Role of *Helicobacter pylori* in gastric cancer following partial gastrectomy for benign ulcer

**Introduction**

During the 1970s, Correa (1) formulated his theory on the sequence of histological changes from type B chronic gastritis to gastric cancer, through intermediate atrophic gastritis, intestinal metaplasia, and dysplasia stages. Based on epidemiological studies, it was suggested that the initial stage in this process, that is, initial gastritis, could result from environmental factors such as diets rich in salt and nitrates, and poor in vegetables and fresh fruits. In 1983, Marshall and Warren (2) demonstrated that mucosal inflammation was caused by the organism *Helicobacter pylori* (*Hp*), and thus they first related gastric cancer to *Hp*, a view that was supported by case-control studies and meta-analyses (3-5) showing a 2 to 4-fold increase in the risk for gastric cancer among the infected population when compared to the non-infected population. In 1994, IARC (International Agency for Research on Cancer dependent of the World Health Organization) defined *Hp* as a type I carcinogen (6), matching it, for instance, with the association between smoking and lung cancer.

All studies suggest that cancer development requires the presence of *Hp* for many years; in other words, it is required that infection be initiated at an early age. Furthermore, some studies suggest that the association between *Hp* and cancer is more obvious in early versus advanced cancer (7). Similarly, this correlation is more apparent if infection was diagnosed years before the diagnosis of cancer (4,8), which suggests that their relationship may be underestimated because of potential infection clearance during disease development. A recent German study (9) compared 68 patients with gastric cancer (excluding cardia cases) versus 360 control individuals; a serology performed a few years before had shown that 78% of patients with cancer were infected versus 63% among controls, which represented an odds ratio (OR) of 3.7 that may reach 5.7 in patients with *Hp* CagA + infection.

A Spanish study (10) demonstrated that the prevalence of infection was not different for intestinal-type and diffuse-type gastric carcinoma (incidence, 69%), but significant differences were found in the prevalence of *Hp* for distal cancer, which was of 73.6% versus only 48.6% for cardial cancer, the latter with no differences versus the prevalence of infection in the control population.

While infection is present in more than 80% of patients with gastric cancer, most infected persons will not develop the latter condition, which suggests that *Hp* is a nearly necessary but insufficient factor. In fact, the prevalence of gastric cancer does not always correlate with the prevalence of infection; for example, areas with a high (Japan) or low (sub-saharian Africa) incidence of gastric cancer have a similar prevalence of infection. Even in regions with a high incidence of *Hp* and cancer, the latter will only develop in 2% of infected individuals. It is widely accepted that less
than 1% of all infected subjects will eventually develop gastric cancer. Thus, research efforts should focus on the identification of factors leading to gastric cancer in a few, but not most *Hp*-infected patients.

What factors may influence the potential development of gastric cancer?

1. **Bacterial factors.** Experimental and epidemiological studies (9) demonstrate a higher association of CagA + germs with gastric cancer. In cell cultures (11), *Hp* CagA + showed its ability for cell invasion, activating MMP-9 (Matrix MetalloProteinase-9), VEGF (Vascular Endothelial Growth Factor) and COX-2 (Cyclooxygenase), and the disruption of apical junctions in superficial gastric cells (12); both characteristics lead to a higher direct or indirect ability for inflammation induction. A meta-analysis (13) identified 16 qualified studies comprising 2,284 patients with gastric cancer and 2,770 control subjects. Both *Hp* and CagA, increase the risk for gastric cancer by 2.28 and 2.87, respectively. Cardial cancer is associated with none of these two parameters. In a Swedish study (14) differences were more apparent –81/100 (81%) patients with gastric cancer are infected: 86% with CagA + germs *versus* 58% and 54%, respectively, for controls (OR 7.4 among *Hp* CagA + patients vs. non-infected subjects).

2. **Environmental factors.** *Helicobacter pylori* may induce gastric cancer in experimental animals, while the presence of a prior carcinogen is a requirement in most studies (15,16). Studies searching for the cellular origin of cancer in *Hp*-infected rats led to the surprising finding that gastric cancer may originate in the so-called BMDC (Bone Marrow-Derived Stem Cells) (17). Similarly, achlorhydria has been shown to produce hypergastrinemia and bacterial overgrowth in the rat, which in turn increases inflammation and atrophic gastritis. However, no evidence worldwide has ever proven that the inhibition of secretion using PPIs (proton pump inhibitors), which elevates blood gastrin and induces no bacterial overgrowth, will increase the incidence of gastric cancer (18). We already discussed that a diet rich in vegetables and fresh fruits containing ascorbic acid and tocopherol has protective effects, while a diet rich in animal proteins and nitrites favors the development of cancer, as does smoking (OR = 2.3), but only in infected subjects (19).

3. **Immune-hereditary factors.** *Hp*-infected first-grade relatives of patients with gastric cancer have a higher proportion of atrophic gastritis and other precancerous factors when compared to infected control subjects with no family history of gastric cancer (20), and have increased interleukin-1-β (II-1-β) and TNF-α, and decreased II-10 levels, which rises the risk for gastric cancer in infected *versus* non-infected subjects 27 fold (21). Such evidence has led to recommend eradication in *Hp*-infected first-grade relatives of patients with gastric cancer.

Is eradication indicated for prevention of gastric cancer?

There is no definite evidence to answer this question, and such evidence will likely be difficult to obtain, since thousands of citizens randomized to eradication or placebo with many years of follow-up would be required. However, indirect evidence available may help reasonably answer this question, however with insufficient strength.
A Japanese study (22) in 132 * Hp * + patients undergoing endoscopical resection for early gastric cancer is interesting. Infection was eradicated in 65 patients who had no tumor relapse at 5 years, whereas 9/67 (13%) patients who received no eradication relapsed. This finding is suggestive but has limitations, since the study design was not double-blind. Another Japanese study (23) followed for a mean 3.5 years 1,120 patients with ulcer disease; 8/944 (0.8%) patients with successful eradication developed gastric cancer versus a higher percentage –4/176 (2.2%)– who had persistent infection; differences did not reach significance. It could be acknowledged that all patients who developed cancer had suffered from gastric ulcer. No patient with duodenal ulcer developed gastric cancer.

Despite the difficulties suggested regarding an interventional study in both healthy and infected subjects to demonstrate preventive efficacy for gastric cancer using eradication in both healthy and symptomatic individuals, one such study (24) has been reported in China, in a high-risk region for gastric cancer and in “only” 1,630 individuals who were followed for 7.5 years. Eighteen cases of gastric cancer were identified during the study period, with no significant differences between those who received eradication (n = 7) and those who received placebo (n = 11) (p = 0.3). Despite this scarcely encouraging result, none of the eradicated patients lacking histological mucosal lesions considered precancerous at baseline eventually developed cancer, versus 6 patients in the placebo group (p = 0.02), which suggests that in the absence of such histological lesions eradication seems to prevent cancer development, while a point of no return seems to exist when therapy occurs once these changes have already developed.

In the recent Spanish consensus conference on the indications of eradication (25) it was recommended that “given the high prevalence of * Hp * worldwide, eradication cannot be performed to prevent gastric cancer, and its yield in terms of cost-effectiveness is unwise”; it may only be accepted, as previously suggested, for first-grade relatives of patients with gastric cancer.

Is eradication indicated in the gastric remnant following partial gastrectomy for gastric cancer?

From evidence discussed in previous sections, the benefits of * Hp * eradication in the remaining gastric stump following gastrectomy for gastric cancer are easily deductible. Furthermore, clinical studies demonstrate that following gastrectomy for cancer there are greater neutrophil infiltrates and increased COX-2 in the * Hp *-infected mucosa versus the non-infected gastric mucosa in the gastric remnant, and these findings suggest a higher potential for malignant relapse in the presence of * Hp * (26).

A recent study (27) in a group of patients with gastrectomy for early gastric cancer and presence of * Hp * at the stump, eradication dramatically reduced mononuclear cell infiltrates, virtually erased neutrophil infiltrates, and significantly diminished IL-8 and Ki-67 tissue levels. The authors concluded that, prior to eradication, the gastric remnant mucosa of patients operated on for gastric cancer (even early gastric cancer) exhibits histological changes considered to confer a high risk of carcinogenesis as a result of inflammation, a risk that at least theoretically may be minimized with * Hp * eradication.

Therefore, the recommendation by the Spanish consensus conference (25) seems appropriate, as it indicates eradication in patients operated on for gastric cancer by means of partial gastrectomy where the presence of infection is demonstrated; even
if this recommendation has only an evidence level of 4 (evidence 4 is based on case report series, cohort studies, and case-control studies).

Is eradication indicated in the gastric remnant following partial gastrectomy for benign gastric ulcer disease?

Patients undergoing partial gastrectomy for benign peptic ulcer disease (mainly gastric ulcer) are considered to have an increased risk of cancer development in the gastric remnant, and risk was suggested to be higher at 15 years after surgery. Some authors even recommended endoscopy and multiple biopsies in this subgroup as of 10-15 years after surgery for potential early diagnosis purposes. Bile reflux and the presence of *Hp* were even suggested as pathogenic causes (28).

The following questions may be posed:

1. **Does Helicobacter pylori remain for years in the gastric remnant following gastrectomy for ulcer?** A German study adequately answers this question (29). Endoscopy, biopsy, and *Helicobacter pylori* tests were performed for 57 patients at a mean of 20 years after gastrectomy for peptic ulcer. In 25/57 (43.8%) patients the germ was detected in biopsy specimens. Gastric atrophy was more common in infected subjects, but not gastritis severity. Therefore, fewer than half of patients gastrectomized for ulcer have *Hp* in the gastric remnant.

2. **How is Helicobacter pylori associated with ulcer relapse?** It is a well known fact that ulcer relapse after eradication in non-operated patients occurs almost exclusively in *Hp* + individuals either from reinfection or recrudescence. However, in a recent study (30) in 186 patients gastrectomized for benign ulcer, 83 (44.6%) had ulcer relapse and of these only 36% were *Hp* +, with no significant differences versus those with no ulcer relapse. The authors conclude that in the case of gastrectomy *Hp* infection plays a role not as relevant in relapse as is the case with patients not undergoing surgery; as a result, eradication to prevent ulcer relapse is scarcely supported.

3. **Is there a greater risk for cancer development in the gastric stump, versus the control population, in patients gastrectomized for peptic ulcer, and is that potentially related to Helicobacter pylori?** The role of *Hp* in the development of gastric cancer in the gastrectomy stump for benign ulcer is controversial and has been considered even unlikely, since, as previously discussed, the germ is only present in approximately 40% of patients, perhaps as a consequence of bile reflux conditioning an alkaline environment in the remnant unfavorable for this organism. Alkaline reflux has been even postulated as the most relevant factor involved in the pathogenesis of stump cancer (31).

In this issue of *Revista Española de Enfermedades Digestivas*, Seoane et al. contribute a review of 73 patients undergoing partial gastrectomy for benign ulcer who were examined using endoscopy, biopsies, and adequate histology. First of all, the high percentage of gastrectomized patients with infection (86%), far above that usually described in the literature (40%) is striking; furthermore, 15 (20.5%) patients were diagnosed with cancer in the gastric remnant, with all of them being *Hp* + and with a mean time from gastrectomy to diagnosis of 32 (14-48) years. This percentage of cancer development in the gastric remnant is also one of the highest ever described in the literature.

The authors reached the following conclusions:

—Cancer development in the gastric stump following gastrectomy for benign ulcer is not negligible (20%).
Editorial

—Cancer development in the stump occurs after 15 years following surgery.
—The pathogenesis of cancer is more related to the presence of \textit{Hp} than to bile reflux in view of the high percentage of infected patients (86\%) in their experience.
—As a logical consequence of their findings, an indication for eradication is in-tuited in these patients, much in the same way as in patients gastrectomized for gastric cancer.

The information provided by the authors is relevant and useful. However, we would like to contribute some remarks.

—The 20\% rate for gastric stump cancer as diagnosed by endoscopy refers to gastrectomized patients who presented because of discomfort or at best because of referral by a practitioner for early cancer diagnosis, but who surely are not representative of the whole group. As a result, the overall percentage of cancer development is surely smaller.

—The information that all patients were diagnosed with cancer after 32 years on average is important; even more relevant is the fact that the diagnosis was reached between 14 and 48 years of age, which confirms that cancer development occurs as was traditionally suggested, namely at least at 15 years after resective surgery.

—In our setting, the mean percentage of \textit{Hp} infection in the adult control population is around 50\% (32), and reaches 60-70\% in patients older than 60 years. Therefore, the percentage of infection found by the authors in their patients is not surprisingly high, particularly considering that these are ulcer patients. However, this possible explanation must be qualified, as also gastrectomized patients reported in the literature are ulcer patients with a higher prevalence of infection.

—While the authors do not clearly specify whether they consider eradication as indicated, they seemingly tend towards this possibility in view of their final conclusion—“Infection by \textit{Helicobacter pylori} may play a role in gastric cancer”—, obviously referring to gastric cancer as developing after gastrectomy for peptic ulcer. However, this indication is not included in the Spanish consensus conference (25) or other previous meetings, and further studies are needed to confirm the relevant findings in this review. Anyway, and according to a recently published study (33), eradication in gastrectomized patients results in a higher efficacy rate when drugs are taken in a lying position and with the body turned to the left for some 30 minutes.

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REFERENCES

Editorial


