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Review Article

Which Individuals with Positive Family History of Gastric Cancer Urgently Need Intensive Screening and Eradication of Helicobacter Pylori? A Systematic Review and Meta-Analysis

Gui He [1,2,3], Xuanke Ji [1,2,3], Yali Yan [1,2,3], Kunyan Wang [1,2,3], Chunhua Song [1,2,3], Peng Wang [1,2,3], Hua Ye [1,2,3], Liping Dai [1,2,3], Jianying Zhang [1,2,3], *Kaijuan Wang [1,2,3]

1. *Department of Epidemiology, College of Public Health, Zhengzhou University, Zhengzhou, China*
2. *Key Laboratory of Tumor Epidemiology of Henan Province, Zhengzhou University, Zhengzhou, China*
3. *State Key Laboratory of Esophageal Cancer Prevention & Treatment, Zhengzhou University, Zhengzhou, China*

***Corresponding Author:** Email: kjwang@163.com

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Abstract

Background: Family history may inform individuals that they are at risk of gastric cancer (GC). However, it is too extensive to conduct intensive screening strategies for all individuals with family history of GC instead of average-risk screening. To establish more precise prevention strategies, accurate risk estimates are necessary for individuals with family history of GC.

Methods: We searched PubMed, EMBASE and Cochrane for all relevant studies from their inception to May 21, 2020, for cohort and case-control studies investigating the association between family history of GC and its risk. Relative risk (RR) and 95% confidence interval (CI) were pooled from studies using random-effects or fixed effects.

Results: The RR of GC was 2.08 (95% CI=1.86-2.34) in individuals with family history of GC according to twenty-nine case-control studies and 1.83 (95%CI=1.67-2.01) from six cohort studies. The increased risk was higher in individuals with sibling history of GC than those with parental history of GC (RR=3.18, 95% CI=2.12-4.79 vs. RR=1.66, 95% CI=1.46-1.89, *P*=0.021). For individuals with 2 or more first-degree relatives (FDRs) with GC, the RR was 2.81(95% CI=1.89-3.99). Subjects with both family history and *Helicobacter pylori (H. pylori)* infection confer a higher risk of GC (RR = 4.03, 95%CI=2.46-6.59).

Conclusion: The RR of GC among FDRs is lower than in previous studies. However, the risk of GC is markedly increased in individuals having a sibling with GC, more than 2 FDRs with GC. Intensified screening and eradication therapy for *H. pylori* could be considered for these individuals.

Keywords: Family history; Gastric cancer; Risk; Meta-analysis; *Helicobacter pylori*

Introduction

Globally, Gastric cancer (GC) is the fifth commonest cancer, and the third leading cause of cancer-related death (1). Especially in Eastern Asia, high incidence and mortality pose considerable public health challenges in terms of healthcare

costs. Therefore, identification of high-risk population is crucial for preventing GC and reducing healthcare costs (2). Some screening guideline for GC recommends screening for all individuals with a family history of GC (3). However, these recommendations may be too wide to accurately guide the primary prevention of GC.

Epidemiologic studies have demonstrated that a family history of GC increases risk for GC (4, 5). This increased risk may be related to inherited genetic factors and shared environmental factors between family members (6, 7). Thus, for individuals with a positive family history of GC, the risk of developing GC is affected by various factors, such as the degree, number and type of family members developed GC, or the diagnostic age of GC. However, there is a lack of evidence-based estimates to quantify the risk of GC based on these factors. Otherwise, whether individuals with sibling history of GC have a higher risk than those with parent history of GC remains inconclusive. Individuals with family history of GC and colonized with *H. pylori* are rarely considered. Therefore, quantitative estimates and further stratified analyses are needed to determine in which individuals with family history of GC have a higher risk of GC.

Methods

This analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (8). The protocol was registered at PROSPERO [CRD 42020163421] (https://www.crd.york.ac.uk/prospero/).

Search strategy and study selection

We searched PubMed, EMBASE and Cochrane for all relevant studies from their inception to May 21, 2020. The search terms included four main categories: "gastric cancer", "family", "cohort study" and "case-control study". No publication status and language restrictions were imposed. Moreover, the reference lists of selected articles were examined for additional eligible studies. The following studies were excluded: 1) case reports, reviews and conference abstracts; 2) studies did not define family history of GC clearly; 3) controls had other malignant diseases; 4) The Newcastle-Ottawa Scale (NOS) <6; 5) studies with duplicated data.

Data extraction and Quality assessment

Two reviewers independently extracted data from all included studies. The following data were extracted: name of the first author, year of publication, country, study design, number of cases, variables adjusted in the analysis, type of family history exposure, effect estimates (odds ratio, relative risk, standardized incidence ratio and 95% confidence interval) and other stratified data. The odd ratios (ORs) were collected as good estimates of relative risk (RR) because of extremely low incidence of GC in symptomatic populations (9). The adjusted estimates were extracted if a study reported both crude and adjusted risk estimates. Stratified data were also collected for subgroup analysis such as degree, number, age, site of GC and type of family history exposure. Quality assessment was independently assessed using NOS by two investigators. The NOS scores ranging 0 to 9 based on eight items. Studies with scores≥6 were included. (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

Statistical analysis

The pooled estimates RR as the effect of outcomes. Assessment of heterogeneity between the included studies was tested using the I^2 statistic of chi-square test. The RR estimate was pooled by random-effects model, when I^2>50% (suggested high heterogeneity), otherwise, the fixed-effects model was used. Subgroup analyses and meta-regression were conducted to explore potential sources of heterogeneity (10). Sensitivity analysis was performed to evaluate the robustness of the results by sequentially omitting one study at a time. Possible publication bias was assessed using Begg's regression test and funnel plot, and P<0.05 was considered to reflect statistically significant. All these statistical analyses were calculated using STATA/SE 15.1 (Stata Corp, College Station, TX).

Subgroup analysis

Since 35 studies showed high heterogeneity, stratified meta-analysis on risk of GC was further performed by the following subgroups: 1) degree of affected relatives (at least 1 FDR versus at least 1 SDR); 2) number of FDR affected (1 FDR versus at least 2 FDR); 3) the types of FDR (parent, father versus sibling); 4) age of person at risk(younger than 60 versus 60 yr or older); 5) gender of person at risk; 6) anatomic site of GC (cardia versus non-cardia); 7) Lauren classification (intestinal versus diffuse); 8) study design (cohort studies versus case-control studies); 9) geographic region of study (Asia versus Americas, Europe); 10) the covariates adjusted. These subgroup analyses are necessary because we perceive them as potential sources of heterogeneity of this meta-analysis.

Results

Literature search

Overall, 2331 articles were identified from the search strategy in PubMed, EMBASE and The Cochrane Library (Fig. 1).

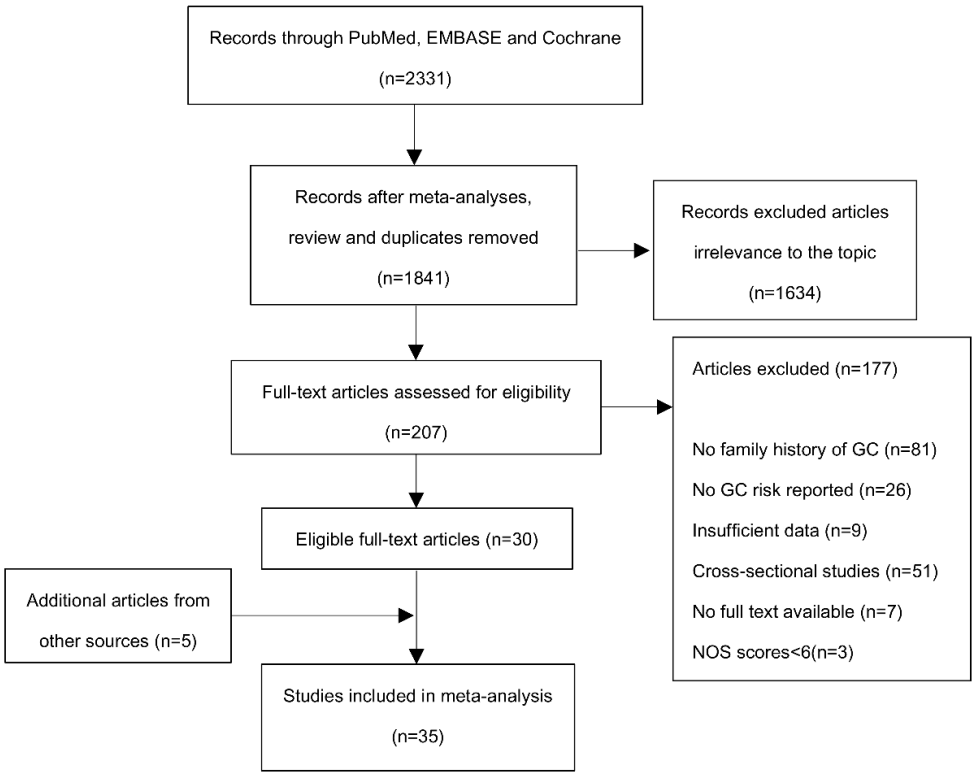

Fig.1: Flow diagram of selection of studies for meta-analysis

After the removal of meta-analyses, review and duplicate articles, 1841 articles remained. After the exclusion of 1634 irrelative articles based on title and abstract, 207 articles were reviewed for full texts screening. The 177 articles were excluded because of following reasons: No family history of GC (n=81), No GC risk reported (n=26), Insufficient data (n=9), Cross-sectional studies (n=51), No full text available (n=7), NOS scores <6 (n=3). Therefore, 30 articles from PubMed, EMBASE and The Cochrane Library, and 5 additional articles from references of eligible studies. Finally, 35 articles were included in this meta-analysis (4-6, 11-42). Characteristics and NOS score of selected studies were summarized (Table 1).

Table 1: Characteristics and NOS score of selected studies in the meta-analysis

Author(year)	*Country*	*Type of design*	*No. of case*	*Adjusted variables*	*NOS*
Shen, J.(2001)	China	Cohort	448	Age and Sex	6
Wang, G. P.(2012)	China	PBC	772	Age, sex and occupation	8
Shin, C. M.(2010)	Korea	HBC	497	*H. pylori* infection, residency during childhood, smoking, current income, and spicy food diet	7
Lin, Y.(2019)	China	PBC	622	Age, sex, BMI, education, occupation, income, smoking, alcohol drinking, drinking tea , chronic atrophic gastritis, reflux, and *H. pylori* infection	8
Luo, H. Z.(2005)	China	PBC	251	None	7
Behnampour, N.(2014)	North Iran	PBC	156	Age, sex, smoking, Charred flesh, *H. pylori* infection,	8
Zhao, J. K.(2017)	China	PBC	2216	Age, sex, county of residence, education, income, pack-years of smoking, alcohol drinking	8
Wang, N.(2010)	China	PBC	285	Age and sex	7
Gao, S.(2011)	China	PBC	398	Age, sex, or histological classification.	8
Yatsuya H.(2004)	Japan	PBC	220	The number of siblings smoking status, drinking habit, consumption of vegetables, *H. pylori* infection, citrus fruits green tea and educational level	9
Song, H.(2018)	Swedish	Cohort	1302	Age, sex, family size and stratified by pathology department	8
Song, M.(2018)	Finland	Cohort	307	Age, type of assigned intervention, BMI, pack-years of smoking, vegetable intake, alcohol drinking, highest level of education , fruit	9
Dhillon, P. K.(2001)	America	PBC	1143	Age, sex, race, pack-years of smoking, gender-specific quartile of BMI, income and proxy status.	8
Hassan, M. M.(2008)	America	HBC	740	Age, sex, and race	7
Safaee, A.(2011)	Iran	PBC	1010	Age and sex	7
Lissowska, J.(1999)	Poland	PBC	464	Age, sex, education, smoking, fresh, fruits/vegetables	8
La Vecchia, C.(1992)	Italy	HBC	628	Age, sex, area of residence, education, and number of siblings.	7
Foschi, R.(2008)	Italy	HBC	230	Age, sex, education, BMI, smoking	8
Hagy, G. W(1954)	America	HBC	106	None	6
Zanghieri, G.(1990)	Japan	HBC	970	Age, sex, education, BMI, smoking	7
Toyoshima, H.(1997)	Japan	Cohort	907	None	7
Huang, X.(1999)	Japan	HBC	850	Age and sex	6
Huang, X. E.(2004)	Japan	HBC	1988	Age and Sex	7
Ikeguchi, M.(2001)	Japan	HBC	926	None	6
Ihamaki, T.(1991)	Finland	Cohort	301	Age and Sex	7

Muñoz, N.(2001)	Vene-zuela.	PBC	292	Age, Sex, BMI and socio-economic status	8
Palli, D.(1992)	Italy	PBC	819	Age, Sex, smoking, alcohol drinking, and BMI	8
Palli, D.(2000)	Italy	Cohort	84	Age, Sex, area of residence, smoking, alcohol drinking, BMI, Social class and histological classification.	9
Brenner, H.(2000)	Germany	PBC	68	Age, sex, education and *H. pylori* infection	8
García, M. A.(2007)	Spain	PBC	404	Age, Sex, smoking and alcohol drinking	9
T Bakir(2000)	Turkey	PBC	1240	Age and Sex	7
Nagase，H(1996)	Japan	HBC	136	Age and Sex	6
Minami, Y.(2003)	Japan	HBC	614	Age, sex, year of survey, alcohol consumption, occupation	8
Chen, M. J.(2004)	China	HBC	176	Age, sex, education, income, smoking	8
Gong, E. J.(2014)	Korea	PBC	237	Age and Sex *H. pylori* infection	9

PBC: Population-based case-control; HBC: Hospital-based case-control; BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; NOS: Newcastle-Ottawa Quality Assessment Scale

Risk of gastric cancer and family history

From included studies, subjects with family history of GC were significantly more likely to develop GC (RR=2.00, 95%CI=1.83–2.20; P<0.001) compared to subjects without family history (Fig. 2). Thirty-five studies showed high heterogeneity (I^2=57.1%; Q=79.33; $P_{\text{heterogeneity}}$ <0.001). The sensitivity analysis meant that the result of meta-analysis was robustness. The Begg's test provided that no publication bias was observed (Begg's regression test P=0.256; funnel plot in Fig. 3).

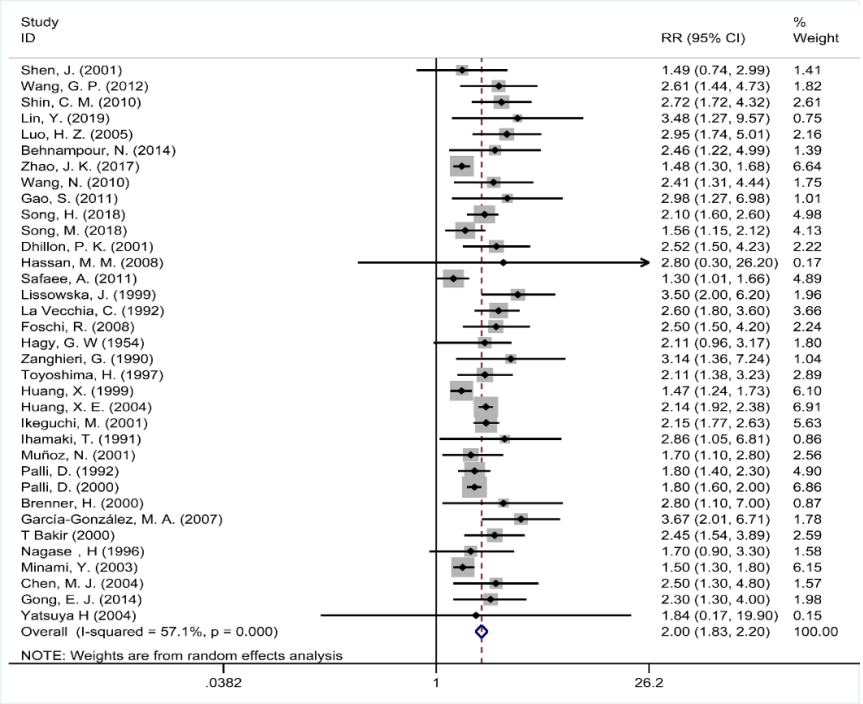

Fig.2: Forest plot of individuals with family history of gastric cancer and gastric cancer risk

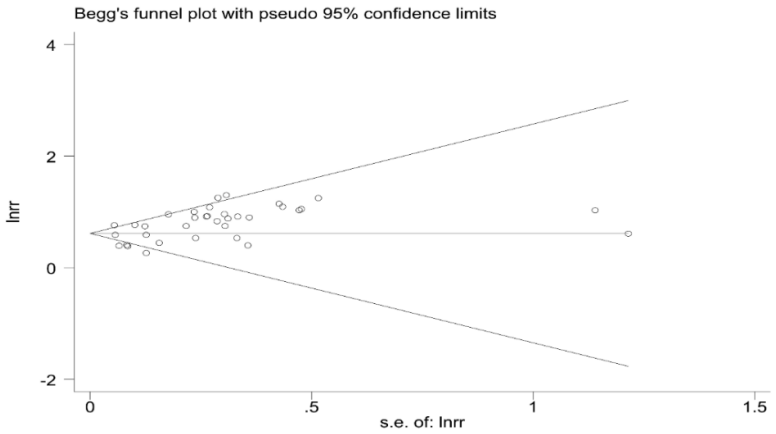

Fig.3: Begg's plot for publication bias of all studies (P=0.256>0.5)

Risk of gastric cancer based on degree of family members

Family history of GC in first-degree relatives (FDRs) conferred an increased risk of GC (RR=2.07, 95%CI=1.88-2.29, P<0.001). The heterogeneity was high (I^2=52.6%, Q=54.85, $P_{heterogeneity}$ <0.001). No publication bias was observed (Begge's regression test P=0.279). Subjects having second-degree relatives (SDRs) with GC were 1.84-fold (95%CI=1.06-3.02, P=0.031) increased risk of GC compared to without such a family history. High heterogeneity was observed (I^2=54.8%, Q=6.64, $P_{heterogeneity}$ =0.084). When individuals with at least one third-degree relatives (TDRs), the two studies corrected RR was not statistically significant (P=0.214). (Fig. 4)

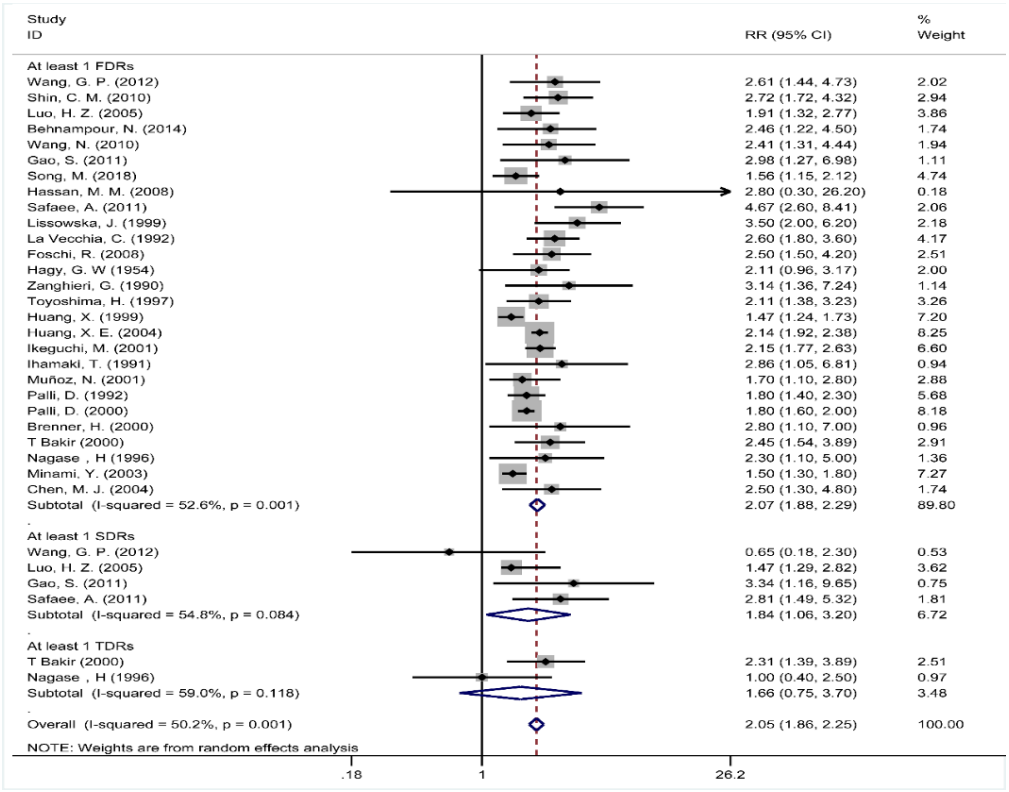

Fig.4: Pooled relative risk of gastric cancer in individuals based on degree of family members

Risk of gastric cancer according to type of first-degree relative

Since the impact of at least one FDR with GC was statistically significant and very robustness, we further analyzed the pooled effect of type of FDR. The risk was higher in individuals having sibling with GC than those having parent with GC (RR=3.18, 95%CI=2.12-4.79, I^2=81.9% versus RR=1.66, 95%CI=1.46-1.89, I^2=21.5%, P=0.021) (Fig. 5). Considered separately, paternal history of GC was statistically significant (RR=1.58, 95%CI=1.23-2.03, P=0.004, I^2=38.0%), whereas maternal history was non-significant (RR=1.50, 95%CI=0.77-2.93, P=0.238, I^2=78.6%).

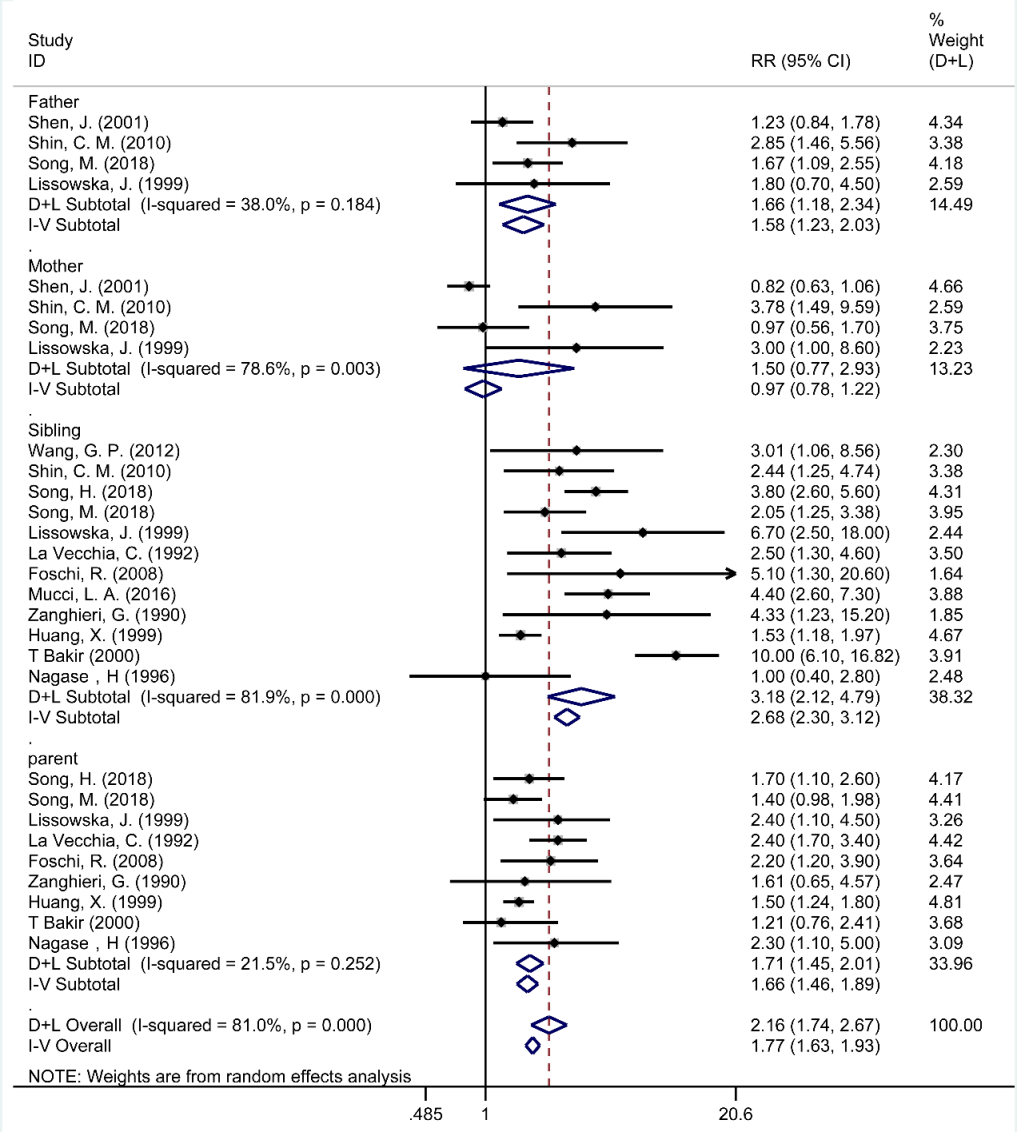

Fig.5: Pooled relative risk of gastric cancer in individuals based on type of first-degree relative

Subgroup and meta-regression analysis

Stratified analyses were performed according to number of FDRs, age and gender of person at risk, anatomic site, study design, geographic area of study, and *H. pylori* infection (Table 2).

Table 2: Stratified analysis of family history and risk of gastric cancer

Category	*Studies(n)*	*RR(95%CI)*	*Heterogeneity*		*P-value*
			I^2 (%)	*P*	
Gender of person at risk					
Male	3	2.29(1.80-2.91) **	0.0	0.373	Ref
Female	3	2.40(1.83-3.14) **	0.0	0.454	0.818
Age of person at risk					
Higher than 60	3	2.20(1.58-3.08) **	0.0	0.714	Ref
Lower than 60	3	2.93(1.81-4.47) **	0.0	0.374	0.398
No. of FDR					
1 FDR	3	1.82(1.53-2.15) **	22.8	0.274	Ref
At least 2 FDR	6	2.81(1.98-3.99) **	36.1	0.166	0.132
Anatomic subsite					
Cardia	5	1.65 (1.24-2.20) **	21.7	0.276	Ref
Non-cardia	4	2.23 (1.87-2.67) **	39.6	0.174	0.171
Lauren classification					
Intestinal	4	4.08 (3.49-4.76) **	81.3	0.001	Ref
Diffuse	4	3.89 (3.26-4.64) **	66.4	0.030	0.803
Design					
Cohort	6	1.83(1.67-2.01) **	0.0	0.549	Ref
Case-control	29	2.08(1.86-2.34) **	62.8	<0.001	0.410
Region					
Asia	18	1.99 (1.73-2.27) **	64.9	<0.001	Ref
Americas	3	2.35 (1.60-3.45) **	0.0	0.897	0.449
Europe	9	1.94 (1.78-2.10) **	49.6	0.037	0.753
Adjust smoking					
Yes	14	2.09(1.79-2.45) **	59.0	0.003	Ref
No	21	1.97(1.75-2.22) **	56.4	0.001	0.559
Adjust alcohol consumption					
Yes	7	1.65(1.54-1.76) **	42.6	0.107	Ref
No	28	2.04(1.91-2.17) **	44.8	0.001	0.016
Adjust *H. pylori* infection					
Yes	6	2.61(1.96-3.47) **	0.0	0.985	Ref
No	29	1.96(1.78-2.16) **	61.6	<0.001	0.126
Factor					
Family history positive	35	2.00(1.83-2.20) **	57.1	<0.001	Ref
Family history and *H. pylori* positive	4	4.03(2.46-6.59) **	0.0	0.517	0.015

The"*"indicate statistically significant levels: **P≤0.001.
RR: relative risk; 95%CI: 95% confidence interval; FDR: first-degree relative, *H. pylori*: *Helicobacter pylori*

The RR of GC was 2.08(95%CI=1.86-2.34) in individuals with family history of GC according to twenty-nine case-control studies and 1.83 (95%CI=1.67-2.01) according to six cohort studies. The RR of GC was 4.03 (95%CI=2.46-6.59, I^2=0.0%) in subjects with both a family history and *H. pylori* positive compared with the uninfected subjects without a family history. Individuals with at least 2 FDRs with GC were more likely to develop GC (RR=2.81, 95% CI=1.89-3.99, I^2=36.1%). The higher risk of GC is associated with a family history of GC for individuals who is younger than 60 yr old, compared with those who is older than 60 yr (RR=2.93, 95%CI=1.81-4.47, I^2=0.0% compared with RR=2.20, 95%CI=1.58-

3.08, I^2=0.00%), but there was no statistically significant (*P*=0.398). The RR of GC among those with family history of GC remained statistically significant when studies were further stratified by the adjusted variables for smoking, alcohol consumption, and *H. pylori* infection. Meta-regression analysis found alcohol consumption (coefficient=-0.251, 95%CI=-0.443-0.059, *P*=0.012) was a source of heterogeneity (Table 3).

Table 3: Meta-regression of potential moderator variables

Factors	*Single factor*		*Multiple factors*	
	Coefficient (95%CI)	*P*-value	Coefficient (95%CI)	*P*-value
Publication Year	-0.003(-0.013,0.007)	0.549	–	–
No. of case	-0.00008(-0.00029,0.00006)	0.205	–	–
Adjusted for age	0.843(0.639,1.112)	0.218	–	–
Adjusted for gender	0.069(-0.241,0.426)	0.592	–	–
Adjusted for BMI	0.013(-0.225,0.251)	0.912	–	–
Adjusted for smoking	0.063(-0.155,0.281)	0.559	–	–
Adjusted for alcohol consumption	-0.250(-0.451,-0.050)	0.016	-0.251(-0.443,-0.059)	0.012
Adjusted for race	0.259(-0.157,0.674)	0.214	–	–
Adjusted for income	0.022(-0.283,0.327)	0.885	–	–
Adjusted for education	0.153(-0.115,0.421)	0.254	–	–
Adjusted for *H. pylori* infection	0.281(-0.083,0.644)	0.126	0.301(-0.047,0.648)	0.087

BMI: Body mass index; *H. pylori: Helicobacter pylori*; 95%CI: 95% confidence interval

Discussion

According to this systematic review, a positive family history of GC was associated with a 2-fold increased risk of GC compared to those without such family history. The RR of GC was 2.07-fold for individuals having at least 1 FDR with GC, and almost 3-fold for having sibling with GC and having at least 2 FDRs with GC. Moreover, there was 4.03-fold increased risk of GC in subjects with both family history and *H. pylori* infection, and it was higher than the sum of risks for each risk factor alone (13, 43). Individuals with a positive family history of GC might be at high risk groups for developing GC. We suggest *H. pylori* eradication should be considered for these individuals, especially those having sibling with GC.

There are many problems in detecting and eradicating *H. pylori* infection in the general population, such as lack of a robust study with cost-effective proof, abuse of antibiotics and antibiotic resistance of *H. pylori* (44), however, a recent study demonstrated that *H. pylori* treatment can reduce the risk of GC in individuals with a positive family history (45). Therefore, it is necessary to separate individuals with family history of GC from the general population as high-risk groups for *H. pylori* screening and eradication therapy. For individuals having sibling with GC and more than 2 FDRs with GC, this need is more urgent. However, the data on age of person at risk were limited in this meta-analysis, the best age of the *H. pylori* eradication might be determined cautiously.

To our knowledge, there was a published meta-analysis that assessed the association between risk of GC and family history of GC in FDRs. Data on relative risk for number and type of family members affected in FDRs, SDRs, TDRs and *H. pylori* infection were not analyzed. The individuals having FDRs with GC were about 2.5-fold more likely to develop GC (46). The relative risk was lower than the reported in this meta-analysis, especially based on cohort studies. This may be because the previous meta-analysis only included case-control study, with greater recall bias compared to the cohort study. Furthermore, we also demonstrated a 1.84-fold risk when individuals have SDRs with GC, whereas having TDRs with GC was non-significant. This may be the result of interactions between genes and environment. FDRs and SDRs

may have more opportunities to share exposure to many environmental factors, such as smoking, drinking, salt intake and *H. Pylori* infection (47). We further estimated the pooled RR among studies that adjusted for smoking, alcohol consumption and *H. pylori* infection factor, and the significantly increased risk of GC and family history persisted. In addition, positive family history was strong risk factor of GC regardless of *H. pylori* infection (20, 21, 48). Seventeen studies adjusted for lifestyle and other potential confounding factors such as income, smoking, alcohol drinking, drinking tea, vegetable intake, and *H. pyloric* infection in this meta-analysis. Therefore, the observed increased risks are creditable and less likely to be affected by known confounding factors.

The reasons why the increased risk of GC conferred by individuals having sibling with GC was higher than those having parent with GC remain speculative. The higher risk with sibling history may be due to critical causal exposures are more shared between siblings from childhood to adulthood, for example, *H. pylori* infection general occurs in childhood (43, 49). The stronger association with paternal history of GC compared to maternal history may be due to the small sample size and need to be further studied.

Several strengths should be acknowledged. Firstly, our meta-analysis is the first study to examine the association between risk of GC and family history of GC according to the degree of affected relatives, number and type of family history exposure. Secondly, this study includes a large number of individuals from 35 studies in Western and Asian population. Thirdly, adequate subgroup analyses were performed according to various effect modifiers. Furthermore, all studies included in this meta-analysis met the inclusion criteria and were assessed by NOS scale.

There are several limitations in the meta-analysis. Firstly, as with other meta-analyses, high heterogeneity was observed. However, alcohol consumption was partially accounted for the heterogeneity. Secondly, both case-control and cohort designs included the current analysis, but case-control study was more likely to have a recall bias. Thirdly, the data on the TDR and age for the diagnosis of affected relative were limited in this meta-analysis. Because of the lacking of studies, we were unable to conduct a more detailed meta-analysis to estimate the risk of GC for subjects with both sibling history and *H. pylori* infection. The association between sibling history and risk of GC was stronger if subjects with *H. pylori* infection. Two studies have shown that GC risks were higher in individuals with relative diagnosed at a younger age (5, 50). The age of diagnosis of relatives is important to evaluate the GC risk in family history of GC. Therefore, more studies should be conducted to examine these issues.

Conclusion

This meta-analysis is likely to be of clinical relevance to inform individuals with a family history of GC that they have increased risk to develop GC, especially those having sibling with GC and more than 2 FDRs with GC. More intensified screening and eradication for *H. pylori* are urgently needed for these individuals. Further studies should focus on analyzing more detailed family history such as how risk estimates change when relatives are diagnosed with different ages.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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