Does *Helicobacter pylori* protect against oesophageal adenocarcinoma, and if so, how?

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Helicobacter pylori infection is becoming less common in developed countries. As expected, the diseases it causes – peptic ulceration and gastric adenocarcinoma – are also becoming less common, although both are still major public health problems. Over a similar timeframe, the incidence of oesophageal adenocarcinoma (but not oesophageal squamous cell carcinoma) has risen sharply.[1–3] There is now good evidence of a causal link explaining these opposing time trends: at a population level, lifelong *H. pylori* infection protects against oesophageal adenocarcinogenesis. The mechanisms underlying this appear straightforward and the supporting evidence is strong and consistent.

Oesophageal adenocarcinoma is a complication of long-standing uncontrolled gastro-esophageal reflux disease (GORD).[4,5] The squamous epithelium of the oesophagus, when chronically damaged by acid refluxate, undergoes gastric metaplasia and subsequently intestinal metaplasia; it changes to a Barrett's oesophagus. This is a risk factor for oesophageal adenocarcinoma but not squamous cell carcinoma. GORD results from loss of lower oesophageal sphincter function. Many patients will have a hiatus hernia, a lax lower oesophageal sphincter and/or increased transient lower oesophageal sphincter relaxations (TLOSRs). Superficially it is unclear how *H. pylori* could contribute as it has no demonstrated effect on lower oesophageal sphincter structure or function.[6] It does have an effect on gastric acidity, however, and the acidity of the gastro-oesophageal refluxate is clearly an important contributor to disease – suppressing it with drugs is effective treatment for GORD.

Helicobacter pylori and acid

Helicobacter pylori infection can result in increased or reduced gastric acidity. Some infected people have an antral-predominant inflammation and these people have increased stimulated gastric acid output from the parietal cells in the un-inflamed gastric corpus, and are prone to duodenal ulceration.[7,8] However, it is more common to have a degree of inflammation in the gastric corpus and many people have severe inflammation here. This results in reduced gastric acid production and a proportion of these people develop gastric atrophy, intestinal (and other types of) metaplasia and sometimes distal gastric adenocarcinoma.[9] The atrophy itself further lowers acid production. Thus, in patients who have gastro-oesophageal reflux due to structural or functional impairment of the lower oesophageal sphincter, *H. pylori* infection may increase or reduce oesophageal acid exposure. At an average level in the population, as reduced acid secretion by *H. pylori* is more common, oesophageal acid exposure will be reduced.

H. pylori and GORD complications in East Asia

The above hypothesis predicts a complicated relationship between *H. pylori* infection and the acidity of gastro-oesophageal refluxate and so a complicated relationship between *H. pylori*, GORD and its complications (although with a net negative association between *H. pylori* and GORD prevalence[10]). However, in some populations a simpler association is expected. In Japan and China, gastric adenocarcinoma is very common because, firstly, nearly all strains are of the most virulent pro-inflammatory cagA-positive cytotoxic type and secondly because such strains usually cause a pan- or corpus-predominant gastritis in these populations with associated reduced acid secretion.[11] Thus in these populations, *H. pylori* would be expected more predictably to have a negative association with GORD and its complications, Barrett's oesophagus and oesophageal adenocarcinoma. This is indeed the case: studies from these countries consistently show a strong negative association.[12–17]

The effect of cytokine gene polymorphism

In developed countries, a major determinant of gastric cancer risk is pro-inflammatory genetic polymorphisms in the *IL-1b* gene (encoding interlukin-1β) or in other pro-inflammatory cytokine genes.[18] In the case of *IL-1b*, these same polymorphisms are an even stronger risk factor for gastric hypochlorhydria, and this is thought to be on the causal pathway to gastric adenocarcinoma.[18] Several studies have shown that these polymorphisms, as would be expected, offer relative protection against reflux oesophagitis and its complications in *H. pylori*-infected people.[19–21]

In developed countries, individuals are infected with *H. pylori* strains of differing pathogenicity. The most pathogenic strains increase the risk of peptic ulceration and gastric adenocarcinoma largely through increasing gastric inflammation, and as the corpus is often involved these strains most commonly suppress acid production.[8] Thus, at a population level they would be expected to reduce the acidity of gastro-oesophageal refluxate in people who have reflux and thus to have a more pronounced negative association with GORD and its complications than less pathogenic strains. This is found to be the case.[2,19,22–25]

As the initial cause of gastro-oesophageal reflux is sphincter disturbance, whereas its severity is contributed to by high acid levels in the refluxate, it is to be expected that the negative association with *H. pylori* will be stronger for more severe disease. For example, it should be stronger for oesophageal adenocarcinoma than for Barrett's oesophagus; stronger for long segment than short segment Barrett's; and stronger for severe reflux oesophagitis than more mild disease. This has been found in published studies.[14,17,22,2] Furthermore, there is a stronger negative association between *H. pylori* infection and endoscopically-

demonstrated reflux oesophagitis than between *H. pylori* and GORD without macroscopic oesophagitis.[26–28]

H. pylori treatment studies

The most confusing and controversial studies concerning the association of *H. pylori* with reflux oesophagitis are *H. pylori*-treatment studies. As *H. pylori* infection can increase or reduce gastric acidity and so the acidity of gastro-oesophageal refluxate, it is to be expected that the results of such studies should be complex. However, also as expected, they are simpler in Far Eastern populations where *H. pylori* infection is consistently associated with reduced acid secretion. In these countries treatment at a population level provokes or worsens reflux and at an individual level may provoke or worsen it or (most commonly) not affect it at all.[29–33] This is because increasing gastric acidity following *H. pylori* treatment will not affect oesophageal symptoms unless the individual is prone to gastro-oesophageal reflux – that is they have a deficient lower oesophageal sphincter.[34] The studies are entirely consistent with this: it is people with a hiatus hernia or with a weak lower oesophageal sphincter who develop reflux oesophagitis after *H. pylori* treatment.[29–33]

In Western countries, the effects of *H. pylori* treatment on precipitating or worsening GORD are much more variable and this has lead to considerable controversy.[30,35,37] However, varying responses of GORD to *H. pylori* treatment are to be expected given the complex and differing effects of *H. pylori* on gastric acidity, the fact that some people will have changed gastric acidity after treatment but some (for example those with gastric atrophy) may not, and the fact that different individuals have varying degrees of impairment of the lower oesophageal sphincter.

Practical patient management

Given that most clinicians treating *H. pylori* will not assess pre-treatment gastric acid secretion or take biopsies to compare inflammation due to *H. pylori* in the gastric antrum and corpus, should concerns about precipitating or worsening reflux oesophagitis affect the decision of whether or not to treat *H. pylori*? A commonsense approach is to treat *H. pylori* if there is an indication to do so as, at an individual level, there will likely be no effect on reflux symptoms and if there is an effect it will be unpredictable. If GORD is precipitated or worsened, this can easily be treated using acid suppressing drugs.

In patients with demonstrated GORD who have *H. pylori*, the decision on whether to treat the infection is controversial. In favour of treatment, if the patient requires proton pump inhibitors (PPIs) there is evidence that gastric atrophy may be induced if they are *H. pylori* positive, and this is a known risk factor for gastric carcinogenesis.[38,39] Although no studies have demonstrated an increase in gastric adenocarcinoma incidence in patients with *H. pylori* given PPIs, the pessimists would argue that the timeframe has so far been too short and that such an increase may occur in the future.[40] On the other hand, acid suppression with PPIs is often more effective in people with *H. pylori* infection, leading to better symptom control.[41–43] Also, if PPIs are stopped, rebound acid hypersecretion occurs in *H. pylori* negative but not *H. pylori* positive individuals.[44] My own practice is to treat *H. pylori* in young and early middle-aged individuals who will require long-term PPI treatment to control their GORD but not to do so in the elderly. However, I accept that this is an area in which more evidence is needed to develop a logical management plan. Perhaps, as Professor Rhodes says of *H. pylori* and oesophageal adenocarcinoma, this should be 'another story'.

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