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Prevention of gastric cancer:
a challenging but feasible task
Lucia C Fry, Klaus Mönkemüller, Peter Malfertheiner

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Summary
Despite its declining incidence gastric cancer still ranks as the second most common malignancy of the digestive tract, accounting for 10% of cancer deaths worldwide. At the time of the diagnosis less than 15% of the patients are in the stage of early cancer, the only stage in which a definite cure of gastric cancer is possible. Therefore the challenges are either early detection or even better prevention of gastric cancer. H. pylori has become recognized as the major risk factor for gastric adenocarcinoma. Epidemiological, biological, histomorphologic, molecular-genetic, epidemiological evidence and more recently few clinical trials have shown that H. pylori eradication has the potential to prevent the development of gastric cancer. Currently, H. pylori eradication is an indication for the prevention of gastric cancer in patients and groups of individuals with strongly increased risk, but further investigations are still required before an implementation of a global and global policy to eradicate H. pylori for the prevention of gastric cancer can be instituted. At present time, the main challenge remains to find out at what point mucosal abnormalities are no longer reversible and gastric cancer development cannot be prevented despite H. pylori eradication.

Key words: H. pylori - gastric cancer - prevention

Prevención del cáncer gástrico: una tarea difícil pero factible

Resumen
A pesar de la disminución en su incidencia, aún hoy el cáncer gástrico se presenta como la segunda causa más común de muerte por enfermedad maligna del tubo digestivo, siendo responsable del 10% de las muertes por cáncer a nivel mundial. Al momento del diagnóstico menos del 15% de los pacientes se encuentran en la etapa de cáncer gástrico temprano, el único estadio en el cual es posible su curación. Por lo tanto, el desafío está en la detección temprana o aún mejor, en la prevención del cáncer gástrico. H. pylori ha sido reconocido como el factor de riesgo más importante para el desarrollo del adenocarcinoma de estómago. Evidencia epidemiológica, biológica, histológica, molecular y más recientemente algunos estudios clínicos han demostrado que la erradicación del H. pylori tiene el potencial de prevenir el desarrollo de lesiones premalignas y del cáncer gástrico. Actualmente la erradicación del H. pylori está indicada para la prevención del cáncer gástrico en pacientes y grupos de individuos con alto riesgo, pero futuras investigaciones son aún necesarias antes de que sea establecida una política global para la erradicación del H. pylori en la prevención del cáncer gástrico. Actualmente el mayor desafío radica en encontrar en qué punto los cambios en la mucosa gástrica se tornan irreversibles, siendo el cáncer gástrico no prevenible a pesar de la erradicación del H. pylori.

Palabras clave: H. pylori, cáncer gástrico, prevención.

Gastric cancer continuous to be a major challenge, largely because in the majority of cases it is recognized only in stages in which a curative therapy is no longer possible. Therefore the efforts should be directed to early detection and prevention. H. pylori is the main risk factor for gastric cancer which offers the chance to battle against this disease by the preventive measure of H. pylori-eradication. The implication of a global gastric cancer prophylaxis strategy offers a unique chance against gastric cancer but should be evaluated taking health-economic aspects in consideration as well.

Epidemiology of the H. pylori infection

H. pylori is one the most common chronic bacte-
H. pylori and gastric carcinoma

Adenocarcinoma of the stomach is divided in two main histological types according to the Lauren classification: a) well-differentiated or intestinal type and b) diffuse or signet ring cell type. The intestinal type is associated with gastric atrophy and intestinal metaplasia and corpus-dominant gastritis, while the diffuse type frequently originates in pan-gastritis without atrophy. A decrease in the incidence of the intestinal type and an increase in the diffuse type of gastric carcinoma, especially the signet ring cell type have been noticed. According to localization different etiology can be considered. In patients with distal gastric cancer, a chronic atrophic H. pylori-induced type B-gastritis is the main etiological factor. Also adenocarcinomas of the proximal stomach including cardia may be related with a H. pylori infection, but for this location there are other H. pylori-independent factors which are not well known yet. In addition, there are other defined but uncommon conditions associated with gastric cancer: atrophic gastritis associated with pernicious anemia, hypertrophic gastropathy or Ménétrier’s disease and gastric adenomatous polyps. But nowadays it has been accepted that all these forms of gastritis are also linked with an H. pylori infection. At the present time, intestinal as well as diffuse type of gastric cancer are both considered strongly associated with chronic H. pylori infection. The association between H. pylori infection and gastric cancer has been confirmed by epidemiological, cell-molecular, animal and interventional studies.

Epidemiologic evidence

The association between H. pylori infection and the development of gastric cancer has been recognized in several epidemiological studies. In retrospective case-control studies, patients with serologically confirmed H. pylori infection had an increased relative risk from 1.2 to 4.2 of developing gastric cancer. In prospective studies, patients with gastric cancer and previous seropositivity for H. pylori, an increased relative risk from 2.8 to 6 was demonstrated. In addition a meta-analysis performed in 2001 including only prospective cohort studies established the association between H. pylori infection and non-cardia gastric cancer (odds ratio 2.97). Newer epidemiological investigations using immunological methods such as serum CagA antibodies showed that H. pylori infected patients have a 20-times higher risk to develop a gastric cancer. In a study from Germany it was demonstrated that H. pylori infection is a sine qua non condition for the development of gastric cancer.
term follow-up prospective studies which also include a study arm with non-infected population.

**Molecular studies**

Cell biological investigations prove a direct influence of *H. pylori* on cellular signal cascades which are involved in the process of the carcinogenesis.\(^{14-21}\) The cell biological phenomena which occur due to infection with *H. pylori* include the activation of growth factors, reduction of the apoptosis, induction of replication, increase of angiogenesis and disruption of cell-cell contacts (table 1). *H. pylori* regulates the activity of growth factor receptors promoting epithelial cell growth, survival, dissociation and motility.\(^{18}\) These significant observations, documented under *in vitro* conditions, demonstrate that *H. pylori* affects cell physiology contributing to uncontrolled growth which leads to an aggressive behavior of the cell and promoting malignant transformation. The intracellular cascades, which lead to an increased and uncontrolled cell proliferation can regress after *H. pylori* eradication (table 2). Knowledge of the intracellular pathways related with malignant behavior is crucial to understand whether *H. pylori* eradication prevents the development of gastric cancer.

**Table 2. Influence of *H. pylori* eradication on cellular events.**

- Reduction of free radicals
- Reduction of COX2 and expression of ornithine decarboxilase (in atrophic preneoplastic and malignant lesions)
- Reduction of epidermal growth factors and their receptors (EGF and EGFR)
- Improvement of metaplasia and genomic instability
- Reversion of aberrant expression of cyclin D2 and p27 in intestinal metaplasia.
- Decrease of cell turn-over
- Elimination of DNA damage through free radicals
- Increase of gastric acid secretion
- Increase of ascorbic acid secretion

**Animal experimental data**

Gastric carcinogenesis has been evaluated in several animal models including ferrets, mice and mongolian gerbils.\(^{28-31}\) In 1998, Watanabe et al presented evidence showing *H. pylori* as a gastric carcinogen in Mongolian gerbils. Further studies demonstrated that *H. pylori* alone is a weak carcinogenic factor, but the presence of nitrosamine together with *H. pylori* infection increases significantly the carcinogenic potential of *H. pylori*.\(^{8,18}\) Furthermore, this carcinogenic potential has been shown to be increased in combination with a high-salt diet.\(^{28}\) Histopathological studies in mongolian gerbils demonstrated that after *H. pylori* infection, gastric glands start to proliferate into the submucosa (named heterotopic proliferative glands) with a slightly dysplastic change of constituent cells.\(^{30}\) After eradication, these heterotopic proliferative glands presented an evident reduction as well as an improvement of mucosal gastric lesions.\(^{8,13,30}\) In the standard mouse model to assess the *H. pylori* infection, it was shown that male mice infected with *H. pylori* regularly developed atrophy, intestinal metaplasia, dysplasia and carcinoma.\(^{31}\)
Interventional studies

Eradication of *H. pylori* is at present time accepted to heal gastritis and dramatically reduce the incidence and recurrence of peptic ulcer disease. Furthermore, the influence of *H. pylori* eradication on the development of gastric cancer has been demonstrated in observational as well as in interventional studies\(^{32-37}\) (table 3). In a study from Japan which included 1526 patients (82% *H. pylori* positive) who were followed-up prospectively for 7.8 years, gastric cancer developed in 36 patients (2.9%) of the infected group but in none of the *H. pylori*-negative patients.\(^{34}\) One study from China showed that gastric cancer development is preventable by *H. pylori* eradication only if gastritis has not yet reached the degree of atrophic changes or intestinal metaplasia (i.e. preneoplastic lesions)\(^{35}\) (table 3). A recently published study followed 1131 patients with peptic ulcer disease who had received *H. pylori* eradication therapy. After a mean follow-up of 3.9 years, gastric cancer was developed in 9 of 953 (0.9%) patients cured of the infection and in 4 of 178 (2.2%) who had persistent *H. pylori* infection.\(^{37}\) The risk of developing gastric cancer after receiving *H. pylori* eradication therapy was increased according to the grade of baseline gastric mucosal atrophy. The effect of *H. pylori* eradication on gastric preneoplastic lesions has been also evaluated in several studies (table 4).\(^{38-46}\) In a study evaluating *H. pylori* positive patients with moderate and severe atrophic gastritis with a 5-years follow-up period Ito et al. demonstrated regression of gastric atrophy and intestinal metaplasia in some *H. pylori*-positive patients.\(^{47}\) Another randomized, controlled, chemopreventive study evaluating patients with increased risk for gastric cancer showed that *H. pylori* eradication led to a decrease of 15 to 30% of atrophic gastritis and intestinal metaplasia.\(^{39}\) In another study it was demonstrated that

### Table 3. *H. pylori* eradication and gastric cancer incidence.

<table>
<thead>
<tr>
<th>Autor/Jahr</th>
<th>Patients</th>
<th>Follow-up (years)</th>
<th>Study</th>
<th>End point</th>
<th>Incidence of gastric cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uemura 1997</td>
<td>132</td>
<td>3</td>
<td>Prospective, placebo-controlled</td>
<td>Incidence of gastric cancer, reversibility of preneoplastic lesions</td>
<td><em>Hp</em> neg: 0/65 (0%) <em>Hp</em> pos: 6/67 (9%) (p=0.011)</td>
</tr>
<tr>
<td>Saito 2000</td>
<td>64</td>
<td>2</td>
<td>Prospective, placebo-controlled</td>
<td>Progression of adenoma in <em>Hp</em>-positive patients</td>
<td><em>Hp</em> neg: 0/32 (0%) <em>Hp</em> pos: 4/32 (12.5%) (p=0.05)</td>
</tr>
<tr>
<td>Uemura 2001</td>
<td>1526</td>
<td>7,8</td>
<td>Prospective, placebo-controlled</td>
<td>Development of gastric cancer in <em>Hp</em>-infected patients</td>
<td><em>Hp</em> neg: 0/280 (0%) <em>Hp</em> pos: 36/1246 (2.9%) (p&lt;0.001)</td>
</tr>
<tr>
<td>Wong 2004</td>
<td>1630</td>
<td>7</td>
<td>Population based, prospective, randomized, placebo-controlled</td>
<td>Incidence of gastric cancer after <em>Hp</em> eradication</td>
<td>Patients without preneoplastic lesions*: <em>Hp</em> neg: 0 vs <em>Hp</em> pos: 6 pts (p=0.02) No difference in pts with preneoplastic lesions.</td>
</tr>
<tr>
<td>Zhou 2005</td>
<td>1006</td>
<td>8</td>
<td>Population based, prospective, randomized, placebo-controlled</td>
<td>Incidence of gastric cancer after <em>Hp</em> eradication</td>
<td><em>Hp</em> neg: 1/1968 (0.4%) <em>Hp</em> pos: 6/2448 (1.6%) After <em>Hp</em> eradication: significant reduction of atrophy in corpus (p=0.001)</td>
</tr>
<tr>
<td>Take 2007</td>
<td>1131</td>
<td>3,9 (mean)</td>
<td>Prospective, not randomized</td>
<td>Incidence of gastric cancer after <em>Hp</em> eradication</td>
<td><em>Hp</em> neg: 9/953 (0.9%) <em>Hp</em> pos: 4/178 (2.2%) p=0.04</td>
</tr>
</tbody>
</table>

*Hp*: *Helicobacter pylori*  
*Hp*: *Helicobacter pylori*  
1 preneoplastic lesions: gastric atrophy, intestinal metaplasia, dysplasia
improvement of gastritis and intestinal metaplasia was more apparent in patients with lower histological severity levels of gastritis. An important cohort-study with a follow-up of 12 years evaluated 795 H. pylori-infected patients with gastric preneoplastic lesions who were randomized to either H. pylori eradication or antioxidants. Participants without initial antibiotic therapy were offered H. pylori eradication 6 years after the start of the study. After 12 years follow-up, up to 66% of the H. pylori-negative patients showed an involution of preneoplastic lesions, in contrast to only 14% of the H. pylori positive patients. Healing of gastritis was most evident for patients with a lower grade of gastritis. Nevertheless, even if these preneoplastic lesions are not fully reversible, it is possible that H. pylori elimination leads to a detention of further progression of the preneoplastic lesions already present.

At present time it is not clear in which stage of gastric carcinogenesis (atrophy, metaplasia and dysplasia) it is still possible to interrupt the development of gastric cancer. Progression of atrophic gastritis and intestinal metaplasia into gastric cancer can also occur despite a successful H. pylori eradication, pointing to the existence of a "point of no return" in the model of gastric carcinogenesis. Obviously, specific molecular-biological and cell genetic events are already present at this time, which perpetuate themselves so that H. pylori elimination does not result in regression of the carcinogenic process. Therefore, it is very important that the implementation of any interventional and preventive strategies which lead to a reduction of the incidence of gastric cancer are applied before this irreversible "point of no return" has occurred.

**Table 4. Influence of H. pylori eradication on preneoplastic gastric lesions.**

<table>
<thead>
<tr>
<th>Autor</th>
<th>Nº Patients</th>
<th>Follow-up (years)</th>
<th>Atrophy</th>
<th>Intestinal metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepes 1999</td>
<td>63</td>
<td>4</td>
<td>Regression</td>
<td>No change</td>
</tr>
<tr>
<td>Sung 2000</td>
<td>587</td>
<td>5</td>
<td>Prevents progression</td>
<td>Prevents progression</td>
</tr>
<tr>
<td>Rocco 2002</td>
<td>54</td>
<td>8</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Ito 2002</td>
<td>22</td>
<td>5</td>
<td>Reversibility in some patients</td>
<td>Reversibility in some patients</td>
</tr>
<tr>
<td>Zhou 2003</td>
<td>552</td>
<td>5</td>
<td>No regression (antrum p=0.223)</td>
<td>Regression in Antrum p=0.032 no change in Corpus p=0.151</td>
</tr>
<tr>
<td>Lu 2005</td>
<td>179</td>
<td>3</td>
<td>Reduction P&lt;0.01</td>
<td>Progression (p&lt;0.05, NS)</td>
</tr>
<tr>
<td>Salih 2005</td>
<td>21</td>
<td>1</td>
<td>Improvement (NS)</td>
<td>Improvement (NS)</td>
</tr>
<tr>
<td>Mera 2005</td>
<td>795</td>
<td>12</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Arkkila 2006</td>
<td>92</td>
<td>1</td>
<td>Regression in antrum (p&lt;0.05)</td>
<td>Not evaluated</td>
</tr>
</tbody>
</table>

NS: non-significant

Nowadays it is unquestionable that H. pylori-induced chronic gastritis represents a critical predisposition for the emergence of the gastric cancer. Nevertheless, at current time the general prevention of gastric cancer is not yet feasible due to the high prevalence of the infection in the asymptomatic population. The first reason why this strategy cannot be implemented is the costs associated with antibiotic therapy. Nevertheless, there are several studies which show that the economic impact of a generalized H. pylori eradication would be favorable. These studies show that H. pylori eradication would lead to a
reduction of long-term health-costs for the treatment of dyspepsia and ulcer-associated disorders and a lower incidence of gastric cancer would be expected.\(^{46,49}\) The second reason why a generalized H. pylori eradication has not yet been implemented is the lack of the final and undisputed proof that H. pylori eradication significantly reduces the incidence of gastric cancer. But in order to evaluate the influence of H. pylori eradication on the incidence of gastric cancer, a very large multicentric, multinational, prospective, double-blinded, placebo-controlled study with long-term follow-up needs to be performed. But such a study, with today’s knowledge regarding H. pylori infection and its consequences is nearly impossible to accomplish. First of all, many patients must be recruited; secondly, the follow-up must be 10 or more years; and thirdly, it becomes difficult (and unethical) for physicians to recruit patients who remain untreated for many decades infected with a bacterium that they know is a proven carcinogen. At the present time, according to the Maastricht recommendations a pro-active eradication of H. pylori is indicated for first-degree relatives of patients with gastric cancer, patients with dyspepsia and patients with corpus-predominant gastritis.\(^{5,12,18,21}\)

**Conclusion**

Gastric cancer is recognized as the second cause of cancer death worldwide. With today’s level of knowledge, H. pylori infection can be accepted as the main risk factor in the pathogenesis of gastric cancer. Apart from epidemiological, biological, histomorphologic and molecular-genetic references we can rely on various clinical studies which show that H. pylori eradication can prevent the development of preneoplastic lesions and gastric cancer. Groups at risk for the development of gastric cancer should be systematically evaluated and searched for H. pylori infection, and if positive preventively treated. Because most gastric precancerous lesions do not progress or even regress after H. pylori eradication, we recommend H. pylori eradication for H. pylori-positive patients. The chance of success is more feasible if no preneoplastic lesions are present at the time of treatment. The treatment of the gastric cancer is still very unsatisfactory, thus prevention is an important task. The fight against gastric cancer by the preventive measure of H. pylori eradication brings an immense chance to clearly lower the incidence of this deadly disease worldwide.

**References**


