

LEADING ARTICLE

Is gastric cancer preventable?

P Correa

Gastric cancer is a major health burden worldwide and prevention is the most promising strategy to control the disease. The available scientific evidence indicates that curing *Helicobacter pylori* infection results in a modest retardation of the precancerous process but does not prevent all cancers. Individuals at the highest risk should be cured of their infection and monitored endoscopically to detect dysplasia and "early" cancer, amenable to successful treatment.

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prolonged latency period. There is a consensus, accepted by the IARC since 1994,² that infection with *H pylori* is a primary cause of the disease. Such infection usually starts in infancy or early childhood and persists as a chronic gastritis, implying that exposure to this major causative agent lasts for five or more decades in most patients.

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Hypothetically, this provides ample opportunity for intervention to block progressively accumulating cell damage. It is therefore crucial that we understand the precancerous process.

SUMMARY

Gastric cancer is a major health burden worldwide. Conventional treatments have not had major impact on survival. Prevention is the most promising strategy to control the disease. A very prolonged latency period has been well documented. In it, sequential precursor lesions in the gastric mucosa have been identified ("precancerous cascade"). Chronic infection with *Helicobacter pylori* is a major force driving the precancerous process. Antioxidant micronutrients may also play a major aetiological role. Recently completed randomised trials in Colombia, China, and Mexico indicate that curing the *H pylori* infection results in a modest slow down of the precancerous process but does not prevent all cancers. Individuals at the highest risk can be identified by histological, immunological, and molecular markers. They should be cured of their infection and monitored endoscopically to detect dysplasia and "early" cancer, amenable to successful treatment.

INTRODUCTION

In spite of its steady decline, gastric cancer is a major health burden. It is the second most deadly malignant neoplasia worldwide. Approximately 876 000 persons are diagnosed with the disease and approximately 649 000 die from it every year.¹ In most countries, the disease is largely diagnosed after it has invaded the muscularis propria. In such patients the five year survival rate is less than 20%. Surgery and chemotherapy for the most part have only little impact on the prognosis. Prevention therefore is the best hope of controlling the disease. Is it possible? This question is examined in this article in the light of recent developments.

LATENCY

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THE PRECANCEROUS CASCADE

The gastric precancerous process eventually leading to non-cardia adenocarcinoma, sometimes compared with a "cascade", has been the focus of attention by pathologists for at least a century^{3–6} and was proposed as a model in 1975.⁷ Its basic steps are identified as histopathological patterns: gastritis → atrophy (loss of glands) → intestinal metaplasia → dysplasia. As in a cascade, each step can be broken down into smaller steps in terms of extension of the mucosal surface involved, as well as in phenotypic and genotypic epithelial characteristics. Multiple publications from different countries have supported the model, especially in high risk populations, in which the intestinal-type of adenocarcinoma is predominant. Strong support was given in a recent publication in which a cohort of 4655 healthy subjects were monitored for 7.7 years with blood pepsinogen levels (markers of atrophy) and anti-*H pylori* antibodies.⁸ In this model, the cancer risk increased with precancerous markers in a stepwise fashion, with the most advanced stage (low pepsinogen levels and loss of active *H pylori* infection) carrying a relative risk of 61.85 (confidence interval 5.6–682.6). Intermediate end points are useful in evaluating cancer risk. The use of gastric cancer as an end point poses major logistic obstacles. Given an incidence rate measured in terms of number of cases per 100 000 population, it would require follow up of cohorts of tens of thousands of subjects for several decades in order to achieve a sufficiently large number of cases.

Although the ultimate mechanism of carcinogenesis remains unknown, it seems clear that infection with *H pylori* is the major driving force in the process. It follows that eradicating the infection is a sound strategy for prevention.

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Recent support for this strategy is accumulating, as illustrated by Uemura *et al* who failed to detect cancer after 7.8 years of follow up in a cohort of 253 infected patients treated and cured of the infection, contrasting with 36 cancers found in 971 patients with persistent infection.⁹

RANDOMISED TRIALS

The litmus test of the efficacy of intervention, by convention, is the double blind, placebo controlled, randomised trial. These are logistically laborious time consuming efforts. A number of these studies have been recently completed and the much awaited results are now making their way to the medical literature. One such trial was completed in Colombia and reported a beneficial effect of anti-*H* treatment in terms of increased odds of regression of intestinal metaplasia (odds ratio (OR) 3.1 (CI 1.0–9.3)) and non-metaplastic multifocal atrophy (OR 4–8 (CI 1.6–14.2)). Curing the infection increased the odds of regression of atrophy (OR 8.7 (CI 2.7–28.2)).¹⁰ When extension of atrophic changes was evaluated with morphometric techniques, significantly reduced scores of atrophy were reported after anti-*Helicobacter* treatment (number of glands per ×40 microscopic field: 8.50 in untreated subjects versus 9.74 in treated subjects; $p = 0.01$).¹¹

A recent randomised trial in Chiapas, Mexico, followed up subjects for one year. It used an index score, assigning weights for degree of severity and extension of preneoplastic lesions in gastric biopsies.¹² The average reduction in score between biopsies obtained six weeks and one year after *H pylori* eradication was -0.07 in the placebo group and -0.84 in the treatment group ($p = 0.02$).

Two groups of Hong Kong based investigators have carried out randomised trials in China. One group has studied populations of Changle, Fujian province. They reported the results of treatment after five years of follow up.¹³ A significantly lower rate of progression of atrophy in the antrum was found in the treated group (29%) than in the placebo group (50%) ($p = 0.01$). Utilising cancer incidence as an end point, no significant difference was found between treated patients ($n = 7$) and those not treated ($n = 11$).¹⁴ In a subgroup of patients without precancerous lesions at the start of the trial, none developed gastric cancer during the 7.5 years of observation compared with six cases in the placebo group ($p = 0.02$).

“Curing the infection in adults with intestinal metaplasia should not be expected to prevent all cancers”

Another group of Hong Kong investigators has been studying populations of Yantai, Shangdong province. Utilising precancerous end points, after one year of observation they reported, as expected, a decrease in inflammatory scores in the treated group.¹⁵ The results after five years of observation are presented by Leung and colleagues¹⁶ in this issue of *Gut* (see page 1244). Several remarkable findings illustrate the value as well as the limitations of randomised trials using intermediate end points. The intervention succeeded in curing the infection in 74.5% of patients, demonstrating that triple therapy can be successful in high risk populations of low socioeconomic strata. During the period of observation, four cancers developed in the treated group and six in the placebo group, a non-statistically significant outcome, as expected when cancer end points are utilised. This finding also illustrates the point that curing

the infection in adults with intestinal metaplasia should not be expected to prevent all cancers. However, curing the infection did reduce the risk of progression of the precancerous process: the OR of progression of intestinal metaplasia was 0.63 (CI 0.43–0.93) in treated patients compared with the placebo group. Patients with persistent infection had a 2.14 risk of progression of metaplasia (CI 1.45–3.16) compared with the placebo group. The study identified patients with extensive antral atrophy as the highest risk group. This finding to some extent contrasts with reports from European populations in which atrophy of the corpus has been emphasised as a high risk factor.¹⁷ In most high risk populations, not of northern European extraction, antral atrophy is the dominant cancer precursor lesion.

EPILOGUE

The available scientific evidence indicates that curing *H pylori* infection results in a modest retardation of the precancerous process. All available trials have been conducted in adults in a rather advanced stage of atrophy and intestinal metaplasia. The study subjects most probably had been infected for five or more decades. The mechanisms by which the infection induces gastric cancer are mostly unknown. It has been proposed that oxidative damage induced by the inflammatory process may be involved.¹⁸ If that is the case, such oxidative insult may have been present in the gastric mucosa for decades before anti-*Helicobacter* treatment, and in prevention trials molecular events eventually leading to neoplasia might have reached a point of no return. Intervention to cure the infection at an earlier stage in high risk populations, before atrophy and metaplasia take place, may reduce cancer risk more markedly than has been reported in trials conducted to date. It is also possible that supplying adequate antioxidants have a role in cancer prevention, as suggested by the results of some trials.¹⁰

“The mechanisms by which the infection induces gastric cancer are mostly unknown”

Given the magnitude of *H pylori* infection (approximately 50% of the population worldwide), the most promising strategy for prevention should focus on high risk populations defined in terms of histopathology, pepsinogen levels, and molecular biology. Combining human polymorphisms of susceptibility¹⁹ and bacterial virulence²⁰ may further identify groups at the highest risk. Targeting earlier stages of the premalignant process in younger individuals may increase the likelihood of cancer prevention. As older subjects have entered the precancerous cascade, curing the infection does not guarantee 100% prevention. Endoscopic monitoring of identified high risk individuals is mandatory.

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EDITOR'S QUIZ: GI SNAPSHOT

Robin Spiller, Editor

Complications of an Addisonian crisis

Clinical presentation

A 60 year old man was admitted to our hospital with dehydration and fever, suggestive of the beginning of an Addisonian crisis. The pituitary had been resected for a prolactinoma 20 years previously. The patient could not take his hormone substitution medication due to severe gastroenteritis with nausea and vomiting. Blood pressure of 80/40 mm Hg, haemoglobin of 20 mg/dl, and haematocrit of 60% revealed haemoconcentration. Gastroscopy was performed to assess the upper gastrointestinal tract and showed that the longitudinal folds of the duodenum were covered by fibrinous erosions (fig 1A). Histopathological examination revealed an erosion with loss of superficial epithelial, inflammatory cells (neutrophils), necrotic epithelium, and fibrin. One week following treatment, endoscopy showed resolution of the lesions with flattening of the folds but no residual erythema or erosions. Histology now presented a normal duodenal mucosa with regular crypts and villi and no signs of inflammation (fig 1B).

Question

What was the pathophysiology of the mucosal damage and how should it be treated?

See page 1234 for answer

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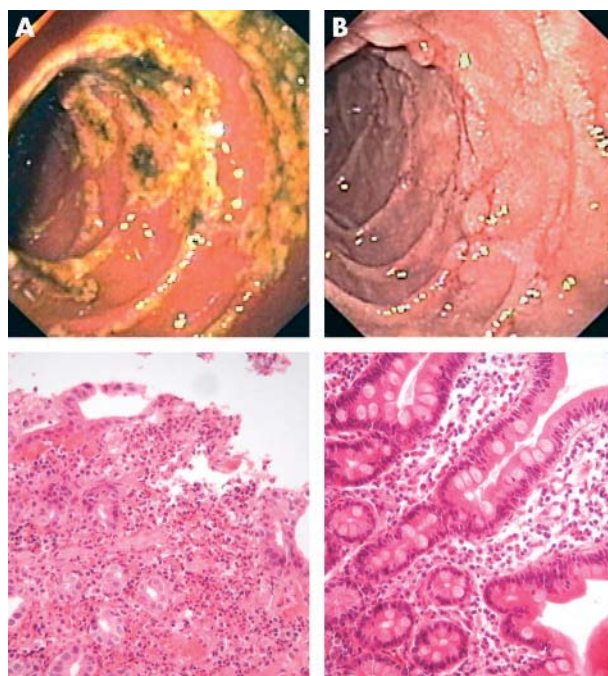


Figure 1 Endoscopic and histological appearance of the mucosal lesion before (A) and after (B) treatment.