2. Studies of Cancer in Humans

2.1 Descriptive studies

2.1.1 *Geographical correlations*

(*a*) *Gastric carcinoma*

Table 2 lists eight studies in which the prevalences of *H. pylori* infection were compared in geographical regions with different gastric cancer rates. The presence of infection was

Table 2. Geographical correlation studies of the prevalence of *Helicobacter pylori* infection and incidence or mortality rates for gastric cancer

Country	Populations	Total number of people surveyed	Gastric cancer		*H. pylori* infection		Results of comparison	Reference
			Period	Range of occurrence (rate)	Period	Range of prevalence (%)		
Colombia	Gastrointestinal patients, aged 15–84; 1 low-risk, 1 high-risk city	78	1972–81	Incidence, 26–150/100 000	NR	63–93	$p = 0.01$	Correa *et al.* (1990a)
Costa Rica	Healthy individuals, aged 7–20; 1 low-risk, 1 high-risk rural area	282	1984–88	Incidence, 20–49/100 000	NR	66–72	$p > 0.05$	Sierra *et al.* (1992)
Italy	Population sample, aged 35–74; 3 high-risk, 2 low-risk areas	930	1975–77	Mortality, 3–43/100 000	1985–88	44–45	$p > 0.05$	Buiatti *et al.* (1989a); Palli *et al.* (1993)
China	Gastrointestinal patients, aged 17–72; 1 low-risk, 1 medium-risk, 1 high-risk area	690	1985–87	CM, 8–60/ 100 000	NR	13–63[a]	$p < 0.01$	Lin *et al.* (1989)
Japan	Blood donors, aged 16–64; 4 prefectures	1815	1982–87	SM, 48–136 (M), 40–117 (F)	NR	50–60 (M) 41–60 (F)	[$r = 0.01$, $p > 0.05$ (M) $r = -0.57$, $p > 0.05$ (F)]	Fukao *et al.* (1993)
Japan	Population sample, aged 40–49, men, 5 areas	624	1985–89	CM, 0–74, 2.2–5.7%	NR	63–86	$r = 0.75$ [$p = 0.14$]	Tsugane *et al.* (1993)
China	Population sample, men aged 35–64; 46 rural counties	1882	1973–75	CM, 0–64, 0.3–6.9%	1983	28–96	$r = 0.34$[c] [$p = 0.02$]	Forman *et al.* (1990)
13 countries	Population sample, aged 25–34 and 55–64; 17 areas or cities (16 with data on mortality, 11 with data on incidence)	3194	Early–mid-1980s	CI, 0–74, 0.9–9.9% (M) 0.3–4.0% (F) CM, 0–74, 0.6–5.7% (M) 0.2–2.1% (F)	NR	8–70 (25–34 years) 31–87 (55–64 years)	$\beta = 1.79$ ($p = 0.002$) (M) $\beta = 2.68$ ($p = 0.001$) (I)	EuroGast Study Group (1993b)

NR, not reported; CM, cumulative mortality; SM, standardized mortality; CI, cumulative incidence; (M), males; (F), females

[a]Based on gastric biopsy

[b]Other cancer sites also studied

[c]$r = 0.40$ after adjustment for within-county variability

determined in most studies by ELISA for IgG antibodies to *H. pylori* in serum. In all studies, infection rates were compared with cancer rates in contemporaneous time periods, although a more appropriate comparison would be between infection prevalence rates and cancer rates several years or even decades later. Such a comparison would reflect the time sequence involved if there were a causal relationship between infection and cancer.

Four of the studies were comparisons of regions of high and low risk for gastric cancer within a single country; two showed a significant difference between *H. pylori* prevalence rates, with an increase in the high-risk region (in Colombia, Correa *et al.*, 1990a; and in China, Lin *et al.*, 1989), while the other two showed no significant difference between the two regions (in Italy, Palli *et al.*, 1993; and in Costa Rica, Sierra *et al.*, 1992). Two studies from Japan (Fukao *et al.*, 1993; Tsugane *et al.*, 1993) compared populations within five and four areas, respectively; neither showed a significant association between *H. pylori* seropositivity and gastric cancer mortality.

Forman *et al.* (1990) examined the prevalence of *H. pylori* IgG antibodies in 1882 residents of 46 rural counties in China and compared them with the gastric cancer mortality rates in the same counties. The correlation between *H. pylori* antibody prevalence rate and gastric cancer mortality rate was 0.34 ($p = 0.02$). The significant positive correlation remained after adjustment for dietary factors associated with risk for gastric cancer (Kneller *et al.*, 1992).

The EuroGast Study Group (1993b) examined the seroprevalence of *H. pylori* IgG antibodies in 3194 randomly selected subjects resident in 17 centres in 13 countries, chosen to reflect the global range in gastric cancer incidence. In regression analyses, in which the two sexes were combined, there were significant relationships between the prevalence of *H. pylori* antibodies and both log-transformed gastric cancer cumulative mortality ($p = 0.002$) and incidence ($p = 0.001$) rates. Exclusion of the regions with highest and lowest mortality rates (Japan and the USA, respectively) reduced the strength of the relationship with mortality from gastric cancer to a nonsignificant ($\beta = 0.62; p = 0.3$) level (Forman *et al.*, 1993).

It has been noted (Holcombe, 1992) in Nigeria and other African countries (e.g. Sudan, Uganda and Zimbabwe) that gastric cancer rates are relatively low (< 2–3% of all malignant tumours) despite a very high prevalence of *H. pylori* infection. The populations of other developing countries with low incidence rates of gastric cancer, but for which no estimates of the prevalence of infection are available, include Kuwaitis, non-Jews in Israel, Malays in Singapore and those of Ahmedabad, Bangalore, Madras and Bombay in India. Gastric cancer incidence rates in the three population-based cancer registries in Africa (Sétif, Algeria; Bamako, Mali; and the Gambia) range from 3.9 to 19.4 per 100 000 in males and from 1.5 to 10.3 per 100 000 in females (Parkin *et al.*, 1992). These rates are substantially below those in high-risk regions of the world (e.g. Costa Rica: 46.9 in males and 21.3 in females) and are comparable to the rates in US blacks (12.4 in males and 5.6 in females) and in England and Wales (16.9 in males and 6.8 in females).

(*b*) *Gastric lymphoma*

Doglioni *et al.* (1992) compared the incidence of primary gastric lymphoma, determined from endoscopy clinic records, in an area of northeastern Italy with that in three communities

in the United Kingdom. In the Italian city of Feltre, the estimated incidence rate for gastric lymphomas was 66/100 000 per five years for the period 1986–90 (37 cases). In three districts in the United Kingdom, the comparable rates were 6/100 000 (six cases), 4/100 000 (seven cases) and 6/100 000 (20 cases). The *H. pylori* infection rate of all patients undergoing endoscopic biopsy was 87% in Feltre in 1991 and 50–60% in the United Kingdom. [The Working Group noted that this was a hospital-based study with no information about the referral patterns to the local endoscopy units. There is, therefore, uncertainty about the denominator populations used in this study.]

(c) *Other cancers*

In the study of Forman *et al.* (1990) (see above), correlation coefficients were calculated for associations between *H. pylori* IgG antibody prevalence and mortality rates from cancers at 12 sites other than the stomach. None was significant. The correlation with lymphoma (all types) was 0.32 and of borderline significance.

2.1.2 *Time trends*

Gastric cancer incidence and mortality rates have been declining rapidly in nearly all developed countries for several years. There are few data for developing countries, but the same trend has generally been observed (Coleman *et al.*, 1993). Secular trends in the prevalence of *H. pylori* infection have not been investigated extensively, but the one serological study that has been conducted in the United Kingdom (Banatvala *et al.*, 1993) indicated that the prevalence has decreased in recent decades. If *H. pylori* is acquired predominantly in childhood (see section 1.3.2), then data on age prevalence (section 1.3.1) can be interpreted as indicating a declining prevalence rate over much of the 20th century. This is also consistent with observed secular trends in duodenal ulcer disease in the USA (Sonnenberg, 1993), the United Kingdom (Susser & Stein, 1962) and Europe (La Vecchia *et al.*, 1993), a disease strongly associated with *H. pylori* infection. Data from Japan (Blaser, 1993) indicate that mortality from gastric cancer in that country has decreased over the past 50–80 years, an effect consistent with a secular decrease in exposure to an environmental agent. The prevalence of gastric cancer of the cardia, in contrast to that of more distal sites within the stomach, has been shown to be increasing in a number of populations (Powell & McConkey, 1990; Blot *et al.*, 1991; Hansson *et al.*, 1993b). Gastric cancer of the cardia has been shown in some studies (Talley *et al.*, 1991a; Hansson *et al.*, 1993b) not to be associated with *H. pylori* infection (see sections 2.3 and 2.4).

2.1.3 *Socioeconomic trends*

Gastric cancer has been shown consistently in several countries to be commoner in poorer socioeconomic groups (Howson *et al.*, 1986; Buiatti *et al.*, 1989b; Logan, 1982). The same association has been observed consistently for *H. pylori* infection (see section 1.3.2).

2.2 Case series

2.2.1 *Gastric carcinoma*

The presence of *H. pylori* infection has been determined in numerous series of gastric cancer patients, usually by histological examination of biopsy and/or gastrectomy samples

but also by microbiological culture; in some studies, serological tests were used to determine the presence of specific IgG antibodies to *H. pylori*. A number of studies were designed specifically to estimate the prevalence of *H. pylori* infection in gastric cancer patients; the majority, however, were broader surveys of patients with upper gastrointestinal disease and included a small subgroup of patients with gastric cancer. In the latter studies, it is unclear whether adequate mucosa was available to evaluate the presence of *H. pylori*; there was also frequently a subgroup of patients who had dyspeptic symptoms but no lesions in their stomachs and who were used as a control series. In a few studies, the control series were healthy volunteers who had undergone endoscopy. Serologically based studies in which data from matched case and control series were available are summarized in sections 2.3 and 2.4.

Table 3 lists the 11 largest case series. The percentage of gastric cancer patients who had *H. pylori* infection varied from 43 to 83%. Particular interest has focused on the Laurén histological classification of gastric adenocarcinoma into cancers of the intestinal (glandular) type and cancers of the diffuse type (Laurén, 1965). It has been reported that the incidence of the former varies between populations whereas that of the latter remains relatively constant (Laurén, 1965; Muñoz *et al.*, 1968; Muñoz & Asvall, 1971; Correa *et al.*, 1973). Environmental exposures are thought to be more important in the etiology of intestinal-type than of diffuse-type cancers (Howson *et al.*, 1986). Table 4 lists eight series in which the cancer cases were classified into intestinal and diffuse histological categories. In some of these studies, an increased prevalence of *H. pylori* infection was seen in association with intestinal-type cancers (Parsonnet *et al.*, 1991a; Tatsuta *et al.*, 1993), but this difference was not observed consistently.

2.2.2 *Gastric lymphoma*

Wotherspoon *et al.* (1991) examined 110 patients in the United Kingdom with gastric B-cell mucosa-associated lymphoid tissue lymphomas, a subset of primary gastric lymphomas. In this group, 101/110 patients (92%) had histological evidence of *H. pylori* infection.

A total of 205 surgical specimens containing primary malignant B-cell lymphomas were investigated in Germany. *H. pylori* colonization was found in 175/178 (98%) cases in which the mucosa some distance from the tumour could be evaluated (Stolte *et al.*, 1994).

2.3 Cohort studies

2.3.1 *Gastric carcinoma*

Four prospective studies have been reported in which the relationship between *H. pylori* infection and the subsequent risk of gastric cancer has been assessed. All were case–control comparisons nested in prospective cohort studies in which blood samples had been taken from cancer-free individuals and stored. Specific antibodies to *H. pylori* were then measured in blood samples from individuals who subsequently developed gastric cancer, and the proportion of individuals with antibodies was compared with that in a matched control group.

Table 3. Prevalence of *Helicobacter pylori* in series of gastric cancer cases

Country	Gastric cancer cases			Method of assessment	Comments	Reference
	No.	*H. pylori* infection				
		No.	%			
Europe						
Italy	44	26	59	Histology	22/44 cases were 'early' gastric cancer, 17 (77%) positive	Caruso & Fucci (1990) (letter)
Italy	277	216	78	Histology	137/167 (82%) early gastric cancers positive; 79/110 (72%) advanced gastric cancers positive	Fiocca *et al.* (1993)
Netherlands	91	54	59	Histology		Loffeld *et al.* (1990)
Turkey	46	34	74	Histology		Buruk *et al.* (1993)
United Kingdom	136	67	49	Histology		Armstrong *et al.* (1991) (letter)
United Kingdom	224	96	43	Histology		Clarkson & West (1993)
North America						
USA	59	40	68	Histology		Parsonnet *et al.* (1991a)
South America						
Brazil	40	33	83	Histology	18/19 (94%) cases positive by histology and culture	Nogueira *et al.* (1993)
Asia						
Japan	94	66	70	Serology		Takahashi *et al.* (1993)
Japan	41	24	59	Culture	All tumours were 'early' gastric cancers	Tatsuta *et al.* (1993)
Singapore	137	103	75	Histology		Wee *et al.* (1992)

Table 4. Prevalence of *Helicobacter pylori* infection in gastric cancer case series by histological type (Laurén classification)

Country	Histological classification[a]						Reference
	Intestinal			Diffuse			
	Total no.	*H. pylori* infection		Total no.	*H. pylori* infection		
		No.	%		No.	%	
Europe							
Italy	166	119	72	79	71	90	Fiocca *et al.* (1993)
Netherlands	80	48	60	11	5	45	Loffeld *et al.* (1990)
Turkey	26	23	88	20	11	55	Buruk *et al.* (1993)
United Kingdom	120	56	47	69	24	35	Clarkson & West (1993)
North America							
USA	37	33	89	22	7	32	Parsonnet *et al.* (1991a)
South America							
Brazil	31	24	77	5	5	100	Nogueira *et al.* (1993)
Asia							
Japan[b]	24	19	79	17	5	29	Tatsuta *et al.* (1993)
Singapore	87	64	74	50	39	78	Wee *et al.* (1992)

[a]Method of assessment shown in Table 3.
[b]In this study the terms 'differentiated early gastric cancer' and 'undifferentiated early gastric cancer' were used for intestinal and diffuse, respectively.

Forman *et al.* (1991) compared 29 gastric cancer patients with 116 age-matched controls for the presence of IgG antibodies to *H. pylori* using a previously described ELISA (Steer *et al.*, 1987) with a reported sensitivity of 93% and a specificity of 96% (Talley *et al.*, 1991b). The subjects were all men taking part in one of two cohort studies: in one study, 20 179 men, aged 35–64 and living in south-east England, provided blood between 1975 and 1982 during a health check-up. In the other study, 2512 men, aged 45–59 and living in Caerphilly, Wales, provided blood between 1979 and 1982 as part of a population study of cardiovascular disease. Cancers or deaths among cohort participants were notified to the study organizers routinely; 23 men with gastric cancer were identified from the first cohort and six from the second. Cancers were diagnosed between 1980 and 1989, with a mean interval between blood sampling and diagnosis of six years (range, four months to 13 years seven months). The mean age of the cancer patients was 54 years (range, 41–63 years) at blood sampling and 60 years (range, 47–76 years) at diagnosis. Four controls were selected for each case by

matching on cohort, date of birth (within one year), date of blood sampling (within one year) and number of freeze–thaw cycles the blood sample had undergone. Twenty of the 29 (69%) gastric cancer patients and 54 of the 116 (47%) controls had antibodies to *H. pylori*, resulting in a matched odds ratio of 2.8 (95% confidence interval [CI], 1.0–8.0). Stratifying the cases and corresponding controls into those diagnosed within five years of blood sampling and those diagnosed five or more years after sampling did not result in a significant difference in the resulting odds ratios. No information was available on site of cancer within the stomach or on histological subtype.

Parsonnet *et al.* (1991b) compared 109 gastric patients with 109 age-, sex- and race-matched controls for the presence of IgG antibodies to *H. pylori* using a previously described ELISA (Evans *et al.*, 1989) with a reported sensitivity of 91% and a specificity of 98%. The subjects were taking part in a cohort study in which 128 992 participants living in California, USA, provided blood between 1964 and 1969 during a health check-up. A total of 246 gastric cancer registrations and/or hospitalizations for gastric cancer among cohort participants were notified to the study organizers routinely, and 200 of these were randomly selected. Availability of blood samples resulted in final inclusion of 186 patients with gastric cancer. Cancers were diagnosed between 1964 and 1989, with a mean interval between blood sampling and diagnosis of 14.2 years (range, 1–24 years). One control was selected for each case by matching on age at blood sampling (within one year), sex, race, date of blood sampling (within 0.5 year) and site of the health check-up. Of the 186 patients, 109 had histologically confirmed adenocarcinoma of the stomach; of these, 92 (84%) had antibodies to *H. pylori*, as did 66 of the 109 (61%) controls, resulting in a matched odds ratio of 3.6 (95% CI, 1.8–7.3). When the cases and controls were stratified by sex, the odds ratio for women was nonsignificantly higher than that for men; when they were stratified by race, the odds ratio for blacks was nonsignificantly higher than that for whites. Eighty-one patients had the intestinal type of adenocarcinoma (Laurén classification), and 67 (83%) of these were seropositive (odds ratio, 3.1; 95% CI, 1.5–6.6); 28 patients had a diffuse type, and 25 (89%) of these were seropositive (odds ratio, 8.0; 95% CI, 1.0–64). Four patients had an adenocarcinoma at a site in the cardia; one was seropositive, as was one of the four matched controls. An additional 27 patients had adenocarcinoma of the gastroesophageal junction (not included in the main analyses above); of these, 17 (63%) were seropositive, as were 19 (70%) controls (odds ratio, 0.8; 95% CI, 0.3–2.1).

Nomura *et al.* (1991) compared 109 patients with gastric carcinoma with 109 age-matched controls for the presence of IgG antibodies to *H. pylori* using a commercial ELISA. The subjects were all men taking part in a cohort study in which 7498 Japanese–Americans living in Oahu, Hawaii, USA, provided blood between 1967 and 1970 as part of a population study of heart disease. A total of 137 gastric cancer registrations and/or hospital discharges for gastric cancer among cohort participants were notified to the study organizers routinely, all with histologically confirmed gastric cancer. As insufficient serum was available from 26 men and the results of the ELISA were indeterminate for two, a total of 109 were included in the study. Cancers were diagnosed between 1968 and 1989, with a mean interval between blood sampling and diagnosis of 13 years (standard deviation, five years). The mean age of the cancer patients at recruitment was 59 years. One control was selected for each case by matching for age at recruitment and date of blood collection. Excluded from the control

series were men who had had a gastrectomy before blood sampling or who had had a diagnosis of peptic ulcer at any time. The exclusion criteria reduced the pool of available controls by 13%. [The Working Group noted that the exclusion criteria would be likely to reduce the prevalence of *H. pylori* infection in the control group and, hence, bias the estimated odds ratio upwards.] Also excluded were men with cardiovascular disease or any other type of cancer diagnosed at any time. These exclusions reduced the control pool by 33%. Controls had to be alive when the cancer cases with which they were matched were diagnosed. Of the 109 gastric cancer patients, 103 (94%) had antibodies to *H. pylori*, as did 83 of the 109 (76%) controls, resulting in a matched odds ratio of 6.0 (95% CI, 2.1–17). Stratification of the cases into three groups (26, 40 and 43 pairs) on the basis of time between blood sampling and cancer diagnosis resulted in odds ratios of 1.5 (95% CI, 0.3–9.0) for less than 10 years, 6.0 (1.3–27) for 10–14 years and indeterminate (1.7–97) for 15 years or more. Stratification into two birth cohorts resulted in odds ratios of 3.0 (0.8–11) for those born in 1900–09 and 15 (2.0–114) for those born in 1910–19. Eighty-one patients had an intestinal type of carcinoma, and 75 (93%) of these were seropositive (odds ratio, 4.5; 95% CI, 1.5–13); 23 patients had a diffuse type, and all were seropositive (odds ratio, indeterminate; 1.1–64). Five patients had cancer at the cardia, and two were seropositive; after exclusion of these patients, the overall odds ratio was 12 (95% CI, 2.8–51). In this study, a trend was observed ($p = 0.0009$) of an increasing odds ratio with an increase in the quantitative antibody level. [The Working Group estimated that, had the exclusion criteria relating to controls with a history of gastrectomy or peptic ulcer not been used, the prevalence of *H. pylori* infection in the controls would have been increased by approximately 4% and the overall odds ratio would have been decreased by about 20%, i.e. from 6.0 to 4.8.]

In a combined analysis of the three nested case–control studies described above, Forman *et al.* (1994) showed that, overall, 215/247 (87%) gastric cancer patients and 203/334 (61%) controls were seropositive for IgG antibodies to *H. pylori*, resulting in a matched odds ratio of 3.8 (95% CI, 2.3–6.2). When these results were stratified by time between sample collection and cancer diagnosis into four periods—fewer than five years, 5–9 years, 10–14 years and 15 years or more—there was a significant trend ($p = 0.049$) towards an increased odds ratio with increasing time interval. The odds ratio changed from 2.1 (95% CI, 0.6–8.7) to 2.3 (0.9–6.5), 4.4 (1.8–13) and 8.7 (2.7–45) over the four periods, respectively. There were 20/25 (80%), 37/46 (80%), 70/78 (90%) and 88/98 (90%) seropositive cases and 34/58 (59%), 46/85 (54%), 58/93 (62%) and 65/98 (66%) seropositive controls in the four strata, respectively. This trend was interpreted by the authors as indicating that false-negative assessments of *H. pylori* status may have occurred more frequently among cancer cases than among matched controls, especially among those diagnosed soon after providing blood. False-negative assessments were believed to derive from the precancerous conditions, severe atrophic gastritis and intestinal metaplasia, from loss of *H. pylori* colonization and loss of seropositivity.

Lin *et al.* (1993a [abstract]) compared 29 gastric cancer patients in Taiwan, China, with 220 controls matched by age, sex and area of residence, for the presence of *H. pylori* IgG antibodies by an ELISA. The subjects were participants in a cohort study in which 9777 people in Taiwan had provided blood since 1984. The mean interval between blood sampling and diagnosis of cancer was 3.1 years. Sixty-nine percent of the gastric cancer patients and

59% of the controls were seropositive for antibodies to *H. pylori*, resulting in an odds ratio of 1.6 (95% CI, 0.68–2.6).

The four prospective studies are summarized in Table 5.

2.3.2 *Gastric lymphoma*

Parsonnet *et al.* (1994) compared 33 patients with gastric non-Hodgkin's lymphoma with 134 age- and sex-matched controls for the presence of *H. pylori* IgG antibodies using an ELISA with a reported sensitivity of 96% and a specificity of 76% for active gastric infection. The subjects were taking part in one of two cohort studies, one in California, USA, described above (Parsonnet *et al.*, 1991b), and the other of 170 000 participants living in Norway who provided blood between 1973 and 1991 during blood donation and health screening programmes. Cancer registrations between 1973 and 1990 among the Norwegian cohort were notified to the study organizers. Twenty gastric lymphomas were identified from the US cohort and 13 from the Norwegian cohort, with median intervals between blood sampling and diagnosis of 14 and 13 years, respectively. The median ages of the lymphoma patients at diagnosis were 66 and 55 years, and 40 and 69% patients in the two cohorts were men, respectively. Four cancer-free controls were selected for each case and matched on cohort, date of birth, age (five-year groups in the USA; within six months in Norway), sex, date and location of blood collection and ethnic group (only in the USA). Twenty-eight of the 33 (85%) gastric lymphoma patients were seropositive for antibodies to *H. pylori*, as were 74 of the 134 (55%) controls, resulting in a matched odds ratio of 6.3 (95% CI, 2.0–20). There was no significant difference between odds ratios when the cases and corresponding controls were stratified on the basis of cohort, sex, age at diagnosis (< 65 or ≥ 65 years) or time between blood sampling and diagnosis (< 14 or ≥ 14 years). In a separate analysis of 31 patients with non-gastric non-Hodgkin's lymphoma and 61 matched controls, 20 patients (65%) and 36 controls (59%) were seropositive, resulting in a matched odds ratio of 1.2 (95% CI, 0.5–3.0).

2.4 Case–control studies

2.4.1 *Gastric carcinoma*

Nine case–control studies have been carried out in which serological assessment of infection was done retrospectively in cancer patients after diagnosis.

Talley *et al.* (1991a) compared 69 patients with gastric adenocarcinoma with 252 controls for the presence of IgG antibodies to *H. pylori* using a previously described ELISA (Pérez-Pérez *et al.*, 1988) with a reported sensitivity of 96% and a specificity of 94% (Talley *et al.*, 1991b). The cases of cancer had been confirmed histologically and diagnosed between 1982 and 1989 at a single hospital in Minnesota, USA. The median age of the patients was 63 years (25th and 75th percentiles, 56.5 and 71 years), and 52% were men. The controls comprised 76 asymptomatic volunteers with no history of gastrointestinal disease and 176 patients who were treated between 1976 and 1989 at the same hospital as the cancer patients for a variety of non-malignant conditions: 67 for benign musculoskeletal problems, 52 for benign oesophageal disease and 57 for benign lung diseases. The median age of the controls

Table 5. *Helicobacter pylori* seroprevalence rates in gastric cancer patients and matched controls: prospective studies

Country	Cohort	Cases			Controls				Odds ratio[a]	95% CI	Mean follow-up (years)	Reference
		No.	*H. pylori* infection		No.	Matching	*H. pylori* infection					
			No.	%			No.	%				
United Kingdom	English undergoing health check-up; Welsh heart disease study Men	29	20	69	116	Cohort, date of birth, date of blood sampling, no. of freeze–thaw cycles	54	47	2.8	1.0–8.0	6	Forman *et al.* (1991)
USA (California)	Men and women undergoing health check-up	109	92	84	109	Age, sex, rate, date of blood sampling, place of health check-up	66	61	3.6	1.8–7.3	14	Parsonnet *et al.* (1991b)
USA (Hawaii)	Japanese–Americans; heart disease study Men	109	103	94	109	Age, date of blood sampling	83	76	6.0	2.1–17	13	Nomura *et al.* (1991)
China (Taiwan)	General population Men and women	29	20	69	220	Age, sex, residence	130	59	1.6	0.68–2.6	3	Lin et al. (1993a) [abstract]

CI, confidence interval
[a]From matched analysis

was 61 years (25th and 75th percentiles, 54 and 67 years), and 50% were men. Of the 69 gastric cancer patients, 36 (52%) had antibodies to *H. pylori*, as did 96 (38%) of the controls. The odds ratio, after adjustment for age and sex, was 1.6 (99% CI, 0.79–3.4). Adjustment for length of storage of the blood samples had no substantial effect on the results. The odds ratio for gastric cancers at sites other than the cardia ($n = 37$) was 2.7 (99% CI, 1.0–7.1), while that for cancers at sites in the cardia ($n = 32$) was 0.94 (99% CI, 0.34–2.6). For the intestinal type of gastric cancer, according to the Lauren classification ($n = 32$), the odds ratio was 1.9 (99% CI, 0.67–5.1), while for cancers of the diffuse histological type ($n = 22$) it was 2.5 (99% CI, 0.73–8.2). After the cancers of the cardia had been excluded, the odds ratios were 4.6 (99% CI, 0.78–27) for the intestinal type ($n = 13$) and 2.3 (99% CI, 0.63–8.1) for the diffuse type ($n = 19$). There were five additional groups of patients in this study. The proportions with antibodies to *H. pylori* were 44% of nine with benign gastric lesions, 89% of nine with gastric cancers other than adenocarcinoma, 51% of 80 with colorectal cancer, 49% of 41 with oesophageal cancer and 56% of 79 with lung cancer. In comparisons with the cancer-free control group, as used in the study of gastric adenocarcinoma, the odds ratios, after adjustment for age and sex, were 1.5 (99% CI, 0.23–9.1) for benign gastric neoplasms, 13 (99% CI, 0.77–203) for other gastric cancers, 1.8 (99% CI, 0.86–3.4) for colorectal cancer, 1.4 (99% CI, 0.58–3.4) for oesophageal cancer and 1.8 (99% CI, 0.91–3.6) for lung cancer.

Sipponen *et al.* (1992) compared 54 patients with gastric adenocarcinoma with 84 controls for the presence of IgG, IgA and IgM antibodies to *H. pylori* using a previously described ELISA (Kosunen *et al.*, 1989). The cases of gastric cancer were confirmed histologically and occurred in a consecutive series of patients diagnosed in 1988 and 1989 at a single hospital in Finland. Patients with cancers of the region of the cardia were excluded, as were patients who had previously undergone gastric surgery. The mean age of the patients who were included was 65 years (SD, 16 years), and 48% were men. The controls were 35 patients with cancers at gastrointestinal sites other than the stomach (6 in the oesophagus, 7 in the pancreas and 22 in the colon) and 48 patients with cancers at sites other than the gastrointestinal tract. The mean ages of these two groups of controls were 65 years (SD, 12 years) and 66 years (SD, 12 years), respectively, and 57 and 71%, respectively, were men. IgG antibodies to *H. pylori* were found in 38/54 (70%) of the gastric cancer patients and 43/84 (51%) of the patients with other cancers. [The unadjusted odds ratio was calculated by the Working Group to be 2.3 (95% CI, 1.0–5.0).] IgA antibodies to *H. pylori* were found in 76% of the gastric cancer patients and 58% of the controls [the unadjusted odds ratio was 2.3 (95% CI, 1.1–4.8]; IgM antibodies were found in 6% of the cases and 5% of the controls. When the gastric cancer patients were stratified into three age groups, IgG antibodies were found in 8/10 (80%) aged 30–49 years, 13/19 (68%) of those aged 50–69 years and 17/25 (68%) of those aged 70 years or more. For the patients with other cancers, the respective proportions were 5/9 (56%), 22/38 (58%) and 16/37 (43%), resulting in odds ratios for the three strata of [3.2 (95% CI, 0.3–45.4)], [1.6 (0.4–6.2)] and [2.8 (0.9–9.4)], respectively. Thirty-one gastric cancer patients had tumours of the intestinal type, and 22 (71%) of them were seropositive; 21 gastric cancer patients had tumours of the diffuse type, and 15 (71%) of them were seropositive.

Kang and Chung (1992) compared 28 patients with gastric adenocarcinoma in the Republic of Korea with 30 age- and sex-matched controls for the presence of IgG antibodies

to *H. pylori*, using a commercial ELISA kit. The gastric cancer patients had all undergone resection, had histological confirmation of their disease and had been diagnosed in 1991. The mean age of the cases was 50 years (range, 29–67 years), and 66% were men. Controls were hospital patients with a variety of diagnoses other than gastrointestinal disease and included nine patients with non-gastrointestinal cancer. The mean age of the controls was 52 years (range, 28–69 years), and 67% were men. Twenty-five (89%) of the gastric cancer patients had antibodies to *H. pylori*, as did 20 (67%) of the control patients. A matched analysis resulted in an odds ratio of 4.2 (95% CI, 1.0–17). Ten of the patients had intestinal-type cancers, and eight (80%) of these were seropositive; 18 patients had diffuse-type cancers, and 17 (94%) of these were seropositive. All nine gastric cancer patients who had 'early gastric cancer' were seropositive; of the 19 who had advanced cancer, 16 (84%) were seropositive.

Hansson *et al.* (1993a) compared 112 gastric adenocarcinoma patients with 103 controls for the presence of IgG antibodies to *H. pylori* using a commercial ELISA kit with a reported sensitivity of 98.7% and a specificity of 100% (Evans *et al.*, 1989). The cases were confirmed histologically and occurred in a consecutive series of patients diagnosed between 1989 and 1991 at eight hospitals in central and northern Sweden. Patients over 79 years of age and with advanced disease (20% of study base) were excluded, as were patients who refused (3%) or were unable (14%) to give blood. The mean age of the gastric cancer patients was 67 years, and 63% were men. Controls were patients admitted to the same hospitals with a variety of non-gastrointestinal diseases, who were frequency matched to the cases by 10-year age group, sex and hospital. The mean age of the controls was 67 years, and 66% were men. Antibodies to *H. pylori* were found in 90/112 (80%) of the gastric cancer patients and 63/103 (61%) of the controls (odds ratio, 2.6; 95% CI, 1.4–5.0). When the analysis was stratified into three age groups, the odds ratios were 9.3 (1.4–101) for patients aged less than 60 years, 4.3 (1.3–15) for those 60–69 years and 1.2 (0.44–3.0) for those aged 70 or more. The interaction between age and *H. pylori* seropositivity was significant. There was a higher odds ratio in men than in women, but the effect was of borderline significance. The multivariate odds ratio for *H. pylori* seropositivity, estimated in a multiple regression model with adjustment for occupation, diet, smoking and alcohol consumption (multivariate odds ratio, 2.7; 95% CI, 1.3–5.8) showed little difference from the univariate odds ratio. Of patients with gastric cancers at sites other than the cardia, 77/93 (83%) were seropositive (odds ratio, 3.1; 1.5–6.3), while 13/19 (68%) patients with cancers of the cardia were seropositive (1.4; 0.44-4.8). Of patients with intestinal-type gastric cancer, 60/75 (80%) were seropositive (2.5; 1.2–5.4), while 22/28 (79%) of patients with diffuse-type cancer were seropositive (2.3; 0.82–7.6).

Blaser *et al.* (1993) compared 29 gastric adenocarcinoma patients with 58 age- (within one year) and sex-matched controls for the presence of IgG antibodies to *H. pylori*, using a previously described ELISA (Pérez-Pérez *et al.*, 1988) with a reported sensitivity of 96% and a specificity of 94% (Talley *et al.*, 1991b). The cases were confirmed histologically and had been diagnosed between 1990 and 1992 in one city, Ichikawa, in Japan. The median age of patients was 63 years (range, 46–82 years), and 62% were men. Controls were out-patients attending the same hospital as the gastric cancer patients for a variety of illnesses, excluding 'known stomach disease' and chronic liver disease. Twenty-four of the 29 (83%) gastric

cancer patients and 39/58 (67%) controls had antibodies to *H. pylori* (matched odds ratio, 2.1; 95% CI, 0.72–6.4). Exclusion of the three gastric cancer patients with cancers of the cardia and the corresponding controls, justified because of the previously identified specificity of association with cancer other than of the cardia (Nomura *et al.*, 1991; Talley *et al.*, 1991a), resulted in an odds ratio of 2.8 (95% CI, 0.82–9.6) for the patients with cancers at sites other than the cardia. Exclusion of non-cardia gastric cancer patients aged 70 years or over (and corresponding controls), justified because of the previously identified reduced association in the elderly (Nomura *et al.*, 1991), resulted in an odds ratio of 6.0 (95% CI, 1.1–34). Comparisons of cases on the basis of stage or severity of pathological lesions were reported not to affect the odds ratio. [The Working Group noted that the exclusion of patients with known stomach disease from the control group would be likely to reduce the prevalence of *H. pylori* infection in the group and, hence, bias the estimated odds ratio upwards.]

Lin *et al.* (1993b,c) compared 148 gastric adenocarcinoma patients with two series of controls (n = 92 and 823) for the presence of IgG antibodies to *H. pylori*, using a commercial ELISA kit with a reported sensitivity of 96% and a specificity of 93%. The cases were confirmed histologically and occurred in a consecutive series of patients diagnosed in 1992 at a single hospital in Taiwan, China. The mean age was 59 years (range, 24–87 years), and 61% were men. The first control series were part of a group of asymptomatic subjects who had had an endoscopic examination with negative results during a routine health check in 1992. Their mean age was 52 years (range, 22–77 years), and 59% were men. The second control series were randomly selected from household registry files in one precinct and three townships in Taiwan. The subjects included people of all ages, from < 10 years to ≥ 70 years, and 50% were men. [The Working Group noted that the two reports of the study had slightly different numbers of cases: 148 (Lin *et al.*, 1993b) and 143 (Lin *et al.*, 1993c). In the results reported below, the larger number was used, except where stated. The Working Group also noted that the selection of controls for the first series, excluding volunteers who did not have endoscopically normal stomachs, would be likely to reduce the estimated prevalence of *H. pylori* infection in the control group and, hence, bias the estimated odds ratio upwards.] Ninety-two of the 148 (62%) gastric cancer patients and 57/92 (62%) controls in the first series had antibodies to *H. pylori* (age- and sex-adjusted odds ratio, 1.0; 95% CI, 0.59–1.8), as did 448/823 (54%) controls in the second series [unadjusted odds ratio, 1.4 (95% CI, 1.0–2.0); after exclusion of controls from the second series who were aged less than 20 years, 347/527 (65%) were seropositive, giving a calculated unadjusted odds ratio of 0.85 (95% CI, 0.58–1.2)]. Among subjects below the age of 60 years, 44/64 (69%) of gastric cancer cases, 40/66 (61%) of the first series of controls and 280/436 (64%) of the second series of controls (20–59 years) were seropositive; among those 60 years of age or more, 48/84 (57%) of the cancer patients, 17/26 (65%) of the first series of controls and 67/91 (74%) of the second series of controls were seropositive. Twenty-six of the cancer patients had their tumour in the region of the cardia, and 17 of these (65%) were seropositive; 114 cancer patients had their tumour in regions other than the cardia, and 71 of these (62%) were seropositive. Of the 52 patients who had cancers of the intestinal type, 31 (60%) were seropositive, whereas of 96 patients with cancers of the diffuse type, 61 (64%) were seropositive. Of 26 'early' gastric

cancer patients, 16 (62%) were seropositive, and of 122 patients with advanced cancers, 76 (62%) were seropositive.

Kuipers *et al.* (1993c) compared 116 gastric adenocarcinoma patients with 116 age- and sex-matched controls for the presence of IgG antibodies to *H. pylori* using a previously described ELISA (Peña *et al.*, 1989). The cases were confirmed histologically; the patients were resident in the Netherlands and had a median age of 67 years (range, 23–92 years); 56% were men. Controls were subjects undergoing upper gastrointestinal investigations, excluding those with endoscopic and histological abnormalities such as peptic ulcer, atrophic gastritis and intestinal metaplasia. Antibodies to *H. pylori* were found in 89/116 (77%) gastric cancer patients and 92/116 (79%) controls [resulting in an unadjusted and unmatched odds ratio of 0.86 (95% CI, 0.44–1.7)]. Stratification into five age groups (< 50, 50–59, 60–69, 70–79 and > 79 years) did not significantly change the odds ratios for gastric cancer within any strata [figures not available]. Of the 67 gastric cancer patients who had tumours of the intestinal type, 51 (76%) were seropositive; of the 36 patients with tumours of the diffuse type, 28 (78%) were seropositive. [The Working Group noted that, despite the exclusions from the control series, the use of symptomatic gastrointestinal disease patients would be likely to increase the estimated prevalence of *H. pylori* infection among the controls and, hence, bias the odds ratio downwards.]

Estevens *et al.* (1993) compared 80 gastric adenocarcinoma patients with 80 age- and sex-matched controls for the presence of IgG antibodies to *H. pylori* using an ELISA developed in their laboratory on the basis of a previously described assay (Evans *et al.*, 1989). The cases were confirmed histologically and occurred in a consecutive series diagnosed in 1990–91 at a single hospital in Lisbon, Portugal. The mean age was 66 years (SD, 11.9 years), and 58% were men. Controls were blood donors and hospital out-patients attending trauma and orthopaedic clinics. Antibodies to *H. pylori* were found in 56/80 (70%) gastric cancer patients and 65/80 (82%) controls, resulting in an odds ratio of [0.54 (95% CI, 0.24–1.2)]. Of the gastric cancer patients with tumours of the cardia, 67% were seropositive; of the patients with tumours at other sites, 70% were seropositive. Of the patients with tumours of the intestinal type, 64% were seropositive, whereas of those with tumours of the diffuse type, 50% were seropositive.

Archimandritis *et al.* (1993) compared 47 gastric adenocarcinoma patients with 50 controls, matched for age, sex, socioeconomic status and area of residence. The presence of IgG antibodies to *H. pylori* was assessed using a commercial ELISA kit. The cases were confirmed histologically; patients with tumours of the cardia were excluded. Patients were from all over Greece, their mean age was 62 years (SD, 12.6 years) and 62% were men. Controls were healthy people from all over Greece with 'no evidence of peptic ulcer or non-ulcer dyspepsia'; their mean age was 62 years (SD, 14.1 years), and 54% were men. Of the 47 gastric cancer patients, 34 (72%) were seropositive for *H. pylori* antibodies, as were 34/50 (68%) controls (odds ratio, 1.2; 95% CI, 0.51–3.0). When the analysis was stratified by age, the odds ratio for subjects aged < 60 years was 1.5 (0.42–5.0) and that for subjects > 60 was 0.87 (0.23–3.3). Of the 31 gastric cancer patients with tumours of the intestinal type, 22 (71%) were seropositive (1.2; 0.43–3.1); of nine patients with tumours of the diffuse type, seven (78%) were seropositive (0.83; 0.13–5.3). [The Working Group noted that the information provided about control selection was inadequate to allow a judgement about the

adequacy of the control group. The exclusion of controls with peptic ulcer or non-ulcer dyspepsia would be likely to reduce the prevalence of *H. pylori* infection in the control group and, hence, bias the esimated odds ratio upwards.]

The studies are summarized in Table 6.

2.4.2 *Other cancers*

No case–control studies of cancers other than gastric cancer have been reported, although the study of Talley *et al.* (1991a) (see above) compared patients with lung, oesophageal and large bowel cancers.

2.5 Intervention studies

Wotherspoon *et al.* (1993) gave *H. pylori* eradication therapy to six patients (three men, aged 37, 76 and 42, and three women, aged 75, 60 and 57) with histological and molecular genetic evidence of primary gastric low-grade B-cell mucosa-associated lymphoid tissue lymphoma with concomitant *H. pylori* infection. *H. pylori* was eradicated in all six patients, and repeated biopsies, 4–10 months after eradication, in five patients showed no evidence of lymphoma.

Stolte *et al.* (1994a) treated 16 patients with low-grade mucosa-associated lymphoid tissue lymphomas, *H. pylori* infection and gastritis with *H. pylori* eradication therapy. The patients were followed up with repeated endoscopic biopsies 3–12 months after treatment; 12 patients showed regression of the lymphoma. In six of the 12, sparse residual lymphoma tissue was found.

The gastric lymphomas that respond to *H. pylori* eradication therapy, the well-differentiated mucosa-assocated lymphoid tissue lymphomas, were previously called 'pseudolymphomas'. They are known to remain localized for many years before invading other tissues.