COX-2 Inhibition and the Prevention of Gastric Cancer

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Although the incidence of gastric cancer has recently decreased in many Western populations, it is still a highly prevalent disease and a major cause of death worldwide. Because gastric cancer usually presents late, the prognosis remains poor, and thus the main strategy for improving clinical outcomes is through prevention. The recognition that most gastric cancers develop consequent to chronic *Helicobacter pylori* infection, and the relative simplicity of eradicating *H. pylori* with combination antimicrobial chemotherapy have led to the hope that much gastric cancer can be prevented through *H. pylori* eradication. However, the evidence thus far from larger randomized controlled trials of gastric cancer prevention with *H. pylori* eradication in subjects at high gastric cancer risk has provided only limited optimism [1, 2]. In these studies the benefit of *H. pylori* eradication was confined almost entirely to subjects who had not progressed to the stage of intestinal metaplasia prior to receiving *H. pylori* eradication therapy. Unfortunately, all clinical studies of *H. pylori* eradication have been underpowered to demonstrate an effect on gastric cancer as an end point. The difficulties of conducting such large controlled studies over decades in patients in whom withholding *H. pylori* eradication can be regarded as unethical mean that more definitive data from *H. pylori* eradication trials in human subjects are unlikely to be forthcoming any time soon.

In the light of the uncertainties of the effects of *H. pylori* eradication on gastric cancer prevention, and the increasing recognition that any benefit is likely to be limited, there is a clear need to investigate additional chemopreventive strategies. As for many gastrointestinal and other malignancies, a strong body of epidemiological evidence supports the notion that aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have chemopreventive effects in gastric cancer [3]. The mechanisms by which NSAIDs inhibit or prevent neoplastic growth are not fully elucidated but most likely they are related to their ability to reduce cyclooxygenase (COX) expression, to induce apoptosis, and to inhibit cell proliferation and angiogenesis. Elevated expression of COX-2 is frequently observed in cancer, including gastric cancer [4], and selective COX-2 inhibitors have demonstrable antitumor effects in many model systems [5]. Because they are considered less gastrototoxic than nonselective NSAIDs, in recent years, COX-2 inhibitors have been investigated as chemopreventive agents in a variety of premalignant states, including two recent large randomized controlled studies of celecoxib that demonstrated efficacy in the prevention of colorectal adenoma recurrence [6, 7]. However, recent revelations regarding unexpected cardiovascular toxicity have severely dampened enthusiasm for the widespread use of COX-2 inhibitors in otherwise healthy patients [8].

In this issue of *Digestion*, Futagami and coworkers report on their investigations of the effects of the COX-2-selective NSAID celecoxib on the incidence of gastric cancer and the extent of *cdx2*-related intestinal metaplasia in the Mongolian gerbil model of *H. pylori*-associated gastric cancer. Presumably because of the difficulties with reproducing gastric cancer in gerbils following *H. pylori* infection alone, the investigators pretreated all animals with N-methyl-N-nitrosurea to promote carcinogenesis. Consistent with two other similarly designed studies of COX-2-selective agents, investigating etodolac in gerbils [9] and nimesulide in mice [10], celecoxib reduced the incidence of gastric cancer after *H. pylori* infection, and this was associated with increased epithelial apoptosis and reduced gastric COX-2 expression. The novel aspect here was the demonstration that celecoxib also reduced the incidence and extent of intestinal metaplasia, as assessed histologically and by the expression of two markers of intestinal metaplasia, Cdx-2 and Muc2.

COX-2 is readily induced by various stimuli, including proinflammatory cytokines, growth factors, and tumor promoters. Overexpression of COX-2 is observed in intestinal metaplasia, intestinal dysplasia, and gastric adenomas, which are considered precancerous lesions, as well as in the *H. pylori*-infected stomach [11]. *H. pylori* has been shown to upregulate COX-2 mRNA expression in gastric mucosal cells in vitro [12], probably through activation of the transcription factor NF- κ B [13]. Futagami and colleagues suggest that celecoxib might inhibit the development of intestinal metaplasia by inhibiting the activation of NF- κ B by *H. pylori* and/or the associ-

ated inflammatory response, thereby leading to decreased *cdx2* transcription. *Cdx2* is the caudal-type homeobox gene and encodes an intestine-specific transcription factor critical for development, differentiation, and maintenance of the intestinal epithelium [14]. Mice expressing *cdx2* under the control of a gastric-specific transgene develop gastric intestinal metaplasia and then cancer [15], showing that heterotopic *cdx2* expression may be directly carcinogenic. However, relatively little is known about the mechanism of *cdx2* regulation in the intestinalization of the gastric mucosa induced by *H. pylori*, and further studies are necessary to explore the relationship between *H. pylori*, NF- κ B, and *cdx2* and histological progression in gastric carcinogenesis. In one clinical study [16], the *cdx2* expression persisted even after eradication of *H. pylori*, and there is no evidence that intestinal metaplasia is reversible in humans, even after 2 years of COX-2 inhibition by rofecoxib [17].

While the paper by Futagami and coworkers demonstrates that celecoxib may prevent the development of intestinal metaplasia and gastric cancer in *H. pylori*-infected gerbils following exposure to a chemical carcinogen, the question whether it influences cancer development once there is intestinal metaplasia (the more important question in humans) was not addressed. Therefore, caution is necessary before an extrapolation of results of this work to human gastric cancer chemoprevention. Indeed, given the concerns about the cardiovascular toxicity of the COX-2 inhibitors [8], the focus in gastric cancer chemoprevention is likely to be shifted to approaches other than COX-2 inhibition together with *H. pylori* eradication for the future.

References

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