

Canadian Association of General Surgeons Evidence Based Reviews in Surgery. 6. “GERD” as a risk factor for esophageal cancer

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CAGS Evidence Based Reviews in Surgery

In September 2000, the Canadian Association of General Surgeons (CAGS) initiated a program entitled “CAGS Evidence Based Reviews in Surgery” (CAGS-EBRS) to help practising clinicians improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas. The *Canadian Journal of Surgery* will publish 4 of these reviews each year. Each review will consist of an abstract of the selected article and a summary of the methodologic and clinical reviews. We hope that readers will find these useful and learn skills that can be used to evaluate other articles. For more information about the CAGS-EBRS or information about participating in the program, send an email to mmckenzie@mtsinai.on.ca.

Selected article

Lagergren J, Bergstrom R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340 (11): 825-31.

Abstract

Question: Is gastroesophageal reflux a risk factor for the development of esophageal adenocarcinoma? **Design:** A case control study. **Setting:** A population-based study in Sweden between 1994 and 1997. **Participants:** Cases included all patients with gastric or esophageal adenocarcinoma and half of all patients with esophageal squamous cell cancer, under the age of 80 years and living in Sweden between Dec. 1, 1994, and Dec. 31, 1997. Controls were selected randomly from among persons matched for age (within 10 yr) and sex in the entire Swedish population, through the use of a population register, which is computerized and updated continuously. **Assessment of risk factors:** Symptomatic reflux

was assessed according to the severity of the symptoms (heartburn only, regurgitation only, heartburn and regurgitation combined, nightly symptoms), frequency and duration. Adjustment was made for age, sex, body mass index, smoking history, alcohol ingestion, socioeconomic status, intake of fruit and vegetables, overall energy intake, posture and the degree of physical activity both at work and during leisure. **Main outcome measures:** Gastric and esophageal adenocarcinoma and esophageal squamous cell cancer. **Main results:** Among participants with recurrent symptoms of reflux, as compared with those without such symptoms, the odds ratios were 7.7 (95% CI, 5.3–11.4) for development of esophageal adenocarcinoma and 2.0 (95% CI, 1.4–2.9) for adenocarcinoma of the cardia. The more frequent, more severe and longer duration the symptoms of reflux were, the greater was the risk. Among persons with long-standing, severe symptoms of reflux, the odds ratios were 43.5 (95% CI, 18.3–103.5) for development of esophageal adenocarcinoma and 4.4 (95% CI,

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1.7–11.0) for adenocarcinoma of the cardia. The risk of esophageal squamous cell carcinoma was not increased with reflux (odds ratio, 1.1; 95% CI, 0.7–1.9). **Conclusion:** The study identified a strong and probably causal relation between symptomatic reflux as a strong risk factor for esophageal adenocarcinoma and a relatively weak risk factor for adenocarcinoma of the gastric cardia.

Commentary

The article in this issue addresses an important clinical topic. Lagergren and associates looked at gastroesophageal reflux disease (GERD) as a risk factor for esophageal adenocarcinoma. GERD is a common condition in North America. It is estimated that over half of all adults experience intermittent symptoms and 7% experience symptoms daily. The incidence of adenocarcinoma of the esophagus doubled between 1976 to 1987, making it the fastest growing cancer in North America. Affecting predominantly white males, the incidence is currently increasing by 10% per year. Although Barrett's esophagus and obesity are known risk factors for adenocarcinoma, a direct link between GERD and adenocarcinoma of the esophagus had not been confirmed previously.

This is a case control study, which is the design often used by epidemiologists to study causation or risk factors. Clinicians are more familiar with randomized controlled trials where study subjects are randomly allocated to the 2 groups. It would be unethical to randomize people to be exposed or not exposed to a risk factor for disease. In case control studies, there are 2 groups: cases, which include people who have the disease or condition being studied and controls who do not have it. The 2 groups are then compared for the risk factors being studied. Because the study is performed retrospectively (i.e., the outcome of interest is present at the start of the study) and people are not randomly allocated, case control studies

are susceptible to biases. Methodologic issues in case control studies relate to the selection of controls, standardization of data collection, confirmation of a temporal relationship, measurement of a dose-response gradient and measurement of the magnitude of association.

This article describes a population-based study done between 1994 and 1997, looking at everyone in Sweden younger than 80 years of age with newly diagnosed adenocarcinoma of the esophagus, adenocarcinoma of the gastric cardia, and squamous cell carcinoma of the esophagus. Controls, drawn from the entire Swedish population, were age and sex matched. The authors used a standard data collection system to minimize the risk of misclassification of tumour location and histology. Multiple biopsies were performed to obtain the diagnosis and anatomical site. The pathological findings in 97% of all cases were reviewed centrally and the location of the tumour was classified by a consensus board when there was any disagreement.

It is appropriate that the control subjects were randomly selected from the entire Swedish population because reflux is a common symptom and one wants to avoid a common bias in case control studies of using hospital-based controls who are more likely to have medical conditions than those in the normal population.

Both control and case subjects underwent a personal interview lasting approximately 80 minutes. The interviewers asked questions about the severity and frequency of any reflux symptoms of more than 5 years' duration. Interviewers were not blinded to whether subjects were cases or controls but were unaware of the study hypothesis and were trained in a standardized interview technique. This study is somewhat unusual in that most case control studies are performed retrospectively. In this study, although the outcome was present at the outset, cases were accrued

prospectively over 3 years, so people could be interviewed at the time of diagnosis. This is a significant strength of the study because people are less likely to forget details. Blinding of the interviewers to the status of the subjects is considered important but was not done in the study. The authors argue that since the interviewers did not know the study hypothesis and conducted the interview in a standardized fashion, interviewer bias should have been avoided. The study personnel also collected data on potential confounders including age, sex, body mass index, smoking history, alcohol ingestion, socioeconomic status, intake of fruit and vegetables, overall energy intake, posture, and the degree of physical activity both at work and during leisure time. The data were analyzed by univariate and multivariate logistic regression with and without inclusion of potential confounders.

Eighty-five percent of the cases were enrolled in the study, but only 73% of controls. This difference in participation rates is a potential source of bias. However, this nonparticipation rate is quite low, and the authors correctly state that the decreased participation rate in the controls is unlikely to be linked to reflux.

The authors found a strong association between the presence of symptoms of reflux and esophageal adenocarcinoma. The odds ratio was 7.7 for esophageal adenocarcinoma, 2.0 for adenocarcinoma of the cardia and only 1.1 for esophageal squamous cell carcinoma. The odds ratio of 7.0 means that the risk of esophageal adenocarcinoma is 7 times greater in people with GERD than in those without GERD. The precision of the estimate of risk is given by the 95% confidence interval of 5.3–11.4, showing a highly significant increased risk of esophageal adenocarcinoma in patients with reflux even if the lower end of the range (5.3) were the true odds ratio.

The issue of a temporal relationship may be problematic in case control studies. To address this, Lager-

gren and associates focused on symptoms that had been present for more than 5 years. This should be long enough to preclude adenocarcinoma being the cause of GERD, as the 5-year survival of untreated carcinoma of the esophagus is essentially zero.

There does appear to be a dose-response gradient from the analysis performed by these authors. The odds ratio increased with increasing severity and duration of reflux to as high as 20. The risk of adenocarcinoma was higher in patients with nocturnal reflux, which is generally considered to be a more severe reflux symptom, with more frequent reflux symptoms, with a higher reflux symptom score and with a longer duration of symptoms.

Lagergren and associates conclude that there is a strong and probably causal relation between gastroesophageal reflux and esophageal adenocarcinoma. However, from epidemiologic studies, generally one can only make conclusions about there being an association not that the risk factor causes the disease. Merely showing that there is a strong association does not infer causality. The relation between reflux and adenocarcinoma of the gastric cardia is relatively weak.

This is a well-designed paper and the authors have done a good job of addressing the question posed. They have answered many of the questions regarding potential sources of bias, such as failure to blind the interviewers and a difference in the response rate between cases and controls. The authors have addressed the question posed in their hypothesis and the evidence strongly supports their conclusion.

From a clinical point of view we must now decide what to do with this information. We can eliminate some of the symptoms of reflux and esophageal acid exposure with medication or surgery; however, studies to date have not shown a decrease in the risk of Barrett's esophagus or adenocarcinoma with this approach. It must be pointed out though that these studies have been underpowered to address this question. The authors of this paper actually found a slightly increased risk of adenocarcinoma in patients who used medications for reflux versus those who did not. The reasons for this are unknown. One may speculate that this was related to the severity of symptoms or to unopposed pancreaticoduodenal reflux. They also found no difference in the risk of adenocarcinoma in patients who had antireflux surgery.

It was thought that all adenocarcinomas of the esophagus were gastric in origin. However, it became evident in the 1980s that adenocarcinoma could occur in the esophagus, separate from the stomach. The importance of Barrett's epithelium became evident as cases of adenocarcinoma arising in Barrett's esophagus were reported. However, in some resected specimens of adenocarcinoma of esophagus, Barrett's epithelium was not observed. The finding of an association between GERD alone and adenocarcinoma would explain this frequent pathological finding. The findings in this study suggest that the link between esophageal adenocarcinoma and Barrett's esophagus is not necessarily the Barrett's esophagus itself, but rather severe GERD.

Screening endoscopy in popula-

tions with chronic reflux might identify the presence of Barrett's esophagus, but currently few people are known to have Barrett's esophagus before they present with symptoms of cancer. Although ongoing screening is recommended once Barrett's esophagus is present, what do we do with the vast majority of chronic reflux patients without this condition? Lagergren and associates found that the association between GERD and esophageal adenocarcinoma was equally strong in patients with and without Barrett's esophagus. Although it is controversial whether to recommend screening endoscopy for all patients with reflux, perhaps the correct message is that GERD is not a completely benign disease, and all patients with severe GERD are at risk of esophageal adenocarcinoma.

The reason for the rising incidence of esophageal adenocarcinoma is unclear. The authors of this paper comment that there is no evidence that the rate GERD is increasing, suggesting that other factors contribute to carcinogenesis, and GERD alone is not responsible for the increasing incidence of adenocarcinoma of the esophagus. Thus, although this paper is of major clinical importance in establishing a link between severe GERD and esophageal adenocarcinoma, we must now look for other factors that contribute to the development of esophageal adenocarcinoma in the hope that we can treat them or find new ways to prevent GERD.

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