Original Article

Association between eight hypermethylation-related genes and gastric cancer: a systematic review and meta-analysis

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Background: Although multiple gene promoter hypermethylation has been associated with gastric carcinogenesis, data on their specific relationship remains scant. We aimed to investigate the correlation between the status of multiple gene promoter methylation and gastric cancer (GC).

Methods: We searched PubMed, EMBASE, CNKI, Wanfang, Cqvip and Cochrane Library up to May 2021. We systematically assessed the association between methylation status of the CpG islands and the risk of GC. We compared the incidence of DNA methylation between tumor and non-tumor tissues, and evaluated the clinicopathological significance of the DNA methylation in gastric carcinoma. The data was presented by an odds ratio (OR) with an accompanying 95% confidence interval (CI). We then generated forest plots calculated by fixed-effects or random-effects model.

Results: This study enrolled a total of 201 studies (140 papers). Our analysis showed a higher frequency of methylation of the CpG islands in GC tissues compared to non-neoplastic tissues. Besides, the data demonstrated that polygene's aberrant promoter methylation might be linked to the initial development and progression of GC.

Discussion: The genes with altered DNA methylation might serve as epigenetic biomarkers, providing a promising molecular diagnostic and prognostic tool for human GC. However, our findings need further evaluation in large randomized controlled trials.

Keywords: DNA methylation; gastric cancer (GC); risk; tumor suppressor gene; diagnosis

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Introduction

Gastric cancer (GC) is the fifth most common malignant tumor, with an estimated one million new cases worldwide each year. Since diagnosis of GC usually happens at an advanced stage (1), it has a high mortality rate, with China, Japan, and South Korea accounting for highest incidence (2). The risk factors include environmental factors, such as smoking and helicobacter pylori infection, salt, and salted foods (3). In addition, the previous study has shown that genomic DNA alterations and mutations, that contribute to deregulation of metabolic pathways, as well as epigenetic machinery alterations could also lead to GC initiation and progression (4). Epigenetic processes include DNA methylation, chromatin remodeling, histone modification and functions associated with non-coding RNA (ncRNA) (5). Out of all the epigenetic processes, DNA methylation was one of the first identified and extensively

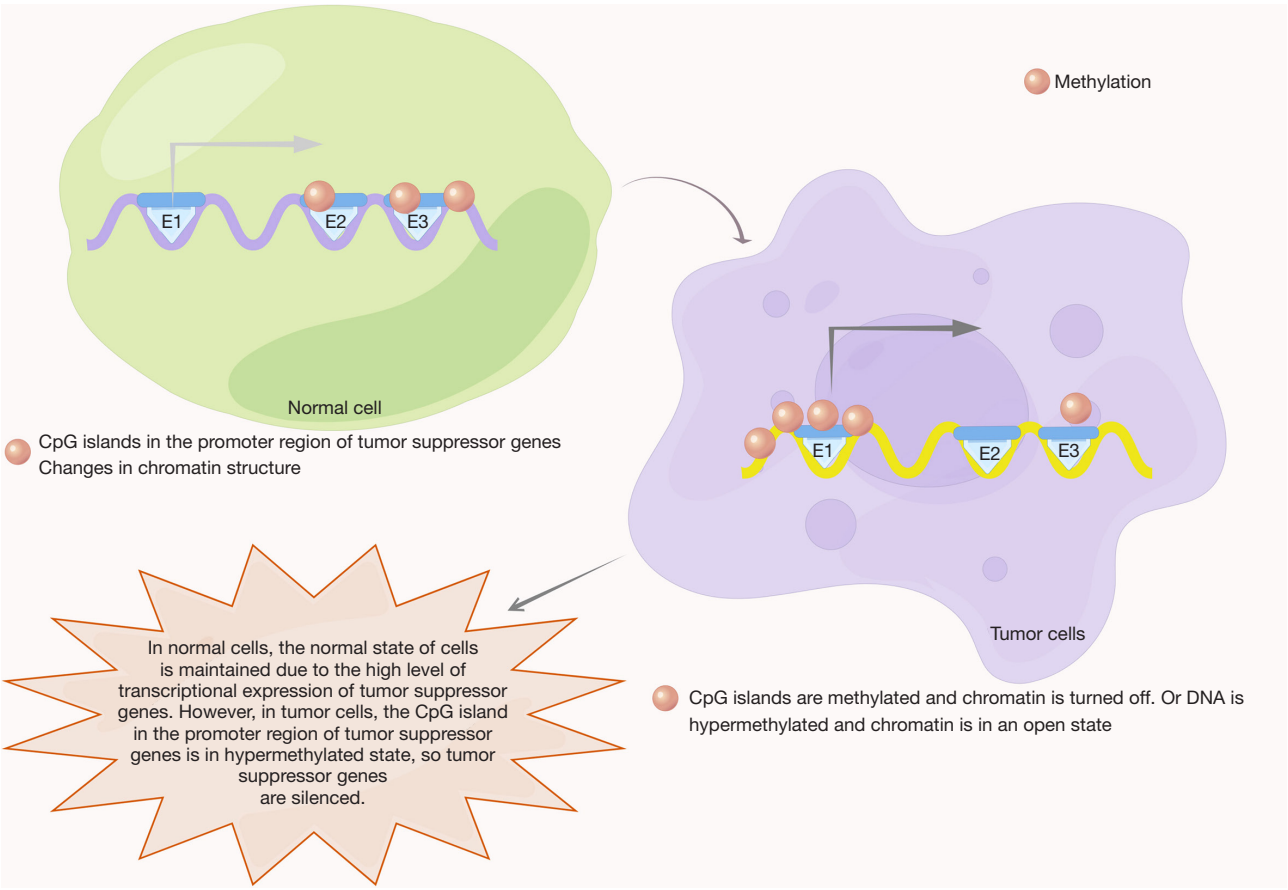

Figure 1 DNA methylation process.

studied epigenetic alterations (6). DNA promoter methylation is a chemical modification where a methyl group is transferred from cofactor S-adenosylmethionine to the C5 position of a cytosine residue in DNA to form 5-methylcytosine (7). Folic acid can provide S-adenosyl methionine (SAM), which can regulate the methylation of CpG island cytosine DNA. The phenotypic changes caused by DNA methylation are related to folic acid metabolism. Folic acid, as a coenzyme of one-carbon unit metabolism, directly participates in the transport of methyl groups in DNA methylation (8).

Hypermethylation of DNA sequences in the promoter region has been shown to modulate GC pathogenesis by silencing tumor suppressor genes (*Figure 1*). Cancer-related genes often control tumor-specific signaling pathways, cell cycle, DNA repair and apoptosis, but promoter hypermethylation can result intogenomic instability (9). Since epigenetic modulation plays a crucial role in cells, any alterations could serve as new clinical biomarkers and therapeutic targets for early detection, diagnosis and treatment of GC. This meta-analysis examined the correlation between the hypermethylation status of polygenes and gastric oncogenesis. We evaluated methylation in genes such as *hMLH1* and *MGMT*; DNA repair genes, *DAPK*; an apoptosis-related gene, *RASSF1A*; a component of RAS pathway, *CDH1*; a cell migration/invasion gene, as well as *RUNX3*; a tumor suppressor gene (10). We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-372/rc).

Methods

Search strategies

We performed systematic search of literature in PubMed, Embase, Cochrane Library, CNKI, Wanfang and Cqvip electronic databases before May 2021, without language

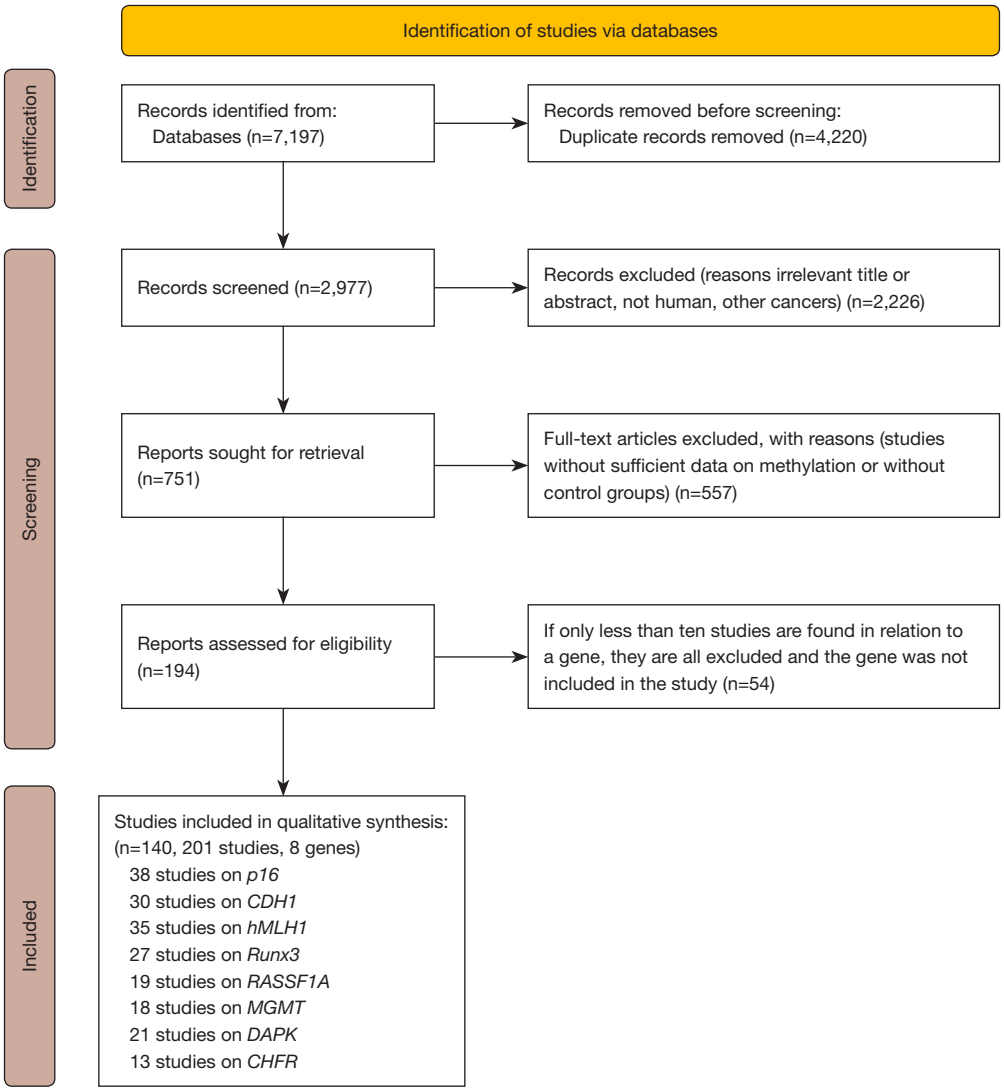

Figure 2 Shows the flow chart of the searches.

restriction. For a comprehensive search, we combined subject words and free words, such as "gastric cancer", "GC", "gastric carcinoma", "methylation", "DNA methylation", "promoter methylation", and then applied slight adjustments according to specifications in different databases. In addition, we screened reference lists of the included articles for any further relevant references. We exported all the searched articles to Endnote citation manager software. After merging the databases, we removed duplicate studies and excluded irrelevant studies following the inclusion and exclusion criteria by reading the titles and abstracts. We then read full texts of potential articles to identify eligible ones. We included studies with detailed information on the frequency of gene methylation for both the cancer and the regular control groups and methylation status on human tissue samples. Articles from animal experiments, cell lines, human xenografts, overlapping databases, and those with same population were excluded for the analysis. Letters, conference abstracts, expert opinions, reviews, editorials, letters and case reports were also excluded. *Figure 2* shows the flow chart of the searches.

Data extraction

We extracted primary data from a customized data-

extraction sheet. The primary data included year of publication, first author, ethnicity, geography location, type of tissues, methods of detection of DNA methylation, number of cases in tumor and non-tumor groups, number of methylation-positive individuals in each group and tumor clinicopathological features. Two authors independently performed the data extraction, and any disagreements were resolved first by consensus, then by consultation with a third investigator in case of disagreements.

Statistical analysis

We calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) for outcome analysis. Cochran's χ^2 test and I^2 statistic were used to explore heterogeneity of the articles included in the meta-analysis. Presence of significant heterogeneity was quantified using the I^2. The heterogeneity was acceptable when the I^2 value was less than 50, with the results measured using a fixed-effects model. When the I^2 value was 50% or greater, a random effect model was used to test for significant heterogeneity. In addition, we employed stratified analysis to further investigate the potential sources of heterogeneity and then implemented a sensitivity analysis to assess the stability of the meta-analysis. Moreover, we performed funnel plots to visually assess any publication bias for asymmetry, and also used Egger's tests to quantify publication bias. The pooled ORs analyzed promoter DNA methylation between the GC and non-tumor gastric mucosa and assessed the relationship between DNA methylation and clinical characteristics. The meta-analysis was performed using Stata12.0 software (Stata Corp, College Station, TX, USA). All P values were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

Study selection and study characteristics

This meta-analysis enrolled a total of 201 studies (140 papers) following the retrieval strategy and the inclusion/exclusion criteria (*Figure 2*). We exclude other genes from the meta-analysis due to their scarcity and lack of enough studies. We evaluated the methodological quality of the included studies according to NOQAS.

Among the included studies, 88% used methylation-specific PCR (MSP) while 5% employed quantitative-MSP (q-MSP) to detect DNA methylation. Other detection methods such as COBRA and Bisulfite hat were rarely used (available online: https://cdn.amegroups.cn/static/application/f73b47ab7360c5fb990f4b694bd229d9/tcr-22-372-1.xlsx). A total of 175 items (87%) were from Asian populations, 18 (9%) studies were from Caucasian populations, and only 4% were from African populations. In sync with previous studies, our analysis showed that the Asian countries had high incidence rate. We summarized the methylation frequency and clinical characteristics of 8 genes (available online: https://cdn.amegroups.cn/static/application/0f268a9be74fa5ede578f9d1a2b6f594/tcr-22-372-2.xlsx).

Relationship between p16 methylation status and GC

This study consisted of 38 studies, with 2,378 GC tissues and 1,991 non-cancer tissues, and investigated the association between the methylation status of the *p16* promoter and tumor histology. Given the substantial heterogeneity between the studies (χ^2=I^2=87%; P<0.001), we applied a random-effects model for the analysis. Results showed that GC had a significantly higher frequency of *p16* promoter methylation compared to the non-neoplastic samples (OR =9.68; 95% CI: 5.41–17.31; P<0.001; *Figure 3*), thus suggesting that *p16* promoter hypermethylation might be contributing to the carcinogenesis of GC.

Relationship between CDH1 methylation status and GC

This analysis included 3,462 cases, with 30 studies evaluating the correlation between *CDH1* methylation status and GC risk. MSP analysis showed that the overall pooled OR was 6.96 (95% CI: 4.07–10.98; *Figure 4*), with a sizeable between-study heterogeneity (χ^2=I^2=80.8%; P<0.001). The data demonstrated that hypermethylation of the *CDH1* promoter increases the risk of GC.

Relationship between hMLH1 methylation status and GC

We employed the random-effects model to estimate the pooled OR with the GC, and noncancerous groups showed substantial heterogeneity (χ^2=I^2=59.1%). The frequency of *hMLH1* methylation was significantly higher in the GC group compared to the nonmalignant group (OR =9.19; 95% CI: 5.73–14.75; P<0.001; *Figure 5*). This finding suggested that *hMLH1* promoter methylation plays a crucial role in the incidence of GC.

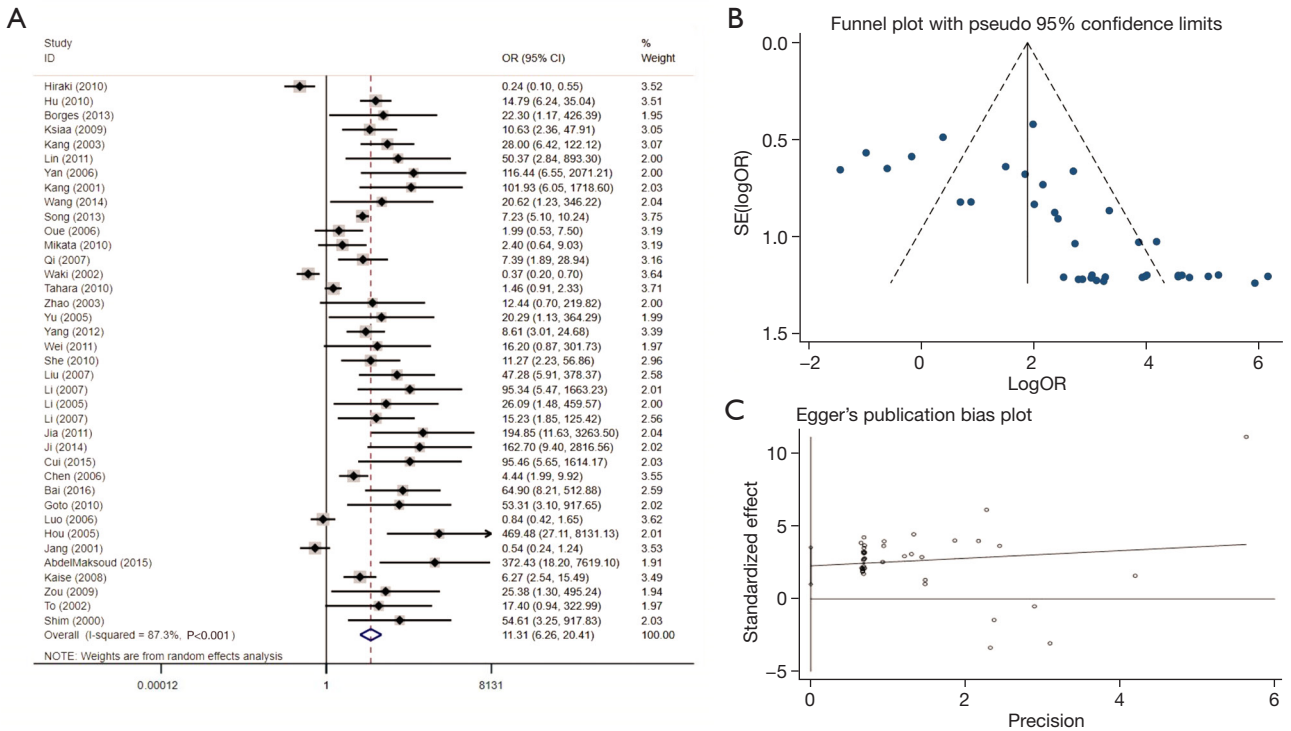

Figure 3 *p16* promoter methylation and GC risk. (A) Forest plot for the association between *p16* promoter methylation and GC risk; (B) funnel plot for the association between *p16* promoter methylation and GC risk; (C) Egger's publication bias plot for the association between *p16* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; GC, gastric cancer.

Relationship between RUNX3 methylation status and GC

We evaluated the relationship between *RUNX3* methylation status and gastric carcinoma risk in 1,580 neoplastic cases and 1,438 controls from 27 selected papers. Using the random-effects model, our analysis showed that the *RUNX3* promoter methylation increases the risk of GC with a pooled OR of 3.48 (95% CI: 2.50–4.86). Moreover, the included studies exhibited statistical heterogeneity (χ^2=I^2=73.7%; P<0.001) (*Figure 6*).

Relationship between RASSF1A methylation status and GC

To assess the relationship between *RASSF1A* promoter methylation status and GC risk, we selected 19 studies which had 1,286 gastric carcinoma cases and 801 controls. Based on the fixed-effect model, the results demonstrated that *RASSF1A* methylation was significantly related to elevated GC risk with a pooled OR of 6.41 (95% CI: 4.68–8.77) (*Figure* 7). Besides, the overall heterogeneity was low across the enrolled studies *Figure* 7.

Relationship between MGMT methylation status and GC

We evaluated the methylation status of *MGMT* in GC using 1,789 GC specimens and 1,754 controls from 18 articles. Based on the random-effects model analysis, aberrant methylation of *MGMT* was a key risk factor for the development of GC with a pooled OR of 4.34 (95% CI: 2.77–6.80). In addition, there was remarkable heterogeneity across the included studies (χ^2=I^2=76.2%; P<0.001) (*Figure 8*).

Relationship between DAPK methylation status and GC

The association between *DAPK* hypermethylation status and the risk for gastric carcinoma was assessed in 21 studies involving 1,233 GC samples and 1,374 controls. The included studies had significant heterogeneity (χ^2=I^2=65.3%; P<0.001). Results indicated that the GC group displayed markedly higher frequencies of DAPK promoter methylation than the control samples (OR =1.74; 95% CI: 1.27–2.39) (*Figure 9*). Thus, the aberrant methylation of *DAPK* might contribute to the initiation of gastric carcinogenesis.

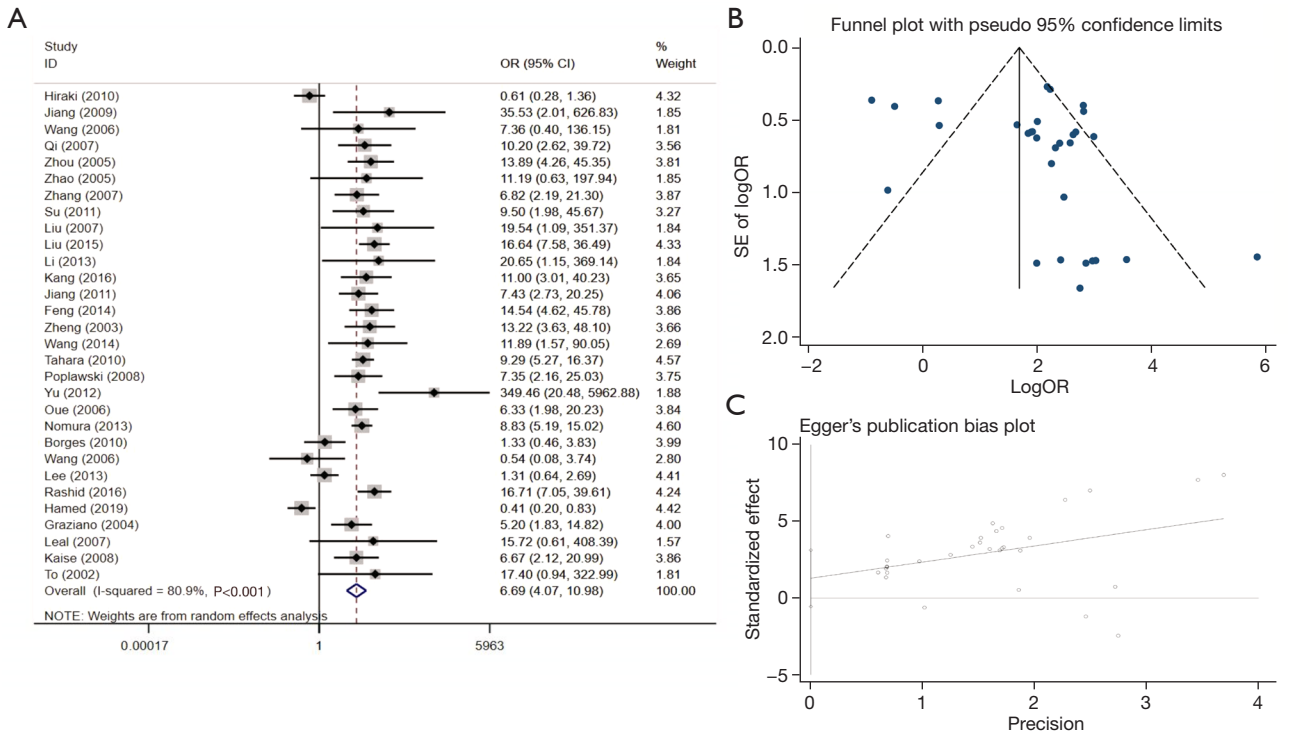

Figure 4 *CDH1* promoter methylation and GC risk. (A) Forest plot for the association between *CDH1* promoter methylation and GC risk; (B) funnel plot for the association between *CDH1* promoter methylation and GC risk; (C) Egger's publication bias for the association between *CDH1* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; GC, gastric cancer.

Relationship between CHFR methylation status and GC

A total of 13 studies with 1,352 cases, including 649 tumor tissues and 603 non-tumor tissues evaluated the role of methylation of *CHFR* gene in gastric carcinogenesis. The results revealed that the frequency of *CHFR* promoter methylation significantly correlated with GC tumorigenesis with a pooled OR of 4.46 (95% CI: 3.29–6.05) (*Figure 10*).

Correlation of gene promoter methylation with GC clinical features

We also examined DNA methylation in precancerous lesions (available online: https://cdn.amegroups.cn/static/application/0282356262afde11c2394cf10f278ace/tcr-22-372-3.xlsx). The risk of methylation of the *p16*, *CDH1*, *hMLH1*, *RUNX3* and *DAPK* genes showed an increasing trend in the regular group—precancerous tissue—cancer tissue. *p16*, *CDH1*, *hMLH1*, *RUNX3* and *RASSF1A* methylation had no statistical significance between precancerous lesions and normal tissues. On the other hand, we investigated the relationship between polygene methylation and clinical features in GC (available online: https://cdn.amegroups.cn/static/application/aac82091af91893855e0efc21dcb4d61/tcr-22-372-4.xlsx). The data showed that *p16*, *CDH1*, *RUNX3*, *RASSF1A*, *MGMT*, *DAPK* and *CHFR* methylation status were unrelated with GC patients' gender or age. However, *RASSF1A* had a markedly higher frequency of promoter methylation in T3/4 GC compared to T1/2 GC. Moreover, gastric carcinoma patients with lymph node metastasis had a considerably higher *p16*, *CDH1*, *RUNX3*, *MGMT* methylation frequency compared to patients without the lymph node metastasis. The frequency of *p16*, *RUNX3* methylation significantly increased in the GC patients with distant metastasis compared to those without distant metastasis. Furthermore, the methylation of *p16*, *CDH1* and *RUNX3* was higher in high-grade GC than low-grade GC. Besides, *p16*, *hMLH1*, *CDH1*, *RUNX3*, had a significantly higher methylation rate in GC patients in stage III/IV than stage I/II GC. In addition, our analysis demonstrated that the degree of methylation of *CDH1* and *RUNX3* genes was significantly higher in intestinal GC compared to that in diffuse GC. There was no significant correlation between

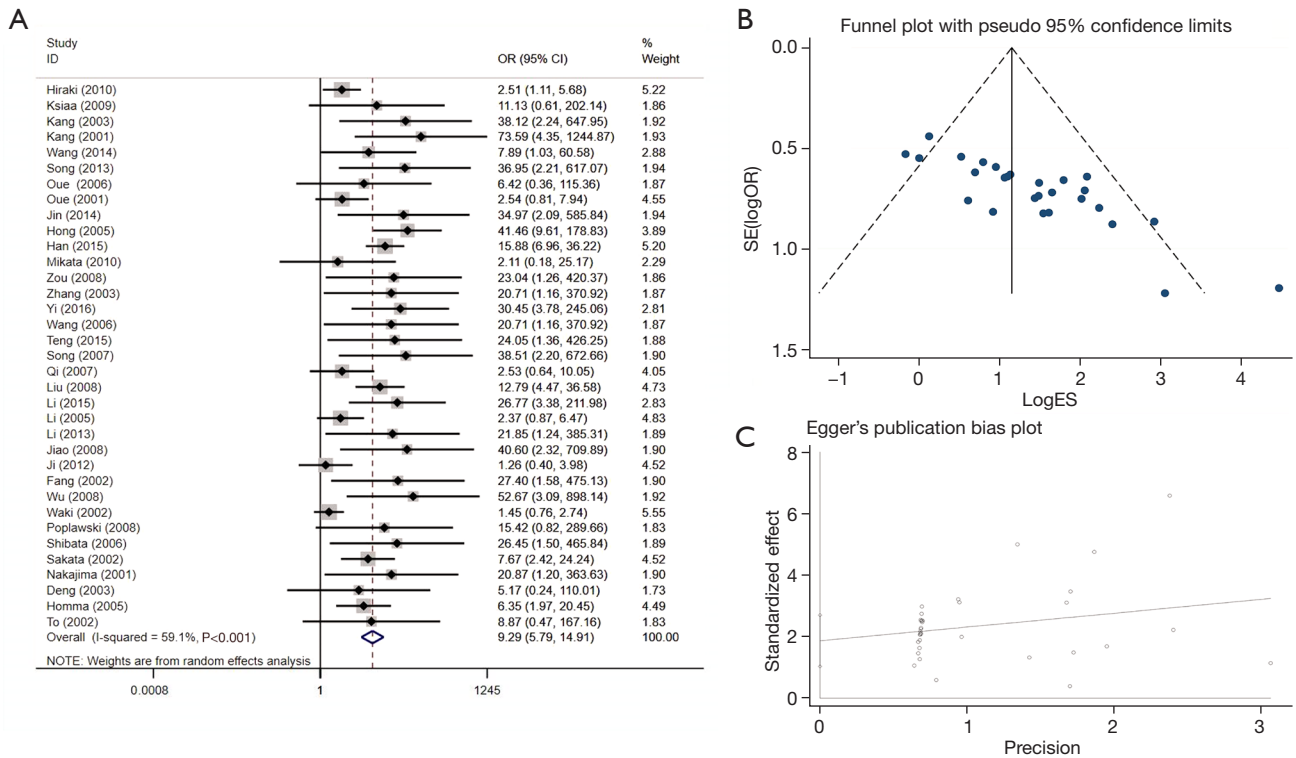

Figure 5 *bMLH1* promoter methylation and GC risk. (A) Forest plot for the association between *bMLH1* promoter methylation and GC risk; (B) funnel plot for the association between *bMLH1* promoter methylation and GC risk; (C) Egger's publication bias for the association between *bMLH1* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; ES, effect size; GC, gastric cancer.

the methylation status of the 8 gene promoters and GC vascular infiltration status or tumor size.

Stratified analysis and sensitivity analyses

We used meta-regression and subgroup analyses to explore the heterogeneity of the analyzed studies. The analysis showed that the methylation detection method, the specimen type and the ethnicity were not sources of heterogeneity in the overall meta-analysis for most of the included genes. In addition, studies from different countries (data not shown) could explain the significant heterogeneity in our meta-analysis ($I^2 \geq 80$; $P<0.05$).

The sensitivity analysis tested the impact of any study on the total estimate by omitting one study at a time. The analysis indicated that removing any of the included studies had no significant effect on the overall results, and this meta-analysis was robust and reliable (available online: https://cdn.amegroups.cn/static/application/aac82091af91893855e0efc21dcb4d61/tcr-22-372-4.xlsx). From the sensitivity analysis results, there were a few heterogeneous studies whose removal had no significant effect on the results.

Publication bias

We used Egger funnel plots with a 95% false confidence limits and Egger tests to estimate the publication bias of the included literature. The funnel plot was used to test the publication bias of the polygene methylation, and the symmetrical distribution of funnel plot indicated that there was no significant publication bias in this study (*Figures 3B*,*4B*,*5B*,*6B*,*7B*,*8B*,*9B*,*10B* and *Figures 3C*,*4C*,*5C*,*6C*,*7C*,*8C*,*9C*,*10C*).

Heterogeneity

The heterogeneity I^2 of sensitivity analysis was 68.5%, and the Q test of sensitivity analysis showed $P<0.001$, indicating that the included studies were heterogeneous.

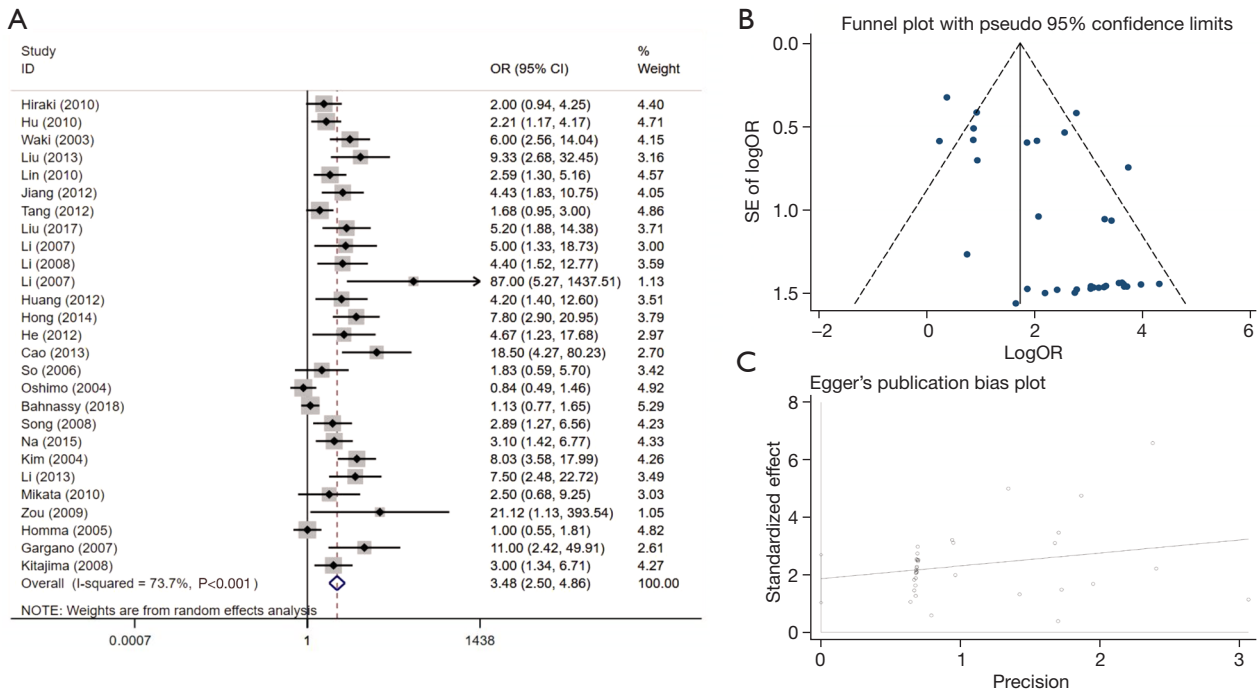

Figure 6 *RUNX3* promoter methylation and GC risk. (A) Forest plot for the association between *RUNX3* promoter methylation and GC risk; (B) funnel plot for the association between *RUNX3* promoter methylation and GC risk; (C) Egger's publication bias plot for the association between *RUNX3* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; GC, gastric cancer.

After referring to the included articles, we summarized the possible sources of heterogeneity: (I) the changes of pathological stages in patients included in the study were from NA to IV. (II) Different groups are included. (III) The cut-off value of GPR set by different studies is quite different. We take heterogeneity into account when conducting the data synthesis.

Publication bias

Analysis of publication bias using STATA 16.1 (Deek's funnel plot) did not reveal obvious publication bias (P=0.48) in the included study.

Discussion

The genes included in this meta-analysis participated in vital cell signaling pathways implicated in apoptosis, cell cycle, DNA repair as well as cell adhesion (9). The *p16* gene is an inhibitor of *CDK4* and *CDK6* kinases, which control cell cycle G1 progression, regulates G1-S cell cycle transition by phosphorylation of Rb signaling modulates the activation of *CDK4*, *CDK6*, and *cyclin D1* as well as the release of *E2F* to drive cell cycle progression (2,5). In addition, homozygous *p16* deletion or silencing via epigenetic methylation is often observed in GC (11), and the inactivation of *p16* has been implicated in gastric carcinogenesis (12). According to this study, there was significant *p16* methylation in dysplasia, intestinal metaplasia, and GC compared to non-neoplastic tissue, implicating the methylation of *p16* promoter as a risk factor of GC, which was consistent with a recent study (13). This study also demonstrated that the abnormal methylation state of *p16* correlated with GC's clinical and pathological characteristics. For instance, the frequency of abnormal methylation of the *p16* gene promoter was significantly higher in GC patients with lymph node metastasis, distant metastasis, and TNM stage III/IV cancer tissues than in cancers without lymph node metastasis, no distant metastasis, and TNM stage I/II organization. Thus, the methylation status of the *p16* promoter in GC tissue could help predict the potential of malignance and progression of GC.

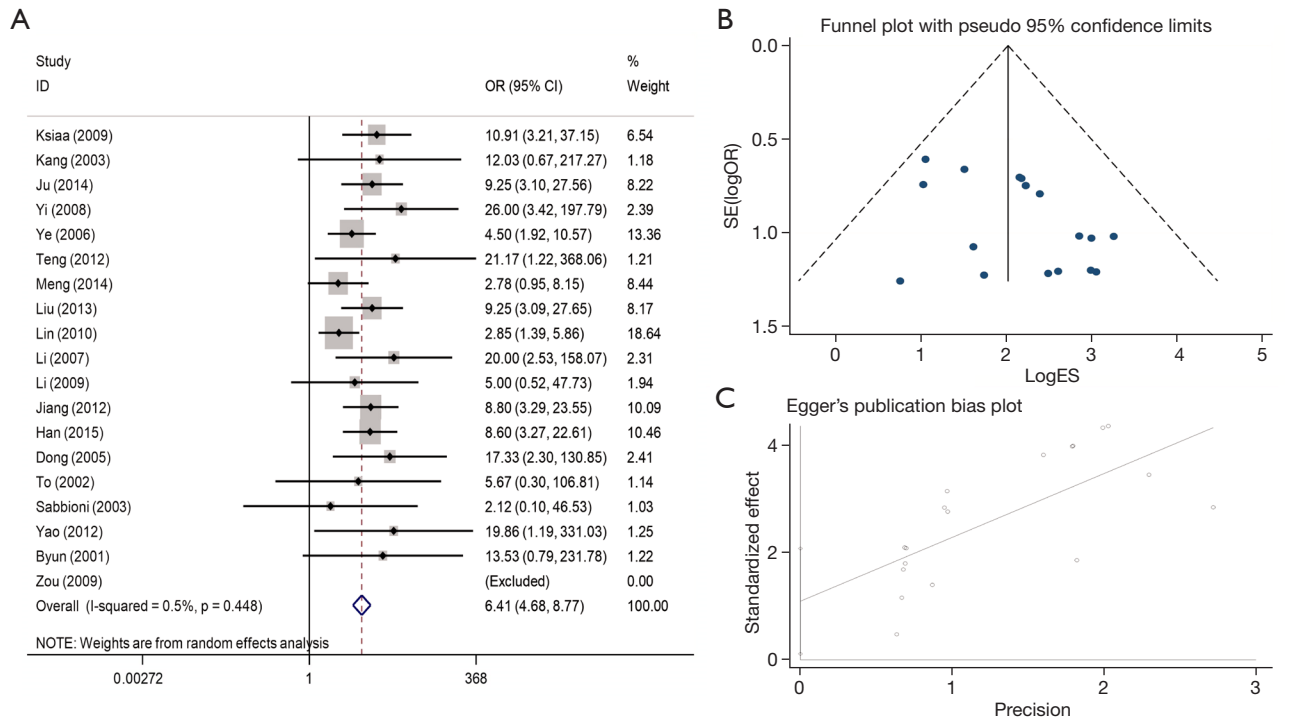

Figure 7 *RASSF1A* promoter methylation and GC risk. (7A) Forest plot for the association between *RASSF1A* promoter methylation and GC risk; (B) funnel plot for the association between *RASSF1A* promoter methylation and GC risk; (C) Egger's publication bias for the association between *RASSF1A* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; ES, effect size; GC, gastric cancer.

CDH1 is essential in the maintenance of cell morphology and regulation of cell adhesion (14). *CDH1* gene encodes *E-cadherin* (*E-cad*), which participates in the inhibition of migration and invasion of tumor cells (15). Interestingly, our study did not observe any relationship between the *CDH1* methylation and GC Lauren classification, which merits further investigation. Epigenetic alterations have been shown to lead to *CDH1* inactivation through an array of complex mechanisms. For instance, low *E-cad* expression in GC has been linked with methylation of *CDH1* CpG islands, indicating that the *CDH1* promoter methylation might be a critical molecular event in the initiation of GC (16). In addition, we showed that the methylation rate of *CDH1* promoter in gastric carcinoma was higher than that in non-cancerous specimens, thus inactivation of the *CDH1* by methylation could result into GC. The abnormal methylation status of the *CDH1* gene was also correlated with GC's clinical and pathological characteristics. The aberrant methylation frequency of *CDH1* was considerably higher in T3/4, high grade, stage III/IV and intestinal GC than that in the T1/2, low grade, stage I/II as well as diffuse GC. The methylation status of the *CDH1* gene in gastric carcinoma tissues could predict the progress and prognosis of gastric carcinomas.

hMLH1 and *MGMT* are mismatch repair (MMR) genes of DNA, which affect the endogenous repair function of cells, maintain genome stability, and inhibits GC (17-19). The *MGMT* gene could serve as a predictive biomarker in neuro-oncology and esophageal carcinoma (20,21). Besides, *MGMT* and *hMLH1* correlated with GC clinicopathology. The methylation frequency of *hMLH1* was higher in the age ≥60 GC group than in age <60 patients. In addition, the methylation frequency of *MGMT* was higher in lymphatic metastasis GC group compared those without lymphatic metastasis, suggesting that the methylation of *hMLH1* or *MGMT* could lead to GC initiation and progression.

RUNX3 regulates the proliferation of GC cells by participating in the TGF and Wnt pathways (22-24). In addition, *RUNX3* promotes the angiogenesis of GC by regulating the level of vascular endothelial growth factor (*VEGF*) (25). Previous experiments in animal models showed that *RUNX3* dysfunction is related with the

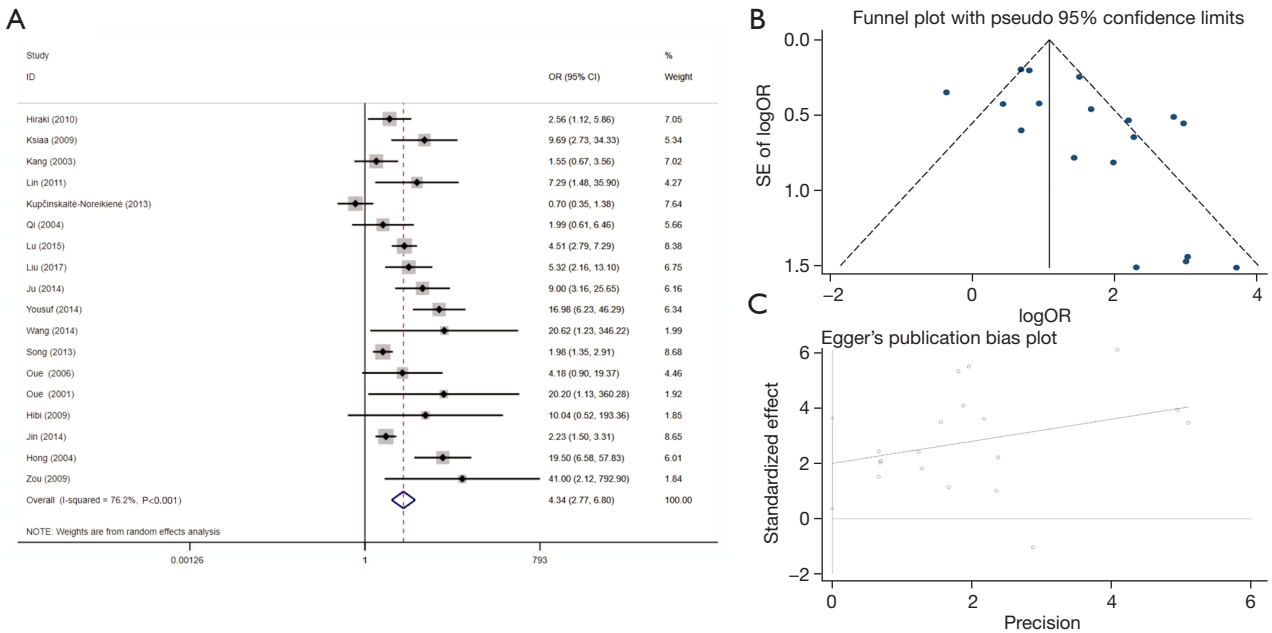

Figure 8 *MGMT* promoter methylation and GC risk. (A) Forest plot for the association between *MGMT* promoter methylation and GC risk; (B) funnel plot for the association between *MGMT* promoter methylation and GC risk; (C) Egger's publication bias for the association between *MGMT* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; GC, gastric cancer.

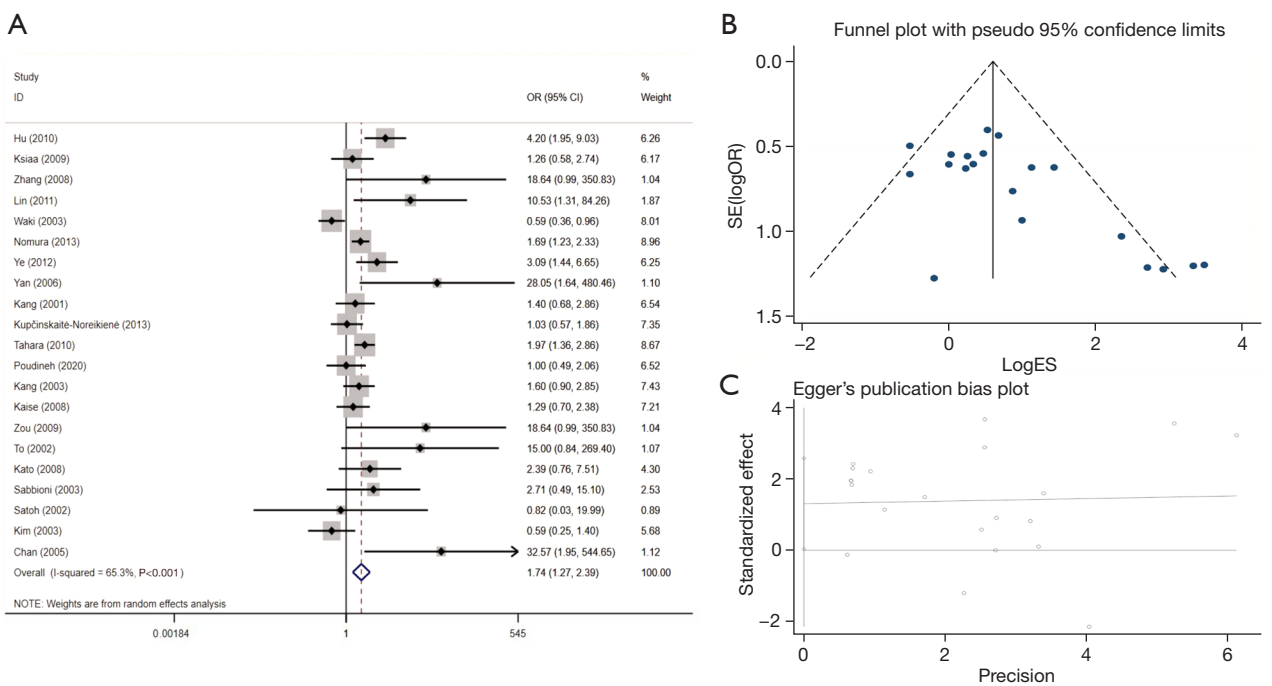

Figure 9 *DAPK* promoter methylation and GC risk. (A) Forest plot for the association between *DAPK* promoter methylation and GC risk; (B) funnel plot for the association between *DAPK* promoter methylation and GC risk; (C) Egger's publication bias for the association between *DAPK* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; ES, effect size; GC, gastric cancer.

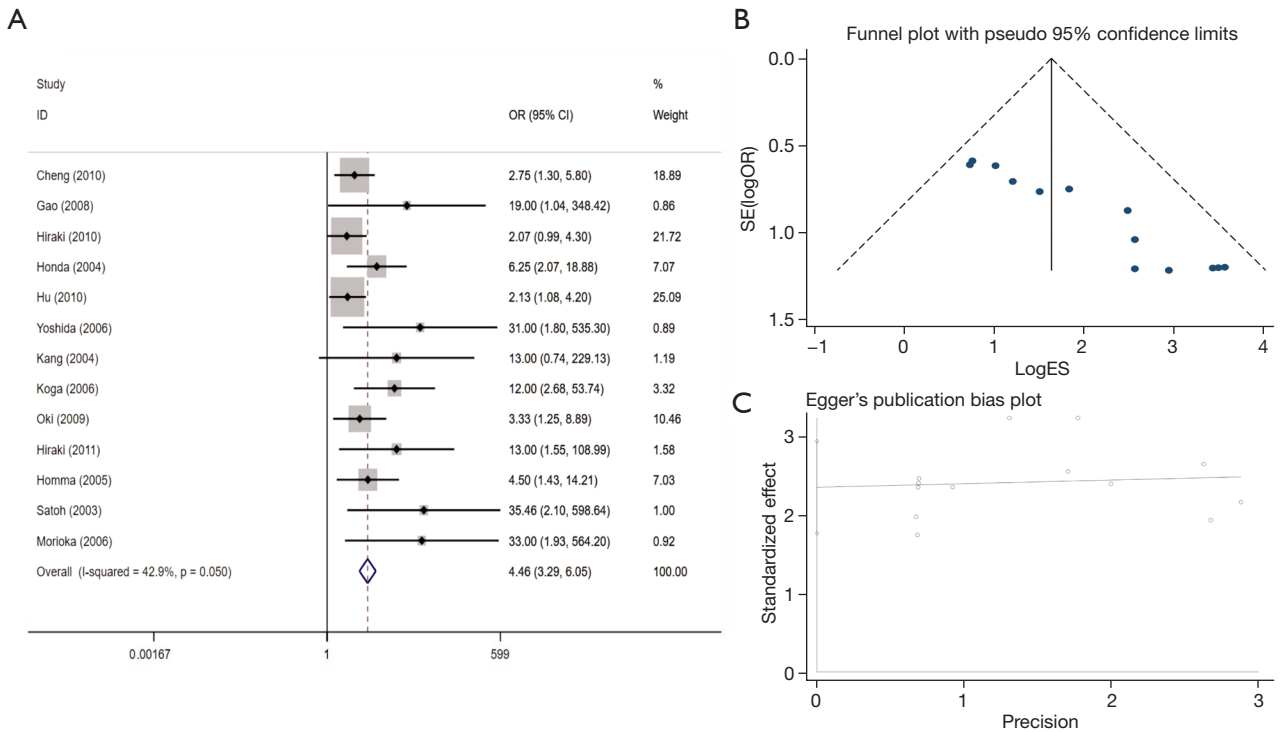

Figure 10 *CHFR* promoter methylation and GC risk; (A) Forest plot for the association between *CHFR* promoter methylation and GC risk; (B) funnel plot for the association between *CHFR* promoter methylation and GC risk; (C) Egger's publication bias for the association between *CHFR* promoter methylation and GC risk. OR, odds ratio; CI, confidence interval; SE, standard error; ES, effect size; GC, gastric cancer.

occurrence and progression of cancer (26,27). There was significant reduction in the expression of *RUNX3* in GC, and the level of *RUNX3* was positively correlated with the methylation of *RUNX3* in the promoter region 6. In sync, our study showed that the methylation of *RUNX3* affects GC and its clinicopathology. The methylation degree of the *RUNX3* promoter was higher in patients with high grade, lymph node metastasis, distant metastasis, stage III/IV and intestinal GC, than in patients with low grade, stage I/II and diffuse GC. These results suggest that the degree of methylation of the *RUNX3* promoter might help predict the progression of malignant GC.

RASSF1A suppresses tumor growth and is essential in apoptosis, cell cycle regulation as well as microtubule stability through the Ras signaling pathway (28,29). Methylation of *RASSF1A* promoter CpG island plays a significant role in the initiation and progression of GC (30). Likewise, our data showed that the abnormal methylation of the *RASSF1A* gene was related to GC and its clinical features. The methylation frequency of *RASSF1A* was higher in stage T3/4 GC than in stage T1/2 GC. The GC patients with lymph node metastasis were more likely to develop *RASSF1A* methylation compared to those without lymph node metastasis, suggesting that *RASSF1A* methylation could help predict the malignant potential and progression of GC. Overall, our results are consistent with and added more data to the prior study. (31).

The *DAPK* play a vital role in regulating cellular process and serve as positive mediators of apoptosis via extrinsic and intrinsic death-regulating signaling pathways (32). Moreover, *DAPK* has an essential function in mediating apoptotic signaling during tumorigenesis (33). The decreased expression of *DAPK* may lead to abnormal cell proliferation and even malignant tumors (34). Hypermethylation of *DAPK* is the leading cause of low expression in tumors (35). Coupled with previous meta-analysis, we suggest that methylation of *DAPK* was associated with gastric carcinogenesis (36). Our study demonstrated that the frequency of *DAPK* methylation in GC is not associated with clinical characteristics.

CHFR is a cell cycle regulator (30), a tumor suppressor gene (37), and controls cell division (38). We observed that methylation of the *CHFR* promoter in GC exceeded that in non-tumor tissues. The correlation between GC and its methylation status was consistent with the previous results in cell experiments (39).

In our meta-analysis, precancerous lesions showed increased frequency of methylation of *MGMT*, *CDH1*, and *DAPK*. Thus, gene methylation occurred at the initial stage of malignant transformation of the gastric mucosa and accumulated changes with the disease development. In addition, the levels of *p16*, *CDH1*, *RUNX3*, *hMLH1*, *RASSF1A*, *MGMT* and *CHFR* in GC were significantly higher than the hypermethylation levels in non-cancerous tissues, suggesting that the methylation of these genes might be a risk factor for GC. In addition, methylation of promoters of genes such as *p16*, *CDH1*, *RUNX3*, *hMLH1*, or *RASSF1A* were related with the clinicopathological characteristics of GC. Therefore, the level of methylation of these gene promoters in tissues can be used as prognostic indicators of GC.

Epigenetic alterations are potential biomarkers used to evaluate the risk of cancer, early identification of tumors, and predict patient's prognosis and response to therapy (40). In addition to DNA promoter methylation of single genes or gene sets in tissues, other study shows they can be detected in liquid biopsy (biological fluids like urine, blood, saliva, and cerebrospinal fluid, among others) (41). However, no gene set is widely used for GC screening currently. Moreover, epigenetic therapeutics can be combined with traditional chemotherapies, targeted therapies, other epigenetic agents and immunotherapy modalities to broaden response rates among patients with hematologic cancers and could extend such treatments to solid tumors (42,43). Recently, various epi-drugs have been developed and tried in clinical use (44), and two classes of the epigenetic drugs, namely *DNMT* inhibitors (DNMTi) and *HDAC* inhibitors (HDACi), have shown positive results in experimental GC treatment. Nevertheless, these therapies have not yet reached clinical practice (5).

Our study was limited by the fact that we only included Chinese and English literature without retrieving other possible languages. Besides, the methylation of gene sets in plasma are potential serum biomarkers, which were not captured in our discussion. The serum biomarkers might support early detection of GC development and monitor disease progression dynamically. This article did not analyze Helicobacter pylori infection and almost all the included studies were case-control designs. In addition, most of the included literature was from the Asian population and estimates from the other areas were based on small numbers and should therefore be interpreted with caution.

Conclusions

Taken together, our data indicated that methylation of the polygene promoter perturbs gastric carcinogenesis and development. The study provides new insights into the occurrence of GC, suggesting that the methylation status of the polygene promoter could act as a new biomarker for GC diagnosis and prognosis. However, our conclusion needs further verification in large randomized controlled trials.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-372/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-372/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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