The Effect of Proton Pump Inhibitors on Barrett's Esophagus

Kerry B. Dunbar, MD, PhD*, Rhonda F. Souza, MD,
Stuart J. Spechler, MD

KEYWORDS

• Barrett's esophagus • Proton pump inhibitor • Dysplasia • Esophageal cancer
• Gastroesophageal reflux disease

KEY POINTS

- Gastrointestinal societal guidelines agree that, for patients with Barrett's esophagus, PPIs should be prescribed in whatever dose is necessary to control GERD symptoms and heal reflux esophagitis.
- Routine esophageal pH testing to assess the adequacy of acid suppression with PPIs, and the routine use of high-dose PPIs (beyond what is needed to control GERD), are not recommended by gastrointestinal societies for patients with Barrett's esophagus.
- In Barrett's esophagus, acid reflux can lead to increased cell proliferation, decreased apoptosis, production of reactive oxygen species, DNA damage, and esophageal production of proinflammatory and proproliferative cytokines.
- Although there are no randomized, controlled trials proving that PPI treatment reduces the risk of neoplastic progression in Barrett's esophagus, the bulk of clinical studies published on this issue support a cancer-preventive effect for PPIs.
- The indirect evidence supporting a cancer-protective role for PPIs is strong enough to warrant PPI treatment of virtually all patients with Barrett's esophagus after they have been informed of the potential risks of long-term PPI therapy.

INTRODUCTION

Barrett's esophagus is a major risk factor for the development of esophageal adenocarcinoma, a tumor whose incidence has increased profoundly over the last 40 years in Western countries.[1] The pathogenesis of Barrett's esophagus involves chronic gastroesophageal reflux disease (GERD) wherein the reflux of acid and bile into the

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Division of Gastroenterology and Hepatology, Department of Medicine, Dallas VA Medical Center, University of Texas Southwestern Medical Center, 4500 South Lancaster Road, GI Lab – CA-111-B1, Dallas, TX 75231, USA
* Corresponding author.
E-mail address: Kerry.Dunbar@utsouthwestern.edu

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esophagus damages the esophageal mucosa and leads to its repair through the process of metaplasia. The specialized intestinal metaplasia of Barrett's esophagus is predisposed to malignancy, and ongoing GERD is likely to contribute to that carcinogenesis. Because chronic GERD plays a role in the pathogenesis of Barrett's metaplasia and in its malignant progression, it makes sense that aggressive treatment of GERD might prevent adenocarcinoma in Barrett's esophagus. The modern medical therapy for GERD is directed primarily at decreasing gastric acid production, and proton pump inhibitors (PPIs), which were introduced into clinical practice in the United States in 1989, are the best medications available for that purpose. This article reviews the effects of PPIs that might impact on the neoplastic progression of Barrett's metaplasia, and the clinical evidence that PPIs may prevent the development of dysplasia and cancer in patients with Barrett's esophagus.

CELLULAR EFFECTS OF ACID REFLUX AND PROTON PUMP INHIBITORS IN BARRETT'S ESOPHAGUS

There are several broad categories of PPI effects that might be expected to protect against carcinogenesis in Barrett's esophagus. First, PPIs heal reflux esophagitis. Chronic inflammation is known to predispose to cancer in several organs, and the elimination of chronic esophageal inflammation by PPIs might protect against malignancy. Next, PPIs decrease esophageal exposure to acid, which can cause cancer-promoting DNA damage and increase proliferation in Barrett's metaplasia. Finally, PPIs can prevent the release of cancer-promoting cytokines by esophageal epithelial cells through mechanisms independent of their acid-suppressive effects. Numerous studies have documented the efficacy of PPIs in healing reflux esophagitis; these data are not reviewed here. Rather, we focus on the latter two mechanisms whereby PPIs might prevent cancer in Barrett's esophagus.

In one study, acid exposure of nondysplastic Barrett's epithelial cells led to the production of reactive oxygen species (ROS) with double-strand breaks in DNA, which can result in genomic instability and carcinogenesis.[2] Those acid-induced DNA double-strand breaks could be prevented by pretreating the Barrett's cells with an ROS scavenger or a compound that inhibited intracellular acidification. These data suggest that refluxed acid can enter Barrett's epithelial cells, leading to the generation of ROS that cause DNA damage. Agents that induce DNA double-strand breaks are considered carcinogens and, thus, PPIs might reduce the risk of cancer by limiting exposure to carcinogenic gastric acid.

Acid also may contribute to cancer by causing increased cellular proliferation in Barrett's esophagus. This has been suggested by studies using Barrett's biopsies maintained in organ culture and using Barrett's biopsies taken before and after acid perfusion of the esophagus.[3,4] Taken together, these studies suggest that acid exposure can cause increased expression of cyclooxygenase-2 and activation of the protein kinase-C and mitogen-activated protein kinase pathways in Barrett's metaplasia, resulting in increased proliferation and decreased apoptosis.

Several clinical studies in patients with Barrett's esophagus have found that protracted treatment with PPIs can cause improvements in markers of proliferation and other potentially beneficial effects. In one study of patients who had biopsies of Barrett's metaplasia taken before and after 6 months of PPI therapy, those patients who achieved normalization of esophageal acid exposure with PPIs showed a significant decrease in proliferation as determined by the biomarker proliferating cell nuclear antigen, unlike the patients who had persistently abnormal esophageal acid exposure despite PPI treatment.[5] Another study compared the proliferative activity