P = .946 | 0.84 (0.54–1.30); P = .437 |
| Female            | 35/26       | 61/29        | 17/13        | 1.00        | 1.59 (0.81–3.13); P = .180 | 0.96 (0.40–2.35); P = .936 | 1.40 (0.74–2.63); P = .305 | 0.74 (0.33–1.64); P = .452 |
| Age               |             |              |              |             |              |              |              |               |               |
| <64               | 50/34       | 111/60       | 35/27        | 1.00        | 1.27 (0.73–2.21); P = .389 | 0.89 (0.45–1.76); P = .744 | 1.16 (0.68–1.96); P = .587 | 0.76 (0.43–1.33); P = .335 |
| ≥64               | 73/58       | 110/78       | 37/32        | 1.00        | 1.12 (0.71–1.77); P = .620 | 0.96 (0.53–1.73); P = .882 | 1.07 (0.70–1.65); P = .743 | 0.89 (0.53–1.52); P = .676 |
| Smoking status    |             |              |              |             |              |              |              |               |               |
| Never             | 87/72       | 160/99       | 60/34        | 1.00        | 1.30 (0.87–1.95); P = .198 | 1.44 (0.85–2.44); P = .175 | 1.34 (0.91–1.96); P = .135 | 1.22 (0.77–1.95); P = .396 |
| Ever              | 36/20       | 61/39        | 12/25        | 1.00        | 0.83 (0.42–1.64); P = .587 | 0.25 (0.10–0.61); P = .002 | 0.60 (0.32–1.16); P = .127 | 0.29 (0.13–0.61); P = .001 |
| Alcohol consumption|             |              |              |             |              |              |              |               |               |
| Never             | 103/83      | 181/117      | 63/47        | 1.00        | 1.22 (0.84–1.77); P = .302 | 1.08 (0.67–1.74); P = .765 | 1.18 (0.83–1.68); P = .366 | 0.95 (0.63–1.45); P = .825 |
| Ever              | 20/9        | 40/21        | 9/12         | 1.00        | 0.86 (0.33–2.28); P = .764 | 0.30 (0.09–1.00); P = .050 | 0.65 (0.26–1.64); P = .364 | 0.33 (0.12–0.90); P = .030 |
| BMI (kg/m²)       |             |              |              |             |              |              |              |               |               |
| <24               | 79/56       | 151/92       | 52/34        | 1.00        | 1.17 (0.75–1.80); P = .491 | 1.08 (0.62–1.88); P = .794 | 1.14 (0.75–1.73); P = .531 | 0.98 (0.60–1.58); P = .919 |
| ≥24               | 44/36       | 70/46        | 20/25        | 1.00        | 1.26 (0.70–2.27); P = .432 | 0.69 (0.33–1.45); P = .331 | 1.06 (0.62–1.84); P = .828 | 0.60 (0.31–1.17); P = .133 |

Note: Bold values are statistically significant (P < .05). Abbreviations: AEG, esophagogastric junction; BMI, body mass index; CI, confidence interval; OR, odds ratio.

aFor INSR rs1799817 G > A, the genotyping was successful in 705 (97.92%) EGJA cases.

bAdjusted for multiple comparisons (age, sex, smoking status, BMI and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
coding-synonymous variant, it is proposed that a G → A nucleotide substitution in this locus may influence the expression of INSR molecule by altering mRNA processing or translation. For these possible reasons, rs1799817 G > A polymorphism may be a functional variant for INSR gene.

Sokhi et al28 reported that INS rs689 polymorphism was associated with an increased risk of T2D. In addition, Lempainen et al29 found that this polymorphism, cooperated with PTPN22 rs2476601 and IFIHI1 rs1990760 loci, might be correlated with the β-cell autoantibodies. A previous study has focused on the association of INS rs689 polymorphism with the risk of colorectal cancer.22 However, the null association was found for INS rs689 polymorphism to colorectal cancer. In the present study, a tendency of increased risk to AEG was found in overall comparison. In a subgroup analysis, this association was more significant in stage III/IV subgroup compared with controls. In the future, the relationship of INS rs689 T > A polymorphism with cancer risk should be explored in more case-control studies.

Although well designed, the present study has some potential limitations and they should be taken into account when interpreted our findings. First, the included sample size was modest, which limited drawing strong conclusions and performing more detailed analyses. Second, we only studied four loci in these genes, the coverage could be insufficient. In the future, a tagging SNP study should be conducted. Third, for lack of the levels of serum proinsulin, insulin, glucagon and so on, we could not carry out further analysis on the association of these SNPs with the biochemistry characteristics. Finally, a functional study is needed to explain the mechanism of these identified SNPs. In summary, this is the first study to explore the possible correlation between rs7903146 and rs290481, INS rs689 and INSR rs1799817 polymorphisms and the development of AEG. Our findings highlight that TCF7L2 rs290481, INS rs689, and INSR rs1799817 polymorphisms may increase the risk of AEG. In addition, TCF7L2 rs290481 and INSR rs1799817 SNPs may influence the lymph node metastasis in AEG patients.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

ORCID

Weifeng Tang http://orcid.org/0000-0002-4157-4057

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