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

Myueng Guen Oh¹, Jin Hwa Kim¹, Mi Ah Han²*, Jong Park², So Yeon Ryu², Seong Woo Choi²

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 $\chi^2$ test statistics and quantified by I².

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:

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(“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.

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 I² 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 studies remain. The results of the search strategy for the study are summarized in Figure 1. In total, we assembled 5 studies eligible for final meta-analysis.

Table 1. Study and Patient Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Recruitment period</th>
<th>No. of patients</th>
<th>Hereditary cancer</th>
<th>Age (years)</th>
<th>Gender (m/f)</th>
<th>Follow-up time</th>
<th>Assessment of family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fang et al., 2013</td>
<td>Taiwan</td>
<td>1988-2004</td>
<td>326 GA patients who received surgery</td>
<td>HNPCC exclude</td>
<td>Mean (SD)</td>
<td>237/89</td>
<td>NS</td>
<td>Self-reporting</td>
</tr>
<tr>
<td>Gao et al., 2009</td>
<td>China</td>
<td>1997-2005</td>
<td>598 with GCA who received surgery</td>
<td>NS</td>
<td>Median (inter-quartile): GCA: 61 (55-66) GNCA: 57.5 (50-63)</td>
<td>GCA: 491/107 GNCA: 239/77</td>
<td>Median: 3 years</td>
<td>Self-reporting</td>
</tr>
<tr>
<td>Gao et al., 2013</td>
<td>China</td>
<td>2003-2005</td>
<td>145 with GCA who received surgery</td>
<td>NS</td>
<td>Mean 58.9</td>
<td>115/30</td>
<td>Median (range) 5.5 (1.5-7) years</td>
<td>Self-reporting</td>
</tr>
<tr>
<td>Han et al., 2012</td>
<td>Korea</td>
<td>2001-2005</td>
<td>263 stage III, IV GA who received surgery</td>
<td>NS</td>
<td>Mean (SD)</td>
<td>167/96</td>
<td>Median: 60.8 months</td>
<td>Self-reporting</td>
</tr>
<tr>
<td>Palli et al., 2000</td>
<td>Italy</td>
<td>1985-1987</td>
<td>382 with GC who received surgery</td>
<td>NS</td>
<td>No of patients &lt;50 yrs: 30 50-64 yrs: 130 &gt;64 yrs: 222</td>
<td>239/143</td>
<td>Mean (range) 134 (120-150) months</td>
<td>Self-reporting</td>
</tr>
</tbody>
</table>

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

Figure 1. Flow Diagram of Identification of Relevant Studies

Table 1. Study and Patient Characteristics

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 (I²=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

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

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

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.
Family History and Survival of Gastric Cancer Patients

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

References


