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Gastric carcinoma risk index in patients infected with *Helicobacter pylori*

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Abstract Epidemiological data show an association between *Helicobacter pylori* gastritis and gastric carcinoma. However, most people infected with *H. pylori* do not develop gastric cancer. We have therefore evaluated histological criteria indicating an increased risk for gastric cancer. *H. pylori* gastritis was investigated in 117 patients with small (∅<2 cm) early gastric carcinomas and in 117 age-matched duodenal ulcer patients infected with *H. pylori*, who are known to have a low risk for developing gastric carcinoma. The results showed that infiltration with lymphocytes/plasma cells and infiltration with neutrophils predominating in the corpus, and intestinal metaplasia in antrum and corpus were associated with both types of gastric carcinoma (intestinal and diffuse, $P< 0.0001$). If an index is computed by giving one point to each of these features, the predictive value for the presence of gastric carcinoma was 0.79 with a score of 2, and 0.94 with a score of 3 (all points on the index used). Application of this index might be a simple method of identifying patients infected with *H. pylori* and carrying a higher risk for gastric carcinoma.

Key words Gastritis · Cancer · *Helicobacter pylori* · Cancer risk

This paper is dedicated to Professor Dr. Kurt Elster, pioneer of gastroenterological pathology in Europe, on the occasion of his 80th birthday

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Introduction

The results of sero-epidemiological studies investigating the relationship between *Helicobacter pylori* (*H. pylori*) serum IgG antibodies and the incidence of gastric carcinoma have suggested that chronic infection with *H. pylori* is associated with an elevated risk of developing gastric carcinoma [4, 8, 13]. However, there is a striking contrast between the number of persons infected with *H. pylori* and those subsequently developing gastric cancer. In the US population, 30–40% are reported to be infected with *H. pylori*, but less than 1% of these will develop gastric cancer [8, 12].

With this huge contrast in mind, the question arises of whether treatment of the infection to prevent gastric cancer is a sensible undertaking. It has been noted in a report by Parsonnet et al. that screening and treatment for *H. pylori* infection can be cost-effective only in populations with a comparatively high risk of gastric cancer [14].

Fiocca et al. and our group have been able to show that the expression of *H. pylori*-associated gastritis in patients with gastric cancer is high in the corpus and is frequently associated with intestinal metaplasia and atrophy [3, 11]. We considered whether *H. pylori* gastritis differs in two populations with contrasting risks for developing gastric cancer, in the hope of establishing common histological criteria that could be used to identify *H. pylori*-infected persons who have an increased risk of developing gastric carcinoma.

Methods

Between January 1991 and January 1995, a study was performed to investigate *H. pylori* gastritis prospectively in patients undergoing gastrectomy for early gastric cancer. After termination of the study, 190 *H. pylori*-infected patients with small early gastric carcinoma not exceeding 2 cm in diameter (as determined macroscopically by measurement of the size of the tumour) were evaluated. The patients with either diffuse-type or intestinal-type carcinoma were matched with *H. pylori*-infected duodenal ulcer patients by age (± 2 years) and gender. Since we were not able to find a corresponding control patient for every cancer patient, 73 cancer patients had to be excluded from analysis at a later time. The mean age of the remaining 117 patients was 59.98 years (SD of mean: 11.69), and that of the 117 matched duodenal ulcer patients, 57.94 years (SD of mean: 9.12). All control patients were recruited from a group of duodenal ulcer patients who were examined during the same time period at the Pathology Institute at Bayreuth. Matching was done by workers who were blind to the gastritis diagnosis.

Expression of gastritis in duodenal ulcer patients was evaluated in four biopsy specimens obtained at endoscopy, whereas in patients with early gastric carcinoma four 2-mm biopsy specimens were cut out from each gastrectomy specimen, two samples from the antrum (2 cm away from the pylorus), and two from the corpus (greater curvature, middle third). Specimens with infiltrating tumour cells were excluded from the evaluation. In five patients, the histological evaluation of gastritis was therefore based on only one of the required two antrum or corpus specimens. Paraffin-embedded samples were sectioned and stained with haematoxylin and eosin, as well as with the Warthin-Starry stain to detect *H. pylori* colonisation. All biopsies were examined using a semiquantiative score to measure infiltration with lymphocytes/plasma cells (degree of gastritis) and neutrophils/polymorphs (activity of gastritis) in accordance with the guidelines of the Sydney System [15], but with minor supplementation. The range of this score was from 0 (none) to 4 (high grade) [17]. Intestinal metaplasia, as a marker for gastric atrophy in antrum or corpus, was scored as Yes or No. Notice of presence or absence of intestinal metaplasia was therefore cumulative in antrum and corpus biopsies. All specimens were investigated by one histopathologist (M.S.). Studies of the pathologist intra-observer variation in the grading of the various parameters have previously shown a high degree of reproducibility with kappa coefficients of 0.78 (grade of gastritis), 0.82 (activity of gastritis), and 0.74 (presence of intestinal metaplasia) [unpublished findings].

Statistical calculations were done using the χ^2-test for comparison of the gastritis parameters investigated. Logistic regression analysis was performed using the SPSS 6.1.3 for Windows software package (SPSS, Chicago, USA).

Results

In the early gastric cancer group, 55 patients had an intestinal type and 62 a diffuse type of carcinoma according to the classification of Lauren [9]. Carcinomas were located in 26 cases in the middle third of the stomach, and in 91 cases in the lower third of the stomach. Neither type of carcinoma nor location resulted in significant differences of gastritis parameters (χ^2, $P>0.2$).

The expression of the grade and the activity of gastritis in the corpus was significantly greater in the early gastric cancer group than in duodenal ulcer patients (grade: median score 3 vs 2; activity: 3 vs 1; $P<0.0001$, respectively). There was no such difference in the expression of gastritis in the antrum (grade: median score 3 vs 3; activity: 3 vs 3).

However, when instead of the grading of gastritis per se, we considered rather the antrum/corpus ratio of the inflammatory response in the two groups, we found that infiltration with lymphocytes/plasma cells in the corpus was greater than or equal to the infiltration in the antrum in 53.8% of the patients with early gastric cancer (diffuse type: 40.3%, intestinal type: 69.1%) and in only 12.8% of the patients with duodenal ulcers (χ^2, $P<0.0001$). Also, neutrophil infiltration in the corpus was more pronounced or at least equal to that in the antrum in 55.5% of the early gastric cancer group (diffuse type: 46.8%, intestinal type: 65.5%) and in only 13.7% of the duodenal ulcer group ($P<0.0001$). Intestinal metaplasia was present in 68.4% of all patients with cancer (diffuse type: 56.5%, intestinal type: 85.5%) and 28.2% of those with duodenal ulcer ($P<0.0001$). Seventeen patients with gastric carcinoma had intestinal metaplasia in both regions of the stomach, whereas in all other patients with intestinal metaplasia it was located in the antrum only.

On the basis of these highly significant results, a logistic regression analysis was done, which showed that the rounded standardised coefficients were similar for all three features. Therefore, we developed a gastric carcinoma risk index assigning one point to each of these factors (Table 1). The predictive values for gastric carcino-

Table 2 Number of patients and predictive values for the presence of gastric carcinoma as a function of the number of points scored on the index (*DU* duodenal ulcer, *EGC* early gastric carcinoma: diffuse and intestinal type)

	DU	EGC		Predictive Value	
		Diffuse	Int. type	Diffuse	Int. type
No points	68	12		0.166	
		11	1	0.254	0.061
One point	35	37		0.464	
		23	14	0.518	0.389
Two points	13	33		0.791	
		18	15	0.771	0.815
Three points	1	35		0.943	
		10	25	0.915	0.973

Table 1 Gastric cancer risk index in patient infected with *Helicobacter pylori*

Finding	Score
1. Infiltration with lymphocytes/plasma cells is more pronounced in the corpus mucosa than in the antral mucosa, or at least equally distributed	1 point
2. Infiltration with neutrophils/polymorphs is more pronounced in the corpus mucosa than in the antral mucosa, or at least equally distributed	1 point
3. Presence of intestinal metaplasia in antrum or corpus	1 point

ma (logistic regression analysis) were calculated as a function of the number of points scored on the index, as shown in Table 2.

Discussion

Since we investigated only small early gastric carcinomas, it is very likely that the different expression of *H. pylori*-associated gastritis in this group precedes gastric carcinoma rather than simply being concomitant with it. We therefore believe that high-grade corpus gastritis in association with intestinal metaplasia are markers for an increased risk of development of both types of gastric carcinoma.

A review of the literature shows that intestinal metaplasia is a precursor in a sequence leading to gastric cancer of the intestinal type [2], or is at least associated with early malignant changes of the mucosa [7]. However, only very sparse data are available about possible precursor lesions for gastric cancer of the diffuse type.

Sipponen et al. suggested that *H. pylori*-induced corpus gastritis might be associated with an increase in gastric pH [16], which might then lead to decreased intragastric levels of ascorbic acid and to production of *N*-nitroso compounds as a result of bacterial overgrowth in the stomach, thus setting the scene for both types of gastric cancer [10]. Axon and Lynch, however, thought that an increased pH might result in a suppressed defence mechanism against de-differentiated epithelium – since atypical cells are very acid sensitive – and thereby lead to persistence of atypical cells and progression of the atypia [1].

However, although epidemiological data strongly suggest that *H. pylori* is involved in the development of gastric carcinoma [4, 8, 13], antimicrobial treatment of all infected patients does not seem feasible, mainly for economic reasons. In addition, widespread uncritical use of antibiotics may give rise to the major problem of increasing resistance rates. Hence, to date, treatment of the infection is recommended mainly in patients with peptic ulcer disease, who are only a minority of all those infected. It therefore seems necessary to develop criteria for identifying those who have no peptic ulcers but who are possibly at an increased risk of developing gastric carcinoma. We believe that the proposed gastric carcinoma risk index (Table 1) may be a useful tool in solving this clinical problem, particularly, since the total number of patients who meet the selection criteria for gastric cancer prevention by curing the *H. pylori* infection appears to be rather small. When the index was tested prospectively in a German pathology unit it was found that of all the patients with *H. pylori* gastritis alone (n=500, mean age: 57.96 years ± 16.77), only 3% (n=15) scored three points on the index (M. Stolte, unpublished results 1997).

We may be criticised for using duodenal ulcer patients for the development of the suggested gastric cancer risk index rather than patients with *H. pylori* gastritis only. However, our purpose was to establish a method of identifying patients infected with *H. pylori* and having a kind of gastritis that might predispose to gastric cancer, which makes the comparison with duodenal ulcer patients reasonable, since among all those with *H. pylori* infection these patients are known to have a decreased risk of developing gastric cancer [6, 13, 16]. Hence, 'duodenal ulcer gastritis' probably has characteristics that are associated with a lower risk of the development of gastric carcinoma than *H. pylori* gastritis only.

In relation to the histological examination of gastritis, it might also be worth mentioning that since semi-quantitative grading of gastritis is not necessary in determining our three features, the reported bias among histopathologists due to inter-observer variability is also reduced [5]. Hence, the index can be used by all, and standardisation of histopathological examinations appears to be very likely.

We are aware that this index cannot be used to screen the general population. There is no justification for biopsy of the stomach in all patients with *H. pylori* infection, and there is also limited value in general screening for high-risk individuals in view of the costs of endoscopic and histological examinations. Nevertheless, using the proposed gastric cancer risk index might help physicians to give their patients undergoing endoscopy a prognostic statement about the risk of gastric cancer in association with *H. pylori* gastritis. It might help to reduce the uncertainty about which *H. pylori*-infected patients not suffering from peptic ulcer disease should be treated, with the aim of reducing the risk of gastric carcinoma.

Even though data on reduction of intestinal metaplasia – one of the features in our index – following *H. pylori* eradication are sparse and not convincing, the two other features (infiltration of the mucosa with either lymphocytes or neutrophils) have been shown to be reducible after cure of the infection [18]. In addition, according to our data, intestinal metaplasia without the finding of a comparably highly expressed *H. pylori* gastritis in the corpus occurred almost as often in cancer patients as in duodenal ulcer patients (n=26 vs n=25). Hence, we speculate that intestinal metaplasia per se appears to be an indicator of long-standing proliferation (implying a higher risk for the development of gastric cancer in certain conditions) but that it is not necessarily a specific precancerous lesion. However, in the case of an increasing inflammatory response to *H. pylori* in the corpus, treatment of the *H. pylori* infection may lead to a reduced risk of developing either type of gastric cancer. In Germany and Austria, a large prospective gastric cancer prevention trial selecting high-risk patients as defined by our index has recently been started to test this hypothesis.

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