Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts

Helicobacter and Cancer Collaborative Group

Abstract
Background—The magnitude of the association between Helicobacter pylori and incidence of gastric cancer is unclear. H pylori infection and the circulating antibody response can be lost with development of cancer; thus retrospective studies are subject to bias resulting from classification of cases as H pylori negative when they were infected in the past.

Aims—To combine data from all case control studies nested within prospective cohorts to assess more reliably the relative risk of gastric cancer associated with H pylori infection. To investigate variation in relative risk by age, sex, cancer type and subsite, and interval between blood sampling and cancer diagnosis.

Methods—Studies were eligible if blood samples for H pylori serology were collected before diagnosis of gastric cancer in cases. Identified published studies and two unpublished studies were included. Individual subject data were obtained for each. Matched odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated for the association between H pylori and gastric cancer.

Results—Twelve studies with 1228 gastric cancer cases were considered. The association with H pylori was restricted to non-cardia cancers (OR 3.0; 95% CI 2.3–3.8) and was stronger when blood samples for H pylori serology were collected 10+ years before cancer diagnosis (5.9; 3.4–10.3). H pylori infection was not associated with an altered overall risk of cardia cancer (1.0; 0.7–1.4).

Conclusions—These results suggest that 5.9 is the best estimate of the relative risk of non-cardia cancer associated with H pylori infection and that H pylori does not increase the risk of cardia cancer. They also support the idea that when H pylori status is assessed close to cancer diagnosis, the magnitude of the non-cardia association may be underestimated.

(Gut 2001;49:347–353)

Keywords: gastric cancer; Helicobacter pylori; cardia cancer; pooled analysis

There is substantial evidence that infection with the gastric bacterium Helicobacter pylori plays a role in the development of gastric cancer.1 2 The magnitude of the risk of gastric cancer associated with infection is however unclear and there have been suggestions that this risk varies with sex,3 4 age,3 5 and the histological subtype of the cancer.1 There is also evidence that the excess risk is restricted to cancer occurring at sites other than the gastric cardia.4 5 9

Many studies have been conducted in an attempt to address these issues. Retrospective case control studies are however limited by the fact that H pylori infection is, by necessity, assessed after the development of cancer in the cases. H pylori does not colonise areas of cancer, intestinal metaplasia, or atrophy and there is evidence that with the development of advanced gastric disease the organism can be lost from the stomach.10 With loss of infection, the level of circulating anti-H pylori antibodies will fall so that patients with gastric cancer may be H pylori seronegative even though they have been infected in the past (TU Kosunen, personal communication)11 This will not occur to the same extent in controls and, in the presence of such differential misclassification, estimates of the association between H pylori and gastric cancer will be biased downwards making the results of retrospective studies difficult to interpret.

This problem can be overcome by conducting case control studies nested within prospective cohorts where blood samples used for H pylori serology are collected before the development of cancer. In 1991, three such studies reported odds ratios (ORs) for the association between H pylori infection and the subsequent development of gastric cancer that ranged from 2.8 to 6.0.1 12 A number of other nested case control studies have since been published7 13–18 and these have given less consistent results. Two possible reasons for this inconsistency are differing proportions of cardia and non-cardia cancers, and variable intervals between sample collection and cancer diagnosis with short intervals potentially leading to differential exposure misclassification of cases as may occur in retrospective studies. Initial support for this latter hypothesis comes from a pooled analysis of the data from the first three nested case control studies which suggested that higher ORs were seen when blood samples were collected more than 10 years before the diagnosis of cancer.13

Although there have been three previous meta-analyses of published data examining the association between H pylori infection and gastric cancer,10 25 26 these have combined both prospective and retrospective studies and/or have

Abbreviations used in this paper: CagA, cytotoxin associated gene A; IgA (G), immunoglobulin A (G); OR, odds ratio.
been unable to separate cardia and non-cardia cancers. We have therefore conducted a collaborative reanalysis using individual subject data obtained from published and two unpublished prospective studies. By pooling these data we have been able to evaluate the magnitude of this relationship more precisely than previously and assess the relative risk in relevant subgroups.

Methods

STUDY SELECTION

The analysis was restricted to case control studies investigating the association between H pylori infection and gastric adenocarcinoma where samples for H pylori serology had been collected prior to the diagnosis of gastric cancer in the cases. Eligible studies were identified through a Medline search (1985–1999) and through contact with investigators in the area. By the end of 1999, 11 reports had been published from nine studies. Results have since been published from a study in China and two further studies have been conducted in Iceland (H Tulinius, personal communication) and Finland (TU Kosunen, personal communication). The investigators from all 12 studies agreed to provide their data for the present analysis. Results from an additional prospective study in Japan have also been published recently but individual subject data from this study were not available at the time of the present analyses.

DATASET

For each subject in their study, the investigators provided the following information (or information to allow calculation of the required variables): case or control status, sex, H pylori infection status (diagnosed by serology) and, for cases, age at diagnosis, site and histological type of the tumour (when available), and length of time between collection of the blood sample for H pylori serology and diagnosis of cancer. For some studies, additional information was available concerning cases who had gastric surgery prior to the development of the cancer. Identifiers for the matched sets were also obtained in order to preserve the original matching in the analyses. The matching variables were sex, age, and date of sample collection.

In two studies the controls were not matched to the cases. For the second Finnish study, controls greatly outnumbered cases and individual matched case control sets were created by dividing subjects into groups based on their age when the blood samples were collected (within a three year period). Each control was then randomly allocated to one of the cases of the same age at sample collection to give case control sets matched on sex, age, and date of sampling (both within about three years). In the second Chinese study there was an excess of older cases and younger controls and thus individual age-sex matching was not efficient. For the overall analysis, cases and controls were stratified by sex and age at blood sampling (seven, five year bands) to give 14 matched sets containing variable numbers of cases and controls. For subsite specific analyses, cases within each of the 14 sets were grouped so that each group was homogeneous with respect to age at diagnosis (10 year groups) and interval between blood sampling and diagnosis (five year bands). Controls within each set were then randomly allocated to one of the case groups in the same set so that, as far as possible, each group contained approximately equal numbers of cases and controls. This process was carried out separately for cardia and non-cardia cases so that all 192 controls were matched to the 30 groups of cardia cases and 174 of the controls were also matched to the 21 groups of non-cardia cases (two of the 14 sex-age at sampling sets did not contain a non-cardia case thus these 18 controls were excluded from the non-cardia analyses).

In each of the studies H pylori infection was diagnosed by serology using an assay for anti-H pylori IgG antibodies. Different assays had however been used and the cut off point used to determine H pylori seropositivity was that used by the original investigators. The first Chinese study had originally used an assay developed in the UK. A local assay has since been developed and validated in China (sensitivity 90% and specificity 94%) and used for the update of this study. These data were used in the present analyses. In the first Finnish study, results were based on serology for both H pylori immunoglobulin (Ig) G and IgA but the IgG data were included in the present analyses for consistency.

Table 1 shows the total number of cases and controls and the ORs for the association between H pylori and gastric cancer in each of the studies. The numbers differ in some instances from those originally published. In the Californian study, two cases were subsequently found to have gastric lymphomas and were thus excluded; the original report from the first Chinese study included 85 cases and 80 of these plus 108 new cases were included in the recent update, and while the original report from the UK study included only 29 cases, additional cases have since been diagnosed, bringing the total to 56. The matched analysis used here for the second Chinese study gives slightly different estimates from the original unmatched analysis.

H PYLORI SEROPREVALENCE

The studies had used differing and sometimes variable numbers of matched controls per case. Because the seroprevalence of H pylori varied across the studies, the prevalence in the control group was therefore unduly influenced by studies with the greatest numbers of controls per case. To overcome this problem, the seroprevalence in the controls was weighted by the number of cases contributed by each study.

STATISTICAL ANALYSIS

The majority of analyses were conducted separately for cardia and non-cardia cancers after excluding cases known to have had previous gastric surgery because this is also a strong independent risk factor for gastric cancer.
Table 1 Characteristics of the individual studies and the overall association between Helicobacter pylori and gastric cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Matched OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>USA (California)</td>
<td></td>
</tr>
<tr>
<td>USA (Hawaii)</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td></td>
</tr>
<tr>
<td>Finland I</td>
<td></td>
</tr>
<tr>
<td>China I</td>
<td></td>
</tr>
<tr>
<td>Finland II</td>
<td></td>
</tr>
<tr>
<td>China II</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

*Interval between collection of blood sample used for Helicobacter pylori serology and cancer diagnosis.
†Odds ratios (OR) differ from published results due to changes in study sample (UK and California) and use of matching (China II). Published results are UK OR 2.77 (95% confidence interval (CI) 1.04–7.97) and OR 4.0 (1.9–8.2); California OR 3.6 (1.8–7.3); and China II OR 2.0 (1.3–3.2).
‡Unpublished data.
§Weighted by the number of cases per study to allow for different matching ratios.

Cases where the cancer site was not specified, or where the tumour overlapped two or more sites that included the cardia, were excluded from site specific analyses. The definition of cardia cancer was that used by the investigators in the original studies. This should include only tumours located within 2–3 cm of the oesophagogastric junction and tumours extending across the oesophagogastric border.

Conditional logistic regression was used to estimate the association between Helicobacter pylori and cancer in order to preserve the individual OR for the association between Helicobacter pylori and non-cardia cancer based on 762 cases and 2250 controls. There was however statistically significant heterogeneity among the results (p=0.01) with the individual OR ranging from 1.52 (0.66–3.53) in Iceland up to 11.1 (2.51–49.4) in Sweden.

The results for cardia cancer were somewhat more consistent and the heterogeneity test was not statistically significant (p=0.12). Overall, the OR between Helicobacter pylori infection and risk of cardia cancer was 0.99 (95% CI 0.72–1.35) based on 274 cases and 827 controls. Three studies (the two from China plus Norway) contributed over two thirds of the cardia cancer cases for this analysis.

In some subjects the cancer site was unspecified or the cancer was so widespread it overlapped two or more sites including the cardia. In this group which, like the group where the site was specified, would probably include a majority of non-cardia cancers, the OR for the association between Helicobacter pylori infection was 4.69 (95% CI 2.71–8.11). A high proportion of
Table 2  Association between Helicobacter pylori infection and non-cardia and cardia gastric cancer* data from 12 prospective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Matched OR and 95% CI</th>
<th>Matched OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardia cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>762</td>
<td>86.0</td>
</tr>
<tr>
<td>H pylori +ve (%)</td>
<td>82</td>
<td>62.2</td>
</tr>
<tr>
<td>Controls</td>
<td>2250</td>
<td>68.6</td>
</tr>
<tr>
<td>Matched OR</td>
<td>2.97</td>
<td>(2.34–3.77)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardia cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>350</td>
<td>86.7</td>
</tr>
<tr>
<td>H pylori +ve (%)</td>
<td>331</td>
<td>82.2</td>
</tr>
<tr>
<td>Controls</td>
<td>274</td>
<td>61.9</td>
</tr>
<tr>
<td>Matched OR</td>
<td>0.99</td>
<td>(0.72–1.35)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Excludes all cases known to have had a partial gastrectomy or where the cancer could not be localised to a particular part of the stomach.
†Unpublished data.
‡In the Hawaiian study there were no case control pairs with a positive H pylori test 10 years or more prior to diagnosis in comparison with a risk slightly greater than unity (OR 1.23) when samples were collected less than 10 years before the development of cancer (p=0.01). However, 69% of the cardia cases with 10 or more years follow up came from the Norwegian study.

In contrast, for cardia cancer, lower ORs were seen with longer follow up (p for trend=0.09) (table 4). There was a significantly reduced risk of cancer (OR 0.46) associated with a positive H pylori test 10 years or more prior to diagnosis in comparison with a risk slightly greater than unity (OR 1.23) when samples were collected less than 10 years before the development of cancer (p=0.01). However, 69% of the cardia cases with 10 or more years follow up came from the Norwegian study.

To allow for the possibility that cancers diagnosed in the first few months of follow up could already have been present at the time of sample collection, analyses were repeated excluding cases diagnosed less than six months (23 non-cardia and four cardia cases) or within 18 months of sample collection (95 non-cardia and 26 cardia cases). This did not alter the results.

Considering all the gastric cancer cases, irrespective of subsite, the OR associated with a positive H pylori test 10 years or more prior to diagnosis was 3.12 (95% CI 2.23–4.35) and was significantly greater (p=0.045) than that obtained when samples were collected less than 16 years.

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for the effects of both age and time interval, the OR for the association between *H pylori* and gastric cancer was 2.2 (95% CI 1.3–3.7) times greater among younger subjects (age <60) and 2.7 (1.5–5.1) times greater among those whose blood samples were collected more than 10 years prior to diagnosis. After allowing for variation in both age and time interval, a test for heterogeneity of the *H pylori*-gastric cancer association across the 12 studies was no longer statistically significant (p=0.2).

The association did not vary by sex (table 3). Information on the histological subtype of the tumour was only available for seven of the 12 studies (including Finland II). The association with *H pylori* did not differ greatly between intestinal- and diffuse-type cancers (p=0.5).

There was no statistically significant variation in the relationship between *H pylori* and cardia cancer by age, sex, or histological type (table 4). Although an inverse association was seen only for intestinal-type and not diffuse-type cancers, this difference was not statistically significant (p=0.3).

**Discussion**

This analysis provides evidence that the increased risk of gastric cancer associated with *H pylori* infection is restricted to cancers at sites other than the gastric cardia. Estimates of the risk of non-cardia gastric cancer associated with *H pylori* infection were considerably higher when blood samples for *H pylori* serology were collected 10 years or more before the diagnosis of cancer. This suggests that retrospective case control studies, where *H pylori* status is assessed after the diagnosis of cancer, will underestimate the magnitude of the association between *H pylori* and gastric cancer as a result of loss of infection in cancers with the onset of disease.

Although overall there was an association between increasing time interval between sample collection and cancer diagnosis and higher OR, the OR peaked at 9.6 in the group with samples collected 10–15 years before diagnosis and then fell to 4.2 for the group with samples collected more than 15 years before cancer diagnosis. There was however considerable overlap of the 95% CI for the OR and the difference was not statistically significant (p=0.15). We have considered several possibilities for the drop in OR in the group with longer interval, including differences in the age structure and differential contributions from the individual studies in the two groups, but have not been able to explain this.

The matched analysis controls for potential confounding by age, sex, and time of sample collection. In addition, some of the individual studies were also matched for race and/or area of residence, and the UK subjects were from a cohort that is relatively homogeneous with respect to social class. Information on other potential confounding factors, for example socioeconomic and dietary factors, was not available for the majority of studies included in this analysis. In the original reports from the Norwegian, first Chinese, and Finnish

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**Table 3** Association between *Helicobacter pylori* infection and non-cardia gastric cancer* by interval between sample collection for *H pylori* serology and cancer diagnosis, age at diagnosis, sex, and tumour histology‡

<table>
<thead>
<tr>
<th>Interval between sample collection and cancer diagnosis (y)</th>
<th>Cases</th>
<th>Controls</th>
<th>Matched OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>334</td>
<td>999</td>
<td>2.56 (1.83–3.57)</td>
</tr>
<tr>
<td>5–9.9</td>
<td>205</td>
<td>624</td>
<td>2.09 (1.33–3.39)</td>
</tr>
<tr>
<td>10–14.9</td>
<td>103</td>
<td>293</td>
<td>9.56 (3.77–24.2)</td>
</tr>
<tr>
<td>15+</td>
<td>120</td>
<td>334</td>
<td>4.15 (2.08–8.29)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>539</td>
<td>1623</td>
<td>2.39 (1.82–3.12)</td>
</tr>
<tr>
<td>10+</td>
<td>232</td>
<td>627</td>
<td>5.93 (3.41–10.3)</td>
</tr>
</tbody>
</table>

**Table 4** Association between *Helicobacter pylori* infection and cardia gastric cancer* by interval between sample collection for *H pylori* serology and cancer diagnosis, age at diagnosis, sex, and tumour histology‡

<table>
<thead>
<tr>
<th>Interval between sample collection and cancer diagnosis (y)</th>
<th>Cases</th>
<th>Controls</th>
<th>Matched OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>133</td>
<td>340</td>
<td>1.21 (0.75–1.93)</td>
</tr>
<tr>
<td>5–9.9</td>
<td>93</td>
<td>273</td>
<td>1.26 (0.73–2.17)</td>
</tr>
<tr>
<td>10–14.9</td>
<td>26</td>
<td>108</td>
<td>0.48 (0.19–1.20)</td>
</tr>
<tr>
<td>15+</td>
<td>22</td>
<td>106</td>
<td>0.44 (0.17–1.16)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>226</td>
<td>613</td>
<td>1.23 (0.86–1.75)</td>
</tr>
<tr>
<td>10+</td>
<td>48</td>
<td>214</td>
<td>0.46 (0.23–0.90)</td>
</tr>
</tbody>
</table>

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*Excludes all cases known to have had a partial gastrectomy and cases where the cancer could not be localised to a particular part of the stomach.
†Percentages are not directly comparable across strata because different studies contributed different numbers of cases to each stratum.
‡Information about histological type was only available for seven studies (the two from the USA, the two from Finland, Taiwan, Japan, and Norway).
OR, odds ratio; CI, confidence interval.

10 years before the development of cancer (2.10 (95% CI 1.70–2.58)).

**THE EFFECTS OF SEX, AGE, AND HISTOLOGICAL SUBTYPE**

There was a significant association between *H pylori* and non-cardia cancer in all age groups (table 3) but the magnitude of this association was much greater among subjects aged less than 60 than among those aged 60 or older (p=0.006). This age effect was independent of the variation with time interval between sample collection and diagnosis. In a model allowing for the effects of both age and time interval, the OR for the association between *H pylori* and gastric cancer was 2.2 (95% CI 1.3–3.7) times greater among younger subjects (age <60) and 2.7 (1.5–5.1) times greater among those whose blood samples were collected more than 10 years prior to diagnosis. After allowing for variation in both age and time interval, a test for heterogeneity of the *H pylori*-gastric cancer association across the 12 studies was no longer statistically significant (p=0.2).

The association did not vary by sex (table 3). Information on the histological subtype of the tumour was only available for seven of the 12 studies (including Finland II). The association with *H pylori* did not differ greatly between intestinal- and diffuse-type cancers (p=0.5).

There was no statistically significant variation in the relationship between *H pylori* and cardia cancer by age, sex, or histological type (table 4). Although an inverse association was seen only for intestinal-type and not diffuse-type cancers, this difference was not statistically significant (p=0.3).

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**Table 3** Association between *Helicobacter pylori* infection and non-cardia gastric cancer* by interval between sample collection for *H pylori* serology and cancer diagnosis, age at diagnosis, sex, and tumour histology‡

<table>
<thead>
<tr>
<th>Histological type‡</th>
<th>Cases</th>
<th>Controls</th>
<th>Matched OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal</td>
<td>241</td>
<td>700</td>
<td>4.45 (2.74–7.24)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>114</td>
<td>353</td>
<td>3.39 (1.70–6.76)</td>
</tr>
</tbody>
</table>

**Table 4** Association between *Helicobacter pylori* infection and cardia gastric cancer* by interval between sample collection for *H pylori* serology and cancer diagnosis, age at diagnosis, sex, and tumour histology‡

<table>
<thead>
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<tr>
<td>Diffuse</td>
<td>114</td>
<td>353</td>
<td>3.39 (1.70–6.76)</td>
</tr>
</tbody>
</table>
studies, however, the data were adjusted for potential confounders. In the Chinese and Finnish studies the authors reported that adjustment did not alter the results and, in Norway, adjustment only slightly weakened the positive association with non-cardia cancer while slightly strengthening the inverse association with cardia cancer. Thus although we cannot rule out the possibility of residual confounding in the present analyses, it seems likely that had adjustment for confounding been possible, it would not have had an appreciable effect on the estimated ORs.

There was evidence of heterogeneity across the results of the studies of the risk for non-cardia cancer (p=0.01) although in seven of the 12 studies the 95% CI around the point estimate did not include the null value and in all studies the point estimate was greater than 1.5. Some of this heterogeneity could be explained by variation in the average interval between sample collection and diagnosis and in the average age of the participants in each study as, after allowing for this, the heterogeneity was reduced and was no longer statistically significant (p=0.2).

We suggest therefore that the approximately sixfold increased risk seen in the group followed for 10 years or more is the best estimate of the magnitude of the relative risk of non-cardia gastric cancer associated with H pylori infection. This estimate is considerably higher than the OR of 2.0–3.1 reported in previous meta-analyses.

Results from another study in Japan have been published since this pooling project and could not be included in the analysis. This study reported a positive association for non-cardia cancer (OR 3.66; 95% CI 1.12–11.92) and little effect for the 10 patients with cancer in the “proximal one third of the stomach” (OR 1.29; 95% CI 0.28–6.09). Inclusion of this additional study would thus have had little effect on the results.

A retrospective case control study, conducted in the USA, has shown a lower risk for oesophageal and cardia adenocarcinomas associated with H pylori infection although this was significant only for infection with cytoxin associated gene A (CagA) positive strains of H pylori. CagA serology data are not available for all of the studies included in the present analysis and therefore this question was not addressed in this paper. It is however necessary to explain why, in our results, H pylori appears to have no effect on the development of cardia cancers while increasing the risk of cancers throughout the rest of the stomach. Reflux oesophagitis has been associated with oesophageal and cardia adenocarcinomas and this suggests that gastric acid exposure might play a role in the aetiology of these cancers. The widespread gastritis and atrophy, which are a consequence of H pylori infection and increase the risk of non-cardia gastric cancer, may reduce gastric acidity and the extent of reflux disease. It is also of note that while the seroprevalence of H pylori and gastric cancer incidence rates appear to be falling over time, the incidence of cardia cancer and oesophageal adenocarcinoma appears to be on the increase.

Only four studies in our analysis included more than 20 cases with cardia cancer and, of these, the two from China indicated an elevated risk associated with infection (ORs 1.44 and 1.77) while two from Europe indicated a reduced risk (ORs 0.40 in Norway and 0.61 in Finland II). Overall these results are consistent with the summary odds ratio of 0.99 indicating no effect of infection but it is also possible that there may be a divergence of effect between Europe and China. Although we formally tested for, and found no evidence of, between study heterogeneity for cardia cancer, heterogeneity tests have relatively little power to detect small to moderate variation in effect. It should be emphasised that a conclusion of different effects between populations is entirely data derived and requires independent confirmation from other studies.

Conclusions

We believe that the best estimate of the magnitude of the association between H pylori infection and the subsequent risk of non-cardia gastric cancer is about sixfold seen in the group of subjects whose samples for H pylori serology were collected 10 or more years prior to the development of cancer. Estimates of relative risk appear to be diluted when H pylori infection is assessed closer to the time of cancer diagnosis. The magnitude of this risk varies with age; the effect is reduced in the older age groups, presumably because of increased seroprevalence among the older controls because there is little change in the seroprevalence in cases with age. Assuming an average prevalence of H pylori of 35% in developed countries and 85% in developing countries, an OR of 5.9 suggests that between about 65% and 80%, respectively, of non-cardia gastric cancers are attributable to H pylori infection and therefore potentially preventable by control of the infection. H pylori infection does not however appear to increase the risk of cardia cancer.

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Appendix

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Gastric cancer and H pylori