

Helicobacter pylori infection and colorectal carcinoma: is there a causal association?

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To the Editor,

We would like to thank Dr. Kapetanakis and his colleagues for their interest in our article (1). We specifically appreciate the attention they brought to the importance of environmental factors, particularly *Helicobacter pylori* (*H. pylori*) infection, in the development of sporadic colorectal carcinoma (CRC). While the focus of our article was on the pathologic aspects (2), we would like to take this opportunity to extend our discussion to *H. pylori* as a potential etiopathogenetic factor in colorectal tumorigenesis.

As mentioned by Dr. Kapetanakis and his colleagues, the development of sporadic CRC is associated with a variety of environmental factors including diet and lifestyle. Given that the colon harbors the largest number of microorganisms in the body, it is natural to assume that certain microbial species may play a role in colorectal tumorigenesis. The first reports connecting intestinal microflora with CRC were published back in the early 1950s. *Streptococcus bovis* septicemia was reported to be associated with carcinoma of the sigmoid colon (3). This association was subsequently supported by several publications (4-6). Animal studies have shown that *S. bovis* or its cell wall antigens promote the formation of hyperproliferative aberrant colonic crypts, enhance the expression of proliferation markers, and increase IL-8 production in the colonic mucosa (7). IL-8 is a proinflammatory cytokine that has been shown to promote the growth, angiogenesis and metastasis of colon cancer cells (8-11). Taken together, these observations suggest that *S. bovis* acts as a promoter of colorectal tumorigenesis.

Later on in the mid-1970s, experiments with germ-free rats further showed that intestinal microflora played a modifying role in colorectal tumorigenesis. Germ-free rats developed much fewer colonic tumors compared to conventional rats when challenged with carcinogens (12,13). Since then, a number of commensal bacteria have been

linked to CRC, including *Escherichia coli*, *Enterococcus faecalis*, *Bacteroides* spp. (*B. fragilis*, *B. vulgatus*, *B. stercoris*), *Eubacterium limosum*, and *Clostridium septicum* (14-22).

Ever since the oncogenic properties of *H. pylori* were firmly established in the stomach, studies on its oncogenicity have extended to other parts of the gastrointestinal tract, particularly the colon (23). To date, the link between *H. pylori* infection and CRC remains inconclusive, with some reports showing an association (24-32) while others none (33-37). The results of two meta-analyses published in 2006 and 2008 both suggested a possible small increased risk of CRC in association with *H. pylori* infection (38,39).

Several hypotheses have been proposed to explain the possible link between *H. pylori* infection and CRC. These include: (I) hypergastrinemia, (II) change in colorectal microflora, (III) toxin production, and (IV) chronic inflammation secondary to direct *H. pylori* colonization in the colon.

Hypergastrinemia

Gastrin and gastrin-like peptides received considerable attention in the 1980s and 1990s because of their growth-promoting properties. Early *in vitro* studies demonstrated that gastrins had a direct mitogenic effect on cultured normal and neoplastic colonic cells (40-42). Later researches reported that induced hypergastrinemia resulted in hyperproliferation of colonic mucosa in transgenic mice (43-45). In addition, *gastrin* gene knock-out mice showed decreased proliferation of the colonic mucosa (46). Furthermore, several case-control studies observed elevated serum/plasma gastrin levels in patients with colorectal adenomatous polyps and/or adenocarcinoma (47-50). These observations suggest that hypergastrinemia in the setting of *H. pylori*-associated atrophic gastritis promotes colorectal

tumorigenesis.

However, the link between hypergastrinemia and CRC has been in question from the beginning. Animal studies showed that drug-induced hypergastrinemia had no stimulatory effect on the growth of colonic mucosa or CRC progression (51-53). In fact, omeprazole was found to inhibit colorectal tumorigenesis induced by azoxymethane in rats despite causing hypergastrinemia (54). In humans, chronic hypergastrinemia caused by proton pump inhibitors also showed no effect on the development of colonic adenomas (55). Patients with Zollinger-Ellison syndrome does not show an increased risk of developing CRC despite prolonged and marked plasma elevation of all forms of gastrin (56). Several studies demonstrated that serum/plasma gastrin levels were not significantly different between subjects with and without colorectal neoplasia, and thus unlikely to play a significant role in colorectal tumorigenesis (57-61). It is interesting to note that some studies have demonstrated that CRC tumor cells express gastrins that may function as autocrine growth factors (62-66). In that scenario, gastrin secretion by tumor cells is likely the source of hypergastrinemia observed in CRC patients. In support of this notion, several studies demonstrated a fall in serum/plasma gastrin values in CRC patients following surgical resections of the tumors (48,67,68). While these data may further support a role of hypergastrinemia in colorectal tumorigenesis, they argue against a direct association with *H. pylori* infection.

Change in colorectal microflora

Gastric acid barrier is an important regulator of the population and composition of the intestinal microflora (69-72). Atrophic gastritis secondary to *H. pylori* infection is associated with reduced acid production, which permits a greater number and variety of microbial species to enter and colonize the intestinal tract. It has been proposed that shifts in the composition of colorectal microflora resulted from *H. pylori* atrophic gastritis may facilitate selective growth of bacteria such as *B. fragilis*, *E. faecalis*, and others that are linked to the development of CRC (14-16,18-20). Supporting this hypothesis are studies showing an increased CRC risk following gastric surgery for benign peptic ulcer disease (73,74). However, other studies failed to confirm the association between gastrectomy and subsequent CRC development (75-78).

Toxin production

There are different *H. pylori* strains, some of which are more virulent and more carcinogenic than the others. For

instance, patients infected with *H. pylori* organisms that express *cagA* gene are more likely to develop gastric cancer than those infected with *cagA*-negative strains (79,80). Shmueli *et al.* tested patients with various malignancies for serum antibodies against *H. pylori* and CagA protein and found that CagA seropositivity was associated with an increased risk not only for gastric adenocarcinoma but also for colonic adenocarcinoma, when compared with CagA-seronegative controls (81). However, as the authors pointed out, the findings should be interpreted with caution because the tests for *H. pylori* and CagA were performed at the same time of cancer diagnosis, which raised the question about the temporal relationship between the two conditions. The conclusions of the study were drawn under the assumption that *H. pylori* infection occurred before CRC development, as for gastric adenocarcinoma. A reasonable argument would be that CRC patients may have an altered immune status, which allows *H. pylori* organisms, especially the more virulent strains, to have a greater chance to successfully establish infection in these patients.

If infection by *cagA*-positive *H. pylori* strains does in fact precede and contribute to the development of CRC, the underlying mechanisms remains elusive. It has been shown that infection by *cagA*-positive strains is associated with higher levels of gastrin than that by *cagA*-negative strains (82,83). Overproduction of IL-8, which is known to be a growth factor for human colon carcinoma cells (8-11), may also be implicated (81,84,85). In addition, infection with *cagA*-positive *H. pylori* strains is associated with an increased likelihood of developing atrophic gastritis (86-88), which would be expected to sustain a more drastic disruption of the gastric acid barrier function to allow for an abnormal bacterial colonization in the lower intestinal tract as discussed above.

Chronic inflammation secondary to direct *H. pylori* colonization in the colon

Chronic mucosal inflammation is believed to be a predisposing factor for CRC development, as evidenced by inflammatory bowel disease. Given *H. pylori*'s well-established proinflammatory and carcinogenic effect in the stomach, a "chronic inflammation → dysplasia → neoplasia" sequence, similar to that for inflammatory bowel disease, may occur in the colon initiated by direct *H. pylori* colonization.

In this regard, Kapetanakis *et al.* reported detection of *H. pylori* organisms in malignant tissues from 34 of 41 (82.9%) CRC patients by cresyl violet staining and immunohistochemistry (32). Using the same staining methods, the authors recently extended their study to 50

patients with CRC and 25 patients with colonic polyps and found that *H. pylori* organisms were present in 84% CRC tissues and 64% polyps (1). It is unclear, however, whether the authors have also included nonneoplastic colonic tissues for comparison in their studies, where the organisms were located in the tissues, and what staining characteristics they have observed for the organisms. Soylyu *et al.* examined 51 colonic polyps (39 tubular adenomas, 3 tubulovillous adenomas, 5 villous adenomas, and 4 adenocarcinomas) by immunohistochemistry and demonstrated positive staining in 11 (21.6%) polyps. In 10 (90.9%) polyps, however, the positive staining was interpreted as equivocal and appeared nonspecific (89). Again, no nonneoplastic colonic mucosa was included for comparison. In the study by Jones *et al.*, a total of 176 colorectal specimens (normal 58, adenoma 59, adenocarcinoma 59) were examined by *H. pylori* immunohistochemistry. Positive staining was seen in 1 (1.7%) normal sample, 9 (15.3%) adenomas, and 10 (16.9%) adenocarcinomas (90). However, all the positive cases showed granular and dot-like staining patterns; none of the positive cases demonstrated an unequivocal spiral form of *H. pylori* organisms as typically seen in the stomach. It is thus difficult to determine whether the positive staining represents deformed (dead or partially degraded) organisms or simply staining artifact.

Employing a *Helicobacter* species-specific 16S rDNA PCR assay combined with pyrosequencing analysis, Grahn *et al.* detected the presence of *Helicobacter* DNA sequences in 21 of 77 (27%) CRC biopsy specimens (91). No nonneoplastic colorectal tissues were examined in the study because the authors did not have access to normal colorectal biopsy specimens according to the authors. However, in a different study using the same techniques, the researchers were able to detect *H. pylori* DNA in 5 of 19 colon samples biopsied from 3 patients with microscopic colitis. No *H. pylori* DNA was detected in 12 rectal biopsies that were histologically normal (92).

Although the exact route of *H. pylori* transmission has not been fully understood, person-to-person transmission via either oral-to-oral or fecal-to-oral route is most common. Since *H. pylori* organisms are shed in stools from infected individuals (93-95), it is not surprising that the organisms, which may just simply pass through the intestinal tract with digested contents, can be detected in colonic tissue samples. It should also be noted that *H. pylori*-associated gastric cancer is known to be the consequence of chronic active gastritis that leads to mucosal atrophy, intestinal metaplasia and dysplasia. However, there have been no reports of chronic or active colitis resulted from direct *H. pylori* infection in the colon. Based on our experience, the colonic mucosa in patients with *H. pylori* gastritis shows normal

histology unless other medical conditions are present. Thus, simply identifying *H. pylori* organisms in colorectal tumor samples does not prove a causal relationship.

Conclusions

While the etiopathogenetic role of *H. pylori* in gastric cancer is well-established, its role in colorectal tumorigenesis remains controversial. *H. pylori* infection of the stomach may promote colorectal tumorigenesis indirectly in a variety of ways such as modulating intestinal microflora, enhancing cytokine production and increasing gastrin secretion. These effects may be more pronounced when infected by more virulent *H. pylori* strains. Detection of *H. pylori* antigens and/or DNA in colonic tissue samples does not necessarily mean colonic colonization by the organisms, and should not be viewed as direct evidence of causal association with colorectal tumorigenesis.

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