Risk for gastric cancer in patients with gastric atrophy: a systematic review and meta-analysis

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Background: The risk for gastric cancer among patients with gastric atrophy is unclear. We investigated the association between the risk for gastric cancer and gastric atrophy.

Methods: We performed a comprehensive literature search in the PubMed and Embase databases and extracted relevant data from eligible studies. A fixed- or random-effects model was applied to pool study-specific risk according to heterogeneity across studies.

Results: Thirteen cohort or nested case-control studies with 655,937 participants and 2,794 patients with gastric cancer were analyzed. The pooled results suggested that gastric atrophy was associated with an elevated risk for gastric cancer [pooled risk ratio (RR) = 2.91, 95% confidence interval (CI): 2.58–3.27]. The pooled RR (3.10, 95% CI: 2.58–3.73) of studies that used serum levels of pepsinogen for diagnosis of gastric atrophy was similar to that of those that used (pooled RR = 2.79, 95% CI: 2.37–3.27) (for endoscopy). Gastric atrophy was positively associated with the risk for gastric cancer in both prospective and retrospective studies. Moreover, the pooled RRs did not significantly vary by country of origin (Asia and Europe) or gastric cancer subtype (cardia and non-cardia).

Conclusions: Gastric atrophy is associated with an elevated risk for gastric cancer, and endoscopy and serum levels of pepsinogens can be used to predict the risk.

Keywords: Gastric cancer; gastric atrophy; risk; meta-analysis

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Introduction

Although its incidence has decreased, gastric cancer remains the fifth most common malignancy and a leading cause of cancer-related death worldwide (1). The incidence of gastric cancer varies among countries, being lower in Western countries than in nations of East Asia, such as Japan and China (2). Helicobacter pylori is the most important risk factor for gastric cancer; the others include smoking and dietary habits (3,4). The survival rate of patients with early-stage gastric cancer is high; however, most patients are diagnosed at a late stage and have a poor overall survival rate. The survival of patients with gastric cancer is enhanced by early detection, and thus surveillance of patients at high risk for gastric cancer is important.

Gastric cancer is a multifactorial disease and is closely associated with H. pylori infection (5). H. pylori infection can lead to chronic non-atrophic gastritis, followed by gastric atrophy and intestinal metaplasia, dysplasia, and ultimately gastric cancer (5,6). Gastric atrophy typically begins at the antrum and expands to the corpus (7), and may be associated with the development of gastric cancer. In addition, atrophic gastritis diagnosed by serological examination can be used to identify patients at high
risk for gastric cancer (8-12). However, the association between gastric atrophy and gastric cancer is unclear. Therefore, we systematically evaluated this association.

**Methods**

**Data sources and study selection**

Systematic searches for eligible publications were performed in the PubMed and Embase databases up to November 2017. The following key words were used: (“stomach” OR “gastric”) AND (“cancer” OR “adenocarcinoma” OR “carcinoma” OR “tumor” OR “malignancy”) AND (“atrophy” or “atrophic gastritis”). We also searched the reference lists of relevant articles and reviews for eligible works. The retrieved articles were carefully assessed to exclude overlapping data or duplicate studies. The titles and abstracts of citations were screened, and full reports were reviewed if necessary. The eligibility of studies for inclusion was assessed by two investigators independently based on the following criteria: cohort or nested case-control study, association between the risk for gastric cancer and atrophy investigated, and estimated hazard ratio (HR) or risk ratio (RR) with 95% confidence intervals (CIs) provided or could be calculated. Only articles in English were included. The review was conducted according to the PRISMA statement (13).

**Data extraction**

Data extraction was performed independently by two reviewers, and any disagreement was resolved by discussion or by the decision of a third reviewer. For each study, the following variables were extracted: last name of the first author, year of publication, country of origin, study design, sample size, number of gastric cancer patients, gastric atrophy diagnostic method, and HR or RR with corresponding 95% CIs. The HRs (RRs) that reflected the greatest degree of control for potential confounders were used in this meta-analysis.

**Statistical analyses**

Heterogeneity across individual studies was evaluated using chi-square and I² tests, and significant heterogeneity was defined as a P value ≤0.05 and/or an I² value >50% (14). Summary risk estimates (HRs or RRs) and 95% CIs were calculated using a random-effects model when the heterogeneity was significant, and a fixed-effects model otherwise. Subgroup analyses were performed to identify the sources of heterogeneity and to assess the effect modification of cancer subtype, geographic region, study design, and gastric atrophy diagnostic method. To assess the risk for publication bias, a Begg funnel plot was generated and an Egger test was conducted. Stata software (v. 11.0; StataCorp, College Station, TX) was used for statistical analyses, and a value of P<0.05 was taken to indicate statistical significance.

**Results**

**Study characteristics**

The systematic literature search identified eligible 2,047 articles, of which 37 were reviewed for inclusion. Ultimately, 13 articles were included in the meta-analysis (Figure 1) (7-12,15-21). Studies were excluded from the meta-analysis for the following reasons: inappropriate topic or design (n=14), not an original article (n=6), and insufficient data (n=4).

Among the 13 included studies, 4 were performed in Europe and the others were conducted in Asia (Table 1). Ten were prospective studies and three were retrospective. The sample size ranged from 594 to 360,000, and the number of patients with gastric cancer ranged from 12 to 1,452. One study enrolled only male participants, and the others enrolled both male and female participants. Seven studies used the circulating pepsinogen level for diagnosis of gastric atrophy, five used endoscopy, and one study used a database.

**Association between gastric atrophy and gastric cancer risk**

Thirteen studies assessed the association between gastric
Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Design</th>
<th>Country</th>
<th>Sample size</th>
<th>No. of patients with GC</th>
<th>Age (years) (mean or median)</th>
<th>Gender</th>
<th>Years of follow up</th>
<th>Atrophy diagnostic method</th>
<th>Adjusted factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shichijo/2016 (7)</td>
<td>Retrospective</td>
<td>Japan</td>
<td>748</td>
<td>21</td>
<td>58.4</td>
<td>M/F</td>
<td>6.2</td>
<td>Endoscopy</td>
<td>Age, gender, intestinal metaplasia</td>
</tr>
<tr>
<td>Sekikawa/2016 (15)</td>
<td>Retrospective</td>
<td>Japan</td>
<td>1,823</td>
<td>29</td>
<td>17.7% patients ≥65 years</td>
<td>M/F</td>
<td>5.3</td>
<td>Endoscopy</td>
<td>Age, gender, gastric xanthelasma</td>
</tr>
<tr>
<td>Mori/2016 (16)</td>
<td>Prospective</td>
<td>Japan</td>
<td>594</td>
<td>79</td>
<td>66</td>
<td>M/F</td>
<td>4.5</td>
<td>Endoscopy</td>
<td>Gender, smoking, location and number of initial gastric cancer</td>
</tr>
<tr>
<td>Chen/2016 (17)</td>
<td>Prospective</td>
<td>Germany</td>
<td>9,506</td>
<td>27</td>
<td>50-75</td>
<td>M/F</td>
<td>10.6</td>
<td>PGI &lt;70 ng/mL and PGI/II ratio &lt;3</td>
<td>Age, gender, education level, smoking status and alcohol consumption</td>
</tr>
<tr>
<td>Song/2015 (18)</td>
<td>Prospective</td>
<td>Sweden</td>
<td>14,285</td>
<td>12</td>
<td>60.3</td>
<td>M/F</td>
<td>10.1</td>
<td>Register database</td>
<td>None</td>
</tr>
<tr>
<td>Mizuno/2010 (8)</td>
<td>Prospective</td>
<td>Japan</td>
<td>2,859</td>
<td>61</td>
<td>Nr</td>
<td>M/F</td>
<td>9.3</td>
<td>PGI ≤70 ng/mL and PGI/II ratio ≤3</td>
<td>Age, gender</td>
</tr>
<tr>
<td>Ren/2009 (9)</td>
<td>Prospective</td>
<td>China</td>
<td>29,584</td>
<td>1452</td>
<td>40-69</td>
<td>M/F</td>
<td>15</td>
<td>PGI/II ratio ≤4</td>
<td>Age, sex, cigarette smoking, alcohol consumption, body mass index, and H. pylori seropositivity</td>
</tr>
<tr>
<td>Take/2007 (19)</td>
<td>Prospective</td>
<td>Japan</td>
<td>1,342</td>
<td>13</td>
<td>50</td>
<td>M/F</td>
<td>3.9</td>
<td>Endoscopy</td>
<td>None</td>
</tr>
<tr>
<td>Palli/2007 (20)</td>
<td>Prospective</td>
<td>Europe</td>
<td>360,000</td>
<td>233</td>
<td>Nr</td>
<td>M/F</td>
<td>6.1</td>
<td>PGA &lt;22 ng/mL</td>
<td>Age, gender, education, smoking history, weight, total vegetables, fruit, red and preserved meat</td>
</tr>
<tr>
<td>Hansen/2007 (10)</td>
<td>Retrospective</td>
<td>UK</td>
<td>101,601</td>
<td>173</td>
<td>45.6</td>
<td>M/F</td>
<td>11.9</td>
<td>PGI/II ratio &lt;2.5</td>
<td>None</td>
</tr>
<tr>
<td>Sasazuki/2006 (11)</td>
<td>Prospective</td>
<td>Japan</td>
<td>123,567</td>
<td>511</td>
<td>40-69</td>
<td>M/F</td>
<td>9</td>
<td>PGI ≤70 ng/mL and PGI/II ratio ≤3</td>
<td>Age, gender, resident area, blood donation date, and fasting times at blood donation, smoking, consumption of fish, gut, green and yellow vegetables, other vegetables, fruit, green tea, body mass index, and family history of gastric cancer</td>
</tr>
<tr>
<td>Ohata/2004 (12)</td>
<td>Prospective</td>
<td>Japan</td>
<td>4,655</td>
<td>45</td>
<td>49.5</td>
<td>M</td>
<td>7.7</td>
<td>PGI ≤70 ng/mL and PGI/II ratio ≤3</td>
<td>Age</td>
</tr>
<tr>
<td>Inoue/2000 (21)</td>
<td>Prospective</td>
<td>Japan</td>
<td>5,373</td>
<td>117</td>
<td>Male: 50.7; Female: 49.9</td>
<td>M/F</td>
<td>10</td>
<td>Endoscopy</td>
<td>Age, gender and family history of gastric cancer</td>
</tr>
</tbody>
</table>

Nr, not reported; M, male; F, female.
Table 2 Subgroup analyses of gastric atrophy and risk of gastric cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Studies</th>
<th>Pooled OR (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal cancer subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCC</td>
<td>4</td>
<td>2.84 (1.52–5.31)</td>
<td>55.4</td>
</tr>
<tr>
<td>GNCC</td>
<td>3</td>
<td>3.12 (2.17–4.49)</td>
<td>34.6</td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>10</td>
<td>2.86 (2.54–3.23)</td>
<td>0</td>
</tr>
<tr>
<td>Retrospective</td>
<td>3</td>
<td>3.90 (2.67–5.70)</td>
<td>33.0</td>
</tr>
<tr>
<td>Country of Origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>9</td>
<td>2.89 (2.38–3.51)</td>
<td>14.7</td>
</tr>
<tr>
<td>Western countries</td>
<td>4</td>
<td>3.17 (2.47–4.08)</td>
<td>32.2</td>
</tr>
<tr>
<td>Diagnostic method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopy or database</td>
<td>6</td>
<td>2.79 (2.37–3.27)</td>
<td>13.6</td>
</tr>
<tr>
<td>Pepsinogen level</td>
<td>7</td>
<td>3.10 (2.58–3.73)</td>
<td>18.7</td>
</tr>
</tbody>
</table>

GCC, gastric cardia cancer; GNCC, gastric non-cardia cancer.

atrophy and the risk for gastric cancer. Those studies had 655,937 participants, among whom 2794 developed gastric cancer. The pooled RR was 2.91 (95% CI: 2.58–3.27) with no significant heterogeneity ($I^2=7.2\%$, $P=0.374$) (Figure 2), suggesting that gastric atrophy was associated with a high risk for gastric cancer. No publication bias was detected based on a Begg funnel plot and Egger test ($P_{\text{Begg's test}}=0.161$, $P_{\text{Egger's test}}=0.151$).

Next, we performed subgroup analyses according to cancer subtype, geographic region, study design, and gastric atrophy diagnostic method (Table 2). The pooled results indicated that gastric atrophy was positively associated with the risk for both non-cardia gastric cancer (pooled RR =3.12, 95% CI: 2.17–4.49) and gastric cardia cancer (pooled...
Gastric atrophy is positively associated with the risk for gastric cancer. In this meta-analysis, both histologically diagnosed (pooled RR =2.79, 95% CI: 2.37–3.27) and pepsinogen-diagnosed (RR =3.10, 95% CI: 2.58–3.73) atrophy were associated with an elevated risk for gastric cancer. This suggests that the serum levels of pepsinogens can be used for gastric cancer screening.

Gastric cancer is classified anatomically as gastric cardia or non-cardia cancer; in this study, gastric atrophy was associated with the risk for both types. The risk factors for those two types of gastric cancer are not necessarily similar. For example, *H. pylori* plays an important role in the development of non-cardia gastric cancer, but its association with cardia cancer is less clear (27). The association between atrophy and gastric non-cardia cancer is supported by strong evidence, while the role of atrophy in the development of gastric cardia cancer is unclear. It has been hypothesized that gastric cardia cancer has two etiologies: one associated with *H. pylori* atrophic gastritis, and another that resembles esophageal adenocarcinoma and against which gastric atrophy does not have a protective effect (10).

Further studies of this issue are warranted.

We systematically analyzed the risk for gastric cancer in patients with gastric atrophy and the findings supported the effects of gastric atrophy gastric cancer surveillance. The included studies were of cohort or nested case-control design, and most were prospective, reducing the risk of bias and increasing the reliability of the pooled results. However, this systematic review and meta-analysis had several limitations. First, the small number of included studies, particularly for some subgroup analyses, may have reduced the accuracy of the estimates. Second, control of confounders was inadequate, and so the risks might be over- or underestimated. For example, *H. pylori* infection and intestinal metaplasia are risk factors for gastric cancer, but we were unable to evaluate the joint effects of these factors and atrophy on the risk for gastric cancer due to the sparsity of the data. Similarly, there were insufficient data to examine the effects of grade of atrophy and peptic ulcer on the association between atrophy and the risk for gastric cancer. Third, the studies that used serum levels of pepsinogen to diagnose gastric atrophy applied nonuniform diagnostic criteria. Most of the studies used a PGI level <70 ng/mL and a PGI/II ratio <3 to diagnose gastric atrophy, while others used different criteria. In addition, the follow-up time, which may be important in cohort studies,
varied among the included works. Moreover, the included studies were performed in East Asia or Europe; therefore, caution is required when generalizing the findings to other populations.

In conclusion, gastric atrophy was associated with an elevated risk for gastric cancer. The evidence suggests that gastric atrophy diagnosed by endoscopy or serum levels of pepsinogen can be used for surveillance of gastric cancer.

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Footnote

Conflicts of Interest: 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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Sui et al. Gastric cancer risk in patients with gastric atrophy
