

## ***Helicobacter pylori* infection and gastroesophageal cancer: unveiling a Hamletic dilemma**

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In the last decades, the incidence of gastric cancer has decreased in Western countries, whilst that of gastroesophageal junction has progressively increased [1]. This has triggered a lot of studies aiming to unveil environmental causes potentially involved in these trends [2]. The reduction in *Helicobacter pylori* (*H. pylori*) infection rate in the general population, mainly due to improvement in socio-economic conditions, was postulated to be one of the most likely factors for these opposite phenomena. Indeed, data on the causal role of *H. pylori* infection in distal gastric cancer are consistent, so it has been classified as a type I carcinogen [3]. On the other hand, some epidemiological data suggest that the prevalence of *H. pylori*, particularly cytotoxin-associated gene A (CagA)-positive strains, is lower in erosive esophagitis, Barrett's esophagus, and in patients with cancer of the gastroesophageal junction [4-6].

To elucidate the possible mechanism involved, an interrelationship between *H. pylori* infection, atrophic gastritis and the reflux disease spectrum (from non-erosive esophagitis to cancer of the gastroesophageal junction) has been proposed [7]. Basically, the protective role of *H. pylori* has been attributed to a bacterial-induced corpus-predominant gastritis, responsible for a reduced gastric acid output [8]. The healing of this type of gastritis following bacterial eradication restores the acid secretion and consequently should produce increased acid reflux, causing symptoms and/or lesions, and progressively cancer [4,7]. Therefore, persistent *H. pylori* infection should be, at least in theory, advantageous in patients with corpus-predominant gastritis in terms of prevention of cancer of the gastroesophageal junction. However, it is widely accepted that *H. pylori*-related corpus-predominant gastritis, particularly with CagA-positive strains, is the main risk for distal gastric cancer development [9], which still represents the third cause for cancer-related mortality worldwide [10]. Therefore,

*H. pylori* eradication would be particularly advantageous in patients with corpus-predominant gastritis in terms of distal gastric cancer prevention [11,12]. Consequently, a physician with a patient presenting with *H. pylori*-associated corpus-predominant gastritis, at least in theory, is faced with a Hamletic dilemma: curing the infection to prevent distal gastric cancer or not curing the infection to potentially reduce the risk of tumor of the gastroesophageal junction?

The decision-making process becomes even foggier when different recommendations by the experts currently available in the literature are considered. According to one point of view, the increasing incidence of gastroesophageal cancer is strictly due to the global reduction in *H. pylori* prevalence and, consequently, the convenience of bacterial eradication in all dyspeptic patients without gastroduodenal lesions should be at least reconsidered [13]. On the other hand, the Maastricht IV Consensus Report suggests eradicating the infection even in patients with reflux disease [14]. Indeed, a prolonged proton pump inhibitor therapy, frequently required in these patients, could favor the development of corpus-predominant gastritis, atrophy and, ultimately, distal gastric cancer onset [11].

What do physicians have to do in such a conflicting scenario? By looking at the available data in more detail, some consistent information could help make the proper decision. A recent study found that *H. pylori* infection (OR 0.53; 95%CI 0.29-0.97), particularly with the CagA-positive strains (OR 0.36; 95%CI 0.14-0.90), was associated inversely with Barrett's esophagus, but not significantly associated with either reflux symptoms or erosive esophagitis [15]. A meta-analysis of 10 trials showed that the incidence of either reflux symptoms or erosive esophagitis did not significantly differ between patients cured for *H. pylori* infection and those receiving placebo at long-term follow up [16]. Furthermore, at least 5 pH-metric studies not only failed to demonstrate acid reflux in the esophagus following bacterial eradication but in some cases an improvement was even reported [17]. Similarly, manometric studies found either no difference in basal lower esophageal sphincter (LES) pressure between *H. pylori*-infected and matched uninfected controls or lower basal LES pressure and higher rate of ineffective esophageal motility in infected patients [18]. All these data seem to suggest that *H. pylori* is protective for Barrett's esophagus, but not for reflux symptoms. However, a long-lasting history of reflux symptoms was found to be an independent risk factor for esophageal adenocarcinoma [19]. The reasons for which active *H. pylori* infection does not prevent reflux symptoms (risk factor), whilst, at the same time, is not able to prevent Barrett's esophagus

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Conflict of Interest: None

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Received 5 July 2014; accepted 7 July 2014

(precancerous condition for cancer of gastroesophageal junction) remains unclear. A recent retrospective study on 152 gastric cancer patients showed that prevalence of both *H. pylori* infection (78.1% vs. 82.3%) and CagA-positive strains (77.2% vs. 84.6%) were similar in proximal (gastroesophageal junction plus fundus) and distal gastric cancers patients [20]. Furthermore, *H. pylori* bacteria are frequently detected on the cardia mucosa where they provoke so-called 'carditis' [21]. Such a chronic inflammatory process could be involved, at least in theory, in the carcinogenesis of the gastroesophageal junction. Finally, the potential role of a complex microbiome of distal esophagus in the development of the cancer of the gastroesophageal junction is of current interest [22]. Therefore, the inverse relationship between cancer of the gastroesophageal junction and *H. pylori* prevalence could merely represent a spurious association, and alternative pathogenetic pathways should be explored. For instance, the prevalence of obesity is relentlessly increasing in developed countries [23]. There is evidence that such a condition favors chronic gastroesophageal reflux, and an epidemiological association between visceral obesity and gastroesophageal cancer has been also reported [24]. Obviously, this would marginalize the protective role of *H. pylori* infection. Nevertheless, some data suggest that the reduction in *H. pylori* infection prevalence would be the *primum movens* causing obesity which, in turn, is associated with reflux disease [24,25]. Therefore, the culprit bacterium, according to an Italian popular saying, 'just got away from the window and suddenly entered from the door', so the saga continues!

While waiting for a definitive solution, following common sense would appear to be the best approach. From an epidemiological point of view, the actual data suggest that the risk of distal gastric cancer in patients with persistent *H. pylori* corpus-predominant gastritis is distinctly higher than the risk of developing cancer of the gastroesophageal junction following bacterial eradication. For the patient, the clinical advantage of *H. pylori* eradication is greater than the reduced distal gastric cancer risk. Indeed, curing the infection clears dyspeptic symptoms in nearly 40% of cases, reduces peptic ulcer incidence and abolishes its recurrence, strongly reduces the risk of gastric lymphoma onset, idiopathic thrombocytopenic purpura, and idiopathic iron deficiency anemia development, and in addition prevention of synergistic damage with the contemporary use of non-steroidal anti-inflammatory drugs is also expected [26-28]. All these clinical advantages surely counterbalance the potential onset of reflux diseases in a subgroup of patients who, ultimately, may be successfully controlled with proton pump inhibitor therapy.

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