Virchows Arch (2000) 436:585–587

ORIGINAL ARTICLE

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Evaluation of the applicability of the gastric carcinoma risk index for intestinal type cancer in Japanese patients infected with *Helicobacter pylori*

Received: 6 October 1999 / Accepted: 22 December 1999

Abstract The gastric carcinoma risk index is a histological criteria to *Helicobacter pylori*-infected patients with a high risk of gastric cancer. The aim of this study was to examine the applicability of this index for the intestinal-type gastric cancer in Japanese patients with *H. pylori* infection. In 55 patients with early intestinal-type gastric cancer and 69 control subjects, we calculated the gastric cancer risk index score by evaluating the grade of mononuclear cell (MNC) and polymorphonuclear cell (PMN) infiltration and the presence of intestinal metaplasia. The gastric cancer index score was significantly higher in patients with gastric cancer ($P<0.01$). The presence of intestinal metaplasia was significantly more frequent in cancer patients than in controls, while infiltration of MNCs or PMNs in the corpus was not different in the two groups. Within the gastric cancer risk index, the presence of intestinal metaplasia was the only criteria associated with the development of intestinal-type gastric cancer in Japan. The gastric cancer risk index may not be applicable to identify *H. pylori*-positive patients at high risk of developing intestinal-type gastric cancer in Japan.

Key words Gastric cancer risk · *Helicobacter pylori* · Intestinal metaplasia

Introduction

Infection of *Helicobacter pylori* is a well-recognized risk factor for development of gastric cancer [4, 15]; however, most *H. pylori*-infected subjects will not develop gastric cancer [9]. Therefore, it is important to identify patients at high risk of more severe clinical outcome. This is particularly relevant in Japan, because the incidence of gastric cancer is much higher than in Western countries. There is increasing evidence that *H. pylori* strains are highly diverse genomically and that infection of virulent genotype strains has been associated with the development of gastric cancer in Western countries [1, 2]. However, in Japan, since most strains are of a virulent genotype, the bacterial genotype is not a useful marker for prediction of the clinical outcome [5, 17].

Differences in host responses to *H. pylori* infection may also affect the clinical outcome. The gastric carcinoma risk index, proposed by Meining et al., is a histological criteria to define high-risk subjects for gastric cancer in patients with *H. pylori* infection [13]. However, they compared histological gastritis between patients with gastric cancer and duodenal ulcer (DU). Thus, this index might define the high-risk group for DU if it is not different between those patients with gastric cancer and those with only chronic gastritis. Therefore, it should be determined whether this index is able to delineate patients with gastric cancer from patients with chronic gastritis. Since most gastric cancers are of the intestinal type in Japan, we examined the applicability of this index for intestinal-type cancer. Advanced cancer was excluded because the prevalence of *H. pylori* is usually decreased [16] and the degree of inflammatory infiltration in the stomach is possibly affected.

Materials and methods

Patients with intestinal-type gastric cancer in an early stage (excluding cancers in cardia) and control subjects were recruited from the subjects undergoing routine endoscopy at Hirosaki University Hospital between March 1996 and August 1998. Patients and control subjects were included in the study if they were infected with *H. pylori*. Infection of *H. pylori* was considered positive if (1) *H. pylori* was isolated from biopsy specimens or (2) *H. pylori* was serologically and histologically positive. Patients and control subjects were excluded if they had received anti-ulcer agents or anti-

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biotics during the 2 months before the endoscopy or had previous histories of gastric tumor, gastric or duodenal ulcer, or gastric surgery. Full histological diagnosis of the tumor type and stage were undertaken on resected specimens [11]. Early gastric cancer (EGC) was pathologically diagnosed by the growth of tumor confined to the mucosa or submucosa of the stomach [6]. Subjects were considered to be eligible for inclusion as controls when their endoscopic diagnosis was normal or revealed only atrophic gastritis. All cancer patients and control subjects provided their informed consent before their endoscopy, and this study was approved by the ethics committee of Hirosaki University.

In cancer patients and controls, biopsy specimens were obtained from the greater curvature of the antrum and the middle portion of the corpus of the stomach. When the tumors were close to the above-mentioned site, biopsy specimens were taken at least 2 cm away from the tumors. The specimens were embedded in paraffin and stained with hematoxylin and eosin. Also, the Warthin-Starry method was used. Grading of mononuclear cell (MNC) infiltration, polymorphonuclear cell (PMN) infiltration, and intestinal metaplasia were performed by an experienced pathologist (M.T.) according to the updated Sydney System [3]. We compared MNC and PMN infiltration between the corpus and the antrum, and evaluated the presence of intestinal metaplasia to calculate the score of the gastric cancer risk index as described previously [13].

Statistically, chi-square analysis was used to compare the grade of each histological feature between patients and control subjects, and the Mann-Whitney U test was performed to compare the cancer risk index. A P value less than 0.05 was considered statistically significant.

Results

The study included 55 patients with early intestinal-type gastric cancer (mean age 63.4±8.6 years; 43 male and 12 female) and 69 control subjects (mean age 60.8±9.9 years; 37 male and 32 female). The gastric cancer index score was significantly higher in patients with gastric cancer (Table 1, $P<0.01$). Pronounced or equal infiltration of MNCs in the corpus was seen in 41 patients (75%) and 49 control subjects (81%). PMN infiltration was equal or enhanced in the corpus in 38 patients (69%) and 46 controls (67%), respectively. The differences were not statistically significant (Table 2). However, the presence of intestinal metaplasia was 76% in cancer patients, whereas it was only 30% in control subjects ($P<0.001$).

We selected an age- (±3 years) and sex-matched control subject for each cancer patient in order to analyze the data as a case-control study. Similar results were obtained from 41 age- and sex-matched pairs. A higher gastric cancer index score was also observed in patients with gastric cancer (Table 1, $P<0.05$). The proportions of pronounced or equal MNC or PMN infiltration in the corpus was not different between patients and control subjects while intestinal metaplasia was present more frequently in cancer patients (Table 2, $P<0.01$).

Table 1 Number of patients divided by points scored on gastric cancer risk index

	0	1	2	3	*P* value*
Total					
Cancer patients	0	11	22	22	<0.01
Control subjects	11	16	26	16	
Case-control					
Cancer patients	0	9	15	17	<0.05
Control subjects	7	6	19	9	

* Mann-Whitney U test

Discussion

In the present study, we examined the applicability of the gastric carcinoma risk index in Japanese patients with *H. pylori* infection retrospectively. Since most gastric cancers are of the intestinal type in Japan and the risk index includes assessment of intestinal metaplasia, we focused on intestinal-type cancer. As in the previous German study, the index score was significantly higher in patients with intestinal type EGC than in control subjects [13], but there were also differences between the two studies.

Previous Western studies have suggested that severe expression of corpus gastritis is a characteristic in gastric cancer patients infected with *H. pylori* [12, 14]; however, no microbiological investigations were performed in those studies. *H. pylori* strains are highly diverse genomically, and infection of virulent strains is associated with a more severe clinical outcome in Western populations [1, 2]. Thus, bacterial genotypic variation is possibly responsible for the differing degree and distribution of gastritis. In Japan, however, most strains have a virulent genotype [5, 17]. Therefore, patients and control subjects are likely to be exposed to similar virulent factors. The present results suggest that infection with virulent *H. pylori* is associated with corpus dominant gastritis even in patients who do not develop gastric cancer. In a recent Japanese study, higher gastritis scores were observed for fundic mucosa than for pyloric mucosa both in patients with intestinal-type cancer and in control subjects [8]. Severe expression of corpus gastritis does not therefore seem to be a specific characteristic of patients with gastric cancer in Japan.

Table 2 Histological findings for gastric cancer risk index. *MNC* mononuclear cell; *PMN* polymorphonuclear cell

	Total		Matched (n=41)	
	Cancer (n=55)	Control (n=69)	Cancer	Control
Corpus dominant MNC infiltration (yes/no)	41/14	49/20	31/10	29/12
Corpus dominant PMN infiltration (yes/no)	38/17	46/23	30/11	28/13
Presence of intestinal metaplasia (yes/no)	42/13*	21/48	29/12*	14/27

* Significantly different from control subjects ($P<0.01$)

Meining et al. [13] calculated the gastric carcinoma risk index using DU patients as the control group. Since infection with virulent *H. pylori* strain is more common both in patients with gastric cancer and in those with DU, the effects of strain diversity might be reduced in their study. However, *H. pylori*-induced gastritis in DU patients is different from that observed in non-ulcer patients. Infiltration of MNC and PMN is greater in the antrum of DU patients than in non-ulcer patients [7]. In DU patients with increased acid secretion, *H. pylori* colonization of the corpus is reduced and this is associated with reduced inflammatory infiltration. It is recognized that *H. pylori*-associated corpus gastritis is increased during acid suppressive therapy [10]. Therefore, it was necessary to examine the value of the gastric carcinoma risk index using adequate control subjects lacking high acid secretion, as suggested by Stachura [18]. Even in case-controlled subjects, our results demonstrated that the frequency of greater MNC and PMN infiltration in the corpus was almost the same in patients with EGC and control subjects. As Japanese subjects have lower acid secretion than Western subjects, corpus predominant gastritis is likely to be characteristic of populations that have a high incidence of gastric cancer and a low incidence of DU. Furthermore, we studied only intestinal-type cancer, so the studied subjects tended to be older than in the German study. Prospective studies using younger populations are required to understand the real values of detecting corpus dominant gastritis.

In contrast to the lack of difference in corpus dominant inflammatory infiltrates, intestinal metaplasia was more frequently observed in patients than in control subjects. Intestinal metaplasia is a well-established risk of intestinal-type gastric cancer in both Western and Asian countries [19]. Since all cancers were of the intestinal type in our study, patients were likely to have extensive intestinal metaplasia. Intestinal metaplasia was frequently present in cancer patients, but the extent of atrophic gastritis was similar in both cancer patients and control subjects. This suggests that individuals with the ability to generate intestinal metaplasia in their atrophic mucosa are at high risk for gastric cancer.

In conclusion, the gastric cancer risk index indicated that the presence of intestinal metaplasia was the only feature which was associated with the development of intestinal-type gastric cancer in Japan. The gastric cancer risk index, therefore, may not be applicable to define patients at high risk of developing intestinal-type gastric cancer in Japan.

Acknowledgement We thank Dr. Jean E. Crabtree for her linguistic advice.

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