RESEARCH ARTICLE

Family History and Survival of Patients with Gastric Cancer: A Meta-Analysis

Myueng Guen Oh[1], Jin Hwa Kim[1], Mi Ah Han[2]*, Jong Park[2], So Yeon Ryu[2], Seong Woo Choi[2]

Abstract

Background: Previous studies have generated conflicting evidence regarding associations between family history and survival after gastric cancer surgery. In this study, we investigated this question using a meta-analysis. Materials and Methods: To identify relevant studies, PubMed and Embase databases were searched up to June 2013. Two reviewers independently assessed search results and data extraction of included studies. Hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival (OS) were calculated based on fixed- or random-effects models. Homogeneity of effects across studies was assessed using x^2 test statistics and quantified by I^2. Results: A total of five studies were selected according to the inclusion criteria. The total number of patients included was 2,030, which ranged from 145 to 598 per study. There was no significant difference in OS by family history of cancer (HR=0.83, 95%CIs=0.50-1.38), but subgroup analysis of patients with a first-degree family history of cancer (HR=0.74, 95%CIs=0.60-0.93) and gastric cancer family history (HR=0.56, 95%CIs=0.41-0.76) tended to show better OS in these patients. Conclusions: This meta-analysis suggests that a first-degree family history of cancer or gastric cancer family history is associated with better survival of gastric cancer patients after surgery, after a systematic review of five previous studies. These results can be applied by clinicians when counselling patients regarding their risk of death from gastric cancer. Further study is needed to investigate the underlying mechanism between family history and survival in gastric cancer patients.

Keywords: Family history - meta-analysis - prognosis - stomach neoplasms - survival

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Introduction

Although the incidence of gastric cancer is decreasing globally, it remains the second leading cause of cancer death, particularly in Asia and especially in China, Japan, and Korea (Yoo, 2010; Jiang et al., 2013).

Family history of cancer is well accepted as an important risk factor for the development of several types of cancer (Eberl et al., 2005). With regard to gastric cancer, family history of gastric cancer was the major risk factor for gastric cancer development, as is also seen in other types of cancer (Foschi et al., 2008; Shin et al., 2010). In the majority of studies, the risk ratio for the development of gastric cancer by family history was between 1.5- and 3.5-fold (Yaghoobi et al., 2010; Mansour-Ghanaei et al., 2012).

However, the effect of family history on gastric cancer survival is controversial. A study of 145 gastric cardia adenoma (GCA) patients who received surgery showed that a positive upper gastrointestinal cancer family history had a worse 8-year overall survival time (Guo et al., 2013). Another study reported that family history had no effect on survival in gastric cancer patients (Gao et al., 2009). On the other hand, Han et al. (Han et al., 2012) reported that a first-degree family history of gastric cancer was associated with improved survival in patients with stage III or IV gastric cancer.

Furthermore, conflicting reports have created controversy with respect to the effects of a positive family history on the survival of patients who are diagnosed with gastric cancer; to our knowledge, no qualitative reviews summarizing these studies have been found. The objective of the present study was to conduct a systematic review and meta-analysis of the published literature, investigating family history and its effect on survival of patients with gastric cancer.

Materials and Methods

Search strategy

Studies reporting the survival of patients with gastric cancer after surgery with or without a family history of cancer were identified through a PubMed and Embase search up to June 2013 using the following keywords:

*[1]Department of Internal Medicine, Chosun University Hospital, [2]Department of Preventive Medicine, College of Medicine, Chosun University, Gwangju, Korea *For correspondence: mahan@chosun.ac.kr*

("gastric tumor" or "gastric tumour" or "gastric cancer" or "gastric neoplasm" or "stomach tumor" or "stomach tumour" or "stomach cancer" or "stomach neoplasm") and ("family" or "familial" or "family history") and ("recurrence" or "death" or "survival" or "prognosis" or "mortality").

Study selection

Two reviewers (M.G.O and J.H.K) independently assessed every retrieved study for inclusion. Inclusion criteria were the following: (1) Articles were published in English; (2) Observational studies reported hazard ratios (HRs) with 95% confidence intervals (CIs), or the information can help infer the survival results in the papers; (3) Family history of cancer was assessed as the prognostic marker of gastric cancer; and (4) Histologically or cytologically confirmed gastric cancer. Reviews, non-original articles, and studies on cancer cell lines and animal models were excluded from our review.

Outcome definition

The primary outcome measures were overall survival (OS), recurrence-free survival (RFS), and the disease-free survival (DFS). OS was defined as the time from surgery to death from any cause or to the last follow-up visit. RFS was defined as the time from surgery to tumor recurrence, death with evidence of recurrence, or occurrence of a new primary gastric tumor. DFS was defined as time from surgery to tumor recurrence, occurrence of a new primary gastric cancer, or death as a result of any cause.

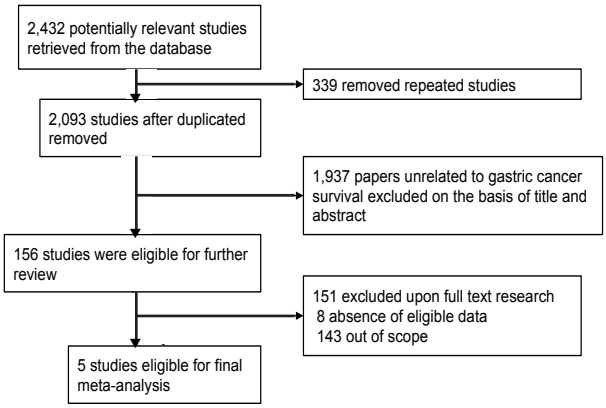

Figure 1. Flow Diagram of Identification of Relevant Studies

Data extraction

The same two reviewers independently extracted data from the included studies using standard data extraction forms. Disagreements between the reviewers were resolved by consensus. The following data were extracted from each study: study name, year of publication, location of study, study period, mean age, sample size, follow-up time, definition of family history, cancer type of family history and study endpoints.

Statistical analysis

Statistical analysis was performed with the Revman Version 5 software package (Cochrane Collaboration, Oxford, UK). For each study, HR and 95%CI were extracted from the manuscript. Study estimates, along with pooled estimates, are presented as forest plots. We examined heterogeneity in results across studies using I^2 statistics, which measures the percentage of total variation across studies. When statistical heterogeneity was not observed, the pooled estimate was calculated based on the fixed-effects model. When statistical heterogeneity was observed, the pooled estimate was calculated based on the random-effects model. Subgroup analysis was used to explore possible sources of heterogeneity. The following items were considered for possible subgroup analysis: degree of family history, location of gastric cancer, and cancer type of family history.

Results

Identification of relevant studies

The searches of PubMed and Embase provided a total of 2,432 citations. After adjusting for duplicates, 2,093 articles remained. The results of the search strategy for the study are summarized in Figure 1. In total, we assembled

Table 1. Study and Patient Characteristics

Study	Country	Recruitment period	No. of patients	Hereditary cancer	Age (years)	Gender (m/f)	Follow-up time	Assessment of family history
Fang et al., 2013	Taiwan	1988-2004	326 GA patients who received surgery	HNPCC exclude	Mean (SD) Diffuse type GC cases FH(-): 65.4 (12.8) FH(+): 54.1 (15.0) Intestinal type GC cases FH(-): 70.8 (9.8) FH(+):60.2 (13.4)	237/89	NS	Self-reporting
Gao et al., 2009	China	1997-2005	598 with GCA who received surgery 316 with GNCA who received surgery	NS	Median (inter-quartile): GCA: 61 (55-66) GNCA: 57.5 (50-63)	GCA: 491/107 GNCA: 239/77	Median: 3 years	Self-reporting
Guo et al., 2013	China	2003-2005	145 with GCA who received surgery	NS	Mean 58.9	115/30	Median (range) 5.5 (1.5-7) years	Self-reporting
Han et al., 2012	Korea	2001-2005	263 stage III, IV GA who received surgery	NS	Mean (SD) FH(-): 56.5 (12.4) FH(+): 57.1 (11.6)	167/96	Median: 60.8 months	Self-reporting
Palli et al., 2000	Italy	1985-1987	382 with GC who received surgery	NS	No of patients <50 yrs: 30 50-64 yrs: 130 >64 yrs: 222	239/ 143	Mean (range) 134 (120-150) months	Self-reporting

FH, family history; GA, gastric adenocarcinoma; GC, gastric cancer; GCA, gastric cardia adenocarcinoma; GNCA, gastric non-cardia adenocarcinoma; HNPCC, hereditary nonpolyposis colorectal cancer; SD, Standard deviation; NS, not specified

2,432 papers from the electronic databases. Following deduplication (n=339), the two reviewers independently screened the identified titles and abstracts. After manually screening the titles, abstracts, and keywords, 1,937 studies were excluded (title and/or abstract were not relevant for the endpoint of the study). The full texts of the 156 candidate articles were retrieved. After reviewing the papers, 151 were excluded for the following reasons: 8 studies did not provide the available survival data to calculate HRs and 95%CIs, and 143 studies were out of scope. Thus, five observational studies were chosen for the meta-analysis (Figure 1).

Characteristics of studies included in the final analysis

The main characteristics of the five eligible studies for aggregation are shown in Table 1. In the selected studies, two studies assessed patients from China, and the remaining studies were from Taiwan, Korea, and Italy, respectively. Studies were published between 2000 and 2013. The patients were enrolled in the studies from 1985 to 2005.

Table 2 summarizes the definitions of family history, cancer type of family history, and HR. Having one first-degree relative with gastric cancer was the least restrictive definition for family history used in the studies. Some studies used a higher number of affected relatives or restricted the age of diagnosis of the relative.

The cofactors used in the multivariate models varied widely, and the most common cofactors in the studies that used multivariate analyses to assess the risk of mortality were age, sex, and tumor stage. In the selected five articles, a significant association between family history and better OS was demonstrated in three studies. One study showed worse survival, and two studies showed a lack of statistical significance.

Family history and survival in gastric cancer patients: meta-analysis

The Forrest plots of the meta-analyses for survival are shown in Figure 2. Despite our attempts to limit the between-study heterogeneity through strict inclusion criteria, there was between-study heterogeneity in family history for all of the meta-analyses (I^2=84%). Thus, HRs was calculated using a random-effects model. The pooled HRs for OS were pooled HRs, 0.84 and 95%CIs, 0.50-1.39.

Subgroup analyses

To explore sources of variability between studies, summary HRs were calculated according to family subtype, gastric cancer location, and cancer type of family history. Family history of a first-degree relative was associated with better survival outcome, with pooled HRs being 0.76 (95%CIs 0.60-0.96) for OS (Figure 3A). Subgroup analysis, including studies with gastric non-cardia adenocarcinoma (GNCA) and gastric cancer, and excluding a study with GCA, showed significantly better survival in gastric cancer patients with a family history (pooled HRs 0.70, 95%CIs 0.57-0.86; Figure 3B). Additionally, a family history of gastric cancer, excluding

Table 2. Estimation of the Hazard Ratio according to the Definition of Family History

Study	Survival	Definitions of family history	Cancer type of FH	No. (%) of positive FH	HR (95% CI)	Adjustments
Fang et al., 2013	OS	First- and second-degree	GC	66 (20.2)	0.43 (0.27-0.71)	None
Gao et al., 2009	OS (1)	First-degree	GCA	26 (5.2)	0.88 (0.54-1.42) in GCA patients	Age, gender, geographic region, histologic grade, primary tumor stage, and lymph node metastasis
	OS (2)	First-degree	GNCA	27 (5.4)	0.76 (0.47-1.22) in GCA patients	Same as above
	OS (3)	First-degree	GCA	5 (3.9)	0.66 (0.26-1.64) in GNCA patients	Same as above
	OS (4)	First-degree	GNCA	16 (5.7)	0.96 (0.48-1.91) in GNCA patients	Same as above
Guo et al., 2013	OS	First- and second-degree	Esophageal, cardia, gastric cancer	64 (44.1)	2.11 (1.32-3.36)	Age, gender, tumor stage, RKIP methylation, expression
Han et al., 2012	OS (1)	First-degree	GC	48 (18.3)	0.47 (0.26-0.84)	Age, gender, smoking, drinking, tumor location tumor size, Lauren classification, depth of invasion, and lymph node metastasis
	OS (2)	First- and second-degree	GC	61 (23.2)	0.57 (0.35-0.93)	Same as above
	RFS	First-degree	GC	48 (18.3)	0.51 (0.30-0.87)	Same as above
	RFS	First- and second-degree	GC	61 (23.2)	0.59 (0.37-0.93)	Same as above
	DFS	First-degree	GC	48 (18.3)	0.49 (0.29-0.84)	Same as above
	DFS	First- and second-degree	GC	61 (23.2)	0.57 (0.36-0.90)	Same as above
Palli et al., 2000	OS	First-degree	Esophageal, gastric, or colorectal cancer	84 (28.2)	0.82 (0.62-1.08)	Age, gender, social class, and T and N classification

CI, confidence interval; DFS, disease-free survival; FH, family history; GC, gastric cancer; GCA, gastric cardia adenocarcinoma; GNCA, gastric non-cardia adenocarcinoma; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival

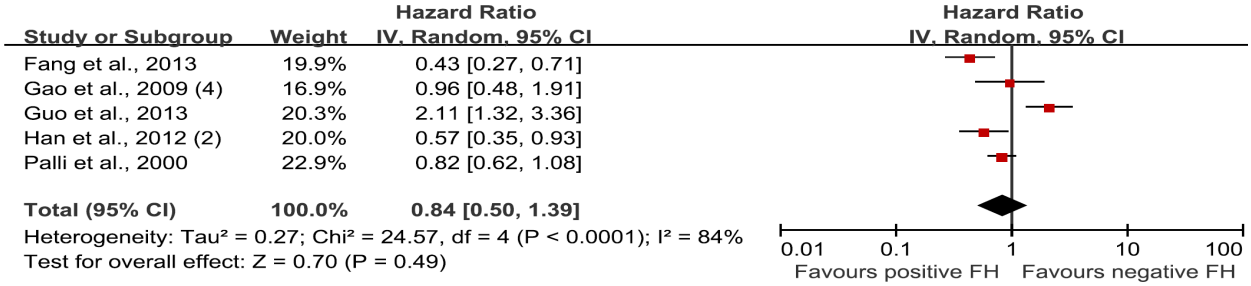

Figure 2. Family History of Cancer and Overall Survival in Gastric Cancer Patients

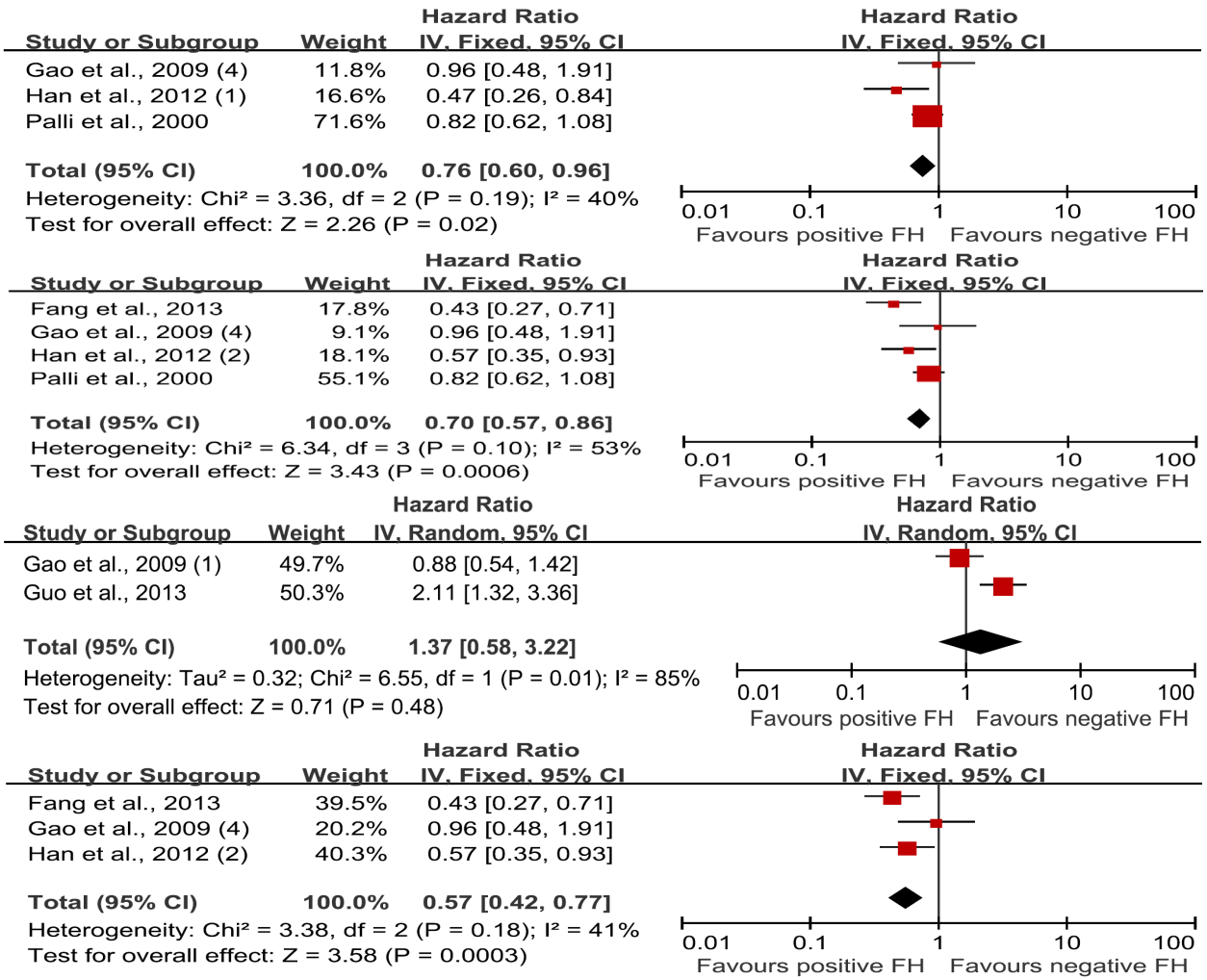

Figure 3. Subgroup analysis. A). First-degree family history of cancer and overall survival in gastric cancer patients **B)**. Family history of cancer and overall survival in gastric adenocarcinoma and gastric non-cardia adenocarcinoma patients **C)**. Family history of cancer and overall survival in gastric cardia adenocarcinoma patients **D)**. Family history of gastric cancer and overall survival in gastric cancer patients

other types of cancer, was associated with better OS (pooled HRs 0.57, 95%CIs 0.42-0.77; Figure 3D).

Discussion

Our meta-analysis showed that there were no significant associations between family history and gastric cancer survival. However, subgroup analysis, including studies with a family history defined as only first-degree relatives and studies with a family history defined as only of gastric cancer, showed significantly better survival in gastric cancer patients after surgery.

With regard to the degree of family history, a first-degree family history was associated with significantly better survival. However, family history, including both first- and second-degree relatives, was not associated with better survival. Only a few of the included studies evaluated risk of death from gastric cancer in patients with second-degree relatives (Han et al., 2012; Fang et al., 2013; Guo et al., 2013), and such information is more prone to error, reducing the magnitude of HRs associated with having second-degree family members affected by cancer. Furthermore, family histories of the studies in this meta-analysis were assessed by self-reporting. In particular, this process might result in under-reporting of a second-degree family history, because reports of family history will always be clearer for those we know better (i.e., first-degree relatives) and will be more uncertain as we extend to second- and third-degree relatives. A recent review showed consistently lower accuracy of reported cancer history in second- and third-degree relatives (Wilson et al., 2009). Therefore, the findings for family history of cancer in distant relatives should also be viewed with caution.

A previous study (Han et al., 2012) showed that degree of family history was an independent factor for survival in gastric cancer patients. This study found that women who had a first-degree family history of cancer experienced a significantly better prognosis, whereas a positive second-degree family history was not associated with better survival. Some previous studies with other types of cancer showed that the associations between family history and survival of cancer patients differed according to the degree of family history and number of affected family members (Bass et al., 2008; Morris et al., 2013) and type of family member affected (such as parents, sibling, etc.)(Slattery and Kerber, 1995). No study included in this meta-analysis considered the HRs associated with the type of family

member affected. A future large study should be carried out to evaluate gastric cancer survival for patients with different degrees of affected relatives and family history.

In the subgroup analysis, when family history was limited to gastric cancer, family history was significantly associated with better survival. A previous study showed that a family history of cancer increased the risk for cancer death at many sites and was not specific to cancer risk within a single site. However, the association between family history and cancer mortality was generally stronger within cancer sites than across cancer sites (Poole et al., 1999). Additionally, a family history of other types of cancer, excluding gastric cancer, was not associated with gastric cancer survival (Han et al., 2012). A study about family history and upper gastrointestinal cancer survival showed a site-specific association (Gao et al., 2009). Thus, family history of a specific cancer type might affect the association between family history and cancer survival.

The subgroup analysis including studies with GNCA and gastric cancer; excluding a study with GCA, the analysis showed significantly better survival of gastric cancer patients with a family history. There are no uniformly accepted criteria of GCA (Jovanovic and Mouzas, 2001). Some previous studies concluded that risk factors, such as dietary habits and H. pylori infection, had different effects on the occurrence and development of GCA and gastric cancer. However, GCA showed some similarities in occurrence when compared with esophageal squamous cell carcinoma (Guo et al., 2013; Jovanovic and Mouzas, 2001; Kim, 2013). The prognosis of esophageal adenocarcinoma was very poor, and the prognoses of GCA and GNCA were quite different. Therefore, the definition of GCA could affect the survival of gastric cancer patients. In this meta-analysis, only two studies (Gao et al., 2009; Guo et al., 2013) analyzed the survival of GCA, and their definitions of GCA were not the same. One study (Guo et al., 2013) defined GCA with its epicenter at the gastroesophageal junction, that is, from 1 cm above to 2 cm below the junction between the end of the tubular esophagus and the beginning of the saccular stomah. The other (Gao et al., 2009) defined GCA as including adenocarcinomas located in the top three centimeters of the stomach. Further studies are needed to investigate survival according to the definition of GCA.

While the noted survival gain in gastric cancer patients with a family history is compatible with genetic predisposition, it may also reflect shared environmental exposures in families.

Unidentified genes and/or known cancer syndromes may have contributed to the survival differences of gastric cancer patients with a family history in the component studies. Although the majority of cases of gastric cancer are sporadic, approximately 1-3% of all gastric cancers occur as part of an inherited cancer predisposition syndrome, including hereditary non-polyposis colorectal cancer (HNPCC), Li-Fraumeni syndrome, familial adenomatous polyposis, and Peutz-Jeghers syndrome (Barber et al., 2006). Although several previous studies mentioned the clinical difference of gastric cancer with sporadic gastric cancer (Masciari et al., 2011), long-term survival data in hereditary gastric cancer syndrome were not yet fully studied. Aarnio et al. (Aarnio et al., 1997) showed that the overall 5-year survival rate in gastric cancer patients with hereditary non-polyposis colorectal cancer was similar to that reported in sporadic cases. Further, the post-operative prognosis for early hereditary diffuse gastric cancer is likely to be excellent (Guilford et al., 2007). In addition, gastric cancer development in patients with familial adenomatous polyposis (Shibata et al., 2013) usually yields a better prognosis. In this meta-analysis, only one study excluded hereditary gastric cancer, such as HNPCC (Fang et al., 2013). However, Han et al. (Han et al., 2012) did not exclude hereditary gastric cancer syndrome (HGCS) and mentioned its possibility. An early age at cancer diagnosis is a characteristic of known HGCS. Two studies showed the mean age of gastric cancer patients by family history. One study showed that familial gastric cancer patients had a younger age (Fang et al., 2013), but another study showed that there was no difference in age by family history (Han et al., 2012). Because the long-term survival data in hereditary gastric cancer syndrome have not yet been fully studied, future studies of survival in gastric cancer patients with a family history could be refined by investigating the possibility of known cancer syndromes.

The differences in survival by family history could also explain the effects of health behaviors of cancer patients by family history. Health behaviors, such as smoking and alcohol drinking, associated with effects on gastric cancer survival. Unhealthy behaviors were more likely to be observed in patients without a family history. Unfortunately, our meta-analysis could not verify the effect of smoking habits, because only one study adjusted for smoking status (Han et al., 2012). Failure to adjust for smoking habits could overestimate the association between family history and gastric cancer survival.

Our meta-analysis has several limitations. One may be that the number of studies included in this analysis is relatively small (only five studies), as several stratified analyses could not be conducted. For example, one study (Han et al., 2012) showed that although a family history of gastric cancer was not associated with survival in stage I and II patients, in stage III and IV patients, a first-degree family history was associated with a significant reduction in the risk of cancer recurrence or mortality in DFS (p=0.003). However, other studies did not show a stratified analysis or restricted analysis by tumor stage. Therefore, we could not evaluate the effect of tumor stage on the final results based only on this study. For the same reason, we also could not evaluate the effects of sex and age. Additionally, no study attempted to confirm the family history through medical records, despite the reliability of self-reported information being a commonly recognized potential source of bias in studies of family history. Finally, the restriction of articles published only in English may also be a source of selective reporting, as restriction to English language articles favors positive studies.

In summary, a first-degree family history or gastric cancer family history was significantly associated with better survival in gastric cancer patients in this meta-analysis. These results can be applied by clinicians when counselling patients regarding their risk of death from

gastric cancer patients. Further studies are needed to investigate the underlying biological mechanism between family history and survival in gastric cancer patients.

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