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

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Selected article

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, 2.3–8.4) for adenocarcinoma of the cardia.
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1.7–11.0) for adenocarcinoma of the
cardia. The risk of esophageal squa-
mous cell carcinoma was not in-
creased with reflux (odds ratio, 1.1;
95% CI, 0.7–1.9). Conclusion: The
study identified a strong and prob-
ably causal relation between sympto-
matic reflux as a strong risk factor for
esophageal adenocarcinoma and a
relatively weak risk factor for adeno-
carcinoma of the gastric cardia.

Commentary

The article in this issue addresses an
important clinical topic. Lagergren
and associates looked at gastro-
esophageal reflux disease (GERD) as a
risk factor for esophageal adenocarci-
noma. GERD is a common condition
in North America. It is estimated that
over half of all adults experience inter-
mittent symptoms and 7% experience
symptoms daily. The incidence of ade-
ocarcinoma of the esophagus dou-
bled 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 adenocarci-
noma, 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 epidemi-
ologists to study causation or risk fac-
tors. Clinicians are more familiar with
randomized controlled trials where
study subjects are randomly allocated
to the 2 groups. It would be unethi-
cal to randomize people to be ex-
posed or not exposed to a risk factor
for disease. In case control studies,
there are 2 groups: cases, which in-
clude 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 be-
ing studied. Because the study is per-
formed retrospectively (i.e., the out-
come of interest is present at the start
of the study) and people are not ran-
domly allocated, case control studies
are susceptible to biases. Method-
ologic issues in case control studies
relate to the selection of controls,
standardization of data collection,
confirmation of a temporal relation-
ship, 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. Con-
trols, drawn from the entire Swedish
population, were age and sex
matched. The authors used a stan-

ard data collection system to mini-
mize the risk of misclassification of
tumour location and histology. Mul-
tiple biopsies were performed to ob-
tain the diagnosis and anatomical site.
The pathological findings in 97% of
all cases were reviewed centrally and
the location of the tumour was classi-
ified 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 symp-
tom and one wants to avoid a com-
mon bias in case control studies of
using hospital-based controls who
are more likely to have medical con-
ditions than those in the normal
population.

Both control and case subjects un-
derwent a personal interview lasting
approximately 80 minutes. The inter-
viewers asked questions about the
severity and frequency of any reflux
symptoms of more than 5 years’ dura-
tion. Interviewers were not blinded to
whether subjects were cases or con-
trols but were unaware of the study
hypothesis and were trained in a stan-
dardized interview technique. This
study is somewhat unusual in that
most case control studies are per-
formed 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 sub-
jects is considered important but was
not done in the study. The authors ar-
ge that since the interviewers did not
know the study hypothesis and con-
ducted the interview in a standardized
fashion, interviewer bias should have
been avoided. The study personnel
also collected data on potential con-
founders including age, sex, body
mass index, smoking history, alcohol
intake, socioeconomic status, intake
of fruit and vegetables, overall energy
intake, posture, and the degree of
physical activity both at work and dur-
ing leisure time. The data were ana-
lyzed 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 nonpar-
ticipation rate is quite low, and the
authors correctly state that the de-
creased participation rate in the con-
trols is unlikely to be linked to reflux.

The authors found a strong asso-
ciation 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 squa-
mous 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 with-
out GERD. The precision of the estimate of risk is
given by the 95% confidence interval
of 5.3–11.4, showing a highly signif-
icant 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 relation-
ship may be problematic in case con-
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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 pancreatic-duodenal 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 populations 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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