Symptomatic Gastroesophageal Reflux as a Risk Factor for Esophageal Adenocarcinoma

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Background
Adenocarcinoma of the esophagus has had the largest increase in incidence than any other cancer since 1970. Specifically, from 1976 to 1987, the incidence of this cancer for men increased from 4% to 10% per year. The reason for this increase remains unclear. While alcohol and cigarette smoking are clearly associated with esophageal cancer and act synergistically to promote malignant transformation, the rates of smoking and alcohol abuse have not changed dramatically and therefore cannot explain the rise in incidence.

Symptoms of gastroesophageal reflux (heartburn) may be related to the onset of esophageal cancer. Heartburn is known to play an important role in the development of Barrett’s esophagus (a pre-cancerous condition of the esophagus), but little evidence exists linking reflux symptoms directly to esophageal cancer. A March 18th report in the New England Journal of Medicine examines the relationship between heartburn and the risk of esophageal cancer and cancer of the gastric cardia.

Methods
All newly diagnosed cases of adenocarcinoma of the esophagus or gastric cardia and half of the newly diagnosed cases of squamous cell carcinoma of the esophagus occurring in Sweden between 1994 and 1997 were entered in this study. A comprehensive catchment strategy was administered to ensure that every potential case throughout the country was identified soon after diagnosis. These patients were matched to a control group randomly selected from persons of the same age and sex.

Tumors were carefully examined endoscopically and pathologically to classify them properly as either gastric cardia cancers or esophageal cancers. Tumors that had their epicenters within two centimeters proximal or three centimeters distal to the gastroesophageal junction were considered gastric cardia. The gastroesophageal junction was defined as the point where the proximal longitudinal mucosal folds begin in the stomach.

Professional interviewers using a computer assisted program obtained data on reflux symptoms including heartburn and regurgitation. The interviewers were not blinded to the patients diagnosis (case or control) but had no knowledge of the study hypothesis. To prevent collecting data on symptoms caused by the cancer, only symptoms that were present for at least five years prior to study entry were included.

Results
618 patients and 820 controls were interviewed for the study. Eighty-five percent of the 618 patients participated in the study. The main reason for nonparticipation was physical or mental impediment or early death. The risk of esophageal adenocarcinoma was eight times higher in persons reporting heartburn, regurgitation or both. The frequency of these symptoms and their severity correlated with the risk of adenocarcinoma. Persons with reflux symptoms greater than three times per week had a nearly 17 fold increase in the risk of esophageal adenocarcinoma. Similarly, the longer the symptoms were present, the higher the risk. Persons with reflux symptoms for longer than twenty years were at higher risk compared to persons with symptoms fewer than twenty years.

Reflux symptoms were associated with adenocarcinoma of the gastric cardia, but not as strongly as with esophageal adenocarcinoma. Symptoms were graded by severity and frequency on a scale from 0-6.5, with higher scores indicating worse and more frequent symptoms. Persons with high scores had an early three fold increase in the risk of adenocarcinoma of the gastric cardia. Duration of symptoms also increased risk; persons with either heartburn or regurgitation greater than twenty years had a four fold increase in the risk of gastric cardia adenocarcinoma.
Esophageal squamous cell carcinoma was not associated with heartburn or regurgitation regardless of the frequency, severity or duration of symptoms. Several confounding factors for esophageal cancer (adenocarcinoma and/or squamous carcinoma) were identified including Barrett's esophagus, age, sex, body-mass index, smoking and alcohol use. However, none of these risk factors significantly changed the risk estimates.

**Conclusion**

The authors documented a strong association between adenocarcinoma of the esophagus and reflux symptoms. A weaker association between reflux symptoms and adenocarcinoma of the gastric cardia was detected and there was no association between reflux symptoms and squamous cell carcinoma of the esophagus. These associations were independent of confounding variables including Barrett's esophagus, age, sex, smoking or alcohol abuse.

The clinical implications of this study are unclear. Should everyone with reflux symptoms be endoscoped to rule-out carcinoma? Since twenty percent of the adult population in the United States complains of heartburn weekly, such a policy would have a remarkably low yield and place a great burden on a medical system already strained financially. Instead, further studies are necessary to define a group of patients with heartburn who are at sufficiently high risk of cancer that screening endoscopy is warranted.

Further studies are also necessary to determine the best treatment of heartburn. Presently, many medications are effective at alleviating reflux symptoms including antacids, H2 blockers (cimetidine, ranitidine, famotidine, and nizatidine) and proton-pump inhibitors (such as lansoprazole and omeprazole).

However whether or not these medications will decrease the risk of cancer is unknown. Clearly, heartburn is not a benign symptom and places patients at risk for esophageal adenocarcinoma and gastric cardia adenocarcinoma. Patients with heartburn, and especially those with severe or long-standing symptoms, should consult a physician for a complete evaluation.