Letter to the Editor

Correspondence re: R. Kim *et al.*, Etiology of Barrett's Metaplasia and Esophageal Adenocarcinoma. Cancer Epidemiol., Biomark. Prev., *6:* 369–377, 1997

Letter

Gareth Morgan[1]

Unit of Chemoprevention, International Agency for Research on Cancer, 69372 Lyon Cedex 08, France

I read with interest the review by Kim *et al.* (1) on the etiology of Barrett's metaplasia and esophageal adenocarcinoma. They described a carcinogenic progression from GERD[2] to Barrett's metaplasia to esophageal adenocarcinoma. Possible explanations cited for the increasing incidence of esophageal adenocarcinoma in the last 2 decades included increased exposure to GERD-provoking agents, such as alcohol and tobacco. GERD is primarily a motility disorder that is associated with reduced resting pressure of the LES, which can lead to the excessive reflux of irritating gastroduodenal juice. Thus, smooth muscle-relaxing drugs used in the treatment of cardiovascular and pulmonary disease could relax the LES and induce idiopathic GERD. Kim *et al.* (1) stated that the use of these agents increased during the same period that incidence of esophageal adenocarcinoma increased. Reversing this hypothesis, it follows that agents that increase LES pressure should be helpful in the chemoprevention of esophageal adenocarcinoma. I write to discuss the potential of NSAIDs for this purpose.

NSAIDs such as indomethacin increase LES pressure (2). Pharmacologically, NSAIDs inhibit the cyclo-oxygenase enzyme and, thus, reduce the synthesis of PGs. It is likely that the NSAID-mediated increase in LES pressure is related to the inhibition of esophageal PGs that physiologically relax the LES.

During GERD, the esophageal mucosa produces increased amounts of PGE2. Similar to its effect on the gastric mucosa, PGE2 may help to protect the esophageal mucosa from injury. At a given threshold of inflammation, however, PGE2 production becomes sufficiently high to exert inhibitory effects on the LES. Excessive PGE2 production is, therefore, a critical factor in the self-perpetuation of GERD because it drives a vicious cycle of inflammation, aggravated LES function, further duodenogastric reflux, and further inflammation (3). Thus, NSAIDs could be expected to prevent the onset of GERD by raising LES pressure and to be helpful in its treatment by breaking the vicious PGE2 cycle. For the latter possibility, low-dose NSAIDs coupled with an acid inhibitor may have potent healing properties (4).

Aspirin is the most widely used NSAID because it is inexpensive and easily available and has value in a wide range of conditions. Theoretically, regular aspirin consumption should be associated with a reduced risk of GERD by raising LES pressure. This hypothesis is supported by the epidemiological study of Funkhouser and Sharp (5), who reported that the regular use of aspirin reduces the risk of fatal esophageal cancer by an astonishing 90%. Other potential mechanisms for aspirin chemoprevention of esophageal adenocarcinoma in Barrett's esophagus include immune stimulation (6) and the replacement of defective tumor suppressor gene function (7).

Further epidemiological studies are required to confirm the results of Funkhouser and Sharp (5). Clinically, low-dose aspirin could be assessed in the treatment of GERD and Barrett's esophagus. It is possible that the chemoprevention of esophageal adenocarcinoma could be another public health benefit of aspirin, together with the chemoprevention of cardiovascular disease (8) and colorectal cancer (9).

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[1] Present address: Department of Public Health, Iechyd Morgannwg Health, 41 High Street, Swansea SA1 1LT, United Kingdom.

[2] The abbreviations used are: GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; NSAID, nonsteroidal anti-inflammatory drug; PG, prostaglandin.