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Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status

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GASTRIC CANCER

Background: Non-cardia gastric adenocarcinoma is positively associated with Helicobacter pylori infection and atrophic gastritis. The role of H pylori infection and atrophic gastritis in cardia cancer is unclear.

Aim: To compare cardia versus non-cardia cancer with respect to the premorbid state of the stomach.

Methods: Nested case–control study. To each of 129 non-cardia and 44 cardia cancers, three controls were matched. Serum collected a median of 11.9 years before the diagnosis of cancer was tested for anti-H pylori antibodies, pepsinogen I:II and gastrin.

Results: Non-cardia cancer was positively associated with H pylori (OR 4.75, 95% CI 2.56 to 8.81) and gastric atrophy (pepsinogen I:II <2.5; OR 4.47, 95% CI 2.71 to 7.37). The diffuse and intestinal histological subtypes of non-cardia cancer were of similar proportions and both showed a positive association with H pylori and atrophy. Cardia cancer was negatively associated with H pylori (OR 0.27, 95% CI 0.12 to 0.59), but H pylori-positive cardia cancer showed an association with gastric atrophy (OR 3.33, 95% CI 1.06 to 10.5). The predominant histological subtype of cardia cancer was intestinal and was not associated with gastric atrophy compared with the diffuse subtype (OR 0.72, 95% CI 0.19 to 2.79) vs (OR 3.46, 95% CI 0.32 to 37.5). Cardia cancer in patients with atrophy had an intestinal: diffuse ratio (1:1) similar to non-cardia cancer (1:9:1), whereas cardia cancers in patients without atrophy were predominantly intestinal (7:1).

Conclusion: These findings indicate two aetiologies of cardia cancer, one associated with H pylori atrophic gastritis, resembling non-cardia cancer, and the other associated with non-atrophic gastric mucosa, resembling oesophageal adenocarcinoma. Serological markers of gastric atrophy may provide the key to determining gastric versus oesophageal origin of cardia cancer.

Several observations indicate that cancers of the cardia region of the stomach are aetiologically different from those of the rest of the stomach. Cancers of the mid and distal stomach (non-cardia cancers) show a strong positive association with Helicobacter pylori infection, whereas cardia cancer has negative, positive or no association with H pylori infection. The incidence time trends of cardia and non-cardia cancer also differ, with the latter falling and the former remaining static or increasing.

Substantial advances have been made in our understanding of the aetiology of non-cardia cancer and, in particular, of the role of H pylori infection. The highest risk of non-cardia cancer is in patients in whom the infection has induced atrophic gastritis and low or absent acid secretion. Non-cardia cancer is the result of progression from H pylori superficial gastritis to atrophic gastritis and hypochlorhydria to dysplasia and finally to cancer.

The aetiology of cancer of the gastric cardia region remains poorly understood. One reason for this may be the anatomical complexity of the cardia. Cardia mucosa extends from the oxyntic mucosa of the body of the stomach to the squamous mucosa of the distal oesophagus. The mucosa consists of columnar mucosa resembling that of the gastric antrum. In neonates, the cardia mucosa is only a few millimetres in length. In adults, the cardia mucosa may be larger, and this expansion may occur by metaplasia of the adjacent mucosa into cardia-like mucosa. Proximal extension of cardia mucosa can occur by metaplastic transformation of the squamous mucosa of the distal oesophagus—a phenomenon that may be induced by acidic gastro-oesophageal reflux. Distal extension of cardia mucosa may arise from atrophic gastritis of oxyntic mucosa with loss of specialised cells and most commonly induced by H pylori infection. When patients present with adenocarcinoma involving the gastric cardia, it is usually impossible to determine whether the tumour has arisen from metaplasia of the distal oesophageal squamous epithelium, from metaplasia of gastric oxyntic mucosa or from the original cardia mucosa.

In a large nested case–control study in the Norwegian population, we found that H pylori infection was associated with an increased risk of non-cardia cancer but with a reduced risk of cardia cancer. The current study was undertaken to compare cancers at those two sites with respect to premorbid gastric mucosal atrophy and acid secretion.

The aim of this study was to examine the association between the state of the gastric mucosa and the risk of subsequently developing cardia versus non-cardia gastric cancer.

PATIENTS AND METHODS

This was a nested case–control study. It comprised 101 601 men and women enrolled in the Norwegian Janus cohort as blood donors in Oslo 1973–86, as participants in the Oslo Study of Cardiovascular Disease 1972–73 and as participants in the Norwegian Counties Study 1974–78 carried out by the National Health Screening Service in the three counties Oppland, Sogn og Fjordane and Finnmark. All solid gastric cancers diagnosed among the cohort members through 1992 were matched. Serum collected a median of 11.9 years before the diagnosis of cancer was tested for anti-H pylori antibodies, pepsinogen I:II and gastrin.

Aim: To compare cardia versus non-cardia cancer with respect to the premorbid state of the stomach.

Methods: Nested case–control study. To each of 129 non-cardia and 44 cardia cancers, three controls were matched. Serum collected a median of 11.9 years before the diagnosis of cancer was tested for anti-H pylori antibodies, pepsinogen I:II and gastrin.

Results: Non-cardia cancer was positively associated with H pylori (OR 4.75, 95% CI 2.56 to 8.81) and gastric atrophy (pepsinogen I:II <2.5; OR 4.47, 95% CI 2.71 to 7.37). The diffuse and intestinal histological subtypes of non-cardia cancer were of similar proportions and both showed a positive association with H pylori and atrophy. Cardia cancer was negatively associated with H pylori (OR 0.27, 95% CI 0.12 to 0.59), but H pylori-positive cardia cancer showed an association with gastric atrophy (OR 3.33, 95% CI 1.06 to 10.5). The predominant histological subtype of cardia cancer was intestinal and was not associated with gastric atrophy compared with the diffuse subtype (OR 0.72, 95% CI 0.19 to 2.79) vs (OR 3.46, 95% CI 0.32 to 37.5). Cardia cancer in patients with atrophy had an intestinal: diffuse ratio (1:1) similar to non-cardia cancer (1:9:1), whereas cardia cancers in patients without atrophy were predominantly intestinal (7:1).

Conclusion: These findings indicate two aetiologies of cardia cancer, one associated with H pylori atrophic gastritis, resembling non-cardia cancer, and the other associated with non-atrophic gastric mucosa, resembling oesophageal adenocarcinoma. Serological markers of gastric atrophy may provide the key to determining gastric versus oesophageal origin of cardia cancer.

Abbreviation: PGII:II, pepsinogen I to pepsinogen II ratio

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identified in The Cancer Registry of Norway. Cases were limited to individuals with available historical serum from whom primary tumour tissue could be verified as gastric adenocarcinoma of unequivocal non-cardia or cardia origin. Of the 230 identified gastric cancer cases, 57 were excluded from the study because of no remaining or wasted serum (n = 7), no tissue (n = 2) or only metastatic tumour tissue (n = 10) available for histological examination, histological type diagnosed or suspected to be other than adenocarcinoma (n = 6), doubt about the stomach being the primary site of the tumour (n = 2), gastric resection before the diagnosis of cancer (n = 16), or disseminated tumour growth precluding determination of cardia/non-cardia subsite origin (n = 14). To each cancer case, controls were matched according to gender, date of birth (within 54 months, 97% within 12 months, median deviation 3 months), date of serum sampling (within 17 months, 99% within 12 months, median deviation 3 months), and serum source (blood donors, the Oslo Study of Cardiovascular Disease, or county within Norwegian Counties Study). In all, three source (blood donors, the Oslo Study of Cardiovascular Disease, or county within Norwegian Counties Study). In all, three

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk of gastric adenocarcinoma for <em>Helicobacter pylori</em> serostatus, quintiles of serum pepsinogen I:II and quintiles of serum gastrin concentration according to different gastric subsites and adenocarcinoma subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td>Cardia (44 cases, 132 controls)</td>
</tr>
<tr>
<td><em>H pylori</em> serostatus</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.00 (reference)</td>
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<tr>
<td>Positive</td>
<td>0.27 (0.12 to 0.59)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum pepsinogen I:II quintiles</td>
<td></td>
</tr>
<tr>
<td>1st 6.060–30.973</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>2nd 4.803–6.055</td>
<td>0.24 (0.07 to 0.75)</td>
</tr>
<tr>
<td>3rd 3.777–4.795</td>
<td>0.68 (0.27 to 1.74)</td>
</tr>
<tr>
<td>4th 2.691–3.774</td>
<td>0.14 (0.03 to 0.71)</td>
</tr>
<tr>
<td>p Value for trend</td>
<td>0.391</td>
</tr>
<tr>
<td>Serum gastrin quintiles (ng/l)</td>
<td></td>
</tr>
<tr>
<td>1st 0.323–2.688</td>
<td>0.78 (0.26 to 2.39)</td>
</tr>
<tr>
<td>2nd 25–30</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>3rd 35–55</td>
<td>1.58 (0.58 to 4.28)</td>
</tr>
<tr>
<td>4th 60–90</td>
<td>0.71 (0.19 to 2.66)</td>
</tr>
<tr>
<td>5th 95–128</td>
<td>1.63 (0.48 to 5.48)</td>
</tr>
<tr>
<td>p Value for trend</td>
<td>0.702</td>
</tr>
</tbody>
</table>

Values are represented as OR (95% CI).

*Including four histologically unclassifiable cases and 12 corresponding controls.*

Statistical analyses

Relative risks of cancer between groups of *H pylori* serostatus, PGI-II and gastrin concentrations were estimated as odds ratios (ORs) with associated 95% CIs using conditional logistic regression analyses. By exploiting the algorithmic equivalence of proportional hazards regression and conditional logistic regression, asymptotic ORs were computed using the Cox module of the SPSS V.7.5 statistical computer software package, with each matched set as a separate stratum. For separate analyses of *H pylori*-seropositive and *H pylori*-seronegative cases and controls, we used unconditional logistic
regression with adjustment for the matching variables in the original study design. Unconditional logistic regression produced estimates similar to comparable conditional regression analyses. Tests of contrasts in ORs between subgroups of subjects were performed by including an interaction term in the statistical model. For tests of linear trend, the categorised variable was treated as a continuous variable, and for tests of homogeneity, the variable was represented with indicator variables. Two-sided p values <0.05 were considered significant.

RESULTS
We studied 131 (76%) men and 42 (24%) women with 390 and 118 matched controls, respectively. In the non-cardia subsites, there were 91 men and 38 women. In the cardia, predominance for men was much more pronounced, with 40 men vs four women. Serum was sampled between 1972 and 1986, with 98% of the samples collected between 1972 and 1977. Median age at serum sampling was 45.6 (range 23.6–63.4) years and median follow-up time to diagnosis of cancer was 11.9 (range 0.3–20.3) years in the cases. Median age at diagnosis of cardia cancer was 57.5 (range 43.6–63.3) years, and median age at diagnosis of non-cardia cancer was 55.8 (range 34.3–68.2) years. The time span over which the serum samples were obtained preceded the introduction of proton pump inhibitor medication in Norway.

As reported previously, the association between H pylori seropositivity and cancer was highly dependent on the gastric subsite14 (table 1). H pylori seropositivity was found in 90% (116/129) of the non-cardia cases and in 43% (19/44) of the cardia cases, as compared with 66% (247/376) and 71% (93/132) in the respective control groups. There was a negative association between the infection and cancer of the cardia (OR 0.27, 95% CI 0.12 to 0.59). This contrasted with the positive association in the non-cardia subsites collectively (OR 4.75, 95% CI 2.56 to 8.81; p < 0.001). The OR in the antrum and pylorus combined (OR 7.95, 95% CI 3.07 to 20.6) was non-significantly higher (p = 0.09) than in the fundus and body combined (OR 2.67, 95% CI 1.14 to 6.25).

SERUM PGI:II
Figure 1 shows the individual PGI:II results. In non-cardia subsites collectively, there was a strong association between PGI:II and the subsequent development of cancer. The risk of non-cardia cancer increased monotonously with decreasing quintiles of PGI:II (table 1). A PGI:II <2.69 (lowest quintile) conferred an overall 11.6 (95% CI 4.91 to 27.5) times higher risk of non-cardia cancer than a ratio >6.06 (highest quintile; p for trend over quintiles <0.001). The associations were similar for the proximal and distal non-cardia subsites (data not shown). With PGI:II values dichotomised, PGI:II <2.5 was associated with a 4.47 (95% CI 2.71 to 7.37) times higher risk of non-cardia cancer than PGI:II >2.5 (table 2). A statistically significant association between low PGI:II and non-cardia cancer was found in both H pylori-positive and H pylori-negative subjects when analysed separately (table 2).

In the cardia, quintiles of PGI:II showed no linear association with risk of cancer (p for trend 0.391; table 1). However, when PGI:II was dichotomised and H pylori-seropositive cases and controls were analysed separately, an association between atrophy and cardia cancer was found. H pylori-positive individuals with a PGI:II <2.5 had a 3.33 (CI 1.06 to 10.5) times higher risk of developing cardia cancer relative to subjects with PGI:II >2.5 (table 2). There were no H pylori-negative cases or controls with PGI:II <2.5 precluding an analogous analysis of H pylori-negative subjects.

SERUM GASTRIN
Figure 2 shows the individual serum gastrin results. In non-cardia subsites collectively, a monotonously increasing risk with increasing serum gastrin quintiles was observed, the risk being 8.99 (95% CI 3.96 to 20.4) times higher for gastrin values >95 ng/l than for values <20 ng/l (table 1). The pattern was similar in proximal and distal non-cardia subsites, with ORs tending to be slightly higher in the distal subsites (data not shown). Length of time between the last meal and serum sampling was known for 120 (93%) of the non-cardia cases and 352 (95%) of corresponding controls. In this subgroup of subjects, the association between serum gastrin concentration and cancer was estimated before and after adjustment for time since the last meal. Overall, the adjustment did not
materially alter the point estimates for cardia or non-cardia subsites. However, the adjustment increased the ORs in the distal non-cardia subsites by approximately 30% within each of the serum gastrin concentration quintiles. In an unconditional logistic regression model with adjustment for the variables used for matching in the study design, dichotomising serum gastrin values at >60 ng/l was most discriminating, conferring a 3.18 (95% CI 2.03 to 4.99) times increased risk of non-cardia cancer relative to gastrin concentrations, ≤60 ng/l. This association was apparent and was of the same order of magnitude in both *H pylori*-positive (OR 2.77, 95% CI 1.69 to 4.54) and *H pylori*-negative (OR 3.05, 0.71 to 13.1) individuals analysed separately (table 2).

In the cardia, there was no linear association between serum gastrin concentration tertiles (p for trend 1.00), quartiles (p for trend 0.41) or quintiles (p for trend 0.70; table 1) and later development of cancer, nor did gastrin dichotomised at various cut-off values show any association with cardia cancer. However, separate analyses for *H pylori*-positive and *H pylori*-negative cases and controls suggested associations proceeding in opposite directions. In an unconditional logistic regression model, hypergastrinaemia (cut-off at 60 ng/l) tended to be positively associated with cardia cancer in *H pylori*-seropositive patients (OR 2.23, 95% CI 0.63 to 7.87) but negatively associated in *H pylori*-seronegative patients (OR 0.38, 95% CI (0.05 to 3.03); a test for homogeneity between ORs gave p = 0.093). Adjustment for time since the last meal did not weaken the associations in the subset of subjects for whom this information was available.

**HISTOLOGICAL SUBTYPES**

The cardia and non-cardia cancers had different distributions of histological subtypes. Of the 129 non-cardia cancers, 59 (46%) were intestinal, 35 (27%) diffuse and 31 (24%) mixed, and four (3%) non-classifiable. In the cardia, 44 (30%) were intestinal and 40 (28%) diffuse, with the remaining 20 (14%) mixed. There were no *H pylori*-seronegative cardia cases or controls with pepsinogen I:II, >2.5.

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**Table 2** Risk of adenocarcinoma for serum pepsinogen I:II, <2.5 (relative to serum pepsinogen I:II, ≥2.5) and serum gastrin concentration ≥60 ng/l (relative to serum gastrin concentration <60 ng/l) according to gastric subsites and *Helicobacter pylori* serostatus

<table>
<thead>
<tr>
<th>Gastric subsite</th>
<th>Risk factor</th>
<th>H pylori serostatus</th>
<th>Seropositive</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardia</td>
<td>Pepsinogen I:II &gt; 2.5</td>
<td>129 cases, 376 controls</td>
<td>116 cases, 247 controls</td>
<td>13 cases, 129 controls</td>
</tr>
<tr>
<td></td>
<td>Pepsinogen I:II ≤ 2.5</td>
<td>4.47 (2.71 to 7.37)</td>
<td>3.45 (2.01 to 5.91)</td>
<td>12.6 (2.25 to 70.7)</td>
</tr>
<tr>
<td></td>
<td>p Value</td>
<td>&lt;0.001</td>
<td>~0.001</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Gastrin &lt; 60 ng/l</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td>p Value</td>
<td>&lt;0.001</td>
<td>~0.001</td>
<td>0.133</td>
</tr>
<tr>
<td>Cardia</td>
<td>Pepsinogen I:II &gt; 2.5</td>
<td>44 cases, 132 controls</td>
<td>19 cases, 93 controls</td>
<td>25 cases, 39 controls</td>
</tr>
<tr>
<td></td>
<td>Pepsinogen I:II ≤ 2.5</td>
<td>1.60 (0.62 to 4.14)</td>
<td>3.33 (1.06 to 10.5)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td>p Value</td>
<td>0.333</td>
<td>0.039</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>Gastrin &lt; 60 ng/l</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td>p Value</td>
<td>0.88 (0.37 to 2.06)</td>
<td>2.23 (0.63 to 7.87)</td>
<td>0.38 (0.05 to 3.03)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>3.18 (2.03 to 4.99)</td>
<td>2.77 (1.69 to 4.54)</td>
<td>3.05 (0.71 to 13.1)</td>
</tr>
</tbody>
</table>

Risk of adenocarcinoma estimated by OR with associated 95% CI in an unconditional logistic regression model with adjustment for the matching variables in the original study design.

*Unconditional logistic regression analysis without adjustment for the matching variables (only three cases with pepsinogen I:II, ≥2.5 precluded adjustment).*

†There were no *H pylori* seronegative cardia cases or controls with pepsinogen I:II, <2.5.
were of undifferentiated histological subtype. By contrast, the 44 cardia cancers comprised 31 (71%) intestinal, seven (16%) diffuse, five (11%) mixed and one (2%) undifferentiated histological subtype. The proportion of intestinal to diffuse subtype was significantly higher in the cardia versus non-cardia subsite (p<0.05).

In the non-cardia region, the risk of each of the three histological subtypes increased similarly with decreasing quintiles of PGI:II and increasing quintiles of serum gastrin (table 1). In the cardia, however, the different adenocarcinoma subtypes showed different associations with both PGI:II and gastrin. For these analyses, the variables were dichotomised because of the limited number of cardia cancers and controls. And for comparison, analogous analyses based on dichotomised variables were performed for the non-cardia subsites (table 3). PGI:II <2.5 (relative to PGI:II >2.5) was associated with an increased risk of the diffuse subtype at both non-cardia (OR 3.21, 95% CI 1.27 to 8.13) and cardia subites (OR 3.46, 0.32 to 37.5). Similarly, there was a tendency towards an association between serum gastrin >60 ng/l (relative to serum gastrin <60 ng/l) and the diffuse subtype in both the non-cardia (OR 2.11, 95% CI 0.92 to 4.86) and the cardia subites (OR 5.30, 95% CI 0.52 to 54.6). With respect to the intestinal subtype, both low PGI:II and high serum gastrin showed disparate effects between the two subsites. Low PGI:II was positively associated with the intestinal subtype at non-cardia sites (OR 6.68, 95% CI 2.79 to 16.0), but apparently not at the cardia sites (OR 0.72, 95% CI 0.19 to 2.79; table 3). The contrast in ORs was highly significant (p = 0.007). Likewise, hypergastrinaemia was positively associated with the intestinal subtype in non-cardia subsites (OR 4.04, 95% CI 2.05 to 7.96), but not at the cardia subsites (OR 0.59, 95% CI 0.22 to 1.58; table 3). This difference in ORs was also highly significant (p = 0.002).

The eight cardia cancers that occurred in patients with atrophic (PGI:II <2.5) stomachs were all H pylori positive (fig 2). Three of these cancers were of intestinal, three were of diffuse and two were of mixed histological subtype, and this distribution of histological subtypes was similar to that of the H pylori-positive non-cardia cancers. The 36 cardia cancers that occurred in patients with non-atrophic (PGI:II >2.5) stomachs were predominantly H pylori negative (69%) and had a distribution of histological subtypes that was different from the non-cardia cancers, the intestinal subtype being more prevalent in the cardia (78%) cancers than in the non-cardia (46%) cancers.

**DISCUSSION**

This study shows the association between the premorbid state of the gastric mucosa and the location and histological subtypes of gastric adenocarcinoma presenting over subsequent years. Cancers of the mid and distal stomach of all histological subtypes were positively associated with H pylori infection, atrophy and hypochlorhydria. Cardia cancer was more complex; it was negatively associated with H pylori infection and the predominant intestinal subtype of cardia cancer was not associated with gastric atrophy. However, in patients with H pylori infection, cardia cancer was positively associated with atrophy and hypochlorhydria. These findings can be explained by cardia cancer being of two distinct aetiologies, some cases being similar to non-cardia cancer and others having a different aetiology.

The findings with non-cardia cancer are consistent with current knowledge that its development is a multistage process. H pylori infection induces superficial gastritis, which progresses to atrophic gastritis with loss of acid secretion and then to dysplasia and cancer. Various bacterial, host and environmental factors are known to contribute to the progress through these different pre-cancerous stages.

The multistage process of non-cardia cancer development has been traditionally more strongly associated with the development of the intestinal histological subtype of cancer, as the diffuse type may develop in subjects with normal gastric mucosa. In the latter cases, there is often a strong hereditary predisposition with inherited germline mutations. Our current study, however, along with that of Uemura et al, indicates that atrophy and hypochlorhydria are associated with increased risk of the diffuse and mixed histological subtypes, as well as with intestinal gastric cancer.

The association between atrophy and non-cardia cancer was apparent in both the H pylori-seropositive and H pylori-seronegative patients, the association being statistically non-significantly stronger in the H pylori-seronegative subjects. H pylori seronegativity in some of these individuals may be explained by atrophy and hypochlorhydria causing loss of H pylori infection and seropositivity. Previous studies have shown that patients with evidence of atrophy and no evidence of H pylori have the highest risk for cancer. Some of the non-cardia cancers may have arisen from gastric atrophy due to causes other than H pylori—for example, autoimmune atrophic gastritis.

In addition to using PGI:II as a marker of atrophy, we also used serum gastrin as a marker of atrophy and hypochlorhydria.

| Table 3 | Risk of adenocarcinoma for serum pepsinogen I:II <2.5 (relative to serum pepsinogen I:II >2.5) and serum gastrin concentration >60 ng/l (relative to serum gastrin concentration <60 ng/l) according to gastric subsites and adenocarcinoma subtypes |
| --- | --- | --- | --- | --- |
| **Histology** | **Overall** | **Intestinal** | **Diffuse** | **Mixed** |
| **Gastric subsite risk factor** | **Non-cardia** | | | |
| Pepsinogen I:II >2.5 | 1.29 (0.81 to 2.05) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| p Value | <0.001 | 0.432 (2.58 to 7.24) | 6.68 (2.79 to 16.0) | 3.21 (1.27 to 8.13) |
| Gastrin <60 ng/l | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| p Value | <0.001 | 2.57 (1.92 to 4.61) | 4.04 (2.05 to 7.96) | 2.11 (0.92 to 4.86) |
| **Cardia** | 0.44 (0.33 to 0.58) | 31 cases, 93 controls | 7 cases, 21 controls | 5 cases, 15 controls |
| Pepsinogen I:II >2.5 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| p Value | 0.365 | 1.56 (0.60 to 4.09) | 0.72 (0.19 to 2.79) | 3.46 (0.32 to 37.5) |
| Gastrin <60 ng/l | 1.00 (reference) | 0.38 (0.20 to 0.79) | 0.59 (0.22 to 1.58) | 5.30 (0.25 to 54.6) |
| p Value | 0.689 | 0.95 (0.38 to 1.88) | 0.59 (0.22 to 1.58) | 6.97 (0.06 to 8.04) |

* Risk of adenocarcinoma estimated by OR with associated 95% CI.
* Including four histologically unclassifiable cases and 12 corresponding controls.
* – not applicable.

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Atrophic gastritis notably impairs the ability of the stomach to secrete acid, which stimulates a rise in the circulating concentration of the hormone gastrin. Serum gastrin has been shown to be an independent predictor of atrophic gastritis in subgroups with and without *H pylori* infection. Similar to PGI:II, serum gastrin is most sensitive to atrophic gastritis affecting the gastric body where the acid-secreting parietal cells are located. Serum gastrin increases linearly with an increase in grade of atrophy of the body mucosa and exponentially with a decrease in peak acid output from normal (>10 meq/h) to zero. In patients with achlorhydria or severe hypochlorhydria (peak acid output <1.1 meq/h), the degree of accompanying hypergastrinaemia decreases linearly with increasing grade of antral atrophy. This moderating influence of antral atrophy is thought to be due to loss of antral G cells, and thus inability to produce the high rate of gastrin secretion stimulated by profound hypochlorhydria.

There was a particularly strong association between increase in serum gastrin level and subsequent risk of non-cardia cancer. It is possible that the rise in serum gastrin level associated with atrophy and low acidity may promote the carcinogenic process. The hypergastrinaemic mouse model develops invasive gastric cancer, an effect that is markedly accelerated by *H pylori* infection and inhibited by gastrin receptor antagonism. The state and function of the gastric mucosa associated with cardia cancer is more complex than that associated with non-cardia cancer. In contrast with non-cardia cancer, there was a negative association between *H pylori* infection and cardia cancer. As *H pylori* infection causes atrophy and hypochlorhydria, we expected to find a lower prevalence of atrophy and hypochlorhydria in patients with cardia cancers than in controls because of the lower prevalence of *H pylori* infection in patients with cardia cancer. This was apparent by using either PGI:II or gastrin as the marker of atrophy. *H pylori* infection is thought to lead to oesophageal adenocarcinoma and to metaplasia of oesophageal mucosa, which is the same process that is thought to lead to oesophageal adenocarcinoma and to be induced by reflux of gastric acid. The mechanism by which *H pylori* infection may protect from this process is unclear, but it may be because it causes a fall in acid output with advancing years owing to the development of atrophy.

The analyses of the histological subtypes provide further evidence of two distinct aetiologies of cardia cancer. Atrophy tended to increase the risk of the diffuse subtype of cardia cancer to an extent similar to which it increased the diffuse subtype of non-cardia cancer. This was apparent by using either PGI:II or gastrin as the marker of atrophy. However, our data suggested that atrophy does not increase the risk of intestinal-type cardia cancer, which was in contrast with the increased risk of intestinal-type cancer in the non-cardia region. The contrast in associations between atrophy and intestinal-type cancer in the cardia versus non-cardia regions was highly significant when using either low PGI:II (*p* = 0.007) or high gastrin (*p* = 0.002) as risk indicators. The diffuse-type cancers at the cardia thus seems to be aetiologically similar to diffuse non-cardia cancers, whereas the intestinal-type cancers at the cardia (or at least most of them) are aetiologically distinct from intestinal-type cancers in the non-cardia region.

The *H pylori*-positive controls. Patients with atrophic gastritis were thus characterised by having a significantly lower prevalence of *H pylori* infection but higher prevalence of atrophy in those with the infection than in the controls. What is the explanation for the complex association between the premorbid state of the gastric mucosa and cardia cancer? The lower prevalence of *H pylori* infection associated with atrophic gastritis supports an additional aetiological pathway in cardia cancer. This was apparent by using either PGI:II or gastrin as risk indicators. The analyses of the histological subtypes provide further evidence of two distinct aetiologies of cardia cancer. Atrophy tended to increase the risk of the diffuse subtype of cardia cancer to an extent similar to which it increased the diffuse subtype of non-cardia cancer. This was apparent by using either PGI:II or gastrin as the marker of atrophy. However, our data suggested that atrophy does not increase the risk of intestinal-type cardia cancer, which was in contrast with the increased risk of intestinal-type cancer in the non-cardia region. The contrast in associations between atrophy and intestinal-type cancer in the cardia versus non-cardia regions was highly significant when using either low PGI:II (*p* = 0.007) or high gastrin (*p* = 0.002) as risk indicators. The diffuse-type cancers at the cardia thus seems to be aetiologically similar to diffuse non-cardia cancers, whereas the intestinal-type cancers at the cardia (or at least most of them) are aetiologically distinct from intestinal-type cancers in the non-cardia region.
the non-cardia cancers. This is consistent with them being of an aetiology similar to non-cardia cancer arising from H pylori-induced atrophic gastritis (fig 2). However, the cardia cancers occurring in patients with non-atrophic stomachs (69% of which were H pylori seronegative) had a much higher proportion of intestinal versus diffuse histological subtype (7:1). This predominant intestinal histological subtype is similar to that reported in oesophageal adenocarcinoma and is consistent with this subgroup being of an aetiology similar to oesophageal adenocarcinoma.

Our observations are relevant to the hypothesis that H pylori infection may protect from oesophageal adenocarcinoma as well as predispose to gastric cancer and that both effects are mediated by gastric atrophy. To demonstrate a possible protective effect of H pylori infection on oesophageal adenocarcinoma via gastric atrophy, it will be essential to study only oesophageal adenocarcinomas well clear of the gastro-oesophageal junction. Inclusion of any cardia cancers will obscure a possible protective effect of atrophy due to the subgroup of cardia cancers associated with gastric atrophy.

Our finding may also be relevant to the conflicting reports on the association between H pylori infection and cardia cancer. In general, the association has tended to be negative in studies originating from the West and positive in studies from the East. Our observation of some cardia cancers aetiologically similar to that reported in oesophageal adenocarcinoma and a predominant intestinal histological subtype arising in patients with evidence of reflux. We have recently proposed that cardia cancers of the intestinal histological subtype are likely to be of an aetiology similar to oesophageal adenocarcinoma and to have arisen from metastatic oesophageal mucosa produced by gastroesophageal reflux. We have recently proposed that cardia cancers of the intestinal histological subtype are likely to be of an aetiology similar to oesophageal adenocarcinoma and to have arisen from original gastric mucosa. By contrast, if the patient has a healthy non-atrophic gastric mucosa, then cardia cancer of the intestinal histological subtype is likely to be of an aetiology similar to oesophageal adenocarcinoma and to have arisen from metastatic oesophageal mucosa produced by gastroesophageal reflux.

One practical implication of our findings is that the state of the gastric mucosa may provide a key to determining the origin of cardia cancer. As already discussed, it is usually impossible to determine the origin of such cancers by examining them grossly or microscopically. However, if examination of the stomach well clear of the cancerous process reveals atrophic gastritis, then cardia cancer of the intestinal histological subtype is likely to be aetiologically similar to non-cardia cancer and to have arisen from original gastric mucosa. By contrast, if the patient has a healthy non-atrophic gastric mucosa. Our finding may also be relevant to the hypothesis that

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Two subtypes of cardia cancer


Single aetiology and dual associations of cardiac cancer

With interest we read the article by Hansen et al. (Gut 2007;56:918–25). The authors have to be congratulated on their contribution which profoundly adds to our understanding of the pathophysiology leading to oesophageal and gastric cancer. In addition, the paper points out the difficulties we have to correctly assign tumours of the oesophago-gastric junction (oesophageal vs gastric?). Cardiac cancers were subtyped for their associations with serum anti-Helicobacter pylori IgG antibody titer and biochemical markers of loss of gastric secretory function associated with atopy (pespinogen I/II ratio and serum gastrin concentration). However, the anatomic criterion to define cardiac carcinoma, that is, tumours centred within 2 cm distal to the oesophago-gastric junction, is inaccurate. Interpretation of the data should be conducted with the inclusion of clear, anatomical and histopathological criteria.

It is well accepted that cardiac cancer and adenocarcinoma of the oesophagus share epidemiological and pathogenetic features. After birth the oesophagus is lined by squamous epithelium, whereas the stomach is lined by gastric oxyntic mucosa (with parietal and chief cells). Due to gastro-oesophageal reflux, squamous epithelium is damaged and replaced by columnar-lined oesophagus (CM). Thus, CM is interposed between squamous and oxyntic mucosa. Via intestinal metaplasia and dysplasia CM may progress towards adenocarcinoma of the oesophagus. Anatomy proves that CM is oesophageal: unlike the stomach, the oesophagus has submucosal glands. Histopathology studies of full-thickness oesophago-gastric specimens revealed that CM is only present above submucosal glands, whereas gastric oxyntic mucosa is not underlined by submucosal glands. CM is columnar-lined oesophagus and not stomach. Using multilevel biopsy sampling around the endoscopic visible oesophago-gastric junction in patients with gastro-oesophageal reflux disease, Ringhofer et al. showed that CM cannot be differentiated from gastric oxyntic mucosa by endoscopy. Reflux-damaged columnar-lined oesophagus was mistaken as proximal stomach in 51% of the patients. Based on histopathology, tumours arising within CM are of oesophageal origin, while those arising within oxyntic mucosa are of gastric origin.

We disagree that authors believe to be a “dual” aetiology are in fact “dual associations”. Their data prove that oesophageal adenocarcinoma arising within CM may be present with or without gastric atrophy and H pylori infection of the stomach. H pylori may also infect columnar-lined oesophagus (ie, CM) and be protective against adenocarcinoma, possibly due to atrophy-induced changes in the composition of the refluxate.

Taken together, the aetiology of cancers at the oesophago-gastric junction can only be defined by histopathological criteria: tumours arising within columnar oxyntic mucosa are of oesophageal and gastric origin, respectively. Consequently, cardiac carcinomas have to be treated as oesophageal cancers and tumours arising from oxyntic mucosa as gastric malignancies. Cardiac cancer has a single aetiology, gastro-oesophageal reflux, but may have associations with H pylori infection and gastric atrophy. The authors are kindly asked to address this issue.

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Authors’ reply

We are grateful to Dr Lenglinger and colleagues for their interest in our paper and thoughtful comments. We disagree with their contention that cardia cancer has a single aetiology and is always a consequence of gastro-oesophageal reflux.

We agree that cardiac cancer shares epidemiological similarities with oesophageal adenocarcinoma but would also point out that there are clear epidemiological differences between these two cancers. Indeed, the epidemiology of cardiac cancer tends to share epidemiological features with both oesophageal adenocarcinoma and non-cardia gastric cancer consistent with these cancers being a mixture of two aetiological subtypes – one being similar to non-cardia cancer and one being similar to oesophageal adenocarcinoma.

We disagree that cardia mucosa always represents a metastatic response. Indeed, cardia mucosa at, or proximal to the angle of His has been shown to be established during gestation and present at birth. Whether this transition zone between the squamous epithelium of the oesophagus and the oxyntic mucosa of the stomach is oesophageal or gastric may in the end be a matter of definition.

We also disagree that the only aetiology of carditis and columnar intestinal metaplasia at the gastro-oesophageal junction is gastro-oesophageal reflux. Helicobacter pylori-induced atrophic gastritis may also produce inflammation, loss of oxyntic glands and intestinal metaplasia at the gastric cardia. Whereas reflux disease causes intestinal metaplasia extending proximally to the original squamo-columnar junction, H pylori atrophic gastritis causes intestinal metaplasia extending distally from the original squamo-columnar junction. In practice, it is very difficult to determine by purely examining the columnar mucosa at the gastro-oesophageal junction whether it has developed from original oesophageal or original gastric mucosa. Contrary to Dr Lenglinger and colleagues’ statement that all cardiac tumours are oesophageal in origin, the latest version of the International Classification of Diseases classifies cardia tumours as gastric tumours (C16.0).

We agree that in the Western world where H pylori and gastric atrophy are relatively rare, the majority of cancers at the gastro-oesophageal junction will have arisen as a consequence of gastro-oesophageal reflux. However, in China and Japan, such cancers are mainly of the other histopathological subtype, suffering a consequence of H pylori-induced atrophic gastritis. Consequently, at a global level, we believe that cancer of the gastro-oesophageal junction and cardia can be of two aetiological subtypes. As proposed in our paper, examination of the gastric mucosa distant from the gastro-oesophageal junction is likely to be helpful in determining the particular aetiology of gastro-oesophageal junction cancer in individual patients.

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