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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 Identified published studies and two unpublished studies were included.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 noncardia 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)

See appendix for details of study group members.

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Accepted for publication
26 February 2001

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.[6] There is also evidence that the excess risk is restricted to cancer occurring at sites other than the gastric cardia.[4,5,7–9]

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.[4,5,12] A number of other nested case control studies have since been published[7,13–18] 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.[19]

Although there have been three previous meta-analyses of published data examining the association between *H pylori* infection and gastric cancer,[20–22] these have combined both prospective and retrospective studies and/or have

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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.[4–6 12–18 23] Results have since been published from a study in China[24] 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[25] 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[24] 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.[15] A local assay has since been developed and validated in China (sensitivity 99% and specificity 94%) and used for the update of this study.[16] These data were used in the present analyses. In the first Finnish study,[14] 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[15] and 80 of these plus 108 new cases were included in the recent update,[16] and while the original report from the UK study[12] included only 29 cases, additional cases have since been diagnosed,[23] bringing the total to 56. The matched analysis used here for the second Chinese study gives slightly different estimates from the original unmatched analysis.[24]

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.[26 27]

Table 1   Characteristics of the individual studies and the overall association between Helicobacter pylori and gastric cancer

Study	Mean (range) age of cases at diagnosis	Sex ratio among cases (% male)	Median interval (y) *	All cases		Controls		Matched OR	(95% CI)
				Total	Hp +ve (%)	Total	Hp +ve (%)		
UK[12 23]	54 (39–69)	100	8.7	56	67.9	174	41.4	3.47†	(1.75–6.85)†
USA (California)[4]	68 (44–90)	69	15.0	111	84.7	111	60.4	3.70†	(1.84–7.44)†
USA (Hawaii)[5]	72 (56–85)	100	13.8	109	94.5	109	76.1	6.00	(2.08–17.3)
Taiwan[13]	63 (43–80)	100	2.0	29	69.0	220	58.6	1.55	(0.68–3.54)
Finland I[14]	62 (32–85)	62	5.1	84	86.9	146	82.9	1.50	(0.70–3.22)
China I[15 16]	63 (49–76)	100	4.8	188	89.4	548	82.3	1.84	(1.08–3.11)
Sweden[7]	56 (38–70)	93	5.1	56	82.1	224	49.1	5.00	(2.34–10.7)
Japan[17]	69 (46–86)	58	3.6	45	91.1	225	75.6	3.38	(1.15–9.90)
Norway[18]	56 (34–68)	75	12.0	208	79.8	983	63.0	2.26	(1.55–3.28)
Iceland‡	72 (55–89)	71	15.0	41	78.0	202	67.8	1.67	(0.76–3.65)
Finland II‡	63 (52–75)	100	4.1	120	85.8	272	69.9	2.26	(1.26–4.05)
China II[24]	61 (36–75)	62	3.6	181	62.4	192	51.6	1.66†	(1.08–2.54)
Total	62 (32–90)	82	6.0	1228	81.2	3406	66.1§	2.36	(1.98–2.81)

*Interval between collection of blood sample used for *H 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)[15] and OR 4.0 (1.9–8.2)[23]; California OR 3.6 (1.8–7.3)[4]; and China II OR 2.0 (1.3–3.2).[24]
‡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 *H pylori* and cancer in order to preserve the individual matching. Results are presented as maximum likelihood estimates of the ORs and 95% confidence intervals (CI). The change in the likelihood ratio statistic on addition to the model of a term for the interaction between *H pylori* status and study centre was used to assess homogeneity across the studies. The same procedure was used to evaluate differences in the effect of *H pylori* by sex, age group, histological subtype of cancer, and time between sample collection and cancer diagnosis. All tests of statistical significance were two sided.

Results

Information from a total of 1228 gastric cancer cases and 3406 controls from the 12 studies was available for analysis. Table 1 and fig 1 show the basic characteristics of each study together with the pooled OR from all studies combined. There was some suggestion of heterogeneity across the individual studies although the statistical test was not conventionally significant (p=0.09). Overall, the matched OR for the association between *H pylori* infection and the subsequent development of gastric cancer was 2.36 (95% CI 1.98–2.81).

Table 2 and figs 2 and 3 show the OR for the association with *H pylori* separately for cardia and non-cardia cancers, after excluding cases known to have had gastric surgery before they developed cancer or where the cancer could not be localised to a particular part of the stomach. Combining the data gave an overall OR of 2.97 (95% CI 2.34–3.77) for the association between *H 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 *H 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 *H pylori* infection was 4.69 (95% CI 2.71–8.11). A high proportion of
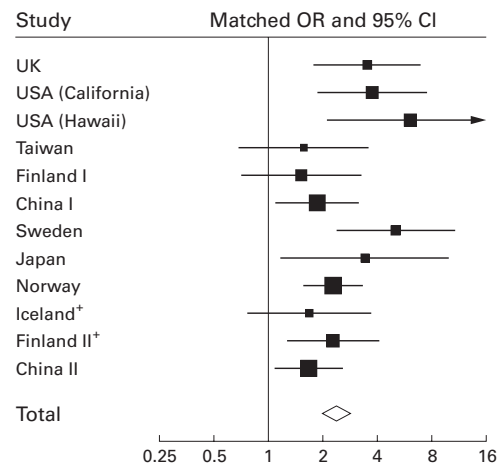

Figure 1   Matched odds ratios (OR) and 95% confidence intervals (CI) for the association between Helicobacter pylori infection and gastric cancer, overall and by study. The area of the square is proportional to the study size. The diamond shows the OR value for all studies combined, with 95% CI represented by the horizontal points. +Unpublished data.

Table 2 Association between Helicbacter pylori infection and non-cardia and cardia gastric cancer* data from 12 prospective studies

Study	Non-cardia cases		Controls				Cardia cases		Controls			
	Total	Hp +ve (%)	Total	Hp +ve (%)	Matched OR	(95% CI)	Total	Hp +ve (%)	Total	Hp +ve (%)	Matched OR	(95% CI)
UK[12 23]	9	66.7	27	44.4	2.88	(0.50–16.5)	12	33.3	36	30.6	1.15	(0.27–4.91)
USA (California)[4]	62	88.7	62	61.3	5.25	(1.80–15.3)	4	25.0	4	25.0	1.00	(0.06–16.0)
USA (Hawaii)[5]	74	95.9	74	75.7	8.50	(1.96–36.8)	5	40.0	5	80.0	—‡	—
Taiwan[13]	21	71.4	160	60.0	1.66	(0.61–4.51)	8	62.5	60	55.0	1.33	(0.31–5.79)
Finland I[14]	75	88.0	130	82.3	1.74	(0.75–4.03)	9	77.8	16	87.5	0.59	(0.08–4.30)
China I[15 16]	114	87.7	331	82.2	1.54	(0.82–2.89)	43	90.7	124	87.1	1.44	(0.43–4.92)
Sweden[7]	27	88.9	108	49.1	11.1	(2.51–49.4)	13	46.2	52	48.1	0.92	(0.27–3.16)
Japan[17]	38	89.5	190	73.7	3.02	(1.02–8.91)	4	100	20	85.0	—‡	—
Norway[18]	132	90.2	614	62.9	5.15	(2.83–9.37)	45	44.4	228	64.9	0.40	(0.20–0.77)
Iceland†	35	77.1	176	68.8	1.52	(0.66–3.53)	5	80.0	22	68.2	1.68	(0.18–15.5)
Finland II†	93	93.5	204	71.1	4.72	(1.98–11.3)	27	59.3	68	66.2	0.61	(0.22–1.70)
China II[24]	82	62.2	174	51.1	1.82	(1.03–3.22)	99	62.6	192	51.6	1.77	(1.05–2.97)
Total	762	86.0	2250	68.6§	2.97	(2.34–3.77)	274	62.0	827	61.9§	0.99	(0.72–1.35)

*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 *H pylori* positive case and a negative control; in the Japanese study there were no *H pylori* negative cases.
§Weighted by the number of cases in each study to allow for the different matching ratios of controls to cases.
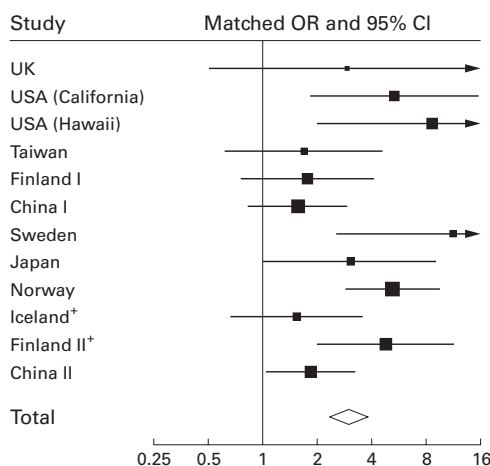OR, odds ratio; CI, confidence interval.

Figure 2 Matched odds ratios (OR) and 95% confidence intervals (CI) for the association between Helicobacter pylori infection and non-cardia gastric cancer, overall and by study. The area of the square is proportional to the study size. The diamond shows the OR value for all studies combined, with 95% CI represented by the horizontal points. ⁺Unpublished data.

Figure 3 Matched odds ratios (OR) and 95% confidence intervals (CI) for the association between Helicobacter pylori infection and cardia cancer, overall and by study. The area of the square is proportional to the study size. The diamond shows the OR value for all studies combined, with 95% CI represented by the horizontal points. ⁺Unpublished data.
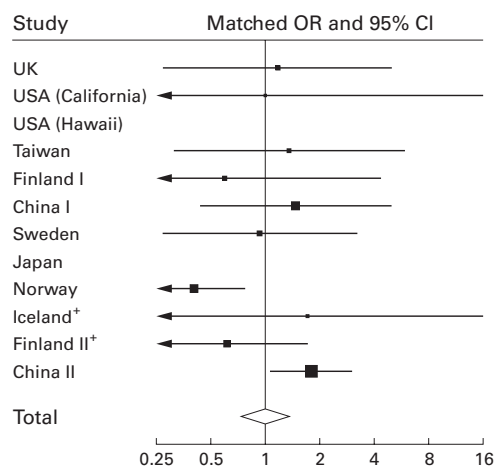
these cases (47%) came from the two American studies[4 5] which could account for the higher OR seen in this group.

INTERVAL BETWEEN SAMPLE COLLECTION AND CANCER DIAGNOSIS

In the combined dataset a significantly increased risk of non-cardia gastric cancer associated with prior *H pylori* infection was seen for each interval between sample collection and diagnosis (table 3). The strength of the association varied significantly however with the time period (p for trend=0.03). There was a 2.1–2.6-fold increase in risk when samples were collected less than 10 years before the development of cancer compared with a 5.9-fold increase in risk associated with a positive *H pylori* test 10 years or more prior to diagnosis (<10 years *v* ≥10 years; p=0.002). A similar pattern was seen when the analysis was restricted to the four studies (Parsonnet and colleagues,[4] Nomura and colleagues,[5] Hansen and colleagues,[18] and the Iceland study) that covered the whole range from less than five to more than 15 years.

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

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‡

	Cases		Controls			
	Total	Hp+ve† (%)	Total	Hp+ve† (%)	Matched OR	(95% CI)
Interval between sample collection and cancer diagnosis (y)						
<5	334	82.6	999	66.2	2.56	(1.83–3.57)
5–9.9	205	85.4	624	72.0	2.09	(1.33–3.29)
10–14.9	103	95.1	293	63.1	9.56	(3.77–24.2)
15+	120	88.3	334	65.9	4.15	(2.08–8.29)
<10	539	83.7	1623	68.4	2.39	(1.82–3.12)
10+	223	91.5	627	64.6	5.93	(3.41–10.3)
Sex						
Male	625	86.4	1839	68.4	2.98	(2.27–3.90)
Female	137	83.9	411	62.5	2.93	(1.76–4.88)
Age at diagnosis (y)						
<50	67	89.6	251	54.2	7.10	(2.93–17.2)
50–59	206	87.4	718	65.2	3.94	(2.46–6.32)
60–69	313	82.7	886	70.9	1.98	(1.40–2.80)
70+	176	88.6	395	71.6	3.13	(1.76–5.56)
Histological type‡						
Intestinal	241	90.5	700	65.4	4.45	(2.74–7.24)
Diffuse	114	90.4	353	69.1	3.39	(1.70–6.76)
Total	762	86.0	2250	67.3	2.97	(2.34–3.77)

*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.

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‡

	Cases		Controls			
	Total	Hp+ve† (%)	Total	Hp+ve† (%)	Matched OR	(95% CI)
Interval between sample collection and cancer diagnosis (y)						
<5	133	68.4	340	66.5	1.21	(0.75–1.93)
5–9.9	93	63.4	273	60.4	1.26	(0.73–2.17)
10–14.9	26	42.3	108	60.2	0.48	(0.19–1.20)
15+	22	40.9	106	60.4	0.44	(0.17–1.16)
<10	226	66.4	613	63.8	1.23	(0.86–1.75)
10+	48	41.7	214	60.3	0.46	(0.23–0.90)
Sex						
Male	210	61.9	680	63.2	0.98	(0.68–1.40)
Female	64	62.5	147	61.2	1.03	(0.55–1.92)
Age at diagnosis (y)						
<50	33	45.5	97	50.5	0.90	(0.37–2.19)
50–59	86	61.6	311	62.1	0.94	(0.55–1.59)
60–69	115	63.5	317	67.5	0.84	(0.52–1.38)
70+	40	72.5	102	62.7	2.23	(0.86–5.80)
Histological type‡						
Intestinal	70	44.3	278	62.6	0.42	(0.24–0.75)
Diffuse	12	75.0	63	73.0	0.93	(0.21–4.10)
Total	274	62.0	827	62.9	0.99	(0.72–1.35)

*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).[4] [5] [13] [14] [17] [18] 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 cases 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 the longest 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,[18] first Chinese,[15] [16] and Finnish

studies[14] 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.[20–22]

Results from another study in Japan[25] 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 cytotoxin associated gene A (CagA) positive strains of *H pylori*.[9] 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[28] 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*[29] and gastric cancer incidence rates[30] appear to be falling over time, the incidence of cardia cancer and oesophageal adenocarcinoma appears to be on the increase.[31–36]

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.

Appendix

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