Gastroesophageal Reflux, Barrett Esophagus, and Esophageal Cancer

Scientific Review

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SYMPTOMS OF GASTROESOPHAGEAL reflux disease (GERD) are among the most common complaints encountered by the generalist physician.1-3 Previously regarded as a so-called nuisance problem, GERD is now recognized to have potentially serious complications, including strictures,4 erosive esophagitis,5,6 and the development of Barrett esophagus,7 a metaplastic change of the lining of the esophagus that is associated with an increased risk of adenocarcinoma of the esophagus.8-10

This article will discuss the pathophysiology of esophageal cancer in the setting of GERD, assess the evidence linking reflux disease to cancer, and examine the potential role of endoscopic screening in individuals with GERD.

Several pertinent clinical questions will be considered, including the prevalence of GERD in the general population, the association between GERD and adenocarcinoma of the esophagus, the appropriate management of Barrett esophagus, and whether endoscopy for those with GERD averts death from esophageal adenocarcinoma.

METHODS

Studies chosen for this review were obtained from MEDLINE searches of English-language literature from 1968 through 2001. Reports were of randomized controlled clinical trials if available, case-control data if trials were unavailable, and cohort studies if case-control data were unavailable. Pertinent bibliographies were also reviewed to find reports not otherwise identified.

Data Sources A MEDLINE search was performed to identify all pertinent English-language reports about GERD, adenocarcinoma, and Barrett esophagus from 1968 through 2001. Reports were of randomized controlled clinical trials if available, case-control data if trials were unavailable, and cohort studies if case-control data were unavailable. Pertinent bibliographies were also reviewed to find reports not otherwise identified.

Study Selection and Data Extraction Studies were selected by using the search terms gastroesophageal reflux, adenocarcinoma, and Barrett’s esophagus, with subheadings for classification, complications, drug therapy, economics, epidemiology, mortality, surgery, and prevention and control. Clinical guidelines for the care of subjects with GERD and Barrett esophagus were retrieved and abstracted.

Data Synthesis Cohort studies demonstrate that symptoms of GERD occur monthly in almost 50% of US adults and weekly in almost 20%. Three large case-control studies demonstrate a positive association between reflux symptoms and risk of adenocarcinoma of the esophagus, with more prolonged and severe symptoms accentuating this risk. However, because of the low incidence of adenocarcinoma of the esophagus and the ubiquity of reflux symptoms, the risk of cancer in any given individual with reflux symptoms is low. No randomized trial data are available to demonstrate either decreased cancer incidence or increased life expectancy in subjects with GERD who undergo screening endoscopy.

Conclusions Strong evidence supports the association of GERD and adenocarcinoma of the esophagus; however, the risk of cancer in any given individual with GERD is low. Barrett esophagus appears to be a common precursor lesion to this cancer. Given the low absolute risk of cancer in those with GERD and the lack of demonstrated efficacy of endoscopic screening, insufficient evidence exists to endorse routine endoscopic screening of patients with chronic GERD symptoms.
through 2001, using the search term *gastroesophageal reflux* with the following subheadings: classification, complications, epidemiology, mortality, and prevention and control. Also, the search term *gastroesophageal reflux* was combined with *adenocarcinoma*. We also searched *Barrett esophagus* with the following subheadings: complications, drug therapy, economics, epidemiology, mortality, prevention and control, and surgery. Additionally, *Barrett esophagus* was combined with *adenocarcinoma*. The bibliographies of pertinent papers were searched for further work appropriate for inclusion. For all clinical questions considered, we present data from randomized controlled trials when such data exist. In the absence of data from randomized studies, we present case-control data, and when no case-control data exist, cohort studies. For each clinical question considered, we identify the type of evidence available to address the topic.

**What is the Prevalence of GERD?**

GERD may be defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. The most commonly recognized manifestation of GERD is heartburn or a substernal burning sensation in the chest. Heartburn is ubiquitous in the United States and other industrialized nations. Several cohort studies have attempted to quantify the burden of reflux symptoms. A Gallup survey demonstrated that 44% of adults in the United States experience heartburn at least once a month. A survey of residents in Olmsted County in Minnesota demonstrated that 18% of respondents experienced heartburn at least weekly. Also, a survey of control subjects and hospitalized individuals reported that 15% of the control subjects experienced reflux symptoms at least weekly. The frequency of other reflux-related symptoms, such as regurgitation, is less well described but also common.

**What Degree of Reflux Is Pathologic?**

Because most asymptomatic individuals usually experience several episodes of undetected acid reflux daily and because many other individuals experience symptomatic reflux only rarely, defining what degree of reflux constitutes disease and what is physiological is necessarily uncertain. If only those who sustain tissue damage are considered to have GERD, the 30% to 70% of individuals who have painful, treatable reflux symptoms but nonerosive disease would be excluded. On the other hand, if all those experiencing any occasional reflux symptom are labeled as having GERD, the problem may be overmedicalized, giving a large portion of the population with relatively trivial occasional symptoms a disease diagnosis. Compounding this problem is the only moderate correlation between reflux symptoms and esophageal acid exposures. Although those with manifestations of severe reflux such as erosive esophagitis, strictures, and Barrett esophagus have, on average, more severe or protracted reflux symptoms than those with nonerosive disease, the degree of overlap of symptoms between those with severe tissue injury and those with nonerosive disease may make it difficult to identify individuals with the potential to develop complications. Even with these ambiguities defined, the data suggest that GERD is common in the adult population, with 10% to 20% of individuals experiencing symptoms of reflux weekly.

**What is the Association Between GERD and Adenocarcinoma of the Esophagus?**

Adenocarcinoma of the esophagus is rapidly increasing in incidence in the United States and other countries. Population-based cohort studies examining the incidence of this cancer suggest a 300% to 500% increase throughout the last 30 to 40 years. Despite this increase, the overall number of individuals with adenocarcinoma in the United States remains low. In 2002, approximately half of the 13 100 anticipated esophageal cancers are expected to be adenocarcinomas. Adenocarcinoma of the esophagus is approximately 8 times more common in white men than white women and 5 times more common among white men than black men, making white men the group at highest risk for the disease. Rates in black women are too low to yield a reliable estimate of trends from the National Cancer Institute’s Surveillance, Epidemiology, and End Results database.

Adenocarcinoma appears to develop from the normal esophageal mucosal lining through a series of steps. Initially, a metaplastic change from the esophagus’s normal squamous epithelium to a specialized or intestinal-type columnar lining, termed Barrett esophagus, occurs. According to animal studies, a necessary prerequisite for this change appears to be destruction of the squamous mucosa to allow for reepithelialization of the lower esophagus. Such destruction may be secondary to acid exposure. The origin of the columnar cells composing the Barrett esophagus is unclear. Because these cells differ histologically from those of the gastric cardia, upward migration of gastric epithelium from the stomach does not explain the condition. Investigators have described a cell that is at the border between the squamous tissue of the esophagus and the Barrett mucosa and has features of columnar and squamous tissue. This cell may be a pluripotential basal cell that is the progenitor of Barrett epithelium. Whether Barrett esophagus is a necessary precursor to all cases of esophageal adenocarcinoma is unknown.

The milieu in which the damaged esophagus heals appears to be important. Dogs with experimentally induced distal esophageal damage regenerate columnar epithelium if the esophagus is exposed to acid and squamous epithelium on exposure to neutral pH. The relative contributions of acid, pepsin, and duodenal refluxate to the development of Barrett esophagus are unclear. The role of reflux of duodenal contents in the development of the dis-
ease is controversial.\textsuperscript{36} Reflux of bile appears more common among individuals with Barrett esophagus than those with uncomplicated reflux disease or among control subjects\textsuperscript{37} and parallels the increased acid reflux also seen in patients with Barrett esophagus.\textsuperscript{38} Therefore, bile may play a synergistic role with acid in the development of Barrett esophagus.

Because of the rare nature of esophageal adenocarcinoma, there are no prospective cohort studies of reflux patients to assess cancer risk. However, 3 case-control studies have examined reflux symptoms as a risk factor for the development of esophageal adenocarcinoma (Table 1). In Sweden, Lagergren et al\textsuperscript{39} performed a population-based case-control study examining the relationship between reflux symptoms and adenocarcinoma of the esophagus. All cases of adenocarcinoma of the esophagus occurring in a 3-year period were eligible for entry, and 85% of those eligible participated. Control subjects were age and sex matched by using a national registry. Case and control subjects were questioned about the frequency and severity of any reflux symptoms they experienced 5 years earlier. After multiple risk factors for cancer were controlled for, subjects with esophageal adenocarcinoma were almost 8 times as likely to report at least weekly symptoms of reflux or regurgitation than were control subjects (95% confidence interval [CI], 5.3-11.4). Furthermore, a dose-response relationship existed, so if an individual’s reflux symptoms were long-term (>20 years) and severe (as defined by a scale accounting for frequency and severity of symptoms), the adjusted odds ratio (OR) for esophageal adenocarcinoma was 43.5 (95% CI, 18.3-103.5). Because recall bias might explain the observed association between reflux symptoms and esophageal adenocarcinoma, a second group with squamous cell carcinoma of the esophagus was also studied. No association was found between reflux symptoms and squamous cell carcinoma risk, suggesting that recall bias did not explain the observed association. This study concluded that long-standing severe reflux symptoms were strongly associated with an increased risk of adenocarcinoma of the esophagus.

Kaiser Permanente in California conducted a review of medical records for all those in the plan who were diagnosed as having adenocarcinoma of the esophagus or gastric cardia from 1986 to 1992.\textsuperscript{40} Controls for these 196 patients were matched for sex, age, and length of time enrolled in the Kaiser system. Medical records were reviewed for a documented history of reflux disease, hiatal hernia, esophagitis, and dysphagia. After several relevant risk factors were adjusted for, patients with adenocarcinoma were at least twice as likely as control subjects to have documentation of 1 of these conditions. A third population-based case-control study using tumor registries in Connecticut, New Jersey, and Washington studied 293 patients with esophageal adenocarcinoma and 695 control subjects derived from random-digit dialing.\textsuperscript{41} As did the study by Lagergren et al,\textsuperscript{39} the study by these investigators demonstrated a dose-response relationship between frequency of reflux symptoms and risk of adenocarcinoma. The adjusted OR for cancer of individuals experiencing at least daily reflux was 5.5 (95% CI, 3.2-9.3).

Although these studies report eye-catching results for relative risk (RR), it is the absolute risk that more accurately describes any individual’s chance of getting cancer. Because the number of US individuals with reflux symptoms is so high and because the incidence of esophageal adenocarcinoma is so low, by necessity the absolute risk to the average person with reflux is low. For example, consider the hypothetical situation that all esophageal adenocarcinomas arise in those who are older than 50 years and who experience reflux symptoms weekly (Figure). According to US census estimates, ap-

Table 1. Association Between Gastroesophageal Reflux Disease Symptoms and Esophageal Adenocarcinoma in Case-Control Studies

<table>
<thead>
<tr>
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*OR indicates odds ratio; CI, confidence interval; and NR, not reported.
†Cases included esophageal adenocarcinoma and adenocarcinoma of the cardia.
proximately 77 million individuals are older than 50 years. If 14% of these individuals experience reflux weekly, approximately 10 million are affected. Of these 10 million individuals, approximately 6500 a year will develop cases of esophageal adenocarcinoma. Therefore, the annual cancer incidence rate for reflux patients older than 50 years is 6500 cases for every 10 million reflux patients at risk, or 0.00065 cases per patient annually. The cancer risk to any given individual with reflux, then, would be extraordinarily low.

Another problem with using reflux symptoms as a marker for increased risk in esophageal adenocarcinoma is that many of those developing the cancer never experience severe chronic reflux symptoms. In the study by Lagergren et al, 40% of those with esophageal adenocarcinoma did not have at least weekly symptoms of reflux before development of their cancer. Therefore, any surveillance program using frequent reflux symptoms as a marker for further investigation would miss these subjects. In the hypothetical but plausible scenario just described, the more than 10 million patients with weekly reflux would have only 3900 of the 6500 annual cases of esophageal adenocarcinoma, translating to a risk of only 0.00039 cases per reflux patient annually.

Esophageal adenocarcinoma is a rare cancer that, although strongly associated with reflux symptoms, is nevertheless uncommon even among those with weekly reflux symptoms. Although the majority of individuals who develop this cancer will report GERD symptoms, the annual incidence of this cancer in those with long-term GERD is less than 1 in a thousand, and 40% of those who develop cancer do not have frequent symptoms. Therefore the use of reflux symptoms to stratify risk for this cancer is associated with multiple epidemiologic and logistical problems.

What Is the Appropriate Treatment for Patients With Barrett Esophagus?

Barrett esophagus is a change in the lining of the esophagus from its usual squamous epithelium to columnar epithelium. Although older definitions of Barrett esophagus allow for any form of columnar epithelium, more recent definitions require that the columnar epithelium be of intestinal type, meaning that it must contain goblet cells. Some investigators have used a length requirement for the definition of Barrett esophagus so that lengths of intestinalized epithelium involving less than 3 cm of the esophagus were not considered Barrett esophagus. Because even short segments of intestinalized metaplasia increase the risk for esophageal adenocarcinoma, the accepted definition of Barrett esophagus is any length of intestinal metaplasia in the tubular esophagus.

Barrett esophagus is strongly associated with reflux symptoms. Endoscopic studies demonstrate that, although less than 1% of the general population has Barrett esophagus, 5% to 15% of those with long-term reflux symptoms will have Barrett esophagus of some length. Although Barrett esophagus is associated with increasing esophageal acid exposures and larger hiatal hernias, individuals experiencing only mild symptoms may also develop the lesion. Duration of reflux symptoms is positively associated with Barrett esophagus. Autopsy studies suggest that the majority of those with the disease are never diagnosed as having the condition, and most of those developing cancer in the setting of Barrett esophagus are unaware of the presence of the disease before their cancer diagnosis.

In longitudinal studies, individuals with Barrett esophagus are at increased risk of esophageal adenocarcinoma relative to either the general public or those with similar reflux symptoms without Barrett esophagus. Additionally, in more than 50% of cases of adenocarcinoma of the esophagus, Barrett esophagus displaying various degrees of dysplasia is found in the mucosa surrounding the esophagus. The disease appears to progress through degrees of dysplasia before the development of frank adenocarcinoma of the esophagus. For these reasons, Barrett esophagus is likely to be a precursor lesion that can evolve into esophageal adenocarcinoma.

The risk of cancer among individuals with Barrett esophagus is unclear. Almost all studies examining the cancer risk of individuals with Barrett esophagus report this risk to be elevated. Most studies report an RR of cancer that is 40 to 125 times higher than that of the general population. Again, the issue of absolute risk is important: although the RR in those with Barrett esophagus is high compared with that of the general population, given the low baseline incidence of the cancer, the absolute risk is less impressive. Estimates of the absolute risk of esophageal adenocarcinoma in the setting of Barrett esophagus vary widely.
from 0% to almost 3% per patient-year. Table 2 displays the longitudinal studies to date reporting the cancer risk in Barrett esophagus. Recent larger studies, as well as a recent meta-analysis of these data, suggest that a reasonable estimate is approximately 0.5% per patient-year. Stated another way, the risk of any given patient with Barrett esophagus developing cancer in a year is approximately 1 in 200. The meta-analysis also suggested that publication bias might be artificially increasing the estimates of cancer risk found in the literature. Small studies describing the cancer risk in Barrett esophagus may have been published only if they reported high estimates of cancer risk.

Because the number of individuals with Barrett esophagus in the United States may be higher than 3 million, investigators have attempted to stratify the risk for progression to adenocarcinoma of the esophagus among those with the disease. If reliable risk factors could be identified, then individuals with those risk factors might benefit from more intensive endoscopic surveillance. To date, the most predictive factor is the degree of dysplasia, or pre-cancerous cellular atypia, in the Barrett esophagus. Although individuals with no dysplasia are unlikely to have adenocarcinoma at subsequent surveillance endoscopies, those with high-grade dysplasia demonstrate a risk of subsequent adenocarcinoma exceeding 25%. Additionally, because the endoscopic biopsies of Barrett esophagus are taken in random locations, sampling error in individuals with high-grade dysplasia is great. When those with high-grade dysplasia undergo esophageal resection, up to 50% of the resection specimens demonstrate previously unrecognized adenocarcinoma. For this reason, several authorities have advocated that individuals with Barrett esophagus and high-grade dysplasia undergo esophageal resection. Others, citing the low incidence of incurable metastatic disease among those developing cancer and observed closely with frequent surveillance endoscopies, have suggested that individuals with Barrett esophagus

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*All studies included required histological confirmation of Barrett esophagus and any resulting cancers. All report a crude cancer incidence rate expressible in cancers per patient-year of follow-up. If multiple reports from the same cohort exist, the most recent report is listed. NR indicates not reported. The table is modified from a previous publication.†Cancer incidence was calculated as the number of carcinomas observed divided by the total number of patient-years of observation.‡The study included subjects with gastric and intestinal metaplasia.
Barrett esophagus is strongly associated with chronic reflux. Although the disease is associated with an increased risk of adenocarcinoma of the esophagus, the magnitude of the absolute risk is low, approximating 0.5% annually. The presence of high-grade dysplasia in Barrett esophagus is ominous and associated with a cancer risk in excess of 25%. Pharmacologic, endoscopic, and surgical therapies have been applied to decrease the cancer risk in the disease. Pharmacologic therapies have been largely unsuccessful in producing reliable regression in Barrett esophagus and have not been proven to decrease the cancer risk associated with the condition. Endoscopic modalities are more promising, and further investigation of the role of these therapies is ongoing.

**Does Endoscopy for Those With GERD Avert Death From Esophageal Adenocarcinoma?**

One question commonly faced in primary care settings is whether the patient with reflux symptoms needs prompt upper endoscopy to rule out cancer or assess for complications of reflux disease, such as stricture, erosive esophagitis, or Barrett esophagus. Certain signs and symptoms are more likely to be associated with underlying esophageal pathology than others. These so-called alarm features include difficulty swallowing (dysphagia), pain on swallowing (odynophagia), anemia, weight loss, and hematemesis. The presence of 1 or more of these in the setting of reflux should elicit further diagnostic testing. Upper endoscopy is commonly pursued in these situations, although a barium swallow is a reasonable diagnostic alternative in the setting of dysphagia.

At present, these therapeutic modalities are considered experimental, and their long-term utility remains uncertain. Given the low risk of progression to adenocarcinoma among individuals who have Barrett esophagus and no dysplasia, these modalities may find their greatest utility among those who have dysplasia and are at higher risk for cancer.3,101

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guidelines recommending that any patient with long-standing GERD symptoms, particularly those aged 50 years or older, have a screening upper endoscopy (Table 3). The primary goal of this endoscopy is to assess the patient for Barrett esophagus. No definition of long-standing was specified. Because Barrett esophagus is associated with an increased risk of esophageal adenocarcinoma, individuals found to have the disease on this screening upper endoscopy would then be eligible to enroll in an endoscopic surveillance program in which periodic upper endoscopies would be performed in the hopes of detecting adenocarcinoma of the esophagus in an earlier and presumably more curable stage.

Despite the American College of Gastroenterology’s recommendations for screening endoscopy for patients with long-term GERD, there are no randomized controlled trials demonstrating the prevention of cancer or an increased life expectancy. Several lines of evidence from cohort studies seem to suggest that endoscopy effectively detects the development of early adenocarcinoma and prevents subsequent death from adenocarcinoma. Patients with carcinomas detected as part of an endoscopic screening and surveillance program have their cancers discovered at an earlier stage and are more often eligible for surgical resection. Additionally, the life expectancy of individuals with cancer diagnosed in endoscopic screening programs is longer than that of those presenting symptomatically. Although these data appear suggestive, several biases, including lead time and length bias, may serve to accentuate the apparent benefits of endoscopic screening and surveillance programs in observational studies. Therefore, the only available data supporting screening endoscopy are observational and subject to bias.

Given the lack of supporting data, the 1997 American College of Gastroenterology guidelines may be too aggressive in their approach to the patient with uncomplicated GERD. The rate of cancer in those with reflux is low, and the overall incidence of this cancer is small. The sensitivity and specificity of upper endoscopy as a screening test in GERD are largely unknown, and it is likely that some cancers would be missed, while others would be detected at a stage too advanced for curative resection. Additionally, although upper endoscopy is a safe procedure with a major complication rate of approximately 1 in 1000 (major complications being perforation, cardiopulmonary events, and aspiration or bleeding requiring hospitalization), mass screening of the more than 10 million patients who are older than 50 years and have heartburn symptoms weekly could be expected to yield approximately 10,000 major complications from the procedures. These 10,000 major complications would be experienced in an effort to detect a cancer with an annual national incidence of approximately 6500 (Figure).

Is detection of Barrett esophagus an adequate goal to justify screening endoscopy in chronic GERD? The answer depends, in part, on the effectiveness of endoscopic surveillance of individuals with Barrett esophagus. We have no prospective randomized data demonstrating that periodic endoscopic surveillance prolongs life expectancy or decreases cancer mortality among individuals with Barrett esophagus. Because no data are available upon which to base an estimate of risk reduction attributable to surveillance programs, no estimate of the number of cancers averted or cancer deaths prevented is available. Because the efficacy is unknown, the cost-effectiveness of the endoscopic surveillance is also unknown, and decision analysis suggests that the cost-effectiveness would be highly dependent on multiple poorly defined variables. Also, even among individuals with Barrett esophagus, the absolute risk of cancer is approximately 0.005 cancers per patient annually. Although this risk is substantially higher than that of the reflux population, it is still low. Finally, we should not ignore the potential psychosocial effects of giving individuals a diagnosis of Barrett esophagus. As one physician notes, “Many patients with Barrett’s esophagus are terrified that they are doomed to develop esophageal cancer....In our zeal to prevent an uncommon cancer, we physicians should not recommend unproved and potentially harmful therapies for our patients with GERD and Barrett’s esophagus.” Even if individuals with Barrett esophagus are identified, it is unclear whether they will derive any significant benefit from that knowledge, and this message must be transmitted to patients choosing to undergo surveillance. For these reasons, it is premature to suggest that performing screening endoscopy on individuals with uncomplicated GERD to find Barrett esophagus is a worthy goal. Further data are necessary with respect to the utility of endoscopic surveillance programs in Barrett esophagus, especially for individuals in whom the disease is found incidentally on upper endoscopy performed for other reasons.

Another concern is whether the cost of any benefit in survival in individu-

### Table 3. American College of Gastroenterology Guidelines for the Diagnosis and Surveillance of Barrett Esophagus

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Suggested Endoscopic Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-standing reflux symptoms, especially in individuals 50 years or older</td>
<td>A single upper endoscopy to rule out Barrett esophagus</td>
</tr>
<tr>
<td>Barrett esophagus, no dysplasia</td>
<td>After a second confirming endoscopy, surveillance every 2-3 y</td>
</tr>
<tr>
<td>Barrett esophagus, low-grade dysplasia</td>
<td>Endoscopy every 6 mo ×2 and then annually</td>
</tr>
<tr>
<td>Barrett esophagus, high-grade dysplasia</td>
<td>Expert confirmation of the histology; if confirmed, consideration of esophageal resection or endoscopy every 3 mo</td>
</tr>
</tbody>
</table>

*The table is based on information from Sampiner. Other organizations, including the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy, have not issued specific recommendations for follow-up of patients with Barrett esophagus.
als undergoing screening endoscopy will be acceptable. Endoscopy is an expensive screening test. Given the low yield of endoscopic screening, even if endoscopic screening programs did avert death from adenocarcinoma, the cost for each cancer diagnosed or life-year saved may well be prohibitive. No prospective data are available by which to judge the cost-effectiveness of this practice. A cost-effectiveness analysis of screening endoscopy found that, under favorable conditions, screening may be a cost-effective strategy but that the conditions might be difficult to meet.118

Any recommendations for screening all individuals with long-term reflux symptoms should be revisited. One way to increase the yield of screening upper endoscopy in individuals with GERD may be to use recently available data to better stratify risk for cancer among those with reflux disease. Sex and race differences exist in the incidence of cancer, which may allow for more targeted use of endoscopy. Also, because increasing body mass index is an independent predictor of risk of esophageal adenocarcinoma,119,120 investigators have attempted to use a combination of body mass index and reflux symptoms to select an extremely high-risk group for endoscopic surveillance. If screening endoscopy were limited to only individuals with severe heartburn (based on a multivariate symptom score) for more than 20 years and a body mass index higher than 25 kg/m², investigators could identify a group that had an adjusted OR of cancer that was 100 compared with that of a lean individual with no reflux disease.121 However, owing to the low absolute risk of cancer, even in such a high-risk group, more than 500 yearly endoscopies would be necessary to find 1 case of esophageal adenocarcinoma. Although this number seems prohibitive, if work can allow for more accurate risk stratification, the yield of screening upper endoscopy might be improved. Efforts are also under way to develop safer and less expensive means of providing sampling of the esophageal mucosa. Small-diameter endoscopes may allow for unsedated or transnasal endoscopy.122 Nonendoscopic methods of obtaining cytologic samples might also decrease cost and risks associated with sedation.123 Currently, these procedures are investigational.

Although the American College of Gastroenterology suggests upper endoscopy for all individuals with longstanding GERD symptoms, no data from randomized trials are available to support this practice, and serious concerns remain about the benefit and cost-effectiveness of this practice. Given the low absolute risk of cancer in those with GERD, the low yield of endoscopic screening in these subjects, and the lack of demonstrated efficacy of endoscopic screening, we do not endorse endoscopic screening of all patients with chronic GERD symptoms without alarm features.

**COMMENT**

GERD is a major risk factor for adenocarcinoma of the esophagus. However, because of the low absolute risk of this cancer and the high prevalence of GERD in the population, the risk of esophageal adenocarcinoma in any given individual with reflux is extremely low. Barrett esophagus, a complication of chronic reflux disease, is also associated with an increased risk of adenocarcinoma of the esophagus. Barrett esophagus is common among those with reflux, with 5% to 15% of individuals with chronic reflux symptoms possessing the lesion. Because of the increased risk of adenocarcinoma of the esophagus associated with reflux disease and Barrett esophagus, endoscopic screening of patients with chronic reflux symptoms has been proposed by the American College of Gastroenterology. Although this approach is widely practiced, no randomized data exist to demonstrate that such an approach improves survival among patients undergoing screening. Furthermore, given the large numbers of individuals with chronic reflux symptoms and the low incidence of adenocarcinoma of the esophagus, as well as the paucity of data demonstrating an effect of endoscopic surveillance in those found to have Barrett esophagus, it is unclear whether the benefits of screening endoscopy outweigh its monetary and quality-of-life costs. For these reasons, we do not endorse routine endoscopic screening in individuals with GERD symptoms. Better methods to stratify risk among the large number of individuals with chronic reflux symptoms would be necessary to improve the yield of endoscopic screening.

**Funding/Support:** This work was supported in part by National Institutes of Health grant K23 DK59311-01.

**Acknowledgment:** We thank Robert Sandler, MD, and Dawn Provenzale, MD, for conceptual help with the article.

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GASTROESOPHAGEAL REFLUX


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