Elevated risk for gastric adenocarcinoma can be predicted from histomorphology

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Abstract
The number of patients with gastric cancer has more than doubled since 1985 in developing countries. Thus, the questions of whether it can be predicted from gastritis morphology, who is at risk and who has a lower risk of developing gastric carcinoma are raised. *H. pylori* infection leads to erosions, ulcerations, carcinoma, mucosa associated lymphoid tissue (MALT)-lymphoma and extragastric diseases only in some individuals. The frequency of ulcerations among *H. pylori*-infected individuals is estimated to be 13%, gastric cancer about 1% and MALT lymphoma around 0.1%. In the literature a multistep model from chronic active *H. pylori*-infection through multifocal atrophy, intestinal metaplasia, dysplasia (intraepithelial neoplasia) and carcinoma has been described. But this model cannot be applied to all routine cases. Since risk factors such as metaplasia and atrophy are paracancerous rather than precancerous conditions, this raises the question whether there is a better morphological marker. Differences in topography, grade and activity of Helicobacter gastritis in the antrum and corpus might be better markers for identifying those who are at risk of developing gastric cancer. It is known that the so-called corpus dominant *H. pylori* gastritis is found more frequently among individuals with early and advanced gastric cancer and within high risk populations. This is valid both for first-degree relatives of gastric cancer patients and for patients with gastric adenoma and hyperplastic polyps. In conclusion, corpus-dominant *H. pylori* gastritis is significantly more common in patients with advanced and early gastric cancer, first-degree relatives of patients with gastric cancer, patients with gastric adenoma and gastric hyperplastic polyps. Therefore, all these patients are at risk of developing gastric cancer. Next, the question of who is at risk of developing corpus-dominant gastritis is raised. It appears that patients with a low acid output more frequently develop gastric cancer. Eradication therapy is never performed too early but probably sometimes too late after the patients pass a “point of no return”. Large prospective long term studies are necessary to prove this and identify new reliable markers for gastric cancer development.

INTRODUCTION

*H. pylori* is recognized as the major pathogenetic factor in chronic active gastritis. Chronic active gastritis not only leads to gastric inflammation in various degrees but also can be the cause of gastric and duodenal ulcer disease and might give rise to gastric mucosa associated lymphoid tissue (MALT) lymphoma (marginal B-cell lymphoma). Interestingly, low grade MALT lymphoma regresses after antibiotic treatment for *H. pylori* eradication in a high percentage of cases.

HISTORICAL BACKGROUND

Prior to the morphological identification of *H. pylori* as the causative agent, gastric inflammation had already been considered a risk factor for gastric carcinoma. Correa postulated in 1988[1] that chronic gastritis may lead via a multistep process to intestinal metaplasia and atrophy as an additional morphological risk factor for the development of carcinoma since these are frequently found to be closely related to the intestinal type of gastric cancer. In addition, today it has become clear that at least 50% of all cases of autoimmune atrophic gastritis which is considered to some varying degree as a precancerous condition, are probably induced by *H. pylori*.[2]

EPIDEMIOLOGICAL EVIDENCE

Mortality of gastric cancer is a significant burden not only on patients but also on the whole health system. There are regional differences depending on the geographical location (Table 1). For example, about 360,000 deaths...
occurs due to gastric cancer each year in China with the world largest population[8]. This means that every 2 min one patient dies of gastric cancer in China.

The knowledge on a pathogenetic association between gastric carcinoma and H pylori infection is mainly based on retrospective studies by observing resected stomachs. H pylori gastritis is usually present in gastric mucosa adjacent to cancerous lesions. Furthermore, a statistically significant correlation between the rate of infection and the incidence of gastric cancer has been observed in a number of populations, although in some populations, especially in Africa, such a correlation is not found[4]. Thirdly, case-control studies demonstrated that the risk of developing gastric carcinoma is significantly higher in the presence of H pylori. Such an association is only described for the distal stomach but not for carcinomas in the proximal stomach, that may arise due to an increasing number of Barrett’s esophagus[5,6]. Many of these studies have methodological problems and weakness of data strength. The situation has improved nowadays. At least some prospective studies are available showing that if certain morphological features are present the patients are at risk of developing gastric carcinoma.

In Germany with 80 million inhabitants, more than 26,000 patients suffer from gastric carcinoma[7]. Approximately 50% of them will not survive for 5 years, which underlines the importance of this disease for the health system.

WHO has classified H pylori as a class 1 carcinogen for the development of gastric carcinoma, but only a minority of individuals infected with H pylori develop gastric carcinoma. It is not clear up till now how the complex interaction occurs between host development of neoplasia in some patients but not in the majority of all others. It has long been known that nutritional factors, high salt intake, smoked meat, few vitamins might increase the risk of gastric carcinoma[8]. From our routine practice we know that cancer develops very rarely in normal gastric mucosa. It is of particular interest to identify risk markers capable of predicting the risk of developing gastric carcinoma. Healing of such high risk gastritis can then decrease the risk of developing gastric adenocarcinoma. Before H pylori was re-introduced into medicine as the causative agent for gastritis, it has been known that the presence of multifocal atrophic gastritis with intestinal metaplasia is a risk factor for gastric carcinoma[1]. Interestingly, the diffuse (signet ring cell) type of carcinomas is not covered by such a hypothesis that gastric cancer might develop even in normal gastric mucosa, especially in very young adults, indicating a genetic background in those patients.

**MORPHOLOGICAL FEATURES OF GASTRITIS WITH HIGHER RISK OF DEVELOPMENT OF ADENOCARCINOMA**

Table 1 Gastric cancer mortality in different populations (Modified from Winawer et al[3])

| Countries  | Yr  | Yr  |
|------------|-----|-----|
| Developed  | 2000| 2020|
| Developing | 334,000| 440,000|
| Developing | 543,000| 983,000|

Initial investigations on the topographic aspects of H pylori showed that H pylori colonization is less frequent and activity is less marked in the gastric corpus compared to the gastric antrum[8,9,10,11]. Recent studies including the gastric cardia also suggest that H pylori colonization is denser in the gastric cardia than in the gastric corpus, in turn leading to more pronounced gastritis in this region[11,12]. Nowadays it is well accepted that H pylori colonizes in the whole gastric mucosa. The infection induces chronic active inflammation anywhere in the gastric mucosa. An important task is therefore, to search for bacteria- and host-related factors that favor the development of gastric carcinoma. The results of studies carried out by our group at the end of the 1980s[13] have prompted us to carry further studies in this field.

**Comparison of gastritis scores in antrum and corpus biopsies**

In a matched control study, our group has compared the gastritis score[14] of individuals with NUD, duodenal ulcer, gastric ulcer, MALT-lymphoma and gastric carcinoma. These studies show that patients with chronic active H pylori gastritis, gastric ulcer and duodenal ulcer have significantly lower scores in the corpus than in the antrum, compared to cases of gastric cancer and MALT-lymphoma (Figure 1)[15], but the scores are significantly lower in MALT lymphoma than in gastric cancer.
Comparison of antral and corpus gastritis in patients with gastric carcinoma or duodenal ulcer
In a next step, our group compared the grade and activity of *H pylori* gastritis in the antrum of 215 patients with gastric carcinoma or patients suffering from duodenal ulcer, showing that there are no differences in the grade and activity of antrum mucosa between the two patient groups, but significant differences in the corpus mucosa. The activity and grade of gastritis in the gastric corpus are significantly higher than those in the antrum of patients with gastric carcinoma, but only in a few patients with duodenal ulcer (Figure 2[19]). An additional study showed that intestinal metaplasia occurs significantly more often both in antrum and in corpus of patients with gastric carcinoma[17]. According to Hattori *et al*[19], intestinal metaplasia might only be a paracancerous condition and just an expression of prior or ongoing severe inflammation, but does not cause cancer.

Gastric carcinoma risk index
In 1998, our group proposed a gastric carcinoma risk index based on previously described results. This index score consists of the presence of intestinal metaplasia (1 point) and the grade and activity of gastritis in the corpus. The maximum point is 3 when all features are present (Table 2). The positive predictive value for the presence of gastric carcinoma is 79% for score 2 and 94% for score 3[19]. Leodolter *et al*[19] found that there is a strong relationship between age and the prevalence of so-called high risk gastritis with a score of 3 (Table 3).

Comparison of grade and activity in first degree relatives of gastric carcinoma patients
Due to the lack of large prospective studies, it can be argued that analyses of the topographic grading of *H pylori*-infected gastric mucosa in patients with gastric carcinoma do not allow transfer of the findings to individuals without gastric cancer since it might influence the status of gastric mucosa. Therefore, our group has analyzed a set of 237 first degree relatives of gastric cancer patients and 237 controls with *H pylori* infection alone[20]. The updated Sydney System for histological classification of gastritis[21] consists of a four-scale semiquantitative grading system with values being not present, slight, moderate and marked.

When the risk profile is analyzed by grading the grade and activity of gastritis according to the updated Sydney System (Figure 3), it becomes clear that the first degree relatives of gastric cancer patients do have more severe grade and activity of gastritis (Figure 3), supporting the familial background of gastric cancer.

Gastritis status in patients with gastric adenomas and hyperplastic polyps
Adenomas of the stomach are unequivocal intraepithelial neoplasms that are limited to the gastric epithelium and can be subdivided into low-grade (adenoma) and high grade intraepithelial neoplasia (formerly dysplasia). From our routine practice, we know that the diagnosis of high grade intraepithelial neoplasia is very rare, and that most
reports on follow-up studies of such lesions show that most of these “high grade lesions” are invasive cancers within a few months \[22\], which probably contribute more to diagnostic uncertainty in biopsy specimens than real neoplastic progression. Adenomas can show a polypoid or a flat growth within the gastric epithelium. For gastric adenomas, the adenoma-carcinoma-sequence \[23\] can also be used to represent a precancerous lesion that should be removed completely to avoid progression to cancer \[24\].

In a series of 118 patients with gastric adenomas, our group showed \[25\] that adenomas occur more frequently in patients with autoimmune gastritis but also in patients with \(H. pylori\) gastritis (Figure 4), and a subsequent analysis showed that patients with gastric adenoma have the same distribution of corpus dominant \(H. pylori\) gastritis like patients with early gastric cancer. In a further study, our group analyzed the gastritis status of gastric pyloric gland adenomas which is also a precancerous condition (approximately 30% show invasive carcinoma at the time of first diagnosis), and found that the proportion of atrophic autoimmune gastritis and corpus dominant \(H. pylori\) gastritis is high in elderly women \[26\] (data not shown).

Hyperplastic polyps are also considered a precancerous lesion. A few case series in the literature and our own data \[27\] indicate that hyperplastic polyps bear a risk of malignant transformation between 0.6% and 6.6%. Therefore, these polyps belong to the group of precancerous lesions and should be removed completely. Follow-up studies showed that gastric carcinoma may develop in 8.6% of the patients at other gastric sites \[28\]. As adenomas, hyperplastic polyps arise quite often in autoimmune gastritis. \(H. pylori\) infection is present in 37% of the cases of hyperplastic polyps. Most of these cases also show corpus-dominant \(H. pylori\) gastritis (data not shown) (Figure 5).

**Gastritis status in populations with different risks of developing gastric carcinoma**

A high incidence of gastric carcinoma is present in Fuzhou in China and in Japan, compared to Beijing in China, Thailand and Vietnam. Corpus dominant gastritis is present in Japan and China (Fuzhou), especially in the elderly whereas antrum predominant gastritis is present in Beijing (China), Thailand and Vietnam. These results correlate with the low incidence of gastric adenocarcinoma in Thai, Vietnamese and certain Chinese populations \[29\] (Figure 6). Interestingly, the activity of corpus gastritis increases with age in Japanese individuals while antrum predominant \(H. pylori\) gastritis does not shift to more severe corpus gastritis in Vietnamese, Thai and certain Chinese populations. This is followed by a more severe colonization of \(H. pylori\) in cases of corpus dominant \(H. pylori\) gastritis. In contrast to the literature, we could not confirm the finding of improved antrum gastritis after proton-pump inhibitor...
(PPI) therapy. We have found aggraved corpus gastritis as described in the literature but decreased colonization in the antrum and corpus[30]. This might explain why increased incidence of gastric carcinoma is not reported among the millions of individuals who use acid-suppressive therapy, although corpus dominant H pylori gastritis is treated with PPI. Future prospective studies especially in China with its large background of individual genetic differences and environmental conditions are necessary to investigate the topography of gastritis in different Chinese populations searching for explanations for different incidences of gastric cancer in China as reported in the literature[31]. It has been speculated that differences in environmental factors might provide a crucial clue to all these questions rather than genetic backgrounds[32].

DISCUSSION

Corpus dominant H pylori gastritis is found more frequently in patients with advanced gastric carcinomas, or early gastric carcinomas and even in first degree relatives of patients with gastric cancer than in patients with duodenal ulcer or functional dyspepsia. While more than 90% of patients with gastric carcinoma are H pylori positive. Combined autoimmune gastritis and gastric cancer is very rarely found. On the other hand, 30% of patients with hyperplastic polyps and gastric adenoma of the intestinal or gastric type (pyloric gland adenoma) suffer from autoimmune gastritis[11,26,28]. Corpus dominant H pylori gastritis is mainly diagnosed in cases infected with H pylori. All the above studies have confirmed that corpus dominant H pylori gastritis bears a higher risk developing gastric neoplasms rather than other forms of H pylori gastritis.

It is difficult to explain the different incidences of gastric cancer in patients with corpus dominant H pylori gastritis and autoimmune gastritis, because at least 50% of autoimmune gastritis are probably induced by H pylori[26], indicating that more than one risk exists in patients with precancerous lesions and patients with corpus dominant H pylori gastritis have a higher risk than those with autoimmune gastritis. Corpus dominant H pylori gastritis is a risk factor for gastric carcinoma in individuals with precancerous conditions and in the first degree relatives of gastric carcinoma patients[20,23]. The predictive value of corpus dominant H pylori gastritis needs to be investigated in future prospective studies.

Lee et al[33] are the first to consider the possibility of differences in acid secreting capacity in answering the underlying causes of corpus dominant H pylori gastritis. According to their hypothesis that low acid output leads to more severe gastritis, which has been confirmed later[34,35]. Moreover, it is important to emphasize that the proposed gastritis-atrophy-intestinal metaplasia- dysplasia-carcinoma sequence by Correa[36] is an ideal model only and fails to be proven in most cases[37]. But intestinal metaplasia (as a paracancerous phenomenon) is frequently picked up in biopsy specimens from individuals with corpus dominant H pylori gastritis, indicating a close relationship.

Whether H pylori eradication is capable of preventing gastric cancer is to clarified in prospective studies such as the German PRISMA study[38]. Eradication stops at least the progression of intestinal metaplasia and atrophy[39] and improves gastritis[40]. However, it has been indicated that “a point of no return” might have been reached before H pylori eradication cures the infection. This possibility is demonstrated by the development of 3 early gastric carcinomas in 92 patients 4 and 5 years after H pylori eradication and complete remission of MALT lymphomas in our German MALT lymphoma study[39] and 3 additional cases having a similar clinical history (Malfertheiner’s personal communication). Further proof is given by the study of Wong et al[40] who showed that the incidence of gastric carcinoma is similar in individuals receiving eradication therapy or placebo during a 7.5-year follow-up period. It was reported that if no precancerous lesions (atrophy/dysplasia/intestinal metaplasia) are present, eradication of H pylori leads to no gastric cancer[40-42]. Another factor that should not be disregarded is a genetic background shown by the analysis of first-degree relatives of individuals with gastric carcinoma[43-48]. Whether metaplasia and atrophy are precancerous or paracancerous lesions[48], they may not have a great clinical impact since these lesions occur especially in individuals with an elevated risk of gastric cancer[49]. Large prospective studies are needed to further analyze the risk factors for gastric cancer and to clarify whether and when eradication therapy is capable of preventing gastric carcinoma.

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