Helicobacter pylori and Gastric Cancer

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ABSTRACT

Gastritis caused by infection with Helicobacter pylori (H. pylori) is one of the most common infectious diseases worldwide. There are data on the epidemiology, pathophysiology, and histology of this disease that show that H. pylori gastritis has an important role in gastric carcinogenesis. However, it has to be considered that only very few of those infected with H. pylori will develop gastric cancer. Hence, it will be a main target of future research to identify individuals who carry a greater risk for developing gastric cancer, and therefore may benefit from eradication of H. pylori in terms of gastric cancer prevention. The Oncologist 1998;3:124-128

INTRODUCTION

Helicobacter pylori (H. pylori) is a causative agent in the pathogenesis of chronic active gastritis of the stomach, on which severe diseases such as duodenal and gastric ulcer may develop [1]. The spectrum of H. pylori-associated diseases is, however, still expanding. There is strong evidence to show that H. pylori infection may also be associated with gastric neoplasms, i.e., carcinoma of the stomach and primary low-grade B cell gastric lymphoma of mucosa-associated lymphoid tissue, known as MALT lymphoma [1]. Our knowledge of the pathogenesis of gastric neoplasms is therefore increasing, and new approaches to the prevention of gastric cancer by antibiotic treatment of a precursor of this disease, namely H. pylori gastritis, can be considered.

EPIDEMIOLOGY

Although incidence of gastric carcinoma is on the decline, it remains the second most common cause of death from malignant diseases. Nevertheless, incidence rates differ from one geographical region to another, being rather high in Japan, China, Columbia, and Costa Rica, and comparatively low in the United States [2]. However, since there is a geographical association between gastric cancer incidence and H. pylori prevalence rates, it has been suggested that gastritis caused by this bacterium may represent an important factor in gastric carcinogenesis [3, 4]. This hypothesis was confirmed by prospective case-control studies investigating the association between infection with H. pylori and gastric cancer which have calculated an approximately three- to sixfold increase in the risk of gastric cancer developing in patients infected with the organism [5, 6]. This odds ratio increases to approximately ninefold if only patients randomized for prospective serological case-control studies with a follow-up period of at least 14 years are considered [7]. In addition, a recent study from Japan in which only patients below the age of 40 were investigated reported an odds ratio of 13.3 for developing gastric cancer associated with H. pylori infection (Table 1) [8].

Nevertheless, there is a striking contrast between the total number of persons infected with H. pylori and those subsequently developing gastric cancer. To date, the ratio of the prevalence of H. pylori infection to the incidence rate of gastric cancer is approximately one to one thousand in Germany, and even less in the United States [1]. This indicates that the epidemiological role of H. pylori infection in the development of gastric carcinoma must be seen only as one factor in a multi-factorial process.

Diet, especially, has been mentioned to be one of these co-factors. Authors who investigated eating habits in relation to gastric cancer risk found that the highest risk of developing gastric cancer was associated with a diet rich in vegetables, fruits, and fish, while a diet high in red meat and processed foods was associated with a lower risk [9].

Table 1. H. pylori and gastric cancer risk/odds ratio

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk of gastric cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients infected with H. pylori</td>
<td>3- to 6-fold risk increase</td>
</tr>
<tr>
<td>Patients infected with H. pylori and randomized for prospective serological case-control studies with a follow-up period of at least 14 years</td>
<td>9-fold risk increase</td>
</tr>
<tr>
<td>Only patients below age 40</td>
<td>13.3 odds ratio</td>
</tr>
</tbody>
</table>

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to gastric cancer incidence rates found that smoked food containing nitrosamines and a high salt consumption in combination with a low-calcium, low-vitamin diet (especially vitamin C, vitamin E, and β-carotene) are associated with an increased risk of developing gastric carcinoma [9, 10]. Regarding socioeconomic factors, it has been mentioned that bad housing conditions and water supply might have a disadvantageous impact on gastric carcinogenesis. In particular, the nitrate content of drinking water is believed to be of importance [11].

PATHOLOGY

We do know that H. pylori infection is always the cause of chronic active gastritis. Infection with the bacterium provokes an invasion of the mucosa by lymphocytes/plasma cells (a marker for the degree of gastritis) and neutrophils (a marker for the activity of gastritis). In addition, inflammation is always accompanied by a replacement of the gastric foveolae by a regenerative type of epithelium and a decrease in the production of mucus [12]. Besides these diffuse parameters, multifocal features such as intestinal metaplasia, atrophy, and lymphoid follicles may be found in association with H. pylori infection.

In terms of gastric carcinogenesis, H. pylori may act either directly or via the inflammatory process that is provoked by the bacterium but determined by the host. It has been reported that H. pylori produces substances such as ammonia, phospholipases, and cytotoxins, which are released into the gastric lumen and are thought to cause epithelial damage [13]. This damage leads to a persistent state of proliferation and regeneration, and thus increases the risk of malignant alterations of the gastric stem cells at the neck region of the gastric tubes [14]. In addition, infection with H. pylori decreases secretion of ascorbic acid into the gastric lumen [15]. Ascorbic acid (as well as vitamin E and β-carotene) serves as an anticarcinogen, since it lowers the levels of potential mutagenic substances such as nitrosamines or free radicals. On the other side, free radicals in the form of NO and reactive oxygen metabolites are produced by neutrophils and therefore determined by the host’s immune response toward infection. Hence, in conclusion, there appear to be interactions among host factors, strain factors, and disadvantageous living conditions/eating habits which all increase the possibility of DNA damage, and finally, the risk of developing gastric cancer (Fig. 1).

MICROBIOLOGICAL ASPECTS

To answer the question regarding why only very few among those with H. pylori infection develop gastric cancer, it has been suggested that there are certain strains of H. pylori, namely those producing the CagA protein, that are thought to play a crucial role in gastric carcinogenesis [16]. In our opinion, however, present data on the role of the CagA in carcinogenesis are not convincing. Performing a “Medline” data survey, we found that prior to November 1997, there were a total of 12 published case-control studies in which the association of the CagA-status on gastric cancer prevalence was investigated. Of these, only three studies reported an increased odds ratio for gastric cancer if an individual is infected with a CagA-positive strain. However, significant odds ratios were only found for developing gastric cancer of the intestinal but not the diffuse type. In addition, it has been reported that the same strain factor (i.e., CagA protein) is involved in the pathogenesis of duodenal ulcers [17], a disease which has been reported to be associated with a reduced risk for developing gastric cancer [18]. Hence, strain factors alone may not suffice to explain why some people develop gastric cancer following infection with H. pylori, whereas others develop a peptic ulcer or stay asymptomatic the rest of their lives.

HISTOPATHOLOGICAL ASPECTS

Another factor involved in carcinogenesis might be the different degree and distribution of gastritis in gastric carcinoma patients. It has been shown that the extent and topography of H. pylori-associated gastritis differs when compared with age- and sex-matched patients having peptic ulcer or merely gastritis. It appears that patients with gastric cancer have much more severe gastritis in the corpus of the stomach in contrast to the antral-predominating gastritis in duodenal ulcer patients [19]. That pronounced gastritis in the corpus may be involved in the development of gastric cancer can be explained by the finding of a decrease in acid production associated with a shift in the distribution of gastritis toward the corpus [20]. This reduction in local acid...
production might then result in the suppression of a defense mechanism against dedifferentiated epithelium—since atypical cells are very acid sensitive—and might thus lead to persistence and progression of atypical cells [21].

Of interest, corpus-predominating “gastric cancer phenotype” of \textit{H. pylori} gastritis also occurs more often in relatives of gastric carcinoma patients [22]. We know, however, that there are hereditary factors that might play a role in the development of gastric cancer [23]. Hence, it may be speculated that there is a genetic susceptibility influencing the expression of gastritis and thereby increasing an individual’s gastric cancer risk. This genetic susceptibility for gastritis of the gastric cancer phenotype may be due to the number of acid-producing parietal cells. If an individual “inherits” a comparatively low number of parietal cells, \textit{H. pylori} gastritis might manifest predominantly in the corpus and thereby increase an individual’s gastric cancer risk.

An alternative pathway could be explained by data of two recent publications which report that in some cases there is a crossreactivity of antibodies directed against \textit{H. pylori} with gastric parietal cells which leads to an increase in the grade of gastritis in the corpus [24, 25]. Since these autoantibodies are found in only a proportion of infected individuals, it may be speculated that their appearance is influenced at least to some extent by hereditary factors. Further studies may help to prove this association. That autoimmune gastritis is associated with an increased risk of gastric carcinoma has been known for many years and has also been confirmed more recently [26, 27]. However, we know that infection with \textit{H. pylori} induces severe inflammation with destruction of the corpus glands (“preatrophic stage”), which finally leads to complete atrophy of the corpus (“atrophic stage”). This latter stage of atrophy and loss of acid production not only increases the risk of gastric carcinoma, but also represents unfavorable living conditions for \textit{H. pylori} [21, 28]. In some cases, therefore, \textit{H. pylori} may no longer be detectable even though infection with the organism induced the mucosal damage. Yet, after the histopathological diagnosis of “preatrophic” and histological or even serological diagnosis of \textit{H. pylori} infection, antimicrobial therapy should be initiated, since our own observations showed that eradicating \textit{H. pylori} not only inhibits a further progression of autoimmune gastritis but also leads to normalization of the gastric glands [29].

**Since prophylacti c vaccination is not available, strategies need to be developed to identify individuals who are at a higher risk and who might therefore benefit from \textit{H. pylori} eradication.**

**Prevention of Gastric Cancer by Cure of the \textit{H. pylori} Infection?**

After what has been reported about the association between gastric cancer and \textit{H. pylori} infection, it sounds reasonable that prevention of \textit{H. pylori} infection might serve to decrease gastric cancer incidence. However, prophylactic vaccination is not available to date. Thus, one of the main aims for future studies will be to investigate the extent to which gastric cancer associated with \textit{H. pylori} infection can be prevented by antibiotic treatment of the organism. There are, however, only very few persons predisposed to develop gastric cancer among those infected with \textit{H. pylori}. In addition, there are the problems with treatment regimens subscribed against the infection: they cost money, they have a number of side effects, and widespread uncritical use may give rise to the major problem of increasing antibiotic resistance rates. Hence, certain strategies need to be developed to identify individuals who are at a higher risk and who might therefore benefit from \textit{H. pylori} eradication.

Relevant important data have recently been reported by Uemura et al. [30]. In a group of patients with endoscopically resected early gastric cancer and subsequent eradication of \textit{H. pylori}, no secondary carcinoma developed during the follow-up period, while in the group with persistent \textit{H. pylori} infection, 9% developed secondary cancers. Hence, prevention of secondary cancer appears possible by treating the \textit{H. pylori} infection and should therefore be performed in individuals following early resection for gastric cancer.

Since there is certainly a hereditary risk for gastric cancer, it may also be advisable to eradicate \textit{H. pylori} in persons with a family history of gastric cancer [31]. This procedure might help to avoid one factor that increases the risk of gastric cancer.

But who else besides the above-mentioned persons might benefit from \textit{H. pylori} eradication in terms of gastric cancer prevention? To date, data on certain strain and host factors are not convincing. Although it has been suggested that serological screening for CagA-status or pepsinogen A/C levels indicates an increased gastric cancer risk, it is still equivocal whether these methods are useful for identifying those persons with \textit{H. pylori} infection who might indeed benefit from \textit{H. pylori} eradication in terms of gastric cancer prevention.
A much broader approach may be given by the use of histopathological examinations of the gastric mucosa. It may be speculated that routine histopathology alone suffices not only to enable reliable detection of a neoplasm but also provides predictive information about the outcome of Helicobacter pylori gastritis in terms of cancer development. We know from Correa’s model that multifocal atrophy arising in H. pylori gastritis is a precancerous condition leading to gastric carcinoma of the intestinal type [32]. Hence, an individual carries an increased risk of gastric cancer if atrophy is detected in gastric biopsy specimens. Subsequent cure of the H. pylori infection may help to stop this process. However, carcinomas of the diffuse type are not included in Correa’s model. Precancerous conditions for this type of gastric cancer have not yet been identified.

Another argument against Correa’s hypothetical sequence derives from data published by Hattori from Japan [33]. Analyzing gastric microcarcinomas of the intestinal type (diameters <5 mm), he found no precursor lesions in the tumor margins. Hence, he concluded that intestinal metaplasia, dysplasia, and carcinomas arise coincidentally. This implies that no precursor is present for each of them. In addition, in disagreement with the role of intestinal metaplasia as a precancerous lesion stands the finding that intestinal metaplasia is found in almost every patient with duodenal ulcer. However, the distribution of intestinal metaplasia/gastric atrophy in these patients is not as expanded as in cancer patients. We do know, however, that a history of duodenal ulcer disease protects from gastric cancer [18]. Hence, it may be speculated that intestinal metaplasia/gastric atrophy appears to be an indicator of long-standing proliferation (and implies, thereby, under certain conditions a greater risk for the development of gastric cancer), but does not necessarily represent a specific precancerous lesion.

An estimation of a person’s risk of developing gastric cancer in association with H. pylori is, however, much easier if diffuse parameters of gastritis such as the degree or activity of gastritis are investigated. There appear to be phenotypes of gastritis characterized by the topographic distribution of these diffuse gastritis parameters in the antrum and corpus of the stomach. A comparatively severe degree and activity of gastritis in the corpus in relation to that in the antrum implies, therefore, an increased risk of gastric carcinoma, while pronounced gastritis in the antrum with only mild inflammation in the corpus is associated with an increased risk of duodenal ulcer and possibly protection against gastric cancer. Hence, it can be noted in summary that the histopathologically determined phenotype of H. pylori gastritis may help to identify individuals who carry an increased (or decreased) risk for developing gastric cancer.

To date, however, final proof of cancer prophylaxis by the eradication of the H. pylori infection is still lacking. Such proof will have to be provided by large-scale long-term interventional studies, and the results of such cannot be expected shortly. What we do have, though, are indirect analogous evidences. Thus, for example, the decrease in H. pylori infection in the developed countries—including Japan—has already led to a reduction in the incidence of gastric cancer in these parts of the world [34]. These data show that gastric cancer is—at least to some extent—an infectious disease which may be prevented by antibiotic treatment.

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