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ARTICLES

An international association between *Helicobacter pylori* infection and gastric cancer

THE EUROGAST STUDY GROUP

Gastric infection with *Helicobacter pylori* seems to be a risk factor for gastric cancer. We have conducted a multicentre epidemiological study to investigate this relation further.

Our study was designed to look at the relation between the prevalence of *H pylori* infection and gastric cancer rates in 17 populations from 13 countries, chosen to reflect the global range of gastric cancer incidence. In each centre, about 50 males and 50 females in each of the two age groups 25–34 years and 55–64 years were selected at random from the local population and provided blood samples. Serum samples were assayed for the presence of IgG antibodies to *H pylori* in a single laboratory. Prevalence rates of *H pylori* seropositivity were related to local gastric cancer incidence and mortality rates using linear regression. There was a statistically significant relation between the prevalence of seropositivity and cumulative rates (0—74 years) for both gastric cancer incidence and mortality with regression coefficients of 2·68 ($p = 0·001$) and 1·79 ($p = 0·002$), respectively.

Our findings are consistent with an approximately six-fold increased risk of gastric cancer in populations with 100% *H pylori* infection compared with populations that have no infection.

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Introduction

There is increasing evidence to suggest that gastric infection with the bacterium *Helicobacter pylori* is a risk factor for gastric cancer. Prospective epidemiological studies have shown seropositivity to *H pylori* associated with a three-to-six-fold increased risk of gastric cancer,[1-3] findings that are compatible with pathological links between *H pylori*-associated gastritis, precancerous lesions, and subsequent cancer of the stomach. Because the prevalence of seropositivity to *H pylori* in adult populations is normally high (47–76%),[1-3] even modestly raised relative risks imply that around 40–60% of gastric cancers could be attributed to infection with this organism.[4]

If the *H pylori*-gastric cancer hypothesis was true, the geographic pattern of cancer incidence would be expected, at least in part, to be correlated with the geographic pattern of *H pylori* infection. Although there have been many studies of the prevalence of *H pylori* infection among patient populations in different countries, together with a few studies of general populations,[5] there has been no systematic attempt to relate the prevalence of *H pylori* infection to international gastric cancer rates.

The EUROGAST study was designed to investigate the relation between gastric cancer and prevalence of *H pylori* infection, as assessed by the detection of *H pylori* IgG antibodies in randomly selected samples of different international populations.

Subjects and methods

The methodology for the EUROGAST study will be described in detail elsewhere. Briefly, 14 populations were initially chosen to be representative of the range of gastric cancer incidence in Europe. Populations from the US and Japan were added later to extend this range. About 200 individuals were selected at random from population-based registers, from general practitioners' lists (UK), drivers' licence rosters (USA), or health-screening programmes (Greece) and were invited by letter and/or telephone to take part. We aimed to recruit 50 males and 50 females in each of the two age-groups 25–34 years and 55–64 years. Non-respondents were followed up with further letters, telephone calls, and home visits. Individuals who could not be contacted or who refused to participate were, in general, replaced by additional subjects in the same age and sex group. All subjects provided a blood sample and answered a short questionnaire by personal interview about sociodemographic details. Serum was collected, stored, and transported according to an identical protocol in each centre. Analysis for *H pylori* IgG antibodies was done in a single laboratory using an ELISA assay,[6] as slightly modified,[7] with duplicate measurements. A threshold of 10 μg/mL was chosen to discriminate *H pylori*-positive from *H pylori*-negative subjects. The sensitivity and specificity of this test was 96% and 93%, respectively, as determined in a trial using sera from the USA.[7]

Cumulative sex-specific gastric cancer incidence and mortality rates[8] for the age range 0–74 years (and, for some analyses, 0–54

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CUMULATIVE (0–74 YEARS) GASTRIC CANCER MORTALITY AND INCIDENCE RATES AND PREVALENCE OF *H PYLORI* SEROPOSITIVITY

Country	Centre	Mortality rate %		Incidence rate %		*H pylori* seropositivity prevalence (%)				Total sample size
						25–34 years		55–64 years		
		Male	Female	Male	Female	Male	Female	Male	Female	
Algeria	Algiers	NA	NA	1·6	0·7	42	44	49	69	200
Belgium	Ghent	1·1	0·7	1·2	0·6	20	17	60	47	208
Denmark	Copenhagen	1·3	0·6	1·4	0·9	23	5	34	27	157
Germany	Augsburg	2·2	1·1	NA	NA	14	22	57	65	187
	Deggendorf	2·6	1·3	NA	NA	40	40	74	76	198
	Mosbach	2·3	0·8	NA	NA	24	33	65	75	158
Greece	Crete	0·6	0·4	NA	NA	53	54	80	70	229
Iceland	S Region*	2·5	0·7	3·2	1·2	31	40	56	62	206
Italy	Florence	3·0	1·2	3·8	1·9	17	14	38	57	205
Japan	Miyagi	4·2	2·1	9·9	4·0	55	64	88	87	186
	Yokote	5·7	2·0	NA	NA	70	54	90	80	200
Poland	Adamowka	3·6	1·3	NA	NA	69	70	79	93	171
Portugal	Gaia	3·9	1·8	5·3	2·6	57	57	73	65	132
Slovenia	Liubljana	2·3	0·8	2·9	1·1	51	27	71	70	201
UK	Oxford	1·4	0·4	2·6	0·9	8	8	49	42	158
	Stoke	3·4	1·3	3·4	1·3	27	10	49	41	200
US	Minneapolis-St Paul	0·6	0·2	0·9	0·3	13	16	36	32	198

*National figures used for cancer mortality and incidence rates. NA = Not available.

years and 55–74 years) were calculated for each study area for a period during the early-mid 1980s. For the Algerian centre, mortality data were not available, while for six centres (three in Germany and one each in Japan, Poland, and Greece) incidence data were not available. The dependency of the cumulative gastric cancer rates on *H pylori* seroprevalence was evaluated by linear regression completed separately for each sex and in a combined model, in which seroprevalence and sex (male = 1, female = 0) were fitted together. Regression coefficients were calculated to represent the slope of the line which best fitted the data under the given model. Cancer rates were log-transformed and the seroprevalence for each centre was calculated as the average of the two age-groups, 25–34 years and 55–64 years.

Results

The table shows the sex-specific, cumulative 0–74 years incidence and mortality rates for gastric cancer, together with the percentage of *H pylori*-positive subjects in the two age groups, for each of the 17 populations. Gastric cancer incidence and mortality rates were lowest in the population from Minneapolis-St Paul (USA) and highest in the two Japanese populations. For males there was an eleven-fold range in gastric cancer incidence and a ten-fold range in mortality, while for females there was a thirteen-fold range in incidence and an eleven-fold range in mortality.

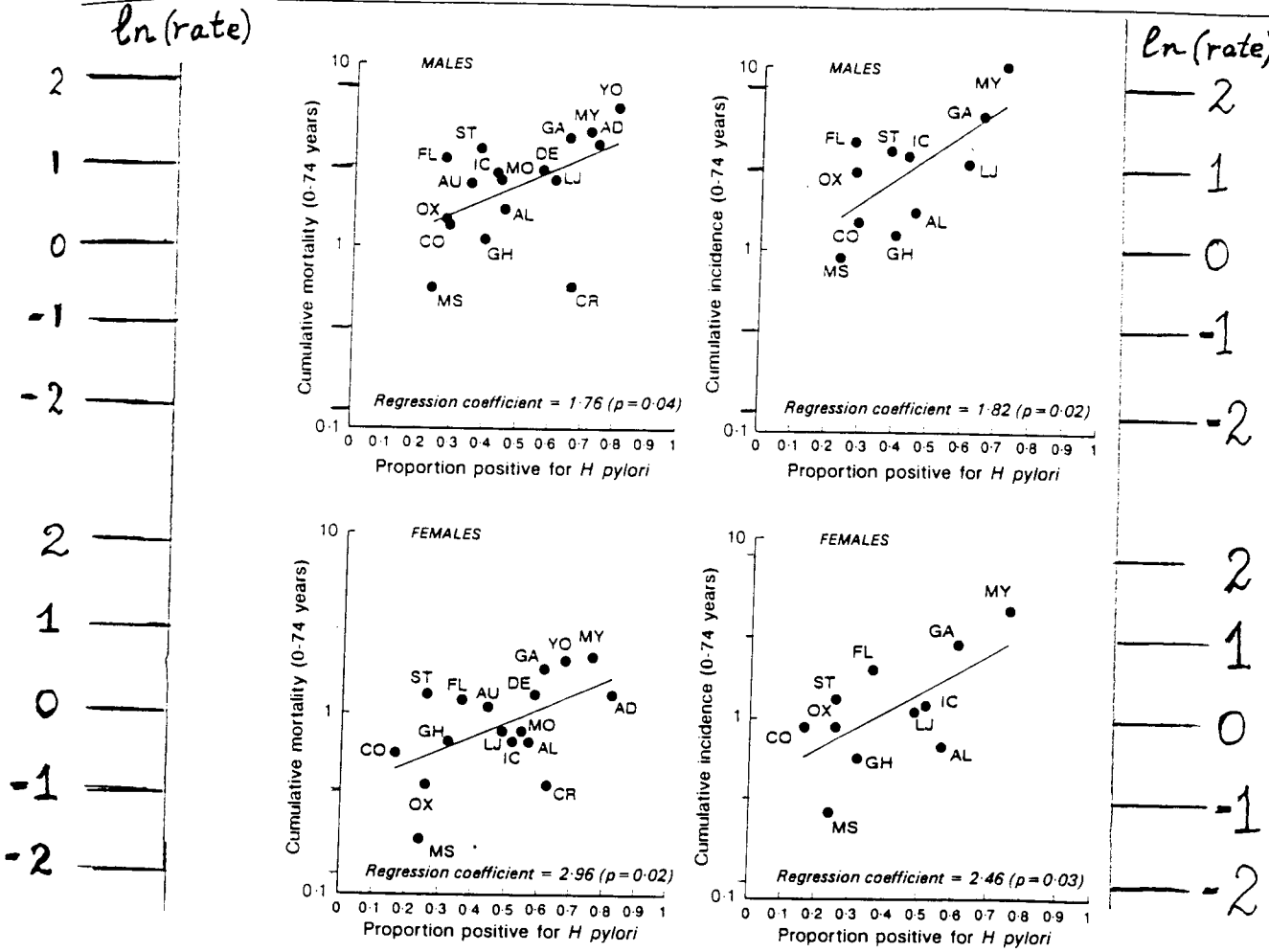
Overall, 1563 of 3194 subjects tested (49%) were *H pylori* seropositive; 543 of 1558 (35%) at 25–34 years and 1020 of 1636 (62%) at 55–64 years. At 25–34 years the prevalence (both sexes combined) of *H pylori* seropositivity varied from 8% in Oxford (UK) to 70% in Adamowka (Poland), while at 55–64 years the prevalence varied from 31% in Copenhagen (Denmark) to 87% in both Adamowka and Miyagi (Japan). There was, therefore, a nine-fold range in prevalence in the younger age group and a three-fold range in the older group. Within each of the individual populations the prevalence was higher in the older age group than in the younger one, but there was a strong correlation between the prevalence at 25–34 years and that at 55–64 years ($r = 0{\cdot}88$, both sexes combined). There was no appreciable difference between the prevalence in males and females (36% and 34%, respectively, at 25–34 years; 62% and 63%, respectively, at 55–64 years; $r = 0{\cdot}88$, both age-groups combined).

For both sexes, there was a statistically significant relation between seroprevalence of *H pylori* and log-transformed cumulative (0–74 years) gastric cancer mortality and incidence rates (figure). In the combined model, the coefficients for *H pylori* seroprevalence were 1·79 ($p = 0{\cdot}002$) for mortality and 2·68 ($p = 0{\cdot}001$) for incidence—ie, a 10% increase in infection prevalence was associated with approximately an 18% increase in log cancer mortality and a 27% increase in log cancer incidence. When the analyses were sub-divided into two age groups, the coefficient estimates and their significance level for combined models were higher for the effect of *H pylori* seroprevalence at 25–34 years on gastric cancer rates from 0–54 years (2·30 [$p = 0{\cdot}001$] for mortality; 3·60 [$p = 0{\cdot}0001$] for incidence) than for the effect of *H pylori* seroprevalence at 55–64 years on gastric cancer rates from 55–74 years (1·73 [$p = 0{\cdot}003$] for mortality; 2·53 [$p = 0{\cdot}003$] for incidence).

For Algiers (Algeria), cancer incidence data were substituted because of the unavailability of mortality data and thus regressions on cancer mortality were based on 34 data points (17 populations, both sexes). Exclusion of the Algiers data had virtually no effect on the estimates of the coefficients or their significance. The regression on cancer incidence was based on 22 data points (11 populations).

Although the regression on cancer incidence rates showed higher coefficients for *H pylori* antibody prevalence than those for cancer mortality, these differences resulted from enforced selection of those 11 centres for which incidence data were available and not from a stronger relation in itself. Analyses of the mortality data restricted to the same 11 centres resulted in very similar coefficients as for the analysis of incidence.

The distribution of data points around the regression line can be seen in the figure, which shows that although there was a clear association between *H pylori* seropositivity and gastric cancer incidence and mortality, there was also considerable scatter. In particular, the populations from Minneapolis-St Paul (USA) and Crete (Greece) had substantially lower cancer rates than would be predicted from the regression model, while the populations from Florence (Italy), Stoke (UK), and Miyagi (Japan) had cancer rates that were higher than predicted. The statistical significance of the regression analyses was not affected by the removal of any single centre. After accounting for sex, the proportion of the variance in the log-transformed cancer



Incidence and mortality rates from gastric cancer by *H pylori* seropositivity (mean of 25–34 years and 55–64 years).

In models in which males and females were combined, regression coefficients were 1·79 (p = 0·002) for mortality and 2·68 (p = 0·001) for incidence.

Centre codes: AL, Algiers; GH, Ghent; CO, Copenhagen; AU, Augsburg; DE, Deggendorf; MO, Mosbach; CR, Crete; IC, Iceland; FL, Florence; MY, Miyagi; YO, Yokote; AD, Adamowka; GA, Gaia; LJ, Ljubljana; OX, Oxford; ST, Stoke; MS, Minneapolis-St Paul.

rates explained by *H pylori* seropositivity was 18·3% for mortality and 31·4% for incidence.

Discussion

Our study has shown a statistically significant association between the gastric cancer incidence and mortality rates and the prevalence of *H pylori* seropositivity in 17 populations. These data suggest that the ten-fold range in gastric cancer rates in these populations is due, at least in part, to the prevalence of *H pylori* infection. Geographical correlation studies such as ours do not provide firm evidence of cause and effect, since the variation in both gastric cancer rates and *H pylori* seroprevalence could be influenced by confounding factors. Socio-economic status was a potential confounder in our study because it is strongly related to the risk of both gastric cancer[9] and *H pylori* infection.[5] After adjustment for average level of education (as a surrogate measure of socio-economic status) the regression coefficients changed from 1·79 to 1·53 (p = 0·009) for mortality and from 2·68 to 2·60 (p = 0·003) for incidence. Although average level of education will only partly reflect socio-economic status, the lack of any appreciable effect of the adjustment on the regression coefficients or their statistical significance weighs against a major confounding influence. Apart from socio-economic status we do not know of any potential confounding factors that correlate as strongly with both gastric cancer risk and *H pylori* infection. Nevertheless, the possibility of confounding by an unknown factor cannot be dismissed.

Our results are consistent with a study that reported a significant correlation between gastric cancer mortality rates and the prevalence of *H pylori* seropositivity in 46 counties in rural China[10] and with a study in Colombia[11] which found a significantly higher infection rate among the adult population of one city than another, gastric cancer rates also being higher in the former. By contrast, a study in Italy[12] found no difference in *H pylori* seropositivity between regions at high and low risk for gastric cancer.

There are certain to be other risk factors involved in the aetiology of gastric cancer apart from *H pylori* infection. Dietary factors are especially important[9] and consideration of these might help explain the scatter of individual populations around the regression line. That certain populations can have a high prevalence of *H pylori* infection yet relatively low rates of gastric cancer has been reported previously,[10] especially in Africa.[13]

A weakness of our study is the implicit assumption that, within a population, the prevalence of *H pylori* seropositivity in the age groups 25–34 and 55–64 years will reflect levels of seropositivity in older generations who contribute most to current gastric cancer rates. Although this assumption may be valid for some populations in the study, it is unlikely to be uniformly true for them all. The transmission of *H pylori* is known to be heavily dependent on socio-economic