HELICOBACTER PYLORI

Risk factors for atrophic chronic gastritis in a European population: results of the Eurohepygast study

The Eurohepygast Study Group

Gut 2002;**50**:779–785

Correspondence to: Dr N Broutet, Unité d'Epidémiologie des Infections Digestives, Laboratoire de Bactériologie-BP 76, Université Victor Segalen Bordeaux 2, 146, rue Léo Saignat, 33076 Bordeaux Cedex, France; nathalie.broutet@labhel.u-bordeaux2.fr

Accepted for publication 29 August 2001

Background and aims: The development of atrophic chronic gastritis (ACG) is multifactorial, involving environment as well as host responses to *Helicobacter pylori* infection. The aim of this study was to determine factors involved in ACG in a European dyspeptic population.

Methods: Data concerning sociodemographics, social behaviour, biological aspects, diet, and virulence factors of *H pylori* strains were collected in a cross sectional study from 19 European centres in 14 countries. Dyspeptic *H pylori* positive patients with ACG or non-ACG (NACG) at histology were included. Anti-CagA antibodies were evaluated by two immunoblot tests and anti-VacA antibodies by one. Logistic regression models were constructed, and estimated odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated from the coefficients.

Results: Of the 451 patients included in the study, 267 were analysed: 202 had NACG and 65 ACG. Mean age was 44.4 years and 63% were women. Risk factors for atrophy identified by multivariate analysis were: age over 60 years (OR 4.14, 95% CI 1.79–9.58), coffee consumption (OR 2.35, 95% CI 1.07–5.16), sedative consumption (OR 2.17, 95% CI 1.04–4.52), and harbouring anti-CagA and anti-VacA antibodies simultaneously (OR 3.09, 95% CI 1.26–7.56), while the odds were significantly reduced for those with an anxiety score of 6 or more (OR 0.45, 95% CI 0.21–0.99).

Conclusion: The simultaneous presence of anti-CagA and anti-VacA antibodies enhanced the risk of ACG in European dyspeptic patients. Failure to discern diet and family history as risk factors for ACG may suggest that diet is homogeneous in Europe and that most of the risk factors for ACG identified so far are identical to risk factors for *H pylori* infection.

Chronic gastritis, both non-atrophic (NACG) and atrophic (ACG), and its relationship with *Helicobacter pylori* infection have been the subject of numerous studies. These diseases were first described in anecdotal reports. Population based surveys were carried out in the 1960s and 1970s[1–4] and it was demonstrated that NACG can progress to ACG. These studies also showed an association between ACG and the pathogenesis of gastric cancer and other gastric diseases.[5 6]

More recently, studies have shown that *H pylori* infection in NACG and ACG varies among countries and populations and is dependent on socioeconomic conditions.[7 8] Although *H pylori* infection seems to be a prerequisite for ACG, it does not explain the full picture.[9–11] Not all subjects infected by *H pylori* will develop ACG and some who do progress to gastric cancer while others do not.

The aim of the Eurohepygast study was to observe the progression of chronic gastritis over a three year period in a European dyspeptic population. Data collected from the Eurohepygast population at inclusion in the cohort were used to better elucidate why patients have ACG. The odds of the presence of ACG were modelled in relation to different variables linked to sociodemographic, host, and environmental characteristics, and antibody response to *H pylori* infection.

PATIENTS AND METHODS

Study design and sample

In this cross sectional analysis, we have compared patients with ACG and NACG based on data collected at inclusion in the Eurohepygast study. Patients consulting for dyspepsia in one of the 19 participating centres from 14 different countries were included. Patients with a diagnosis of non-ulcer dyspepsia, aged between 18 and 75 years, requiring an endoscopy, and with chronic gastritis on histology were included. A detailed questionnaire was filled out by the clinician or a research nurse, and a blood sample was taken from eligible patients.

Endoscopy

Four biopsies were obtained from the mid antrum, two for histology and two for culture. Three biopsies were taken from the mid corpus on the greater curve, two for histology and one for culture. Biopsies for histology were placed in 10% formalin and the remainder immediately frozen at −80°C. Macroscopic findings were recorded as per the Sydney classification for endoscopists.[12]

Histopathological diagnosis

Biopsies were routinely embedded in paraffin blocks, then cut and stained in each local centre. The stained slides were subsequently examined by a single expert gastrointestinal pathologist (PS) using the updated Sydney classification.[13 14] Two histopathological entities were delineated: NACG and ACG. NACG was defined as any grade of inflammation with no atrophy in either the corpus or antrum. ACG was defined as antral atrophy alone, antral intestinal metaplasia (IM) alone, corpus atrophy alone, corpus atrophy associated with corpus IM, or corpus IM alone. Patients with missing or inadequate biopsies were excluded from the analysis.

Culture of *H pylori*

Biopsies obtained from the antrum and corpus were cultured locally according to a common protocol[15] agreed upon by the participating microbiologists.

Abbreviations: ACG, atrophic chronic gastritis; NACG, non-atrophic chronic gastritis; IM, intestinal metaplasia; ELISA, enzyme linked immunosorbant assay; EIA, enzyme immunoassay; BMI, body mass index; OR, odds ratio.

Serological testing

(A) Anti-*H pylori* antibodies by an enzyme immunoassay (EIA): Pyloriset EIA-G test (Orion Diagnostica, Espoo, Finland).[16]

(B) Anti-*H pylori*, anti-CagA, and anti-VacA antibodies by immunoblot Chiron RIBA *H pylori* SIA (Chiron Diagnostics Emeryville, California, USA).[17]

(C) Anti-CagA antibodies by an inhouse immunoblot performed in one of the centralised facilities.[18]

(D) Anti-CagA antibodies only by a modified inhouse enzyme linked immunosorbant assay (ELISA).[19]

Determination of serological status

To be classified as positive for *H pylori* infection, concordant results of two different serological tests were required: the EIA and Chiron immunoblot. If these results were discordant, the results of serology were considered indeterminable. Two of the three tests for CagA had to be positive for the patient to be deemed CagA positive. The first two tests applied were the inhouse immunoblot and the CagA ELISA; in the case of discordance, the Chiron immunoblot alone was then considered. The chiron immunoblot alone was used to determine positivity for anti-VacA antibodies.

Definition of *H pylori* status

Patients were considered to be infected with *H pylori* if one of three tests was positive: culture, serology, or histology. Patients were considered infection free when two of the three tests were negative, and the third result was either negative, indeterminable, or missing.

Variables

The 34 variables included in the analysis were divided into five groups.

The first group included all variables related to sociodemographic factors: age was considered a binary variable—60 years of age or less, or over 60 years. Origin of birth was considered as: (i) Western Europe, (ii) Eastern Europe, and (iii) others (defined as Middle East, Africa, the Americas, or West Indies). Educational level achieved was considered as: (i) illiterate-primary, (ii) secondary, or (iii) apprenticeship, university level. Family composition was considered as: (1) number of siblings: (i), 0, (ii) 1 or 2, or (iii) 3 or more; (2) birth rank: (i) first, (ii) second, or (iii) third and following; and (3) finally, these two variables were coded as: only child or oldest, and second or more. The composition of the actual family was analysed as follows: (1) marital status: single versus married (including widow); (2) number of children: none versus one or more; (3) patient's and patient's partner's profession: higher and intermediate profession-managerial workers; sales-clerical and related workers, services workers; agriculture-production-transport-equipment workers; workers not classified elsewhere or unemployed; and (4) occupational status of the family: upper and middle, intermediate, skilled workers and clerical, semi-skilled, and unskilled workers.

The second group contained variables related to behaviour including: smoking habits (never, ex, or actual), consumption of alcohol (occasionally, weekends only or everyday), sleeping tablets, and tranquillisers, and anxiety. The latter was measured according to the scale proposed by Covi and colleagues,[20 21] with a score of 0–5 representing no anxiety and a score of 6–12 indicating the presence of anxiety.

The third group corresponded to variables related to the patient such as body mass index (BMI kg/m^2; normal value 23.4±3.2 in women and 24.3±3.3 in men[22]) and blood pressure (mm Hg), considered normal, high, or low.[23] Also included were ABO and rhesus blood groups, family history of digestive diseases including stomach cancer or surgery, gastric ulcer, and colon cancer; and a history of the present disease (duration of dyspepsia).

The fourth group included variables related to diet. A self evaluation questionnaire based on the frequency and amount of certain foodstuffs consumed was administered. A principal component analysis was performed using Statbox 2.5 (Grimmer Logiciels, Paris, France 1997) for variables linked to diet in order to determine the patient's nutritional profile.[24]

The fifth group included putative virulence factors of *H pylori*, as measured by anti-CagA and anti-VacA antibodies.

Data analysis

Statistical analysis was performed using STATA 5.0 statistical software (Stata Corporation, Texas, USA 1997). The distribution of ACG and NACG in different strata of the variables was compared using a Mantel-Haenzsel χ^2 test, a Student's *t* test, or ANOVA when appropriate. In each group of variables, the odds for the presence of ACG compared with NACG were calculated. An intermediate multivariate analysis was then performed on each of the five groups of variables independently, including all variables associated with atrophy ($p \leqslant 0.25$) in the univariate analysis. Each of the five models was adjusted for age as a dichotomous variable and sex. All variables associated with the presence of ACG ($p \leqslant 0.05$) in each intermediate model were gathered into a final model. The multivariate analysis was performed by logistic regression using a backward elimination procedure of variables not significantly associated with the presence of ACG ($p=0.05$).[25] Estimated odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated from the coefficients examined. The significance of the coefficient of a variable was tested using the likelihood ratio test, at each step of the construction of the logistic model. Confounding variables and interactions were evaluated as recommended.[25]

Ethics

At inclusion, each patient was required to sign an informed consent and the study protocol was accepted by the local ethics committee of each hospital.

RESULTS

Overall, 451 patients were enrolled in the cohort but 184 were excluded. Forty four had normal mucosa on histological review by the expert gastrointestinal pathologist. The other 122 patients were excluded as their biopsies were inadequate or unobtainable. In 13, *H pylori* status could not be reliably determined and in five with chronic gastritis *H pylori* status was negative. Thus 267 biopsy proven *H pylori* infected patients with chronic gastritis were analysed: 202 had NACG and 65 had ACG. Mean age of the patients was 44.4 years (range 19–72.5; SD 12.5) and 168 (63%) were women; mean age was the same for both sexes. At endoscopy, macroscopically normal mucosa was observed in 166 (82.6%) NACG patients and 47 (72.3%) ACG patients ($p=0.07$).

Analysis of sociodemographic data

As shown in fig 1, there was no apparent trend towards an increase in the proportion of patients with atrophy with age, up to the age of 60 years, and therefore age was entered as a dichotomous variable in the logistic regressions. Among the different variables analysed (table 1), the following were associated with an increased odds for the presence of ACG compared with NACG ($p \leqslant 0.25$): age over 60 years; birth place Eastern Europe, Asia, the Americas, or Africa compared with Northern Europe; a primary school educational level versus university level of education; having more than one child; and being retired. In the multivariate intermediate model, only age proved to be a significant factor in predicting the presence of ACG ($p=0.05$).

Analysis of variables linked to the host

None of the variables studied (blood group, rhesus group, family history of gastric disease, duration of dyspeptic

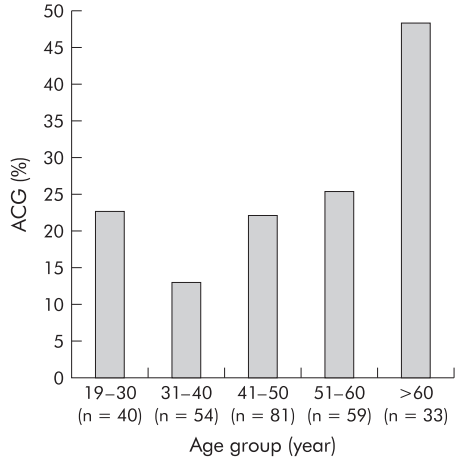

Figure 1 Proportion of atrophic chronic gastritis (ACG) cases according to age group (n=267).

symptoms, blood pressure, or BMI) was linked to the presence of ACG ($p \leq 0.25$) and therefore none was used to construct an intermediate model or to adjust the final model.

Analysis of variables linked to behaviour

Consumption of coffee, tranquillisers, or sleeping tablets was associated with the presence of ACG (p=0.25) (table 2). Conversely, anxiety (score 6–12) was associated with a reduced odds for ACG. Interestingly, among patients not taking tranquillisers or sleeping tablets, the proportion of cases with ACG was not significantly different between those without anxiety (score 0–5) and those suffering from anxiety (score 6–12) (23.7% *v* 17%, respectively; p=0.34) which was not the case among patients taking tranquillisers or sleeping tablets (45.4% *v* 17.8%, respectively; p=0.022). In the intermediate multivariate logistic regression model, adjusted for age and sex, only coffee consumption remained associated with ACG ($p \leq 0.05$). Anxiety score and consumption of tranquillisers or sleeping tablets were maintained in the model because their ORs almost reached significance. No interaction was observed between them. These three variables were included in the final model.

Analysis of variables linked to diet

The principal component analysis did not reveal any association profile. Therefore, consumption and the type of

Table 1 Univariate analysis of sociodemographics factors associated with atrophic chronic gastritis in a European dyspeptic population (n=247)

	NACG		ACG			
	n	%	n	%	Unadjusted OR	95% CI
Age						
60 y or less	171	79.2	45	20.8	1	—
>60 y	16	51.6	15	48.4	3.56	1.64–7.75
Sex						
Male	65	72.2	25	28	1	—
Female	122	77.7	35	22	0.74	0.41–1.35
Country of origin						
Western Europe	67	80.7	16	19.3	1	—
Eastern Europe	111	74.0	39	26.0	1.47	0.8–2.8
Other*	9	64.3	5	35.7	2.32	0.7–7.9
Ethnic status						
Northern Europe	93	76.2	29	23.8	1	—
Southern Europe	74	77.9	21	22.1	0.91	0.5–1.7
Middle Eastern	14	66.7	7	33.3	1.60	0.6–4.3
African, Indian, Mongoloids	6	66.7	3	33.3	1.60	0.4–6.8
Educational level						
Illiterate, primary	38	82.6	8	17.4	1	—
Secondary	117	75.5	38	24.5	1.54	0.7–3.6
University	32	69.6	14	30.4	2.08	0.8–5.6
No of siblings						
0	14	77.8	4	22.2	1	—
1 or 2	90	76.9	27	23.1	1.05	0.32–3.46
3	83	74.1	29	25.9	1.22	0.37–4.01
Rank order						
Oldest or only child	66	75.0	22	25.0	1	—
Second or more	121	76.1	38	23.9	0.94	0.51–1.72
No of children						
None	42	82.4	9	17.6	1	—
1 or more	145	74.0	51	26.0	1.64	0.7–3.6
Marital status						
Single	26	83.9	5	16.1	1	—
Other	161	74.5	55	25.5	1.78	0.6–4.8
Patient's profession†						
Gp 0–1–2–3	46	76.7	14	23.3	1	—
Gp 4–5	31	73.8	11	26.2	1.16	0.5–2.9
Gp 6–7–8–9	28	82.4	6	17.6	0.70	0.2–2.0
Other‡	57	83.8	11	16.2	0.63	0.3–1.5
Retired/not classified elsewhere	21	56.8	16	43.2	2.50	1.03–6.1

NACG, non-atrophic chronic gastritis; ACG, atrophic chronic gastritis; OR, odds ratio; 95% CI, 95% confidence interval.
*Asia, Africa, Americas, overseas.
†0–3: professional, administration, clerical, and related workers; 4–5: sales and service workers; 6–9: agriculture, nature, production, transport workers.
‡Unemployed, no occupation, student, or not classified.

Table 2 Univariate analysis of behaviour and drug intake factors associated with atrophic chronic gastritis in the European dyspeptic population (n=260)

	NACG		ACG		Unadjusted OR	95% CI
	n	%	n	%		
Smoking habit						
Non-smoker	112	76.7	34	23.3	1	—
Ex smoker	26	63.4	15	36.6	1.90	0.9–4.0
Smoker	58	79.5	15	20.5	0.85	0.4–1.7
Consumption (pack/year)						
0	112	76.7	34	23.3	1	—
<20	56	73.7	20	26.3	1.17	0.6–2.2
⩾20	28	73.7	10	26.3	1.10	0.5–2.5
Alcohol consumption						
None	55	75.3	18	24.7	1	—
Yes	125	77.2	37	22.8	0.90	0.5–1.7
Weekends only	16	64.0	9	36.0	1.72	0.6–4.5
Coffee consumption						
None	64	84.2	12	15.8	1	—
Yes	132	71.7	52	28.3	2.10	1.0–4.2
Sleeping tablets or tranquillisers						
No	155	77.9	44	22.1	1	—
Yes	41	67.2	20	32.8	1.72	0.9–3.2
Stress score						
0–5 (not anxious)	128	71.9	50	28.1	1	—
6–12 (anxious)	68	82.9	14	17.1	0.53	0.3–1.0

NACG, non-atrophic chronic gastritis; ACG, atrophic chronic gastritis; OR, odds ratio; 95% CI, 95% confidence interval.

Table 3 Antibodies linked to atrophic chronic gastritis in the European dyspeptic population (n=235)

	NACG		ACG		Unadjusted OR	95% CI
	n	%	n	%		
Anti-CagA						
Negative	56	83.6	11	16.4	1	—
Positive	117	69.6	51	30.4	2.22	1.1–4.6
Anti-VacA						
Negative	121	78.1	34	21.9	1	—
Positive	52	65.0	28	35.0	1.92	1.1–3.5
Anti-CagA-anti-VacA						
CagA and VacA neg	45	81.8	10	18.2	1	—
CagA pos only	76	76.0	24	24.0	1.42	0.6–3.2
VacA pos only	11	91.7	1	8.3	0.41	0.1–3.5
CagA and VacA pos.	41	60.3	27	39.7	2.96	1.3–6.9

NACG, non-atrophic chronic gastritis; ACG, atrophic chronic gastritis; OR, odds ratio; 95% CI, 95% confidence interval.

different foods were analysed using the mean (SEM). Consumption of vegetables and fruit, potatoes, pork, other meats, fish, smoked protein, raw animal protein, cooked vegetable protein, spicy foods, salt, and vitamin C were considered independently. No association was observed between types of food or quantity intake and the presence of ACG. Therefore, construction of a multivariate intermediate model was unnecessary, and none of these variables was included in the final model.

Analysis of markers of *H pylori* pathogenicity

A total of 71.5% of patients had antibodies against the CagA antigen and 34.0% against the VacA antigen (n=235). Most patients with anti-VacA antibodies also had anti-CagA antibodies (68/80 (85%)), and in 55/67 (82%) with no anti-CagA antibodies, anti-VacA antibodies were also absent. A VacA positive-CagA negative profile only occurred in 12/235 (5%) patients. Twenty seven of 68 patients (40%) with anti-CagA and anti-VacA antibodies had ACG compared with 10 of 55 (18%) without the antibodies (OR 3.2, 95% CI 1.4–7.4) (table 3); CagA positive-VacA negative (OR 1.42, 95% CI 0.6–3.2) and VacA positive-CagA negative (OR 0.41, 95%CI 0.1–3.5) cases did not show any association with ACG. Multivariate intermediate analysis was performed, and only one variable was considered from the results of table 3: the combination of anti-CagA and anti-VacA antibodies.

Multivariate analysis

Multivariate analysis included all variables associated with ACG, at a p value ⩽0.05, in the intermediate models. The following variables were included: age 60 or less or over 60 years, sex, consumption of coffee, consumption of tranquillisers or sleeping tablets, stress score (dichotomised as 0–5 *v* 6–12), and anti-CagA and anti-VacA antibody status. All except sex remained significantly associated with the presence of ACG compared with NACG (table 4).

Risk factors were: age over 60 years (OR 4.14, 95% CI 1.79–9.58), consumption of coffee (OR 2.35, 95% CI 1.07–5.16), consumption of tranquillisers or sleeping tablets (OR 2.17, 95% CI 1.04–4.52), and the presence of CagA and VacA antibodies (OR 3.02, 95% CI 1.26–7.56). The presence of anxiety had an inverse effect: patients with a of score 6–12 versus

Table 4 Final logistic regression model for atrophic chronic gastritis in the European dyspeptic population (n=234)

	Unadjusted OR*	Adjusted OR*	95% CI	p Value
Age (over 60 y *v* ⩽60 y)	3.64	4.14	1.79–9.58	0.001
Sex (male *v* female)	0.74	1.09	0.55–2.14	0.809
Coffee consumption (yes *v* no)	2.10	2.35	1.07–5.16	0.033
Sleeping tablet or tranquilliser intake (yes *v* no)	1.72	2.17	1.04–4.52	0.038
Stress score (6–12, anxious *v* 0–5, not anxious)	0.53	0.45	0.21–0.99	0.038
Anti-CagA-anti-VacA (*v* both neg)				
CagA positive VacA negative	1.42	1.39	0.58–3.34	0.454
VacA positive CagA negative	0.41	0.32	0.03–3.06	0.324
CagA and VacA positive	2.96	3.09	1.26–7.56	0.013

OR, odds ratio; 95% CI, 95% confidence interval.
*OR adjusted on all variables of the models.

those with a score of 0–5 had a lower risk of atrophy (OR 0.45, 95% CI 0.21–0.99).

No interaction was identified, particularly between age and the presence of specific antibodies.

DISCUSSION

The onset of ACG is a dynamic process and needs to be followed over time. However, this cross sectional study revealed important factors associated with the presence of ACG in a European population presenting with non-ulcer dyspepsia and chronic gastritis on histology and infected with *H pylori*.

We revealed similar environmental and lifestyle factors related to the presence of ACG, as in other studies.[26–29] In this analysis, the comparator group did not comprise healthy asymptomatic individuals without gastritis and this may have biased the findings. Environmental factors may only have a limited role in the presence of ACG in this study population.

The study emphasised the important role of the pathogenic properties of CagA and VacA of the *H pylori* strain as determinants of ACG. However, the effect of the presence of anti-VacA or anti-CagA antibodies alone on the risk of ACG could not be evaluated due to the small sample size. Most patients with anti-CagA antibodies also had anti-VacA antibodies. Only one patient had ACG and only anti-VacA antibodies. The risk of atrophy was greater when both antibodies were present. This is in agreement with previous studies that have reported an association between anti-CagA antibodies, as a marker of strain virulence, and ACG.[30–34] Currently, few data are available on anti-VacA antibodies as a marker of virulence. It is known that toxin production is dependent on the particular type of gene alleles; for example, strains with the s1m1 genotype are known to produce high amounts of VacA toxin in vitro.[35] The *vacA* gene is always present in *H pylori* while anti-VacA antibodies are present in only a small proportion of infected patients,[35] possibly because antibodies occur only when the amount of toxin produced is high enough to stimulate an immune response. This test may therefore be a pragmatic way to evaluate the production of toxin in vivo.

Serology was performed in this study to avoid as much as possible false negative results of the invasive tests (culture and histology) when ACG was present.[36] *H pylori* serology has been shown to be reliable in the presence of atrophy whereas invasive tests are not.[37] Although bias could not be avoided, inclusion bias in particular, this population is as close as possible to any *H pylori* infected population consulting for dyspepsia in a gastroenterology department and in whom ACG or NACG has been diagnosed. Furthermore, no differences were found between patients included and patients analysed according to the variables studied. To minimise potential centre bias, the country of origin was taken into account in the univariate analysis. No association was found between the variable "country of origin" and the presence of ACG, allowing its division into three groups according to the estimated risk of exposure to *H pylori* infection: Western Europe, Eastern Europe, and other (Iran, Turkey, Africa, and the French West Indies).

Among the sociodemographic variables, apart from age (as expected), no variable was found to modify the odds for ACG. The question remains whether the effect of age on ACG is a cohort effect linked to the dynamics of *H pylori* infection[38] or simply the effect of ageing on the gastric mucosa. One possible explanation for the absence of an association with sociodemographic variables is that, in this study, all patients were infected with *H pylori*. This tends to reduce heterogeneity with regard to exposure to the potential risk factors during childhood. Although the principal recruitment criterion of these patients was the presence of chronic gastritis and not *H pylori* infection, all 272 patients recruited with chronic gastritis, except five, were infected by this bacterium (among these five, four had NACG and one had ACG).

Several previous studies have suggested that the relationship between gastric cancer and family history may be due to genetic factors,[39–43] environmental factors operating in childhood and early adult life,[44] or clustering of *H pylori* infection.[45] In 1986, Bonney *et al* demonstrated that ACG is linked to age and to a history of maternal ACG[46] but this has not been confirmed by others.[47 48] Furthermore, it is suggested that mothers play an important role in the transmission of *H pylori*. In the present study, the effect of a family history of gastric cancer may be masked by the fact that only *H pylori* positive patients with chronic gastritis were enrolled.

The absence of any association between ACG and diet is difficult to explain. There are conflicting reports in the literature.[10 26 27 49] Europe is relatively small and diet is rather homogeneous, principally among urban dwellers. For instance, 89% of patients in the present study ate raw vegetables or fruit at least once a day while 77% had animal protein at least twice per week. From a global stance, the present dyspeptic study population appeared to have a well balanced diet. The questionnaire on diet was designed to make it simple, easy to administer, and easy to answer. This questionnaire was not as detailed as those used by nutritionists and only gave an approximation of dietary factors.

A positive association between stomach cancer and smoking habits was found although the effect was not as strong as in the more usual smoke related cancers.[50–52] The role of smoking in ACG is still a subject of debate. Some studies suggest a relationship[10] while most do not.[28 27] While smoking was not found to be associated with the presence of ACG in this study, we cannot exclude the fact that it may be associated with evolution from ACG to gastric cancer, as has been found in other studies.[10] Jedrychowski and colleagues[53] have emphasised the importance of alcohol and smoking in the transition from gastritis to IM. In the present study, alcohol consumption was not found to be associated with ACG. The number of answers to questions concerning alcohol consumption did not permit analysis of the number of alcohol units drunk over a period of time. Indeed, patients self estimated the number of

alcohol units drunk only if they were daily or weekend drinkers: 14 of 266 patients claimed to be daily drinkers, and 26 weekend drinkers. The protective effect of anxiety and, in particular, in patients taking tranquillisers or sleeping tablets, may be worth exploring in relation to the presence of ACG. It could be linked to secretion of hormones having a protective effect on the gastric mucosa[54] or to a simple sampling effect. Another limitation is the anxiety scale used which was originally created by clinicians for symptomatic volunteers and ambulatory patients enrolling in clinical trials.[20 21 55 56]

In 1986, Sipponen and colleagues[6] noted that both antral and corpus atrophy were independent risk factors for gastric cancer. In their study, the OR for antral atrophy was approximately 18 and that for corpus atrophy 3–6. Indeed, the presence of severe panatrophy (atrophy both in the antrum and corpus) multiplied the marginal risk, and the OR for cancer increased by up to 80–90. In the present study, subgroup analysis was impossible because of the limited number of relevant cases and therefore antral and corpus atrophy were regrouped as one entity (ACG). The dynamics of *H pylori* gastritis suggest that its progression to ACG occurs at a rate of 1–2% per year and continues at the same rate from one grade of ACG to the next.[1 57]

More than half of infected subjects develop some degree of ACG during their lifetime[58] but despite the fact that ACG is a premalignant condition, very few patients develop gastric cancer.[59] Some cases of ACG may even regress.[60 61] It seems plausible that the factors associated with the presence of ACG may be, at least partly, different from those associated with the presence of gastric cancer. Despite this, most studies on risk factors for ACG or gastric cancer have evaluated the same factors.

Indeed, if the presence of strains inducing anti-CagA or anti-VacA antibodies increases the OR for ACG, it is possible that other unknown bacterial pathogenic factors, unexplored environmental factors, or specific host genetic factors[46 62–67] may be involved.

In conclusion, the present observations of a European dyspeptic population with chronic gastritis indicate that the risk of presenting with ACG was enhanced by the simultaneous presence of anti-CagA and anti-VacA antibodies. Our findings also support the fact that most differences between NACG and ACG patients, when *H pylori* infection was not taken into account, may have been due to differences in exposure to the risk factors for the infection. However, the current results were derived from a cross sectional study and therefore should be confirmed in a prospective analysis of the cohort after three years of observation.

APPENDIX

The Eurohepygast Study Group

Project leader

Francis Mégraud

Study coordinator

Nathalie Broutet

Steering Committee

Colm O'Morain, President (Dublin, Ireland), Pentti Sipponen (Espoo, Finland), Ashley Price (London, UK), Peter Malfertheiner (Magdeburg, Germany), Anthony Moran (Galway, Ireland), Francis Mégraud (Bordeaux, France), Nubia Munoz (Lyon, France), Françoi Dabis (Bordeaux, France), Nathalie Broutet (Bordeaux, France).

Centralised facilities

N Figura (Siena, Italy), S Hynes (Galway, Ireland), A Moran (Galway, Ireland), M Plebani (Padova, Italy), A Price (London, UK), P Sipponen (Espoo, Finland), T Wadström (Lund, Sweden).

Data analysis

C Sakarovitch, F Nachit (Bordeaux, France).

Participants

I M Arenas (San Sebastian, Spain), A Blasi (Catania, Italy), J F Bretagne (Rennes, France), S Chaussade (Paris, France), J C Delchier (Créteil, France), J D De Korwin (Nancy, France), D Duda (Wroclaw, Poland), J Dzieniszewski (Warsaw, Poland), B Fixa (Hradec Kralové, Czech Republic), J Gisbert (Madrid, Spain), A Goldis (Timisoara, Roumania), J Guerre, (Paris, France), L Hryniewiecki (Poznan, Poland), G Inserra (Catania, Italy), A L Karvonen (Espoo, Finland), Z Knapik (Wroclaw, Poland), H Kolke (Tartu, Estonia), H Lamouliatte (Bordeaux, France), A Le Coustumier (Nancy, France), K Linke (Poznan, Poland), J Lonovics (Szeged, Hungary), H Maaroos (Tartu, Estonia), P Malfertheiner (Magdeburg, Germany), S Michopoulos (Athens, Greece), J Monés (Barcelona, Spain), C O'Morain (Dublin, Ireland), J G Pajarés, (Madrid, Spain), L Paradowski (Wroclaw, Poland), U Peitz (Magdeburg, Germany), S Pinto (Lisboa, Portugal), M Quina (Lisboa, Portugal), G Trautmann (Nancy, France), K Tchernev (Sofia, Bulgaria).

ACKNOWLEDGEMENTS

Source of funding: Biomed 1 Program of the European Community and a complementary grant from Glaxo Wellcome Laboratories.

REFERENCES

1 **Siurala M**, Varis K,Wiljasalo M. Studies of patients with atrophic gastritis: a 10–15-year follow-up. *Scand J Gastroenterol* 1966;**1**:40–8.
2 **Kirkpatrick JR**, Davis GT, Jacobs A, *et al*. The recognition of atrophic gastritis. *Br J Surg* 1969;**56**:742–6.
3 **Correa P**, Cuello C, Duque E. Carcinoma and intestinal metaplasia of the gastric mucosa in Colombian migrants. *J Natl Cancer Inst* 1970;**44**:297–306.
4 **Strickland RG**, MacKay IR. A reappraisal of the nature and significance of chronic atrophic gastritis. *Am J Dig Dis* 1973;**18**:426–40.
5 **Correa P**. The epidemiology and pathogenesis of chronic gastritis: three etiologic entites. *Front Gastrointest Res* 1980;**6**:98–108.
6 **Sipponen P**, Kekki M, Haapakoski J, *et al*. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. *Int J Cancer* 1985;**35**:173–7.
7 **Parsonnet J**. The incidence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1995;**9**:45–51.
8 **Broutet N**, Gisbert J, Pajares J. Epidemiology of *H. pylori* infection. *Curr Opin Gastroenterol (The Year in Helicobacter pylori)* 1999;**15**(suppl 1):43–8.
9 **Blaser MJ**. Intrastrain differences in *Helicobacter pylori*: A key question in mucosal damage? *Ann Med* 1995;**27**:559–63.
10 **Fontham E**, Zavala D, Correa P, *et al*. Diet and chronic atrophic gastritis: a case-control study. *J Natl Cancer Inst* 1986;**76**:621–7.
11 **Fontham ET**, Ruiz B, Perez A, *et al*. Determinants of *Helicobacter pylori* infection and chronic gastritis. *Am J Gastroenterol* 1995;**90**:1094–101.
12 **Tytgat G**. The Sydney system: endoscopic division. Endoscopic appearances in gastritis/duodenitis. *J Gastroenterol Hepatol* 1991;**6**:223–34.
13 **Dixon MF**, Genta R, Yardley JH, *et al*. Classification and grading of gastritis: the updated Sydney system. *Am J Surg Pathol* 1996;**20**:1161–81.
14 **Price AB**. The Sydney system: Histological division. *J Gastroenterol Hepatol* 1991;**6**:209–22
15 **Mégraud F**, Lehn N, Lind T, *et al*. Antimicrobial susceptibility testing of *Helicobacter pylori* in a large multicenter trial: the MACH 2 study. *Antimicrob Agents Chemother* 1999;**43**:2747–52.
16 **Granberg C**, Mansikka A, Lehtonen OP, *et al*. Diagnosis of *Helicobacter pylori* infection by using pyloriset EIA-G and EIA-A for detection of serum immunoglobulin G (IgG) and IgA antibodies. *J Clin Microbiol* 1993;**31**:1450–3.
17 **Yamaoka Y**, Kodama T, Graham DY, *et al*. Comparison of four serological tests to determine the CagA or VacA status of *Helicobacter pylori* strains. *J Clin Microbiol* 1998;**36**:3433–4.
18 **Figura N**, Cetta F, Angelico M, *et al*. Most *Helicobacter pylori*-infected patients have specific antibodies, and some also have *H. pylori* antigens and genomic material in the bile: Is it a risk factor for gallstone formation? *Dig Dis Sci* 1998;**43**:854–62.
19 **Heikkinen M**, Janatuinen E, Mayo K, *et al*. Usefulness of anti-*Helicobacter pylori* and anti-CagA antibodies in the selection of patients for gastroscopy. *Am J Gastroenterol* 1997;**92**:2225–9.
20 **Covi L**, Lipman R, McNair DM, *et al*. Symptomatic volunteers in multicenter drug trials. *Prog Neuropsychopharmacol* 1979;**3**:521.
21 **Lipman R**, Covi L. Outpatient treatment of neurotic depression: medication and group psychotherapy. In: Spitzer RL, Klein DF, eds. *Evaluation of the psychological therapies*: Baltimore: Johns Hopkins University, 1976.
22 **Goran MI**, Allison DB, Poehlman ET. Issues relating to normalization of body fat content in men and women. *Int J Obes Relat Metab Disord* 1995;**19**:638–43.
23 **The World Health Organization MONICA Project**. Ecological analysis of the association between mortality and major risk factors of cardiovascular disease. *Int J Epidemiol* 1994;**23**:505–16.

24 **Robert C**. *Analyse descriptive multivariée—Application à l'intelligence artificielle*. Paris, France: Flammarion, 1989.
25 **Hosmer DW**, Lemeshow S. Model-building strategies. In: Sons JW, ed. *Applied logistic regression*. New York: A Wiley Interscience Publication, 1989:82–134.
26 **Kuwahara Y**, Kono S, Eguchi H, *et al*. Relationship between serologically diagnosed chronic atrophic gastritis, *Helicobacter pylori*, and environmental factors in Japanese men. *Scand J Gastroenterol* 2000;**35**:476–81.
27 **Namekata T**, Miki K, Kimmey M, *et al*. Chronic atrophic gastritis and *Helicobacter pylori* infection among Japanese Americans in Seattle. *Am J Epidemiol* 2000;**151**:820–30.
28 **Ozasa K**, Kurata JH, Higashi A, *et al*. *Helicobacter pylori* infection and atrophic gastritis—A nested case-control study in a rural town in Japan. *Dig Dis Sci* 1999;**44**:253–6.
29 **Watanabe Y**, Ozasa K, Higashi A, *et al*. *Helicobacter pylori* infection and atrophic gastritis. A case-control study in a rural town of Japan. *J Clin Gastroenterol* 1997;**25**:391–4.
30 **Kuipers EJ**, Perez-Perez GI, Meuwissen SGM, *et al*. *Helicobacter pylori* and atrophic gastritis: Importance of the cagA status. *J Natl Cancer Inst* 1995;**87**:1777–80.
31 **Maaroos HI**, Vorobjova T, Sipponen P, *et al*. An 18-year follow-up study of chronic gastritis and *Helicobacter pylori* association of CagA positivity with development of atrophy and activity of gastritis. *Scand J Gastroenterol* 1999;**34**:864–9.
32 **Oksanen A**, Sipponen P, Karttunen R, *et al*. Atrophic gastritis and *Helicobacter pylori* infection in outpatients referred for gastroscopy. *Gut* 2000;**46**:460–3.
33 **Blaser MJ**, Perez-Perez GI, Kleanous H, *et al*. Infection with *Helicobacter pylori* strains possessing *cagA* is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res* 1995;**55**:2111–15.
34 **Torres J**, Perez-Perez GI, Leal-Herrera Y, *et al*. Infection with CagA+ *Helicobacter pylori* strains as a possible predictor of risk in the development of gastric adenocarcinoma in Mexico. *Int J Cancer* 1998;**78**:298–300.
35 **Atherton JC**, Cao P, Peek RM, *et al*. Mosaicism in vacuolating cytotoxin alleles of *Helicobacter pylori*—Association of specific *vacA* types with cytotoxin production and peptic ulceration. *J Biol Chem* 1995;**270**:17771–7.
36 **Karnes WEJ**, Samloff IM, Siurala M, *et al*. Positive serum antibody and negative tissue staining for *Helicobacter pylori* in subjects with atrophic body gastritis. *Gastroenterology* 1991;**101**:167–74.
37 **Kokkola A**, Rautelin H, Puolakkainen P, *et al*. Diagnosis of *Helicobacter pylori* infection in patients with atrophic gastritis: Comparison of histology, C-13-urea breath test, and serology. *Scand J Gastroenterol* 2000;**35**:138–41.
38 **Sipponen P**, Kimura K. Intestinal metaplasia, atrophic gastritis and stomach cancer: trends over time. *Eur J Gastroenterol Hepatol* 1994;(suppl 1):S79–83.
39 **Brenner H**, Arndt V, Sturmer T, *et al*. Individual and joint contribution of family history and *Helicobacter pylori* infection to the risk of gastric carcinoma. *Cancer* 2000;**88**:274–9.
40 **Lissowska J**, Groves FD, Sobin LH, *et al*. Family history and risk of stomach cancer in Warsaw, Poland. *Eur J Cancer Prev* 1999;**8**:223–7.
41 **Nagase H**, Ogino K, Yoshida I, *et al*. Family history-related risk of gastric cancer in Japan: a hospital-based case-control study. *Jpn J Cancer Res* 1996;**87**:1025–8.
42 **Palli D**, Galli M, Caporaso E, *et al*. Family history and risk of stomach cancer in Italy. *Cancer Epidemiol Biomarkers Prev* 1994;**3**:15–18.
43 **El-Omar E**, Carrington M, Chow W, *et al*. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000;**404**:398–402.
44 **Zhao L**, Blot W, Liu W, *et al*. Familial predisposition to precancerous gastric lesions in a high-risk area of China. *Cancer Epidemiol Biomarkers Prev* 1994;**3**:461–4.
45 **El-Omar E**, Oien K, Murray LS, *et al*. Increased prevalence of precancerous changes in relatives of gastric cancer patients: crtitical role of *H. pylori*. *Gastroenterology* 2000;**118**:22–30.
46 **Bonney GE**, Elston RC, Correa P, *et al*. Genetic etiology of gastric carcinoma: chronic atrophic gastritis. *Genet Epidemiol* 1986;**3**:213–24.
47 **Kekki M**, Siurala M, Ihamaki T. Enrichment of combined antral and corpus atrophic gastritis ("combined AG") in sibs of gastric carcinoma patients. *Scand J Gastroenterol* 1991;**26**:24–8.
48 **Rothenbacher D**, Bode G, Berg G, *et al*. *Helicobacter pylori* among preschool children and their parents: Evidence of parent-child transmission. *J Infect Dis* 1999;**179**:398–402.
49 **Inoue M**, Tajima K, Kobayashi S, *et al*. Protective factor against progression from atrophic gastritis to gastric cancer—Data from a cohort study in Japan. *Int J Cancer* 1996;**66**:309–14.
50 **Mizoue T**, Tokui N, Nishisaka K, *et al*. Prospective study on the relation of cigarette smoking with cancer of the liver and stomach in an endemic region. *Int J Epidemiol* 2000;**29**:232–7.
51 **Doll R**, Peto R, Wheatley K, *et al*. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;**309**:901–11.
52 **Tredaniel J**, Boffetta P, Buiatti E, *et al*. Tobacco smoking and gastric cancer: review and meta-analysis. *Int J Cancer* 1997;**72**:565–73.
53 **Jedrychowski W**, Popiela T, Drews M, *et al*. Effect of *Helicobacter pylori* infection, smoking and dietary habits on the occurrence of antrum intestinal metaplasia. Clinico-epidemiological study in Poland. *Pol J Pathol* 1999;**50**:289–95.
54 **Fixa B**, Komarkova O, Herout V. The beneficial effect of corticosteroids in a patient with simple atrophic gastritis. A case report. *Scand J Gastroenterol* 1967;**2**:269–74.
55 **Lecrubier Y**, Lancrenon S, Ghozlan A. Description selon le DSM III et diagnostic "intuitif" de 1298 déprimés suivis en ambulatoire par des psychiatres français. *Psychiatr Psychobiol* 1986;**1**:75–83.
56 **Derogatis LR**, Covi L, Lipman RS, *et al*. Dimensions of outpatient neurotic pathology: comparison of a clinical versus an empirical assessment. *J Consult Clin Psychol* 1970;**34**:164–71.
57 **Kuipers E**, Meijer G. *Helicobacter pylori* gastritis in Africa. *Eur J Gastroenterol Hepatol* 2000;**12**:601–3.
58 **Valle J**, Kekki M, Sipponen P, *et al*. Long-term course and consequences of *Helicobacter pylori* gastritis—Results of a 32-year follow-up study. *Scand J Gastroenterol* 1996;**31**:546–50.
59 **Sipponen P**, Hyvärinen H, Seppälä K, *et al*. Review article: pathogenesis of the transformation from gastritis to malignancy. *Aliment Pharmacol Ther* 1998;**12**:61–71.
60 **Correa P**, Haenszel W, Cuello C, *et al*. Gastric precancerous process in a high risk population: cohort follow-up. *Cancer Res* 1990;**50**:4737–40.
61 **Kokkola A**, Haapiainen R, Laxen F, *et al*. Risk of gastric carcinoma in patients with mucosal dysplasia associated with atrophic gastritis: a follow up study. *J Clin Pathol* 1996;**49**:979–84.
62 **Capuzzi D**, Santoro E, Hauck WW, *et al*. Fhit expression in gastric adenocarcinoma—Correlation with disease stage and survival. *Cancer* 2000;**88**:24–34.
63 **Yu J**, Miehlke S, Ebert MPA, *et al*. Frequency of TPR-MET rearrangement in patients with gastric carcinoma and in first-degree relatives. *Cancer* 2000;**88**:1801–6.
64 **Sakai T**, Aoyama N, Satonaka K, *et al*. HLA-DQB1 locus and the development of atrophic gastritis with *Helicobacter pylori* infection. *J Gastroenterol* 1999;**34**(suppl 11):24–7.
65 **Baffa R**, Veronese ML, Santoro R, *et al*. Loss of FHIT expression in gastric carcinoma. *Cancer Res* 1998;**58**:4708–14.
66 **Kato S**, Onda M, Matsukura N, *et al*. Genetic polymorphisms of the cancer related gene and *Helicobacter pylori* infection in Japanese gastric cancer patients: An age and gender matched case-control study. *Cancer* 1996;**77**:1654–61.
67 **Correa P**, Fox J, Fontham E, *et al*. *Helicobacter pylori* and gastric carcinoma. *Cancer* 1990;**66**:2569–74.