Relationship between *Helicobacter pylori* gastritis, gastric cancer and gastric acid secretion

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Abstract

Epidemiological evidence strongly indicates that *Helicobacter pylori* infection is an essential factor for the development of most non-cardia gastric cancer. Furthermore, the identification of an effective animal model and a plausible biological hypothesis provide further compelling evidence for its pathogenic role. Nevertheless, it will be some years before prospective studies in humans are able to confirm cause and effect beyond any doubt. In the meantime sceptics point out that the prevalence of *Helicobacter pylori* in different countries do not always correlate with the incidence of gastric cancer. It is unclear why patients with duodenal ulcer (who are almost invariably infected) are protected from the disease. Cancer often develops in patients from whom *Helicobacter* disappeared from the stomach years previously. This paper discusses the relationship between *Helicobacter pylori* infection, the development of gastritis and its evolution to non-cardia gastric cancer. It also addresses possible reasons why the incidence of gastric cancer does not always mirror the prevalence of *Helicobacter* infection throughout the world and why patients with duodenal ulcer may be protected from developing gastric cancer.

Key words: *Helicobacter pylori*, non-cardia gastric cancer, antral predominant gastritis, corpus predominant gastritis, gastric atrophy, gastric intestinal metaplasia, gastric acid secretion.

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Introduction

It is generally accepted that gastric infection by *Helicobacter pylori* was the underlying cause for around 90% of gastric and duodenal ulcers that affected up to 10% of the population of Europe between the end of the 19th century and the middle of the 20th century. It still remains the most important cause of these diseases in many parts of the world. The causal relationship between *Helicobacter pylori* and gastric cancer, however, has been more difficult to prove. Whereas it was relatively simple to demonstrate that its eradication led to lasting cure of peptic ulcer disease, the length of time it takes for gastric cancer to develop following infection has led to logistic and ethical difficulties in designing prospective studies to show the same effect in this disease. Nevertheless, convincing retrospective epidemiological evidence indicates a relative risk of over 20 for patients who have been infected when compared with controls. Animal models show that infection with this class of organism and with *Helicobacter pylori* in particular leads to the development of gastric cancer. A plausible hypothesis for the pathogenesis of the disease based on experimental and observational work with *Helicobacter pylori* has convinced the majority of gastroenterologists that in its absence non-cardia gastric cancer would be rare, whereas this disease is at present the second commonest cause of malignant death in the world.

In spite of the evidence that *Helicobacter pylori* is responsible for the development of gastric cancer, a number of inconsistencies remain. Sceptics have pointed out that although infection with this organism is widespread in the developing world with a prevalence of around 80%, only a minority develop gastric cancer. More particularly the incidence of the disease varies widely from country to country even when figures are corrected for the age of the population and the numbers infected. Another observation is that the incidence of gastric cancer has fallen rapidly in the developed world. Although some of this change can be attributed to the decline in prevalence of *Helicobacter* infection, the fall in the incidence of cancer seemed to start

earlier and has fallen more rapidly than would have been predicted. Another surprising finding is that patients who develop duodenal ulcer and who are almost invariably infected with *Helicobacter pylori* are unlikely to develop gastric cancer even though they have been infected with *Helicobacter pylori* for many years. Furthermore, although gastric ulcer is known to be associated with gastric cancer, duodenal ulcers never become malignant in spite of the long standing, ulceration and inflammation caused by the organism.

Perhaps it is because of these epidemiological observations that the hypothesis stating that *Helicobacter pylori* is the cause of gastric cancer has met with some scepticism within the medical profession and the public health authorities. There has not been a strong lobby advocating total eradication of *Helicobacter pylori* in any country even in those with a high incidence of gastric cancer. This is in contrast to the overwhelming public and political pressure on governments to introduce colonoscopic screening for the prevention of colonic cancer, a policy which is more expensive and carries higher personal risks than a *Helicobacter pylori* eradication campaign.

This paper addresses the relationship between *Helicobacter pylori* infection, the development of gastritis and its evolution to cause non-cardia gastric cancer. The possible reasons why the incidence of gastric cancer does not always mirror the prevalence of *Helicobacter* infection throughout the world are also addressed.

Helicobacter pylori gastritis

Helicobacter pylori a gram negative, flagellated, curved organism is a parasite of the human gastric mucosa. It is adapted to colonize the mucus that overlies the specialized gastric epithelial cells to which it adheres, gaining nutrition and causing damage. During its evolution *Helicobacter pylori* has acquired a powerful urease that protects it from gastric acid and it has also developed mechanisms that enable it to evade the host immune system [1], so it usually persists within the stomach for many years, often indefinitely. All individuals infected with *Helicobacter pylori* have microscopic gastritis characterized by the infiltration of chronic inflammatory cells, with super added neutrophil leucocytes indicative of continued active inflammation. The gastritis varies in its severity between individuals. The pattern of inflammation may be limited to the antral region of the stomach, or it may affect the whole stomach, or predominantly affect the corpus [2].

Long continued inflammation if sufficiently severe causes destruction of the glandular mucosa of the stomach leading to atrophy and hypochlorhydria, and the gastric epithelial cells become metaplastic taking on the characteristics of intestinal mucosa. These changes are patchy initially, but they may eventually coalesce and progress to extensive intestinal metaplasia.

The association of *Helicobacter pylori* with gastric cancer

It has long been recognised that gastric cancer arises in stomachs that have developed atrophy and intestinal metaplasia [3].

Until *Helicobacter pylori* was discovered the only recognised cause of chronic atrophic gastritis was autoimmune gastritis but this accounted for only a minority of cases of gastric cancer. When it was realised that *Helicobacter pylori* caused chronic gastritis, leading to gastric atrophy and intestinal metaplasia, it seemed a reasonable assumption that this organism was responsible for most gastric cancer. Early epidemiological studies demonstrated a positive relationship between the prevalence of *Helicobacter pylori* in European countries and the incidence of gastric cancer [4]. Based on these data the IARC concluded that *Helicobacter pylori* was a Group 1 carcinogen causing gastric cancer by its destructive effect on the gastric mucosa and the development of intestinal metaplasia [5].

More persuasive data favouring the association has been derived from studies in which serum acquired from normal individuals some years previously for the purposes of long-term epidemiological studies in other diseases were analyzed for *Helicobacter pylori* antibodies. The results showed a strong association between the infection and the subsequent development of gastric cancer [6]. The odds ratio gave a relative risk of 2.36. An interesting observation was that those sera taken ten years previously gave a higher risk than those banked later at 5.9. When *Helicobacter pylori* has been present for many years and the stomach becomes atrophic and hypochlorhydric the intragastric environment is no longer optimal for *Helicobacter pylori*. Competing faecal type organisms are able to colonize the stomach at that stage. Furthermore, *Helicobacter pylori* is able to colonize only normal gastric cells, not those that have differentiated into intestinal metaplasia. For these reasons *Helicobacter pylori* disappears from the stomach when atrophy and intestinal metaplasia supervenes. In its absence the antibody titre declines. Thus in patients who are most likely to develop gastric cancer (those with extensive intestinal metaplasia and atrophy) the serology is often negative. Epidemiological research based on ELISA studies for *Helicobacter* serology have therefore underestimated the relative risk of infection. When studies are done on younger patients with gastric cancer, particularly those with early gastric cancer, the risk ratio is as high as 20 [7].

In a recent paper antibodies to the CagA protein were studied [8]. CagA is an antigen present in most of the *Helicobacter pylori* organisms that are responsible for peptic ulcer and gastric cancer. Unlike the antibodies detected by the standard ELISA techniques those to CagA remain in the serum long after the organism has disappeared. When this technique was used to assess *Helicobacter* infection the risk ratio for infection rose to 20, similar to that found in young people with early cancer. This risk is of an order that suggests *Helicobacter* to be essential for the development of non-cardia gastric cancer in nearly all cases.

Animal models

Helicobacter pylori infection in humans is unusual in that it invariably causes inflammation. This is in contrast to the majority of other vertebrates. Although most are infected with species specific *Helicobacter*. In the main these do not cause inflammation. It was some time before a suitable model could

be identified that mirrored the human condition. The most useful one is the *Mongolian gerbil*. This animal can be infected by *Helicobacter pylori* and it causes an inflammation similar to that in humans [9,10]. It causes gastric ulceration, atrophy and intestinal metaplasia. If the animals are kept alive long enough gastric cancer develops [11]. Eradication of the organism at an early stage prevents progression to cancer when compared with those who are not given treatment [12,13].

How does *Helicobacter pylori* cause cancer?

Considerable experimental work has been undertaken to elucidate the pathogenic mechanism that leads from *Helicobacter* infection to the development of cancer. Inflammation induces a hyperproliferative state suggesting that there may be a greater likelihood of mutation [14]. The inflammatory response also stimulates the production of reactive oxygen species [15] that are known mitogens. Apart from the secondary effects of the inflammatory reaction *Helicobacter pylori* itself subverts cell physiology by activating growth factor receptors, increasing cell proliferation, reducing apoptosis and inducing angiogenesis [16]. Some, or all of these factors, may be relevant in the pathogenesis of gastric cancer, however, on their own they do not fully account for the development of gastric cancer.

Non-cardia gastric cancer is associated with gastric atrophy and intestinal metaplasia, however, the distribution of the epithelial damage is of even more importance. A Japanese study has shown that cancer does not arise in patients with antral gastritis such as is found in duodenal ulcer (patients with duodenal ulcer have long been known to have a surprisingly low incidence of gastric cancer). Cancer develops in individuals who have pan or corpus predominant gastritis where the odds ratio is around 34 [17]. If *Helicobacter pylori* had a direct carcinogenic effect through the mechanisms set out above gastric cancer would also be common in patients with antral predominant gastritis. The severity of inflammation in in these cases is similar or more severe than that which occurs in the corpus. If the cancers that arise in patients with corpus predominant gastritis were usually found in the corpus it could be argued that the corpus mucosa has a greater propensity to become malignant than the antral mucosa, however, in these cases, gastric cancer is usually found in the antrum so this theory does not hold.

It seems that the mechanism responsible for inducing cancer results from the physiological changes that accompany the development of atrophy and intestinal metaplasia within the gastric corpus. This implies that *Helicobacter pylori* itself or the inflammation that it produces cannot be the direct cause of gastric cancer.

## The pattern of gastritis in relation to gastric acid secretion

When individuals are first infected with *Helicobacter pylori* there is an acute pan gastritis associated with achlorhydria [18]. The cause of the achlorhydria is not fully understood, but can persist for months or even years. The acute inflammation may impair the ability of parietal cells to secrete acid by a direct effect. However, the generation of the inflammatory response involves secretion of interleukin-1 beta [19]. This is a pro-inflammatory cytokine but is also an extremely powerful acid inhibitor. This may be responsible for the hypochlorhydria. With the passage of time the acute inflammation gradually settles and is replaced by the typical acute on chronic infection seen in patients with long standing *Helicobacter* infection. With the decline in acute inflammation the stomach again starts to secrete acid. It seems that the amount of acid that the stomach secretes is what determines the pattern of the gastritis, i.e. whether the whole of the stomach will be inflamed (pan gastritis) or whether the inflammation will be limited to the antrum. If there is a high acid secretion the inflammation in the corpus diminishes and the parietal cells secrete more acid. Furthermore, the antral inflammation affects the gastrin and somatostatin secreting cells (those that are responsible for controlling the amount of gastrin secreted) the effect is to hyperstimulate the parietal cells. Thus antral predominant gastritis is associated with a high acid secretion, whilst pan gastritis or corpus predominant gastritis is associated with a low acid secretion. Those with antral gastritis have a propensity to develop duodenal ulcer the others with a corpus gastritis may develop gastric ulcer. The long-term effects of these differences are even more profound because in those with an antral predominant gastritis, atrophy and intestinal metaplasia is limited to the antral region where there are no acid secreting cells. Long standing inflammation in the corpus, however, leads to atrophy, intestinal metaplasia which affects the parietal cells and causes a further reduction in acid secretion [20].

The normal stomach is not colonized with bacteria and in the majority of individuals who are infected with *Helicobacter pylori* the only colonizing species is *Helicobacter pylori*. This is because gastric acid serves as a bacteriocidal barrier ensuring that ingested food containing infecting organisms do not pass into the rest of the gastrointestinal tract. In the absence of gastric acid, however, the stomach rapidly becomes colonized. This happens even in normal individuals who take regular proton pump inhibitors or H2 receptor antagonists [21]. Bacterial colonization is more prominent in patients who have corpus atrophy and hypochlorhydria where a wide range of faecal organisms may colonize the stomach. Many of these are metabolically active and produce a variety of potential carcinogens. In the years before *Helicobacter pylori* had been identified it was hypothesized that the direct cause of gastric cancer was the production of N-nitrosamines by colonizing bacteria within the stomach [22]. Nitrosamines are known carcinogens and they induce gastric cancer in the experimental animal. N-nitrosamines are labile chemicals and difficult to work with. Since *Helicobacter pylori* was found to be associated with gastric cancer, the nitrosamine hypothesis has not been promulgated to the same extent that it was in earlier years. Nevertheless, this remains a possible explanation as to why cancer develops in patients with gastric atrophy and intestinal metaplasia.

Ascorbic acid is believed to protect against a number of carcinogens including reactive oxygen species and nitrosated compounds. Normal individuals have a high concentration of ascorbic acid in their gastric juice, indeed the concentration is

Figure 1. **Potential outcomes following *H. pylori* infection**
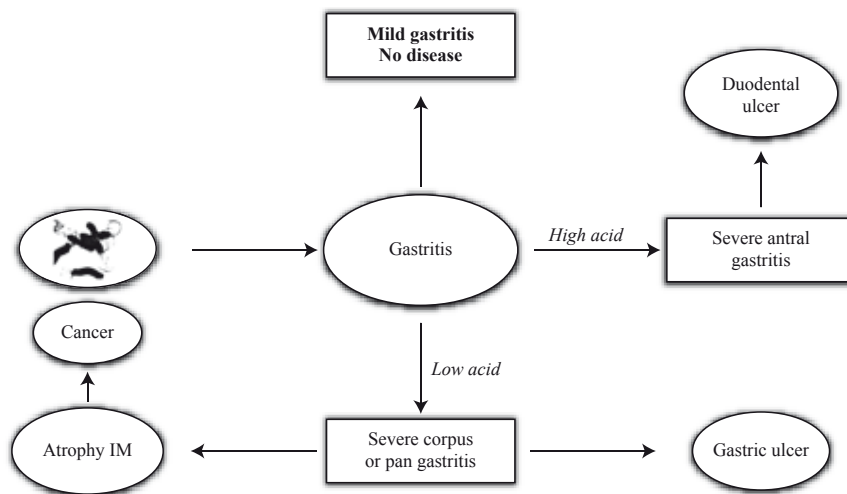
higher than that present in the plasma, it is in effect "secreted" into the stomach. When infected by *Helicobacter pylori* this secretory mechanism disappears, however, in the presence of achlorhydria, not only is there a reduced secretion, but ascorbic acid is rapidly destroyed and is no longer detectable [23].

The presence of faecal organisms within the stomach may be responsible for further damage arising within the mucosa, in particular it may accelerate the development of intestinal metaplasia [24].

Helicobacter pylori may not therefore be directly responsible for gastric cancer. It seems more likely that the organism sets the scene for its development by destroying the ability of the stomach to secrete acid in addition to causing direct injury to the gastric epithelium through inflammation.

Why does the incidence of gastric cancer vary?

There is a positive relationship between the prevalence of *Helicobacter pylori* and the incidence of gastric cancer. However, there are some notable exceptions. The subcontinent of India has a high prevalence of *Helicobacter pylori*, but a modest incidence of cancer. The same applies to parts of Africa, whilst in the Far East where there is a similarly high prevalence of *Helicobacter pylori*, gastric cancer is much more common. The same obtains to a lesser extent in Russia and the Eastern part of Europe. Certain countries in South America have an extremely high cancer rate, but others somewhat lower.

In the Western part of Europe and the United States the incidence of gastric cancer has fallen rapidly over the past century. This has been attributed to the decline in the prevalence of *Helicobacter pylori*. However, the evidence for this is not totally persuasive. It is true that the prevalence of *Helicobacter* has fallen, but the decline is mainly in younger people. When the elderly population is considered (the ones who are currently at risk of gastric cancer) the incidence of cancer has fallen more than would have been anticipated.

Factors other than *Helicobacter pylori* prevalence influence the incidence of gastric cancer. As indicated earlier gastric cancer is found in individuals who have severe corpus atrophy and intestinal metaplasia. It is the pattern of the infection and its severity which is important (*Fig. 1*). Antral predominant infection is not positively associated with the development of cancer. Few studies have addressed the issue as to whether the pattern and severity of gastritis varies between populations. A recent paper prospectively studied age matched cohorts of patients in England and Japan [25]. The incidence of cancer in Japan is substantially higher than that in England. The study showed the prevalence of infection to be only slightly higher in the Japanese group, but the major difference between the populations was the pattern of the gastritis. English patients were more likely to have an antral predominant gastritis as compared to the Japanese where there was a higher prevalence of pan and corpus gastritis. Furthermore corpus atrophy and intestinal metaplasia was enormously higher in the Japanese than in the English patients especially in the older cohorts. It is possible that some international differences in the incidence of cancer may relate not only to the number of individuals infected, but to the phenotype of the gastritis.

The severity of gastritis varies between patients and is influenced by the virulence of the infecting *H. pylori* strain. The presence, for example, of the Cag pathogenicity island increases the pathogenic potential of the organism [26]. There are other variations between the strains including sub-types of the vacuolating cytotoxin that increase the virulence of the organism. *Helicobacter* strains vary considerably and recent work shows that there are geographical differences, for example, a higher percentage of strains in the Far East are CagA positive as opposed to those in Europe [27]. It is likely that there are other strain differences as yet unknown that have a geographical selection, causing a greater severity of inflammation in certain parts of the world than others.

A low acid secretion is associated with a pan gastritis or corpus predominant gastritis and a high acid with antral gastritis. If an acid suppressant is prescribed, the pattern of antral gastritis

changes to a pan gastritis [28]. The amount of acid secreted by individuals varies enormously. Not all of the factors responsible for this are known, however, malnutrition is a recognised cause of hypochlorhydria [29] and gastric acid secretion is proportional to lean body mass [30]. Populations vary in their nutrition and in the size of their citizens so these are possible factors that might influence the pattern of gastritis.

Individuals respond to infection with *Helicobacter pylori* by the production of a series of cytokines. These are subject to variation. In particular, interleukin-1 beta has a number of polymorphisms, that is to say the molecular composition of the protein varies slightly according to the genetic make up of the individual. Tiny changes in these molecules may radically alter their activity. Certain polymorphisms are positively associated with gastric cancer [31] so it is possible that racial differences may influence the inflammatory response that certain populations have to an infecting organism both in terms of the pattern of gastritis and its severity.

Summary

The discovery of *Helicobacter pylori* has revolutionized our understanding of the pathology of the stomach and duodenum. There is strong evidence to suggest that this organism is responsible for nearly all non-cardia gastric cancer. The disease, however arises primarily in individuals who have had a severe corpus predominant inflammation whilst those with an antral predominant gastritis are relatively protected from the disease. This suggests that *Helicobacter pylori* is not directly responsible for the development of cancer, but that by destroying the acid secreting part of the stomach and inducing a generalized inflammation it sets the scene for other mechanisms to act directly on the mucosa and it is these that cause the transition from a diseased, albeit stable mucosa, to neoplasia. It is unclear which factors are ultimately responsible for the malignant change and more work is required in this area to elucidate the pathogenesis of the disease. Nevertheless, *Helicobacter pylori* is responsible for inducing the premalignant lesion that develops into cancer, in its absence gastric cancer would be extremely rare.

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