

## Helicobacter pylori and colorectal cancer: Is there any link?

G.J. Mantzaris

Bacterial infections have, traditionally, not been considered major causes of human cancer. However, specific bacteria may be implicated in the carcinogenesis process via the induction of chronic inflammation and production of carcinogenic bacterial metabolites. *H. pylori* is the first bacterium accepted by the International Agency for Research on Cancer as a definite cause of gastric cancer in humans. This association is supported by epidemiological data and a series of research observations. It is envisaged that *H. pylori* establishes a lifelong inflammation resulting in increased cell proliferation, production of mutagenic free radicals and N-nitroso compounds and, finally, development of gastric carcinoma.<sup>1</sup>

It has been suggested that *H. pylori* has not only local but also systemic effects, including the development of cancer in extra gastric target organs, such as pancreatic and colorectal cancer (CRC). CRC is one of the commonest forms of cancer worldwide and one of the leading causes of death. It has been attributed to genetic, dietary and other environmental factors, and growth factors. In addition, bacterial metabolites with mutagenic propensity, bile salt metabolites, *Bacteroides* species and local bacterial infections may increase the risk of CRC.<sup>1</sup> *H. pylori* and its vacuolating toxin A has been detected in the stools of patients with *H. pylori* infection and *H. pylori* DNA has been identified in the colon of dyspeptic patients, suggesting that *H. pylori* may cause disease in the colon.<sup>2</sup> However, the significance of these observations is questionable and there is no direct link between *H. pylori* infection and the development of CRC. *H. pylori* is not a true invader and does not reside in the human

colon except in unusual circumstances. Therefore, the link of *H. pylori* infection to CRC, if any, is probably exerted via inflammatory mediators, hormones, and/or growth factors which are produced at the site of the primary infection and released into the systemic circulation.

Gastrin is a candidate trophic factor that can possibly mediate the effects of *H. pylori* on tumours. Patients with *H. pylori* infection have increased basal and postprandial serum levels of gastrin. Thus, a plausible hypothesis is that *H. pylori* infection promotes colonic neoplasia by inducing hypergastrinaemia. Then, gastrin increases the expression of cyclooxygenase 2, a pro-inflammatory enzyme that releases excessive amounts of prostaglandin E2, leading to further mucosal proliferation, reduction of apoptosis, angiogenesis and tumour growth.<sup>3</sup> Patients with CRC and *H. pylori* infection have higher serum levels of gastrin compared with non-infected CRC patients and these levels are restored to normal if *H. pylori* infection is successfully eradicated.<sup>4</sup> Siddheshwar *et al* have also reported that plasma levels of progastrin, but not amidated gastrin or glycyl-extended gastrin, are significantly increased in patients with CRC over patients with CRA or healthy individuals.<sup>5</sup> However, gastrin may exert its trophic action at physiological levels or even by an autocrine or paracrine action. Indeed, immunoreactive gastrin, gastrin receptors, mRNA of COX-2, and anti-apoptotic protein Bax are overexpressed in CRC tissues compared with healthy colonic mucosa, whereas expression of the pro-apoptotic protein Bcl2 is down-regulated.<sup>3,6</sup> Thus, part of hypergastrinaemia in CRC patients may be accounted for by gastrin secretion by the tumour itself.

The hypothesis for a true association between *H. pylori* infection and CRC was unexpectedly raised by early uncontrolled studies showing a higher than expected proportion of patients harbouring colorectal adenomas (CRA) and/or CRC to be concurrently infected by *H. pylori*. Actually, it should be emphasized that in some

*A' Gastroenterology Clinic, "Evangelismos" General Hospital, Athens, Greece*

*Author for correspondence*

G.J. Mantzaris, 8b Strymonos street, 145 61 – Kifissia, Athens, Greece, Tel. 0030-210-8086967, e-mail: gman195@yahoo.gr

studies, the seroprevalence of *H. pylori* was higher in patients with CRC or lung cancer than in patients with gastric cancer.<sup>4,7</sup> However, even at those early days, there were controlled studies showing that the relationship between *H. pylori* infection and CRC either did not exist or was not independently associated with CRC.

These preliminary observations triggered worldwide interest in the actual implication of *H. pylori* as a risk factor for the development of CRC. The results of these case-control trials are highly controversial and contradictory. Moss *et al* did not confirm any association between the presence of *H. pylori* infection and the risk of development of CRC.<sup>8</sup> This was also confirmed by Siddheshwar *et al*. In their study logistic regression analysis showed no difference in seroprevalence of *H. pylori* between CRA or CRC patients and controls (OR 1.3 and 1.1, respectively).<sup>7</sup> In contrast, Meucci *et al*, found a significant relationship between seroprevalence of *H. pylori* and the risk of developing colorectal adenomas (CRA) but not CRC (9). Regarding the association of *H. pylori* to CRA, Breuer-Katschinski *et al* reported that patients with *H. pylori* infection had an increased risk of developing CRA compared with population controls but not hospital controls [OR 2.6 (1.3-5.4) and 1.6 (0.80-3.4), respectively].<sup>10</sup> Fireman *et al* found that *H. pylori* infection was more prevalent in patients with colorectal cancer ( $p = 0.05$ ) but no association was found between serum levels of CEA and IgG anti-Hp antibodies, nor between serum gastrin level and CRC.<sup>11</sup> Finally, Konturek *et al* have recently reported that seroprevalence of *H. pylori*, especially that expressing CagA, and levels of IL-1beta, a tumour promoting cytokine, but not other cytokines, were significantly higher in CRC patients than in 100 age, gender, and profession-matched controls and did not change significantly 3-6 months after tumour resection.<sup>6</sup>

All these case-controlled studies (as well as some reports in abstract form) are small and marked by inadequate or inappropriate methodology (selection bias, inadequate matching of patients and controls, especially for age, sex and socioeconomic status, not adjusted for confounding factors, etc), and flaws in interpretation of data. Thus, the currently available data is still limited,

contradictory and, therefore, inconclusive to support an aetiological role for *H. pylori* infection in the pathogenesis of CRC. Until robust data from well-designed case-control studies are available, this association remains purely hypothetical.

## REFERENCES

1. Parsonnet J. Bacterial infection as a cause of cancer. *Environ Health Perspect*. 1995; 103 [Suppl 8]:263-268.
2. Kelly SM, Pitcher MCL, Farmery SM, *et al*. Isolation of *H. pylori* from the feces of patients with dyspepsia in the United Kingdom. *Gastroenterology* 1994; 107:1671-1674.
3. Hartwich A, Konturek SJ, Pierzchalski P, *et al*. *Helicobacter pylori* infection, gastrin, cyclooxygenase-2, and apoptosis in colorectal cancer. *Int J Colorectal Dis*. 2001; 16:202-210.
4. Penman ID, el-Omar E, Ardill JE, *et al*. Plasma gastrin concentrations are normal in patients with colorectal neoplasia and unaltered following tumour resection. *Gastroenterology* 1994; 106:1263-1270.
5. Siddheshwar RK, Gray JC, Kelly SB. Plasma levels of progastrin but not amidated gastrin or glycine extended gastrin are elevated in patients with colorectal carcinoma. *Gut*. 2001; 48:47-52.
6. Konturek PC, Bielanski W, Konturek SJ, *et al*. Progastrin and cyclooxygenase-2 in colorectal cancer. *Dig Dis Sci*. 2002; 47:1984-1991.
7. Siddheshwar RK, Muhammad KB, Gray JC, Kelly SB. Seroprevalence of *Helicobacter pylori* in patients with colorectal polyps and colorectal carcinoma. *Am J Gastroenterol*. 2001; 96:84-88.
8. Moss SF, Neugut AI, Garbowski GC, Wang S, Treat MR, Forde KA. *Helicobacter pylori* seroprevalence and colorectal neoplasia: evidence against an association. *J Natl Cancer Inst*. 1995; 87:762-763.
9. Meucci G, Tatarella M, Vecchi M, *et al*. R. High prevalence of *Helicobacter pylori* infection in patients with colonic adenomas and carcinomas. *J Clin Gastroenterol* 1997; 25:605-607.
10. Breuer-Katschinski B, Nemes K, Marr A, *et al*. *Helicobacter pylori* and the risk of colonic adenomas. *Colorectal Adenoma Study Group. Digestion*. 1999; 60:210-215.
11. Fireman Z, Trost L, Kopelman Y, Segal A, Sternberg A. *Helicobacter pylori*: seroprevalence and colorectal cancer. *Isr Med Assoc J*. 2000; 2:6-9.