STOMACH

Why does Japan have a high incidence of gastric cancer? Comparison of gastritis between UK and Japanese patients

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Background and aims: The incidence of gastric cancer in Japan is four times higher than in the UK. It usually arises in a stomach with corpus predominant or pangastritis that has undergone extensive atrophy and intestinal metaplasia. We hypothesised that a Japanese population would have a more severe gastritis with a corpus predominant or pangastritis pattern and a greater degree of atrophy and intestinal metaplasia than that found in the UK. To test this we designed a comparative trial.

Methods: A total of 252 age matched consecutive patients were recruited from the endoscopy services in Leeds and Tokyo. In each centre, 21 patients were prospectively selected from each decennial, between the ages of 20–80 years. All had epigastric discomfort as their predominant symptom. Patients with peptic ulcer, cancer, and oesophagitis were excluded. Five gastric biopsies were examined by two histopathologists using the updated Sydney system. *Helicobacter pylori* infection was assessed by histology and culture of biopsies and enzyme linked immunosorbent assay and immunoblot of plasma.

Results: Gastritis was found by both pathologists in 59 (47%) UK and 76 (60%) Japanese patients (χ^2 test, p = 0.04). In those patients with gastritis, corpus predominant or pangastritis was commoner in the Japanese (63% Japan v 36% in the UK (χ^2 test, p = 0.003) Atrophy and intestinal metaplasia were more extensive and severe (Mann-Whitney U test, p<0.001) and chronic inflammation and polymorph activity were also greater, especially in the corpus (Mann-Whitney U test, p<0.001). Fifty three of 59 UK gastritis patients (90%) and 67/76 (88%) (χ^2 test, p = 1) Japanese gastritis patients were positive for *H pylori*. Using a previously described ''gastric cancer risk index'' among *H pylori* positive patients, there were significantly more Japanese than UK subjects with a ''high risk'' score.

Conclusion: In Japanese as opposed to English patients, gastritis is more prevalent and severe with more corpus predominant atrophy and intestinal metaplasia. These differences may partially explain the higher incidence of gastric cancer in Japan.

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The incidence of gastric cancer varies throughout the world. It is four times more common in Japan than in the UK and occurs at a younger age.[1] A variety of aetiological factors have been put forward to account for these differences, including *Helicobacter pylori* prevalence[2] and virulence[3] as well as dietary[4] and genetic[5] variations between different populations.

The Correa hypothesis postulates a progression from chronic gastritis to gastric atrophy and intestinal metaplasia (IM), leading to dysplasia and finally cancer.[6] Histologically, gastric cancer is classified as either ''intestinal'' or ''diffuse''. Intestinal cancer is commoner and is associated with atrophy and IM while diffuse cancer tends to arise in areas of active inflammation. Both are strongly associated with *H pylori* infection. The severity and histological appearances of the gastritis are therefore relevant but the pattern of the gastritis seems to be even more important. Patients with a corpus predominant or pangastritis (gastritis affecting the corpus more than the antrum or affecting both equally) have a much higher cancer risk than those with an antral predominant gastritis.[7] Corpus gastritis that is associated with loss of parietal cell mass (atrophy) and hypo- or achlorhydria allows faecal-type bacterial species to colonise the stomach and it is thought that these organisms may convert ingested nitrate to nitrite and then to carcinogenic N nitroso compounds.[6]

It is unclear which factors are responsible for the increased risk of cancer in Japan compared with the UK but it would seem a reasonable hypothesis that whatever the underlying cause the Japanese population should have a more severe gastritis, occurring at an earlier age, and with a corpus, rather than an antral, predominant pattern. Therefore, the aim of this study was to evaluate the pattern and severity of gastritis in patients complaining of dyspepsia in the UK and Japan, matched for age.

PATIENTS AND METHODS

This was a cross sectional comparative study carried out at the General Infirmary at Leeds and the National Cancer Centre Hospital, Tokyo. Three endoscopists (T Gotoda in Tokyo and L Gatta and G Naylor in Leeds) spent two months training together ensuring concordance of patient selection, recruitment and biopsy sites, processing of histological and microbiological specimens, blood sampling, and storage.

Ethics approval for the study was obtained from the local ethics committees. In Leeds, patients were recruited from a ''one stop'' dyspepsia clinic. Patients gave written consent on the day if they agreed to enter the trial. In Tokyo, patients attending the National Cancer Centre Hospital endoscopy department specifically for investigation of dyspepsia were similarly approached.

In order to calculate sample size, we identified existing data on gastritis for the UK and Japan. Results from a previous Japanese biopsy study[8] had shown normal findings

Abbreviations: IM, intestinal metaplasia; IQR, interquartile range; IL, interleukin; TNF-α, tumour necrosis factor α
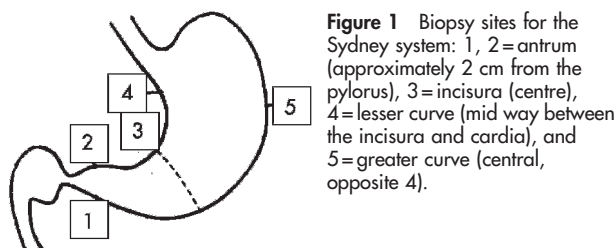
Figure 1 Biopsy sites for the Sydney system: 1, 2=antrum (approximately 2 cm from the pylorus), 3=incisura (centre), 4=lesser curve (mid way between the incisura and cardia), and 5=greater curve (central, opposite 4).

(that is, no evidence of gastritis) in 9.5% of an asymptomatic population aged 20–60+ years. Unpublished data from a Leeds population showed 50.5% of patients in a routine endoscopy series to have normal stomachs. No asymptomatic Western population data existed but as previous studies[9][10] have demonstrated a lack of correlation between symptoms and histological findings in patients with gastritis, we concluded that this comparison was valid for the purpose of our power calculation. This gave a prevalence of 90.5% and 49.5% for gastritis (of any type) for Japan and Leeds, respectively. Therefore, to detect a difference of 41% in prevalence between the Japanese and English patients with a power of 0.80 and a significance level of 0.05 (alpha two sided), at least 126 patients had to be enrolled from each centre. Twenty one patients from each decennial from 20 to 80 years were therefore recruited from Leeds and Tokyo between May 2000 and April 2002. Inclusion criteria were as follows: age 20–80 years, predominant symptom of epigastric pain and no endoscopic evidence of reflux oesophagitis, peptic ulcer disease, or malignancy ("non ulcer dyspepsia"). Patients were excluded if they had received *H pylori* eradication therapy in the past or any non-steroidal anti-inflammatory drugs, proton pump inhibitors, antibiotics, or bismuth containing compounds in the previous two weeks or H_2 receptor antagonists in the previous two days. At endoscopy, five gastric mucosal biopsies were taken as detailed below. Further antral and body biopsies were taken for *H pylori* culture. Blood was also taken for *H pylori* serology.

Histology
Biopsy samples were taken using standard endoscopy biopsy forceps from the five sites specified in the updated Sydney system (fig 1).[11]

Samples were placed in 10% formalin and then embedded in paraffin for sectioning. Three sets of slides were made in each centre; one set was stained with haematoxylin and eosin. These were then assessed by the histopathologist in each centre (Professor M Dixon (MD) in Leeds and Professor

T Shimoda (TS) in Tokyo). A second set was sent unstained to the other centre where haematoxylin-eosin staining took place and the slides were assessed. The pathologists were blinded as to the age and sex of the subjects but because of differences in laboratory identification of the slides, they were aware of their origin. The graded features were scored as absent, mild, moderate, or severe (0–3) according to the updated Sydney system for polymorph activity, chronic inflammation, IM, and atrophy. Thus two sets of histological data were produced on all of the material from Leeds and Tokyo, one from a Japanese pathologist and one from a "Western" pathologist. In addition, two further sets of slides (one each from Leeds and Tokyo) were stained in Leeds by a modified Giemsa for detection of *H pylori* (MD). Patients were considered positive for histological gastritis (consensus gastritis) only if it was diagnosed by both pathologists.

Helicobacter pylori
Three methods were used to detect *H pylori*: histology, culture, and antibody testing. Antral and body biopsy samples were placed immediately into culture medium and then frozen to $-70°C$. They were cultured on 10% (vol/vol) blood agar at 37°C in variable atmosphere incubators under microaerobic conditions in the separate centres. Cultures (Tokyo) or biopsies (Leeds) where then transported to a single centre (London) to be typed for CagA status and VacA genotype.

Two serological tests were performed on samples from all patients. Firstly, an enzyme linked immunosorbent assay of IgG antibodies against *H pylori* (HM-CAP; Enteric Products Inc., Westbury, New York, USA) with a value of 1.8 taken as positive (sensitivity 98.7%, specificity 100%). Secondly, an immunoblot kit assay that included VacA and CagA antibody testing as well as diagnosing infection (Helocoblot 2.1; Genelabs Diagnostics, Singapore) (sensitivity 96%, specificity 95%).

Statistical analysis
Demographic data and pattern of gastritis were compared using Pearson's χ^2 test. The Sydney system approach generates four sets of categorical data each, with four possible grades for the five biopsies from individual patients. Statistical analysis of the gastritis data was restricted to those patients in whom both pathologists had agreed the presence of gastritis (consensus gastritis). In order to carry out the statistical comparisons, we converted the grades to numerical values (0–3) and used medians and non-parametric testing, namely the Mann-Whitney U test. Interobserver agreement between the two pathologists was examined using kappa statistics, a chance corrected coefficient of agreement.

Table 1 Summary of sex and smoking characteristics

	All patients		
	UK (n=126)	Japan (n=126)	p Value
Sex (M/F)	63/63	45/81	0.03*
Age (y) (median (IQR))	49.5 (34–65)	51 (34–65)	0.7†
	Consensus gastritis patients‡		
	UK (n=59)	Japan (n=76)	
Sex (M/F)	29/30	28/48	0.2*
Age (y) (median (IQR))	57 (40–66)	56 (42–66)	0.7†
Smokers/non-smokers	23/33	17/59	0.047*
H pylori negative patients (%; 95% CI)	6 (10; 4.7–20.1)	11 (14.5; 8.3–24.1)	0.60*

IQR, interquartile range; 95% CI, 95% confidence interval.
*χ^2 test; †Mann-Whitney test.
‡Gastritis diagnosed by both pathologists.

Table 2 Number of patients in each decennial in whom a consensus diagnosis of gastritis was made by both pathologists

	Decennial (age)						
	20s	30s	40s	50s	60s	70s	Total
No of patients UK (%)	3 (14)	11 (52)	7 (33)	12 (57)	13 (62)	13 (62)	59 (47)
No of patients Japan (%)	9 (43)	8 (38)	12 (57)	15 (71)	16 (76)	16 (76)	76 (60)

Differences between proportions and their 95% confidence interval (CI) were calculated using the method recommended by Newcombe and Altman.[12] Values of p<0.05 were considered significant. These criteria were determined before commencement of the study. Standard statistical packages were used for the analyses (SPSS version 10.1 (SPSS Science, Chicago, Illinois, USA) and Statsdirect (Statsdirect, Cheshire, UK)).

RESULTS
Demographics
Sex, age, and smoking characteristics of the two patient groups are illustrated in table 1. There was no significant difference in age between the two groups. However, the prevalence of female patients was higher in the Japanese (64.3% (95% CI 55.6–72.1)) than in the UK groups (50% (95% CI 41.4–58.6)), with a difference in prevalence equal to 14.3% (95% CI 2.1–25.9).

Table 3 Kappa coefficients of agreement for all patients' biopsies (Sydney system histology results from a UK and Japanese histopathologist)

Biopsy site	Atrophy	Intestinal metaplasia	Polymorph activity	Chronic inflammation
Antrum 1	0.213	0.549	0.565	0.662
Antrum 2	0.175	0.642	0.643	0.676
Incisura	0.395	0.675	0.552	0.729
Lesser curve	0.706	0.650	0.617	0.573
Greater curve	0.392	0.468	0.646	0.518
Mean	0.376	0.597	0.604	0.632

Prevalence of gastritis
There was consensus agreement between the two pathologists that 76 (60.3% (95% CI 51.6–68.4)) Japanese and 59 (47.6% (95% CI 39.1–56.3)) UK patients had gastritis, with a difference in prevalence equal to 12.7% (95% CI 0.04–24.5; p = 0.0432). Demographic details for these patients are shown in table 1 and details of the consensus diagnosis per decennial in table 2.

Interobserver agreement between the pathologists
Sydney system scores were compared. Mean kappa coefficients varied from 0.376 to 0.632 (table 3). Agreement was poorest for atrophy and greatest for chronic inflammation. Landis and Koch[13] suggest that kappa values >0.20 represent "fair" and >0.40 "moderate" agreement. A previous assessment of interobserver variation in the assessment of gastritis,[14] using a comparable scoring system, found kappa scores of 0.1–0.29 for atrophy.

Severity of gastritis
Total median scores from all five biopsies were compared between the two patient groups for atrophy, IM, activity, and chronic inflammation in subjects with gastritis. The Japanese median atrophy score was 9 compared with 2 in the UK (median difference 6 (95% CI 5–8); Mann-Whitney U test, p<0.001). Median scores for IM were 1.5 for Japan and 0 for the UK (median difference 0 (95% CI 0–3); Mann-Whitney U test, p<0.01). Median scores for polymorph activity were 8 for Japan and 4 for UK (median difference 4 (95% CI 2–5); Mann-Whitney U test, p<0.001). Median scores for chronic inflammation were 13 for Japan and 9 for the UK (median difference 4 (95% CI 2–5); Mann-Whitney U test, p<0.001). Medians for each decennial are illustrated in fig 2. It can be seen that for each parameter there was a trend to a greater
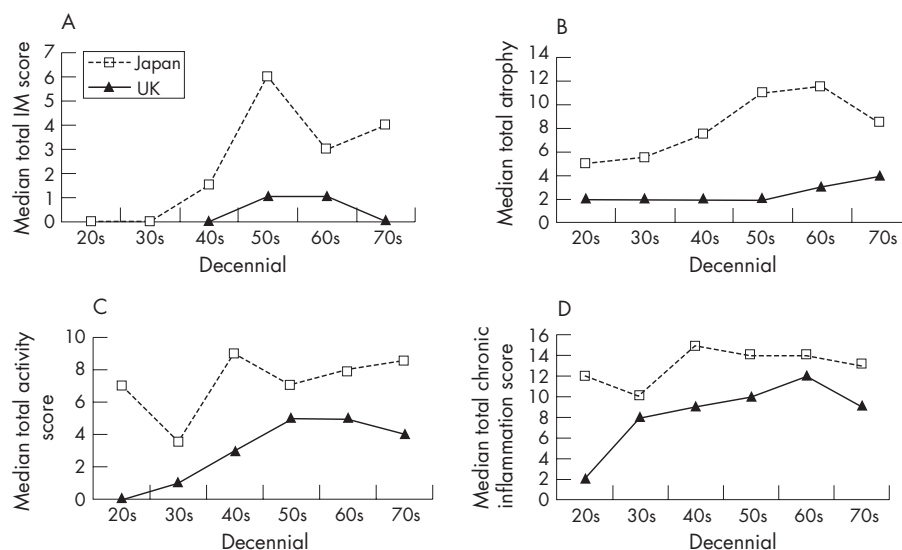

Figure 2 (A–D) Median histology scores for consensus gastritis patients, cumulative scores for all five biopsies. (A) Intestinal metaplasia (IM), (B) atrophy, (C) polymorph activity, and (D) chronic inflammation. (A) Median overall IM scores 1.5 versus 0 (p<0.01). (B) Median overall atropy scores 9 versus 2 (p<0.001). (C) Median overall activity scores 8 versus 1 (p<0.001). (B) Median overall chronic inflammation scores 13 versus 9 (p<0.001).
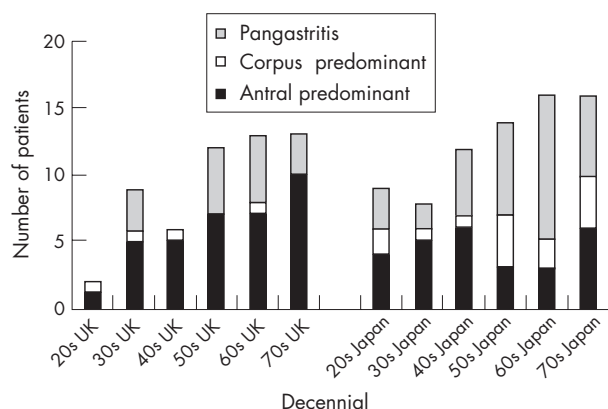
Figure 3 Patterns of gastritis in UK and Japanese patients.

degree of pathological change in each of the age decennials, except for IM in the 20s and 30s where they were the same.

Pattern of gastritis

Cumulative scores for each patient with gastritis were analysed to assess the pattern of inflammation (antral predominant or corpus/pangastritis). The updated Sydney system[11] suggests that chronic inflammation (mononuclear cell infiltration) should be used as the principal tool to assess pattern. The reasoning is that this represents the ''degree'' of gastritis and also does not have the sampling errors that atrophy and IM are prone to.

Therefore, scores from both pathologists for chronic inflammation were added together for biopsies 1 and 2 (antrum) and compared with the equivalent scores from biopsies 4 and 5 (corpus). If the cumulative scores were 2 or more points greater in the antrum biopsies compared with the corpus biopsies, gastritis was classified as ''antral predominant''; if they were 2 or more points greater in the corpus it was classified as ''corpus predominant''; or if they were within one point of each other as ''pangastritis''.

Sixty three per cent of Japanese patients with gastritis had a corpus predominant or pangastritis compared with 36% in the UK (χ^2 test, p = 0.003) (fig 3, table 4).

Differences in the nature and severity of gastritis in the antrum and corpus of those patients with consensus gastritis in the two populations were further explored by comparing the cumulative scores for each of the parameters of the updated Sydney system (chronic inflammation, polymorph activity, atrophy, and IM) given by both pathologists for biopsies 1 and 2 (antrum) and biopsies 4 and 5 (corpus). The results are shown in fig 4. Comparisons for each decennial are shown with patients grouped into <50 and >50 for statistical comparison. Chronic inflammation and activity scores were comparable in the antrum but markedly lower in the corpus of the UK patients. This largely explains the greater prevalence of antrum predominant gastritis in UK subjects; Japanese subjects had the same, or even higher,

scores for chronic inflammation in the antrum but in general had far more corpus chronic inflammation. The degree of corpus atrophy was more marked in the Japanese patients, especially in the older age groups.

H pylori associated gastritis

Gastritis patients were assessed for *H pylori* infection (table 5). Forty six of 59 (78%) UK patients had histological or microbiological (culture) evidence of *H pylori* infection compared with 54 of 76 (71%) Japanese patients (χ^2 test, p = 0.6). However, these values do not include those in whom *H pylori* may have originally caused inflammation but had subsequently disappeared. If serological evidence is taken into account, 53 of 59 (90%) UK patients and 67 of 76 (88%) of Japanese patients may have been infected at some time (χ^2 test, p = 1). Alternatively, if the diagnosis of *H pylori* infection is taken to require *two* positive tests, there were 51 (85%) UK and 56 (74%) (χ^2 test, p = 0.5) Japanese positives (table 5).

H pylori negative gastritis

Seventeen gastritis patients (six UK, 11 Japanese) were negative for all modalities of *H pylori* testing (tables 6, 7). Thirteen of these (four UK, and nine Japanese, all <50 years old) had low levels of gastritis of uncertain significance (median total histology score 3 (interquartile range (IQR) 3–5). Four patients (two UK, two Japanese, all over 50 years) had more marked gastritis (median total histology score 11.5 (IQR 10–15.5)). In these *H pylori* negative cases, activity scores were low and in general histological changes were more marked in the antrum. However, some of the older patients did have evidence of atrophy and IM in the corpus and it is possible that in these cases both the organism and antibody response had disappeared. Alternative aetiologies such as ''chemical'' (reactive) or autoimmune gastritis are possible but recent non-steroidal usage was an exclusion criterion and none of the patients had the typical histological appearances of autoimmune gastritis (however, this is known to be very rare in Japan).

H pylori pathogenicity

CagA status was assessed using an immunoblot assay. Forty seven (37%, mean age 54 years) UK and 72 (57%, mean age 56 years; χ^2 test, p = 0.003) Japanese samples were positive for the 116 kDa protein that corresponds to the presence of the CagA antibody. Histology of the CagA positive patients was compared. There were similar antral activity and chronic inflammation scores in the two populations but greater corpus atrophy, chronic inflammation, and polymorph activity in the Japanese population (fig 5, table 8). The proportions of corpus predominant/pangastritis and antral predominant in CagA positive cases were similar to those found in all cases of gastritis (antral predominant 49% Japan, 67% UK; p = 0.06).

We were able to culture and subtype 53/56 (94%) Japanese *H pylori* positive patients and 29/51 (57%) UK patients. All 53 Japanese patients were VacA subtype s1m1. Fifty two of 53 Japanese patients were CagA positive although one patient had CagA positive antral and CagA negative body cultures.

Table 4 Pattern of gastritis in UK and Japanese patients

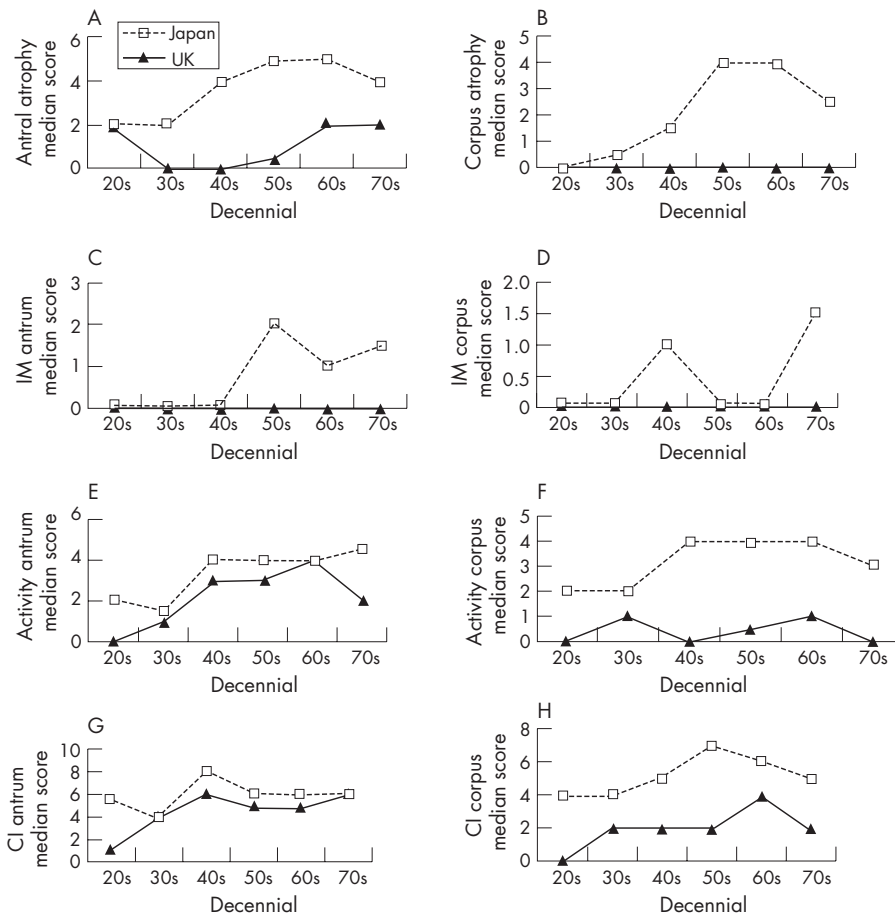| Pattern of gastritis	UK patients (n (%)) (n = 59)	Japanese patients (n (%)) (n = 76)	χ^2 p value (*Fisher's exact test)
Antral predominant	35 (59)	28 (37)	0.0154
Corpus predominant	4 (7)	14 (18)	0.07*
Pangastritis	17 (29)	34 (45)	0.086
Corpus predominant/pangastritis	21 (36)	48 (63)	0.0027
Unable to classify	3	0	

Figure 4 (A–H) Total median scores for atrophy (A, B), intestinal metaplasia (IM) (C, D), polymorph activity (E, F), and chronic inflammation (CI) (G, H) in the antrum (biopsies 1 and 2) and corpus (biopsies 4 and 5). (A) Antral atrophy: median difference age <50 years = 2 (p<0.0001); median difference age >50 years = 3 (p<0.0001). (B) Corpus atrophy: median difference age <50 years = 0 (p=1); median difference age >50 years = 3 (p<0.0001). (C) Antral intestinal metaplasia: median difference age <50 years = 0 (p=0.6); median difference age >50 years = 0 (p<0.017). (D) Corpus intestinal metaplasia: median difference age <50 years = 0 (p=1); median difference age >50 years = 0 (p=0.01). (E) Antral activity: median difference age <50 years = 1 (p=0.013); median difference age >50 years = 1 (p=0.03). (F) Corpus activity: median difference age <50 years = 2 (p=0.0007); median difference age >50 years = 2 (p<0.0001). (G) Antral chronic inflammation: median difference age <50 years = 2 (p=0.03); median difference age >50 years = 0 (p=0.2). (H) Corpus chronic inflammation: median difference age <50 years = 3 (p=0.001); median difference age >50 years = 3 (p<0.0001). p values for Mann-Whitney U testing.

Eleven of 29 UK patients had VacA s1m1 subtype, 13 were s1m2, and five were s2m2. Overall 26/29 were CagA positive.

Histological differences remained when 52 Japanese and 10 UK patients who were CagA positive and VacA s1m1 on antral biopsy culture were compared. It is apparent that the differences seen for all *H pylori* gastritis patients are maintained when like is compared with like. Cag and Vac pathogenicity of *H pylori* does not appear to be the decisive factor explaining the differences in gastritis between the two populations.

Gastric cancer risk scores for *H pylori* positive patients

In order to further explore the histological data, we used a previously validated gastric cancer risk score, as described by Meining and colleagues.[15] They compared gastritis in patients with small early gastric cancers with histologically proven

H pylori infection with a control group of *H pylori* positive duodenal ulcer patients who had a low risk of gastric cancer. Their scoring system was calculated as follows:

(a) Infiltration with chronic inflammatory cells is more pronounced in the corpus mucosa than in the antrum, or is equally distributed = 1 point.

(b) Infiltration with neutrophils (= "activity" in the Sydney system) is more pronounced in the corpus mucosa than in the antrum, or is equally distributed = 1 point.

(c) Presence of IM in the antrum or corpus = 1 point.

In Meining's study, the predictive value for the presence of gastric carcinoma was 0.166 for 0 points, 0.464 for 1 point, 0.791 for 2 points, and 0.943 for 3 points.

Table 5 Patients with consensus gastritis: evidence of *Helicobacter pylori* infection

Decennial	Gastritis UK	JPN	H pylori on histology and/or culture UK	JPN	ELISA positive for H pylori UK	JPN	Immunoblot positive for H pylori UK	JPN	Cag A positive (immunoblot and/or culture) UK	JPN	Any evidence of H pylori (2 tests positive for H pylori) UK	JPN
20s	3	9	1	5	0	5	1	5	1	5	1 (1)	5 (5)
30s	11	8	6	4	7	2	7	4	6	4	9 (8)	6 (3)
40s	7	12	7	9	4	9	5	11	6	10	7 (7)	11 (10)
50s	12	15	9	14	8	12	9	14	11	11	11 (10)	15 (14)
60s	13	16	12	12	10	13	11	13	9	14	12 (11)	16 (12)
70s	13	16	10	12	12	13	12	15	11	15	13 (13)	14 (12)
Total	59	76	45	56	41	54	45	62	44	59	53 (51)	67 (56)

ELISA, enzyme linked immunosorbent assay.

Table 6 Histology scores for the 11 Japanese patients with consensus gastritis who were negative for all forms of *Helicobacter pylori* testing

Age (y)	Sex	Antral activity	Antral CI	Antral atrophy	Antral IM	Corpus activity	Corpus CI	Corpus atrophy	Corpus IM
21	F	0	2	2	0	0	0	0	0
26	F	0	3	1	0	0	1	0	0
27	F	0	4	2	0	0	4	0	0
28	F	0	2	2	0	0	1	0	0
30	F	1	3	0	0	0	0	0	4
33	F	0	2	2	0	0	2	0	4
35	F	0	3	2	0	0	0	0	0
46	M	0	2	1	0	0	4	0	4
61	F	0	3	2	0	0	4	0	3
69	F	0	3	3	3	0	2	6	0
67	F	0	4	2	4	0	4	6	4

CI, chronic inflammation; IM, intestinal metaplasia.

Table 7 Histology scores for the six UK patients with consensus gastritis who were negative for all forms of *Helicobacter pylori* testing

Age (y)	Sex	Antral activity	Antral CI	Antral atrophy	Antral IM	Corpus activity	Corpus CI	Corpus atrophy	Corpus IM
28	F	0	1	1	4	0	0	0	0
29	F	0	2	2	0	0	0	0	0
31	F	1	4	0	0	0	3	0	0
33	F	0	0	2	0	0	0	0	0
58	M	1	6	3	1	1	4	4	0
65	F	0	2	2	4	0	2	2	4

CI, chronic inflammation; IM, intestinal metaplasia.

Histology results of the 45 UK patients and 54 Japanese patients who had histological evidence of *H pylori* infection were analysed (in keeping with the original study).

The sum of the chronic inflammatory scores for both pathologists for biopsies 1 and 2 (antrum) were compared with the scores for biopsy 4 and 5 (corpus). The same approach was used for activity in the corpus and antrum. Finally, IM in the antrum or corpus reported by either pathologist was noted. Again the results for both pathologists were added together and this value used to establish the cancer risk score.
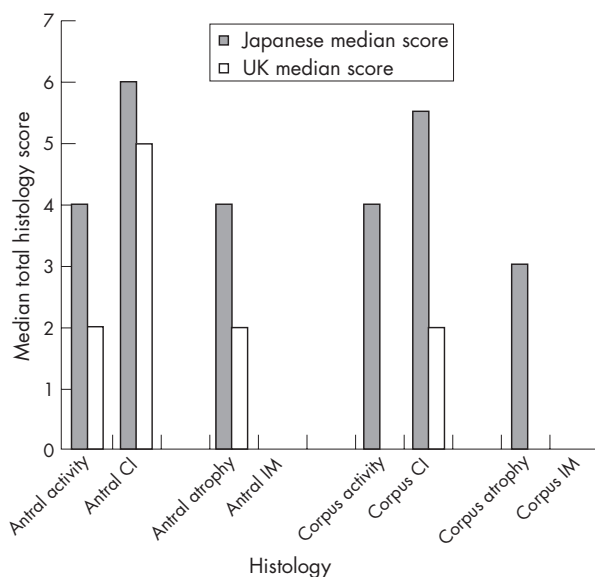

Figure 5 Comparison of histology of CagA positive patients. CI, chronic inflammation; IM, intestinal metaplasia.

Comparing the cumulative scores (table 9), there were significantly more Japanese patients with a score of 3, and conversely more UK patients with a score of 0. The proportion of patients with intermediate scores of 1 and 2 were similar in both patient groups.

DISCUSSION

We believe this to be the first study to prospectively compare the histology of two matched populations from countries with substantially different gastric cancer rates. The selection process excluded patients with macroscopic pathology such as cancer, peptic ulcer, and reflux oesophagitis. Only those with symptoms of "functional" dyspepsia were assessed and the protocol ensured similar age cohorts.

The major weakness of the study is that dyspeptic symptoms were not identical because of differences in culture, language, and health seeking behaviour in the two countries. However, strict adherence to inclusion and exclusion criteria should have minimised this effect; in particular we ensured that the National Cancer Centre patients were attending for investigation of simple dyspepsia and not for possible malignancy. It also proved impossible to "blind" the two pathologists with respect to the source of the material they were examining. The kappa statistics were generally good with the sole exception of antral atrophy in young patients; however, antral atrophy has previously been recognised as a difficult feature to assess.[16] A further weakness of the study was that we were unable directly to compare social class between the two countries because a system of social assessment does not exist in Japan. Nor was it considered possible to obtain an accurate dietary history from the Japanese patients.

The cause of the gastritis was predominantly *H pylori* infection. Other aetiologies are unlikely because of the histological findings, and patients on recent non-steroidal anti-inflammatory drugs were excluded. No patient had the characteristic histological appearance of autoimmune

Table 8 Comparison of histology of cagA positive patients

	Antral atrophy	Antral IM	Antral activity	Antral CI	Corpus atrophy	Corpus IM	Corpus activity	Corpus CI
UK score (median (IQR))	2 (0–4)	0 (0–10	2 (0–4)	5 (3–8)	0 (0–1)	0 (0–0)	0 (0–2)	2 (1–4)
Japan score (median (IQR))	4 (2–6)	0 (0–40	4 (0.5–5)	6 (4–8)	3 (0–5)	0 (0–3)	4 (0.5–4)	5.5 (4–7)
Median difference (95% CI)	3 (1–3)	0 (0–0)	1 (0–2)	1 (0–2)	2 (1–3)	0 (0–0)	2 (1–3)	3 (2–4)
Mann-Whitney U test (p value)	<0.0001	0.9	0.008	0.04	0.0001	0.007	0.0001	0.0001

CI, chronic inflammation; IM, intestinal metaplasia; IQR, interquartile range; 95% CI, 95% confidence interval.

gastritis (a condition that is very rare in Japan anyway) but parietal cell antibodies were not checked.

As this was a cross sectional analysis we must remember that the age of infection with *H pylori* (assumed to be in childhood) is not known. The rate at which patients were infected and at what age would be important factors in determining the future histological changes.

The difference in prevalence (12.5%) of gastritis between the two groups was lower than anticipated and this reflected the unexpected similarity in *H pylori* infection rates. This finding is commensurate with the falling rate of infection in the Japanese population. Our results show that gastritis in Japan is histologically more severe, is present at an earlier age, and is more likely to be corpus predominant or pangastritis. Three possible explanations may account for the differences between the two populations: the genetic constitution of the host, the genotype of the infecting organism, and the environment.

Severity of inflammation

Cytokine production is largely responsible for the host's inflammatory response to *H pylori* infection and is genetically determined. Interleukin (IL) 1β and tumour necrosis factor α (TNF-α) are proinflammatory cytokines that also inhibit acid production. Polymorphisms of the genes controlling production of these cytokines have been linked to different levels of IL-1β and TNF-α production and have been associated with an increased risk of gastric cancer, chronic atrophic gastritis, IM, and gastric ulcer.[5] [17–19]

Bacterial factors are also important. Possession of the *Cag* associated pathogenicity island leads to production of the CagA protein[20] and is associated with an increased severity of gastritis and incidence of peptic ulcer disease and gastric cancer.[21–24] Production of the vacuolating toxin VacA, and the genotype of the *VacA* gene, are also associated with increased pathogenicity.[25]

Another environmental factor likely to play a role in the severity of gastritis is diet. Diet has long been postulated as an aetiological factor for non-cardia gastric cancer, with nitrate and salt intake both being implicated,[1] [2] [26] while antioxidants such as vitamins A, C, and E may be protective.[27] The Japanese diet is higher in salt than a standard Western diet and animal models show that a high salt diet causes an acute gastritis.[28]

Table 9 Comparison of cancer risk scores

	No of pts UK (n (%)) (n = 45)	No of pts Japan (n (%)) (n = 54)	χ^2 p value (*Fisher's exact test if count <5)
Score = 0	20 (44)	11 (20)	0.0186
Score = 1	15 (33)	11 (20)	0.219
Score = 2	9 (20)	14 (26)	0.648
Score = 3	1 (2)	18 (33)	<0.0001*

Pattern of gastritis

The pattern of colonisation of the gastric mucosa by *H pylori* appears to be controlled by acid secretion. Although *H pylori* is much more tolerant of a low pH than most bacteria, it cannot proliferate in areas of high acid production. A low acid output allows spread of inflammation to the gastric corpus resulting in a further decrease in acid production.[29] Acid secretion is directly related to height and weight which determine lean body mass.[30]

Maximal acid secretion varies widely between individuals and it is likely that patients with a constitutionally lower acid secretion are more likely to develop a corpus predominant or pangastritis. Might different levels of acid production explain the different pattern of gastritis in the two populations? Japanese subjects may have a smaller parietal cell mass but direct comparisons of acid secretion have not been performed. Evidence for lower acid output in patients from the Far East was found in a comparison between a Chinese and Scottish population (both normal and duodenal ulcer subjects). Acid output was higher in the Scottish normal and duodenal ulcer patients and the difference was maintained when the results were corrected for weight.[31] The latter study pre-dates the discovery of *H pylori* so the relative infection rates are unknown. However, the data suggest that variation in the level of acid production in different populations may account for our findings.

Atrophy, intestinal metaplasia, and the role of *H pylori*

In Japanese patients, atrophy was more severe than in UK patients. The differences were greatest in the corpus of the middle to older age groups. Intestinal metaplasia was more marked in the older Japanese patients. Even when gastritis was caused by similar pathogenic strains (with regard to CagA and VacA), the differences were maintained but there are other virulence factors for which we have not controlled.

More atrophy was seen in the older Japanese who were *H pylori* histology negative while almost none was seen in their UK counterparts. Serology results suggest that the older Japanese patients with atrophy/IM but no histological evidence of *H pylori* may have been infected with CagA organisms in the past but had cleared their infection leaving its after effects, as has been described elsewhere.[32]

Cancer risk

As corpus atrophy and IM are key steps in Correa's gastritis-metaplasia-dysplasia-carcinoma sequence,[5] differences between the two populations show Japanese gastritis to have a "premalignant" pattern in keeping with their increased cancer risk. The carcinogenic factor or factors that tip the balance towards dysplasia and carcinoma are not completely understood but in the hypochlorhydric or achlorhydric stomach faecal-type bacteria proliferate and carcinogenic n-nitroso compounds may be generated by bacterial metabolism of either dietary nitrate or nitrite derived from endogenously converted nitrate.[5] [33]

The pattern of *H pylori* gastritis in the Japanese was mainly corpus predominant or pangastritis. Conversely, UK patients

had an antral predominant pattern that would tend to maintain, or even increase, acid production from the parietal cells of the corpus. The importance of IM and a corpus predominant pattern of chronic inflammation and polymorph activity in determining cancer risk has been demonstrated within a German population.[15] We have applied the same scoring system making this the first study to show that such factors apply in two populations with widely different gastric cancer rates.

Summary

This study confirms that in age and symptom matched patients, Japanese subjects do develop a more severe and more corpus predominant gastritis than their UK counterparts. This may account for the increased gastric cancer risk in Japan.

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REFERENCES

1 **Neugat AI**, Hayek H, Howe G. Epidemiology of gastric cancer. *Semin Oncol* 1996;**23**:281–91.
2 **The Eurogast Study Group**. An international association between Helicobacter pylori infection and gastric cancer. *Lancet* 1991;**341**:1127–31.
3 **Parsonnet J**, Friedman GD, Orentreich N, et al. Risk for gastric cancer in people with Cag A positive or Cag A negative Helicobacter pylori infection. *Gut* 1997;**40**:297–30.
4 **Joossens JV**, Hill MJ, Elliott P, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol* 1996;**25**:494–504.
5 **El Omar EM**. The importance of interleukin 1 beta in Helicobacter pylori associated disease. *Gut* 2001;**48**:743–7.
6 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992;**52**:6735–40.
7 **Uemura N**, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001;**345**:784–9.
8 **Kimura K**. Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. *Gastroenterology* 1972;**63**:584–92.
9 **Parente F**, Imbesi V, Maconi G, et al. Influence of bacterial CagA status on gastritis, gastric function indices and pattern of symptoms in H pylori-positive dyspeptic patients. *Am J Gastroenterol* 1998;**93**:1073–9.
10 **Schubert TT**, Schubert AB, Ma CK. Symptoms, gastritis, and Helicobacter pylori in patients referred for endoscopy. *Gastrointest Endosc* 1992;**38**:357–60.
11 **Dixon MF**, Genta RM, Yardley JH, et al. Classification and grading of gastritis. The updated Sydney system. *Am J Surg Pathol* 1996;**20**:1161–81.
12 **Newcombe RG**, Altman DG. Proportion and their differences. In: Altman DG, Machin D, Trevor NB, et al, eds. *Statistics with confidences*, 2nd edn. London: BMJ Books, 2000:45–56.
13 **Landis J**, Koch G. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.
14 **El-Zimaity HM**, Graham DY, Al-Assi MT, et al. Interobserver variation in the histopathological assessment of Helicobacter pylori gastritis. *Hum Pathol* 1996;**27**:35–41.
15 **Meining A**, Bayerdorffer E, Muller P, et al. Gastric carcinoma risk index in patients infected with Helicobacter pylori. *Virchows Arch* 1998;**432**:311–14.
16 **Ruiz B**, Garay J, Johnson W, et al. Morphometric assessment of gastric antral atrophy: comparison with visual evaluation. *Histopathology* 2001;**39**:235–42.
17 **Figueiredo C**, Machado JC, Pharoah P, et al. Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst* 2002;**94**:1680–7.
18 **Machado JC**, Figueiredo C, Canedo P, et al. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology* 2003;**125**:364–71.
19 **El-Omar EM**, Rabkin CS, Gammon MD, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 2003;**124**:1193–201.
20 **Segal ED**, Cha J, Lo J, et al. Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by Helicobacter pylori. *Microbiology* 1999;**96**:14559–64.
21 **Kuipers EJ**, Perez-Perez GI, Meuwissen SG, et al. Helicobacter pylori and atrophic gastritis: importance of the cagA status. *J Natl Cancer Inst* 1995;**87**:1777–80.
22 **Parsonnet J**, Friedman GD, Orentreich N, et al. Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. *Gut* 1997;**40**:297–301.
23 **Blaser MJ**, Perez-Perez GI, Kleanthaus H, et al. Infections with strains possessing cagA is associated with an increased risk of developing cancer of the stomach. *Cancer Res* 1995;**55**:2111–15.
24 **van Dorn LJ**, Figueiredo C, Sanna R, et al. Clinical relevance of the cagA, vacA and iceA status of Helicobacter pylori. *Gastroenterology* 1998;**115**:58–66.
25 **Atherton JC**, Peek R, Tham KT, et al. Clinical and pathological importance of heterogeneity in vacA, the vacuolating cytotoxin gene of Helicobacter pylori. *Gastroenterology* 1997;**112**:92–9.
26 **Gonzalez CA**, Riboli E, Badosa J, et al. Nutritional factors and gastric cancer in Spain. *Am J Epidemiol* 1985;**122**:947–59.
27 **Ekstrom AM**, Serafini M, Nyren O, et al. Dietary anti-oxidant intake and the risk of cardia cancer and non-cardia cancer of the intestinal and diffuse type: a population-based case-control study in Sweden. *Int J Cancer* 2000;**87**:133–40.
28 **Fox JG**, Dangler CA, Taylor NS, et al. High salt intake induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonisation in C57BL/6 mice. *Cancer Res* 1999;**59**:4823–8.
29 **Sipponen P**, Hyvarinen H, Siurala M. H. pylori corpus gastritis—relation to acid output. *J Physiol Pharmacol* 1996;**47**:151–9.
30 **Baron JH**. Lean body mass, gastric acid and peptic ulcer. *Gut* 1969;**10**:637–42.
31 **Lam SK**, Hasan M, Sircus W, et al. Comparison of maximal acid output and gastrin response to meals in Chinese and Scottish normal and duodenal ulcer subjects. *Gut* 1980;**21**:324–8.
32 **Kokkola A**, Kosunen TU, Puolakkainen P, et al. Spontaneous disappearance of Helicobacter pylori antibodies in patients with advanced atrophic corpus gastritis. *APMIS* 2003;**111**:619–24.
33 **Ziebarth D**, Spiegelhalder B, Bartsch H. N-Nitrosation of medicinal drugs catalysed by bacteria from human saliva and gastro-intestinal tract, including Helicobacter pylori. *Carcinogenesis* 1997;**18**:383–9.