The continuum of GERD complications

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ABSTRACT

Complications of chronic gastroesophageal reflux disease (GERD) run the gamut from erosive esophagitis to esophageal cancer, but all are linked to repeated exposure of the esophagus to caustic gastric and duodenal acid. Progression from one complication to another is not clearly established across the GERD continuum, although there is a clear progression from the serious complication of Barrett's esophagus to esophageal adenocarcinoma. This review examines the range of complications that can arise from chronic GERD, underscoring the need to view heartburn as a symptom of a potentially serious condition.

It is easy to understand how frequent heartburn and regurgitation can reduce quality of life. Gastroesophageal reflux disease (GERD) symptoms cause discomfort for the sufferer and, in the case of nocturnal reflux, can disturb sleep. For some people who experience mild or moderate GERD, the condition can remain fairly benign and limited to occasional discomfort. For others, GERD symptoms can be signs of serious health problems.

The complications of GERD, from erosions in the esophageal epithelium to esophageal adenocarcinoma, are linked to repeated esophageal exposure to caustic gastric and duodenal juices. Frequent and severe heartburn is often, but not always, an indication of esophageal damage, but damage can occur even in those with mild symptoms or even in the absence of GERD symptoms.

This article explores the complications that arise from chronic GERD. These include erosive esophagitis, esophageal ulcers, esophageal strictures, and Barrett's esophagus. In addition, GERD complications and hiatal hernia frequently occur as comorbid conditions.[1] Erosive esophagitis is the single most common GERD complication, whereas strictures and ulcers occur more often in combination with other conditions or with each other.

In the case of the more serious GERD complications, namely, Barrett's esophagus and esophageal adenocarcinoma, there is a clear progression from the former to the latter. Indeed, Barrett's esophagus is the only recognized risk factor for esophageal adenocarcinoma.[2] Progression is not as clear, however, with other GERD complications. For example, Winters and colleagues[3] found that the prevalence of Barrett's esophagus was 36.3% (95% confidence interval [CI], 0.20 to 0.52) in patients with erosive esophagitis compared with 12.4% (95% CI, 0.06 to 0.18) in patients with GERD symptoms alone.

The following sections focus on the prevalence and pathology of GERD complications, as well as their appearance in the esophagus, diagnostic signs and symptoms, and other issues in their diagnosis.

REFLUX ESOPHAGITIS

In patients with chronic GERD, the material refluxed into the esophagus can cause epithelial changes, marked by polymorphonuclear or mixed polymorphonuclear and round cell infiltration.[4] In some cases, these microscopic changes occur in an otherwise normal-appearing esophagus. Esophageal inflammation caused by GERD is called reflux esophagitis. For some patients with reflux esophagitis, erosions or mucosal breaks of varying severity can develop in the esophagus. Erosion of the esophageal mucosa, or erosive esophagitis, is a common complication of chronic GERD.

Erosive esophagitis, a visible manifestation of

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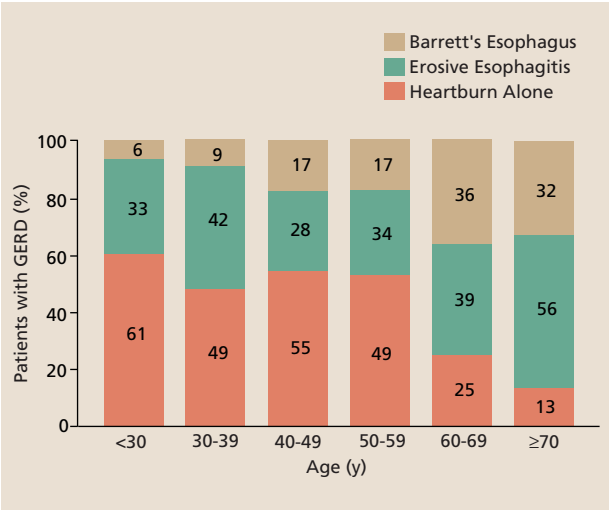

FIGURE 1. Proportions of GERD patients with heartburn, erosive esophagitis, and Barrett's esophagus according to age group. Reprinted from reference 8 with permission from the American College of Gastroenterology.

esophageal damage caused by refluxate, is considered by many to be synonymous with GERD itself.[5] Some clinicians use the term "nonerosive reflux disease" to denote patients with GERD symptoms who have no visible esophageal damage, and the term GERD to denote patients with visible esophageal damage caused by reflux. In fact, healing of erosive esophagitis was considered a primary end point in most early clinical trials of GERD therapy and continues to be an important measure of treatment efficacy. However, people with nonerosive reflux disease experience GERD symptoms that are as severe as the symptoms of patients with esophagitis, impairing quality of life to the same degree and requiring the same treatment as patients with esophagitis. This article will treat erosive esophagitis as a common GERD complication rather than a symptom.

Erosive esophagitis is difficult to predict clinically, as symptom duration, frequency, and severity are poor indicators of its presence.[6] Moreover, the connections between erosive esophagitis and more serious GERD complications, such as Barrett's esophagus and esophageal adenocarcinoma, are similarly problematic. This section discusses the prevalence, pathology, and endoscopic appearance of esophagitis; evidence of the lack of correlation between GERD symptoms and its presence; and the relationship of this condition with other, more severe GERD complications.

Prevalence

The population prevalence of erosive esophagitis is difficult to assess. One study in China demonstrated a prevalence rate of 5%, whereas a study in Sweden showed a prevalence rate of approximately 2.4%. In the United States, two prevalence surveys based on physician contacts yielded a rate range of 0.7% to 1.2%.[7]

The only way to positively identify esophagitis is through endoscopy. Therefore, to assess the prevalence of esophagitis in the general population, all individuals would have to undergo this procedure. Usually, only patients who complain of GERD or other upper digestive symptoms undergo endoscopy, and attempts to determine erosive esophagitis prevalence rates for the general population based on studies conducted in patients with GERD symptoms may result in an overestimation of prevalence. In patients with chronic GERD, the prevalence of erosive esophagitis is estimated to be 20%, although some studies have demonstrated even higher rates.[1]

Whereas uncomplicated GERD tends to be more common in women, GERD complications are more common in men.[1] Age is also an important factor in complication prevalence. Collen and colleagues[8] investigated the relationship between age and GERD severity in 228 patients. The proportions of GERD patients aged less than 60 years with heartburn alone or with erosive esophagitis remained relatively consistent among 10-year age groups, averaging 54% (range, 49% to 61%) and 35% (range, 28% to 42%), respectively. However, among patients aged 60 years or older, the proportion of patients with heartburn alone decreased as the prevalence of erosive esophagitis and Barrett's esophagus increased **(Figure 1)**. The prevalence of erosive esophagitis and Barrett's esophagus was significantly higher in GERD patients aged 60 years or older: 81%, compared with 47% in younger GERD patients ($P = 0.000002$). Symptom severity, however, did not significantly differ among age groups. These data indicate that, although older patients may not experience more severe GERD symptoms than younger patients do, they may present with more severe GERD complications.

As with GERD in general, esophagitis is more common in whites compared with other ethnic groups.[1] However, there are indications that the prevalence of this complication has been underestimated in Asians or may be increasing. A recent study conducted in 464 Asian inhabitants of Taiwan

found that 14.5% of consecutive patients referred for endoscopy for GERD symptoms had erosive esophagitis.[9] The authors postulated that the increased use of endoscopy as a method of detection, instead of less accurate radiologic studies, might explain this higher-than-expected percentage. They also noted, however, that lifestyle changes in this population could underlie the observed increase in prevalence. This study confirmed a higher prevalence of erosive esophagitis in male versus female patients and in older versus younger patients in this Asian population.

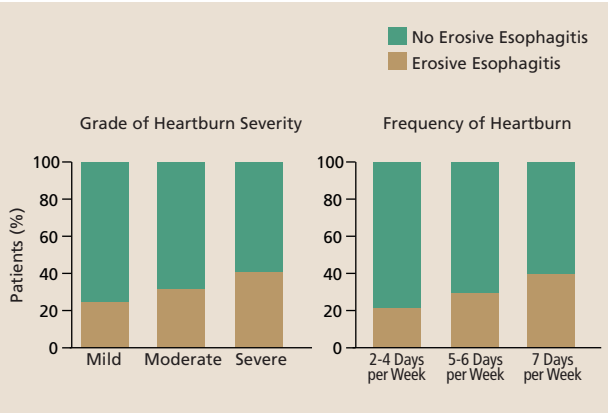

FIGURE 2. Prevalence of erosive esophagitis in a study of 994 GERD patients presenting with varying degrees of heartburn severity and frequency. Reprinted from "Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice," by Venables TL, Newland RD, Patel AC, et al, from Scand J Gastroenterol, www.tandf.no/gastro, 1997, vol. 32, 965-973, by permission of Taylor & Francis AS.[12]

Etiology and symptoms

In 1935, the idea was postulated that exposure to refluxed material could cause inflammation of and injury to the mucosa of the esophagus. For many years, researchers assumed that hiatal hernia was the main cause of reflux esophagitis. Currently, researchers believe that reflux-related esophagitis is caused by multiple factors and that lower esophageal sphincter pressure (LESP) and hiatal hernia are just two of the many factors in its development. Factors involved in the pathogenesis of reflux-related esophagitis include:

- Impaired esophageal clearance and neutralization mechanisms, which control the amount of time refluxed material remains in contact with esophageal mucosa
- Increased volume and causticity of material that is refluxed into the esophagus
- Impaired ability of the esophageal tissue to resist injury.

The contribution of each of these factors to the pathogenesis of reflux esophagitis varies from patient to patient. Thus, the presence of reflux esophagitis in the patient with GERD symptoms is difficult to predict.[3] Research has found that systemic sclerosis, which results in dysfunction of the LES, correlates with an increased risk of erosive esophagitis.[1] The use of nonsteroidal anti-inflammatory drugs has also been associated with an increased occurrence of this complication, possibly because these drugs seem to impair esophageal tissue resistance to injury by refluxate.[1,6]

Material refluxed into the esophagus during sleep, when the person is supine, tends to remain in the esophagus for a longer time. Some investigators have postulated that patients with GERD who experience nocturnal reflux are at greater risk of developing esophagitis, because this complication is directly related to the time of esophageal exposure to caustic refluxed material. However, there is a stronger correlation between the severity of esophagitis and the total time of esophageal exposure to the refluxate than there is between the severity of the esophagitis and the body position at the time of the reflux episode.[10] A study by Orr and colleagues[11] demonstrated that patients with erosive esophagitis had a greater degree of acid reflux and a greater percentage of esophageal acid contact time in both upright and supine positions than did patients without erosive esophagitis. The authors did find that the number of reflux episodes experienced in a recumbent position lasting more than 5 minutes also had predictive value for the presence of esophagitis.

Patients who report having no symptoms or mild symptoms can still demonstrate severe erosive esophagitis on endoscopy. Conversely, patients with severe GERD symptoms often have nonerosive reflux disease. The correlation between the frequency, severity, and duration of symptoms and erosive esophagitis varies from study to study. Venables and colleagues,[12] in a study of 994 patients with chronic GERD symptoms, found that 32% had erosive esophagitis. They noted that, even though most of the study participants did not have erosive esophagitis, the majority indicated that their heartburn was severe enough to disrupt their daily activities. Furthermore, daily heartburn was reported by 49%

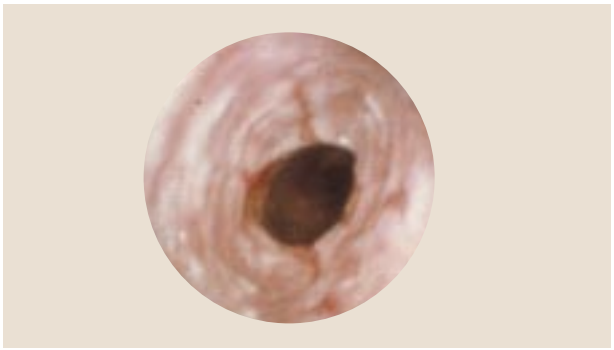

FIGURE 3. Endoscopic view of **isolated erosions** of the esophageal epithelium.

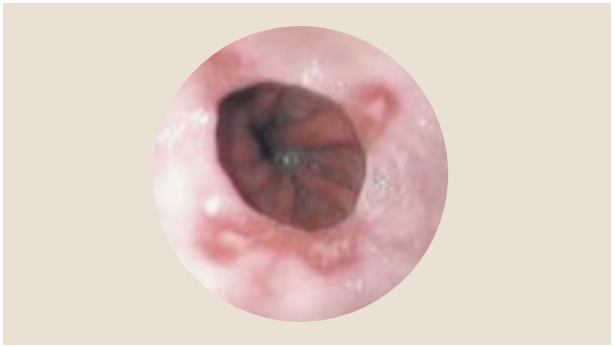

FIGURE 4. Endoscopic view of **confluent erosions** of the esophageal epithelium.

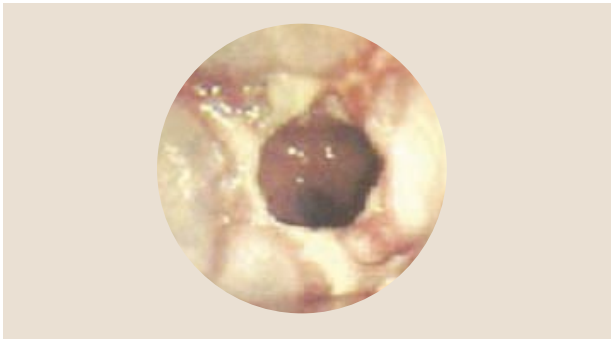

FIGURE 5. Endoscopic view of **circumferential erosions** of the esophageal epithelium.

of the participants. **Figure 2** illustrates the relationship of heartburn severity and frequency with the presence of erosive esophagitis in this study. The researchers concluded that the severity or frequency of chronic GERD symptoms is unreliable in predicting the presence of underlying esophagitis.

Voutilainen and colleagues[6] reached this same conclusion in their study of 1,128 patients with GERD referred for endoscopy. They found that the GERD symptoms of heartburn and/or regurgitation had a high specificity (0.87; 95% CI, 0.85 to 0.89) and negative predictive value (0.90; 95% CI, 0.88 to 0.92), but a low sensitivity (0.44; 95% CI, 0.37 to 0.52) and positive predictive value (0.37; 95% CI, 0.31 to 0.44) for the presence of esophagitis. They also found that the majority of patients aged less than 50 years with GERD symptoms did not have esophagitis.

Other studies have found correlations between the severity of specific symptoms and the presence and severity of erosive esophagitis. Lundell and colleagues[13] pooled results from two large studies involving 716 patients (538 in the first, 178 in the second) with GERD symptoms of varying severity. They found that heartburn severity correlated with esophagitis severity ($P < 0.01$ in the first study; $P < 0.001$ in the second). In a trial designed to evaluate the causes of Barrett's esophagus, Lieberman and colleagues[14] studied the correlation between the occurrence of GERD symptoms and erosive esophagitis. Of 662 patients with GERD symptoms who underwent endoscopy, 39% had no esophageal inflammation, 44% had erosive esophagitis, and 17% had probable Barrett's esophagus. Sixty-one percent of patients reported daily GERD symptoms, and 39% reported intermittent symptoms of lesser frequency. In this study, the presence of daily GERD symptoms was associated with a greater likelihood of erosive esophagitis ($P < 0.001$), but symptom duration was not associated with an increased likelihood. Forty-seven percent of patients who experienced GERD symptoms for less than 1 year had erosive esophagitis, compared with 42% of those who had GERD symptoms for more than 10 years.

Appearance

Erosions in the esophageal mucosa appear as areas of "denuded" epithelium. These erosions are classified into three categories[5] to describe the extent of esophageal damage:

- **Isolated erosions.** These are small and unconnected erosions that occur only on the peaks of the mucosal folds **(Figure 3)**.
- **Confluent erosions.** These are larger breaks in the esophageal mucosa that occur on the peaks of folds and also between folds. The injury to the esophageal mucosa is more extensive, but it does not encircle the entire esophagus **(Figure 4)**.
- **Circumferential erosions.** In this case, the mucosal injury encompasses the entire circumference of the esophagus. Circumferential erosions indicate the most severe form of erosive esophagi-

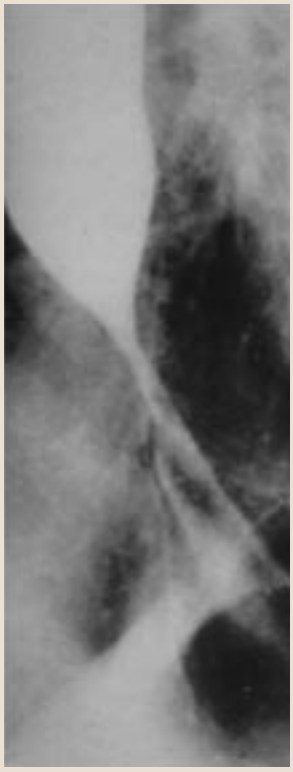

FIGURE 6. Barium esophagram showing a stricture.

tis. Esophageal injury to this extent often occurs with other complications, such as ulcer, stricture, and Barrett's esophagus **(Figure 5)**.

Several classification systems of erosive esophagitis based on the extent of mucosal injury have been developed. The most common methods of classification are discussed elsewhere.[15]

Uncertain role in disease progression

In the past, practice guidelines recommended aggressive treatment of mild erosive esophagitis to prevent progression to more severe forms. A high prevalence of concurrent GERD complications in patients with esophagitis indicates a close pathophysiologic relationship. However, studies have not shown a definite progression. Instead, patients seem to present with either severe or mild forms and then maintain this phenotypic expression of GERD.

For example, a study conducted by El-Serag and Sonnenberg[16] in US veterans found that 39% of patients were initially diagnosed with esophageal ulcer, a more severe GERD complication, whereas only 22% were diagnosed with esophagitis. In a subsequent study,[17] also conducted in US veterans, these researchers monitored 29,500 patients with erosive esophagitis but without further complications (ulcer or stricture) and 5,100 patients with esophagitis as well as ulcers or strictures. After 4 years, no patient in the former group had developed ulcers or strictures, whereas 80% of the latter group still had esophagitis and ulcer or stricture.

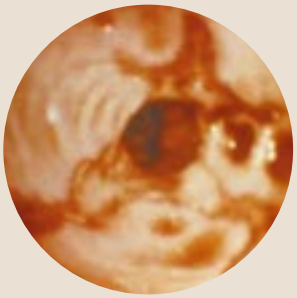

FIGURE 7. Endoscopic view of an esophageal stricture and ulceration.

These findings contradict the logic that repeated and prolonged esophageal exposure to acid reflux, the culprit of initial esophageal injury, causes disease progression. One explanation could be that the most severe grade of esophagitis is reached at onset of the disease.[1] It will be interesting to see how further research into the pathophysiology of this complication resolves this issue.

ESOPHAGEAL ULCERS AND STRICTURES

Esophageal ulcers and strictures are more-severe GERD complications. The above-mentioned study in US veterans by El-Serag and Sonnenberg[16] found that any GERD complication was 10 times more likely to occur with another GERD complication than without. This was true most often with esophageal strictures and ulcers. Strictures rarely occurred without other GERD complications, and ulcers never occurred as the sole complication. Given these observations, ulcers and strictures behave more like "compound complications" than isolated GERD complications, and both represent the most severe forms of esophagitis. However, this does not implicate or prove a progression to severe esophagitis from milder forms.

Figure 6 shows a barium esophagram of a stricture, whereas **Figure 7** shows an esophageal stricture, a narrowing of the esophageal lumen,[18] and ulceration. Ulcers are deeper injuries to the esophageal mucosa than the erosions of esophagitis **(Figure 8)** and can cause bleeding in the esophagus.

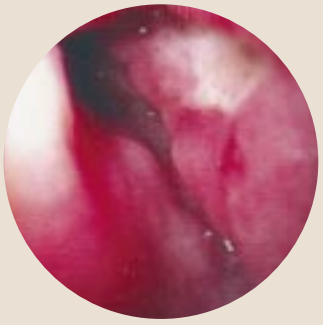

FIGURE 8. Endoscopic view of an esophageal ulcer.

Unlike gastric or duodenal ulcers, esophageal ulcers are not linked to *Helicobacter pylori* infection but are secondary to acid reflux. The prevalence of strictures and ulcers is low in patients with GERD as well as in the general population. This section explores the prevalence, pathology, and symptoms of these two GERD complications.

Strictures

Prevalence. The majority (70% to 80%) of strictures that occur in the distal esophagus are caused by GERD.[18,19] Estimates of the prevalence of strictures in patients with untreated erosive esophagitis range from 7% to 23%.[19] **Table 1** presents the findings of two surveys measuring the prevalence rates of esophagitis, ulcer, and stricture in the general population. The estimated prevalence of erosive esophagitis ranges from 0.7% to 1.2%. In comparison, the prevalence of strictures ranges from 0.07% to 0.12%. Strictures are most prevalent in whites and in men, and prevalence increases with age.[7]

Etiology and pathology. The presence of GERD is the most important etiologic factor for an esophageal stricture. Although decreased LESP is common in patients with uncomplicated GERD or less severe GERD complications, patients with esophageal strictures tend to have a further decrease in LESP. Furthermore, patients with strictures tend to demonstrate more frequent perturbations in motility, such as ineffective peristalsis, which prolongs the duration of esophageal acid exposure. Bile, trypsin, and pancreatic enzymes also play a role in stricture development, and studies have found that strictures are more common in patients with significant alkaline esophageal exposure. Hiatal hernia, found in 85% of patients with esophageal stricture, is another contributing factor to stricture development.

Esophageal strictures form as a result of repeated damage to the esophageal epithelium, leading to mucosal repair with fibrosis. Initially, inflammation causes the lumen of the esophagus to narrow. During healing, fibrosis occurs as the esophagus builds up type III collagen and scar tissue. Esophageal narrowing caused by scar tissue is irreversible. As a GERD complication, strictures occur most often in the distal esophagus, almost always forming at the squamocolumnar junction. They are usually less than 1 cm long. Esophageal strictures in conjunction with Barrett's esophagus often occur in more proximal locations, as the squamocolumnar junction is displaced to a more proximal area of the tubular esophagus.[19]

TABLE 1
Rates of esophagitis, esophageal ulcers, and esophageal strictures from all physician contacts in the United States, based on two 1985 surveys[7]

Survey	Rates per 100,000 population		
	Esophagitis	Ulcer	Stricture
National Disease and Therapeutic Index	1,246	46	125
National Ambulatory Medical Care Survey	797	18	74

Symptoms. Dysphagia is the most common symptom of esophageal strictures, although some patients may also present with odynophagia.[18] Patients often report a feeling of food sticking in the throat, even though the stricture is located in the distal esophagus. Patients presenting with dysphagia with liquids either have a narrow stricture or may have a motility disorder. It is difficult to extrapolate the severity of a stricture from dysphagia symptoms, because patients have usually already altered their diet as a result of the stricture. Therefore, patients should be questioned about the kinds of foods with which they experience dysphagia.[19]

In addition to dysphagia and odynophagia, patients with esophageal stricture can present with a variety of esophageal and extraesophageal symptoms. Most patients with esophageal strictures experience heartburn, although it is absent in approximately 25%.[18] Patients with heartburn may report a steady decline in the severity of this symptom because worsening of the stricture may reduce the amount of material refluxed into the esophagus. Extraesoph-

ageal symptoms include chronic cough and asthma. These symptoms are caused by aspiration and are not typical. Food impaction or esophagitis may cause chest pain in patients with strictures. Weight loss is not common, because patients tend to change their diets to accommodate strictures.[19]

Esophageal ulcers

As shown in **Table 1**, the prevalence of esophageal ulcers in the general population is very low, ranging from 0.018% to 0.046%. Like strictures, GERD-related ulcers increase in prevalence with age and are more prevalent in whites than in other racial groups.[18]

At endoscopy, ulcers appear as deep mucosal injuries and may occasionally bleed. They are not a common complication but may be seen in patients with Barrett's esophagus. In a study conducted in 78 patients with Barrett's esophagus, Murphy and colleagues[20] detected discrete esophageal ulcers in 36 patients over an average 3.3 years of follow-up (range, 1 year to 11 years). The majority of these ulcers were located in the distal esophagus, and 86% occurred within 3 cm of the esophagogastric junction. Gastrointestinal bleeding was present in 24% of patients, and in 76% of these patients, the bleeding was caused by the Barrett's ulcer.

BARRETT'S ESOPHAGUS

The lining of a normal esophagus is composed of a stratified squamous epithelium, in contrast to the columnar cell-lined epithelium found in the stomach and intestine. Barrett's esophagus is characterized by the presence of a metaplastic columnar epithelium in the tubular esophagus. The cellular changes of Barrett's esophagus appear to develop as a result of disordered repair following damage by caustic material refluxed from the stomach.[21]

In patients with Barrett's esophagus, GERD is often severe and may be complicated by esophageal ulcer, hemorrhage, and stricture. Although relatively few patients with GERD develop Barrett's esophagus, this condition merits attention because it is a major risk factor for the development of esophageal adenocarcinoma. This section discusses the pathophysiology, prevalence, and diagnosis of Barrett's esophagus, as well as its progression to dysplasia and adenocarcinoma.

Pathophysiology

Barrett's esophagus is defined as the replacement of the normal squamous epithelium of the esophagus with a metaplastic columnar epithelium. The exact mechanism of this process is not known. However, evidence has linked Barrett's esophagus to repeated and prolonged exposure of the esophageal mucosa to gastric material refluxed into the esophagus. Pluripotential stem cells then appear to differentiate into columnar epithelium during the repair process.[22] Therefore, exposure of the esophagus to acid reflux seems to both precipitate and facilitate development of the metaplastic columnar epithelium.[21]

This process would seem to suggest that the presence of erosive esophagitis is a risk factor for Barrett's esophagus. Csendes and colleagues,[23] in a study of 376 patients with GERD symptoms, found that erosive esophagitis occurred in 64% of participants with short-segment Barrett's esophagus and in 80% of those with traditionally defined, or long-segment, Barrett's esophagus. However, studies investigating a progressive relationship between erosive esophagitis and Barrett's esophagus have not been able to establish a clear link. In the GORGE study[14] of 662 patients with GERD symptoms who underwent endoscopic examination, a history of erosive esophagitis was not found to be an independent risk factor for Barrett's esophagus. Of patients who experienced GERD symptoms for less than 1 year, 47% had erosive esophagitis, although only 4% of this group had probable Barrett's esophagus on endoscopy. However, among patients who experienced GERD symptoms for more than 10 years, only 42% had erosive esophagitis on endoscopy, but 21% had probable Barrett's esophagus **(Table 2)**.

Although patients with Barrett's esophagus have

TABLE 2
Endoscopic findings from the GORGE study: Relation between erosive esophagitis, duration of GERD symptoms, and probable Barrett's esophagus

Duration of symptoms (yr)	Number of pts	Pts with esophagitis	Pts with probable Barrett's esophagus
< 1	127	47%	4%
1–5	236	53%	11%
5–10	81	48%	17%
> 10	140	42%	21%

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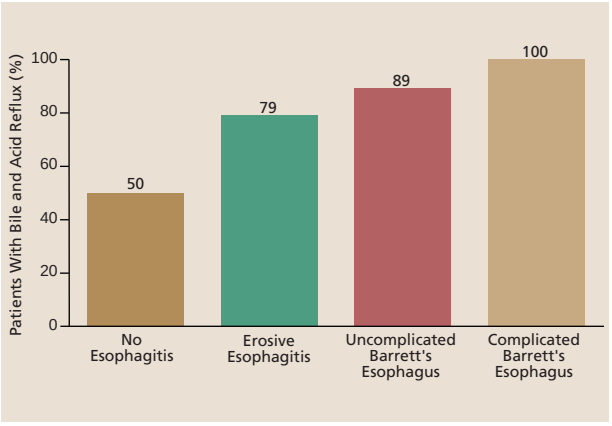

FIGURE 9. Prevalence of gastric acid reflux combined with duodenogastric reflux in patients with GERD, by degree of GERD severity. Reprinted from reference 26 with permission from the American Gastroenterological Association.

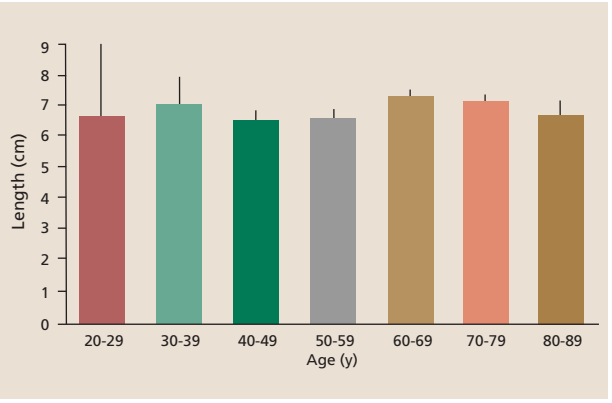

FIGURE 10. Mean length of segments of Barrett's esophagus among different patient age groups. Lines indicate standard error of the mean. Reprinted from reference 27 with permission from the American Gastroenterological Association.

increased esophageal acid exposure, hypersecretion of gastric acid does not seem to be related to Barrett's esophagus. Studies that compared patients with Barrett's esophagus to patients with erosive esophagitis alone found no difference in several acid output measures (basal acid output, gastrin-stimulated peak output, and pepsin output).[24]

The composition of the refluxed material in patients with Barrett's esophagus also has been investigated, particularly the role of duodenal secretions in esophageal injury. Some researchers have postulated that pancreatic enzymes, bile salts, and lysolecithin are important in the development of intestinal metaplasia and esophageal adenocarcinoma. When acid is present, damaging agents of bile salts are potentiated, and the salts are better able to penetrate into the esophageal mucosa.[25]

Vaezi and Richter[26] measured esophageal acid and bile exposure in patients with GERD (n = 30), patients with Barrett's esophagus (n = 20), and 20 control subjects. The refluxed material of most patients with GERD comprised both acid and bile **(Figure 9)**. The percentage of time that esophageal pH was less than 4 and that the bilirubin level was 0.14 or greater increased gradually with increasing disease severity, as did fasting gastric bile acid concentrations. Most episodes of duodenogastric reflux (79% to 91%) occurred when the pH of the esophagus was less than 4. Also, there was a significant correlation between the percentage of time that esophageal pH was less than 4 and the percentage of time that the bilirubin absorbance level was 0.14 or greater ($P < 0.01$).[26]

Although Barrett's esophagus is essentially an acid-reflux–facilitated process of epithelial damage followed by abnormal cellular repair, the condition is rarely progressive. Instead, it tends to develop to its fullest extent early on. The reason for this lack of progression is not known.[21] In a study involving 377 patients diagnosed with Barrett's esophagus from 1976 to 1989, Cameron and Lomboy[27] found that the length of the segment of Barrett's esophagus did not vary significantly among age groups **(Figure 10)**. Barrett's was defined as extension of the columnar epithelium at least 3 cm from the distal esophagus. Also, in 101 patients who underwent follow-up endoscopic examinations (average follow-up interval, 3.2 years), no significant progression of Barrett's esophagus was noted.

Histology

The types of columnar epithelium found in the esophagus fall into three categories[21,22]:

- **Gastric fundic-type epithelium**, which is lined with pits composed of mucus-secreting cells. The glandular layer underneath is composed of chief and parietal cells **(Figure 11)**.
- **Gastric junctional-type (or cardiac-type) epithelium**, which has a foveolar surface. There are no parietal cells, and the glands are composed almost entirely of mucus-secreting cells **(Figure 12)**.
- **Specialized intestinal metaplasia (or specialized columnar epithelium)**, which is required for a diagnosis of Barrett's esophagus and is the only one of these three types of columnar epithelium linked to an increased risk of esophageal adenocarcinoma. It has a villiform surface and mucus-

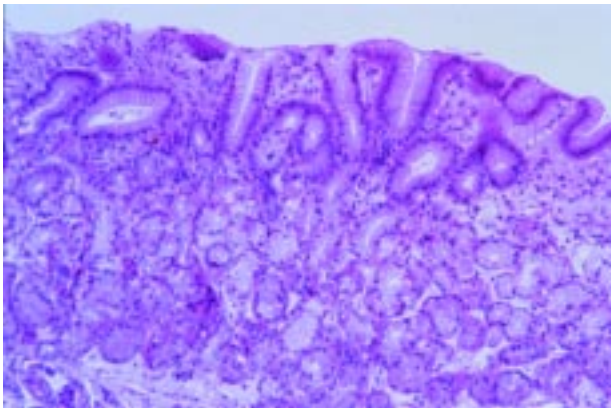

FIGURE 11. Fundic-type epithelium, lined with pits composed of mucus-secreting cells. The glandular layer underneath consists of chief and parietal cells.

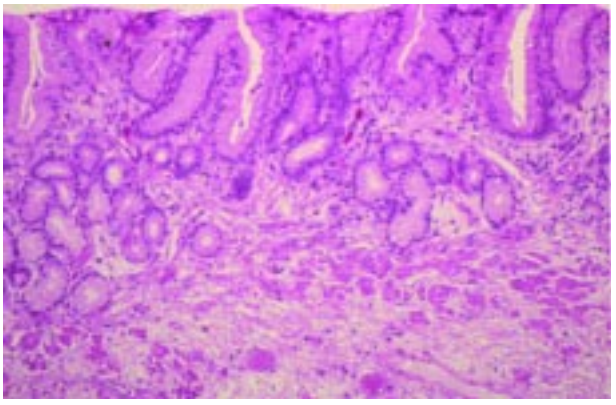

FIGURE 12. Junctional-type or cardiac-type epithelium, with its characteristic foveolar surface. No parietal cells are present, and the glands consist almost entirely of mucus-secreting cells.

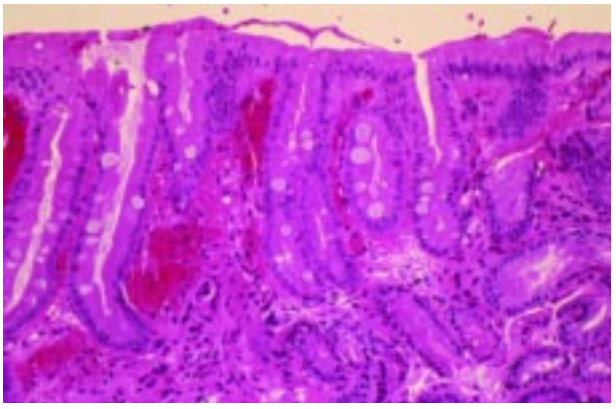

FIGURE 13. Specialized intestinal metaplasia, characterized by a villiform surface and mucus-secreting goblet and columnar cells lining intestinal-type crypts. This is the only type of columnar epithelium linked to an increased risk of esophageal adenocarcinoma.

secreting goblet and columnar cells lining intestinal-type crypts. Chief and parietal cells are usually absent **(Figure 13)**.

The different types of epithelia occurring in Barrett's esophagus look the same on endoscopy, and histologic examination must be performed to differentiate them. Although gastric fundic-type and junctional-type epithelia are sometimes histologically indistinguishable from normal gastric mucosa, specialized intestinal metaplasia is easily identified.[21]

Prevalence

The overall prevalence of Barrett's esophagus is unknown. Its estimated prevalence in the general population is 0.41% to 0.89%,[24] although studies in specific populations have shown higher rates.

Cameron and colleagues[28] conducted a population-based study in Olmsted County, Minn., comparing the prevalence of clinically detected Barrett's esophagus with autopsy findings. The study analyzed the number of county residents who had been clinically diagnosed with Barrett's esophagus from 1968 to 1986. The researchers found that, as of January 1, 1987, the age-adjusted and sex-adjusted prevalence rate was 22.6 cases of Barrett's per 100,000 individuals in the population (95% CI, 11.7 to 33.6 cases). The researchers then prospectively reviewed the autopsy records of Olmsted County residents over an 18-month period ending in September 1987. Using the same diagnostic criteria, the autopsy data yielded a prevalence rate of 376 cases of Barrett's per 100,000 residents (95% CI, 95 to 967 cases)—a 21-fold increase (95% CI, 5 to 54). These findings suggest that, for every case of Barrett's esophagus that is detected antemortem, 20 cases are not detected.

Differences in the parameters used to diagnose Barrett's esophagus also lead to changes in prevalence estimates. In a study of 650 adults in Japan, Azuma and colleagues[29] found that when the traditional diagnostic measures were used (segments of columnar epithelium 3 cm or greater in length), the prevalence rate of Barrett's esophagus was 0.62%. However, when they included the prevalence of short-segment Barrett's esophagus (segments less than 3 cm), the rate was 15.7%.

Barrett's esophagus is most common in white males, appearing less commonly in black and Asian populations.[25] Studies have placed the prevalence of Barrett's esophagus in Hispanic populations at a rate comparable to that in whites. Moreover, a recent study in a Taiwanese population demonstrated a

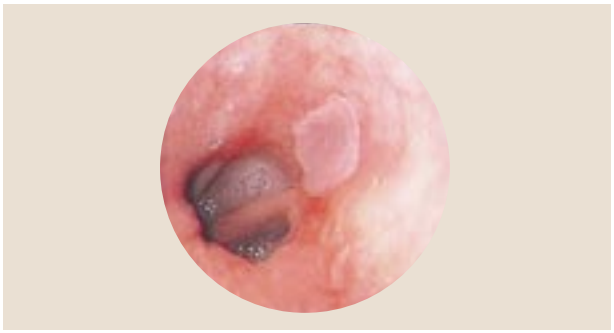

FIGURE 14. Endoscopic view of columnar epithelium in the distal esophagus showing a white, pearly patch of squamous epithelium within Barrett's esophagus.

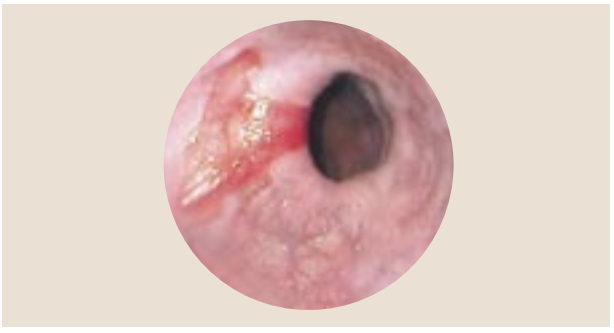

FIGURE 15. Endoscopic view of a red, velvet-like tongue of columnar epithelium among normal pink, glossy epithelium, typical of Barrett's esophagus.

prevalence rate of 2%, suggesting that prevalence may be increasing in populations where the condition previously was thought to be unusual.[24]

Estimates of the prevalence of Barrett's esophagus in patients with chronic GERD symptoms range from approximately 10%[30] to as high as 20%.[14] The prevalence of Barrett's esophagus in this population has been linked to the duration of GERD symptoms. In the GORGE study,[14] 4% of patients who had symptoms for less than 1 year had Barrett's esophagus. For patients who had symptoms for 1 year to 5 years, the odds ratio for Barrett's esophagus was 3.0 (95% CI, 1.2 to 8.0). The odds ratio increased to 6.4 (95% CI, 2.4 to 17.1) for patients who had symptoms for more than 10 years.

Diagnostic issues

Estimates of the average age of the Barrett's patient at diagnosis vary. One common estimate is 55 years.[25] In their population study, Cameron and Lomboy[27] found that the mean age at development of Barrett's esophagus was 40 years, but the mean age at diagnosis was 63 years. One explanation for this gap could be related to symptomatology. Barrett's esophagus is impossible to differentiate from uncomplicated GERD based on symptoms alone,[25] and the signs of Barrett's esophagus can be detected only by endoscopy. A positive diagnosis is made after histologic examination of biopsy samples from the esophagus reveals the presence of intestinal-type epithelium. Patients with GERD symptoms who have Barrett's esophagus develop those symptoms at an earlier age, have more-severe nocturnal reflux, and suffer from more complications, such as stricture, ulcer, and bleeding.[25] Although most patients with Barrett's esophagus are referred for endoscopy for GERD symptoms, there are no antecedent esophageal symptoms in an estimated 25% of cases.[21] In these cases, Barrett's esophagus is discovered when the patient is referred for endoscopy for unrelated conditions.

Also, many patients with Barrett's esophagus appear less sensitive to pain caused by acid reflux. Impaired sensitivity to acid reflux may further hamper efforts to detect Barrett's esophagus. This decreased sensitivity may be age-related or caused by the presence of columnar epithelium.[25]

Appearance. When viewed through an endoscope, the normal squamous epithelium lining the esophagus appears pearly white.[21] Columnar mucosa appears as a salmon-pink–colored epithelium. In most cases of Barrett's esophagus, the columnar epithelium consists of salmon-pink–colored, velvety tongues extending upward from the gastroesophageal junction.[31] **Figures 14 and 15** present typical endoscopic images of columnar epithelium and Barrett's esophagus. Patches of squamous epithelium appear pearly white among the darker columnar epithelium. The esophagus terminates at the gastroesophageal junction, which appears as a pinched closure at the end of the esophagus coinciding with the beginning of the gastric folds. The presence of hiatal hernia, erosive esophagitis, and other GERD complications can make it difficult to fix the exact location of this junction visually on endoscopy.[31]

Short-segment vs long-segment Barrett's esophagus. In the late 1950s, when Barrett's esophagus was first defined as an acquired condition separate from other gastroesophageal abnormalities, such as tubular-shaped hiatal hernia, the length of columnar epithelium required for a diagnosis of Barrett's esophagus was determined to be at least 3 cm.[32] Recent emphasis, however, has been placed on the presence of any length of intestinal-type metaplastic epithelium rather than any specific length of the

columnar epithelium segment. Endoscopic evidence of segments of columnar epithelium less than 3 cm in length in the distal esophagus, paired with histologic findings of intestinal-type mucosa, indicates short-segment Barrett's esophagus. Among patients undergoing routine endoscopy, prevalence rates of Barrett's esophagus 3 cm or more in length are around 1%, but the reported prevalence increases when shorter segments are included, ranging from 6% to 36%.[25]

Short-segment Barrett's esophagus shares many clinical features with traditional, or long-segment, Barrett's esophagus. Patients with GERD symptoms and increased esophageal acid exposure have an increased likelihood of developing short-segment Barrett's esophagus.[31] However, a study by Weston and colleagues[33] of 237 patients undergoing routine endoscopy found that acid reflux symptoms were present in only about half (53%) of patients with histologically confirmed short-segment Barrett's esophagus. Hiatal hernia was present in a majority of these patients (84%).

The degree and incidence of most abnormalities in patients with short-segment Barrett's seem to fall between those of patients with long-segment Barrett's esophagus and patients without Barrett's esophagus. For example, patients with short-segment Barrett's esophagus have increased LESP compared with patients with long-segment Barrett's esophagus, but decreased LESP compared with patients without Barrett's esophagus. Patients with short-segment Barrett's esophagus also experience less esophageal acid exposure than the former group, but more than the latter group.[25]

Detection of short-segment Barrett's esophagus is complicated by its proximity to the gastric cardia in the very distal esophagus **(Figure 16)**. Fixing the exact location of the gastroesophageal junction and comparing it with the squamocolumnar junction is the initial step in recognizing Barrett's esophagus. Intestinal metaplasia of the esophagus is histologically indistinguishable from intestinal metaplasia of the gastric cardia. If the junction is not precisely identified endoscopically and the endoscopist is not exact with the location of the biopsy, a patient who has intestinal metaplasia of the gastric cardia could be misdiagnosed with short-segment Barrett's esophagus.

Short-segment Barrett's esophagus can be missed when small segments of columnar mucosa in the distal esophagus are not recognized visually during endoscopy, when biopsy samples are not targeted accurately from affected areas, or when biopsy specimens are accidentally taken from the gastric cardia.[31]

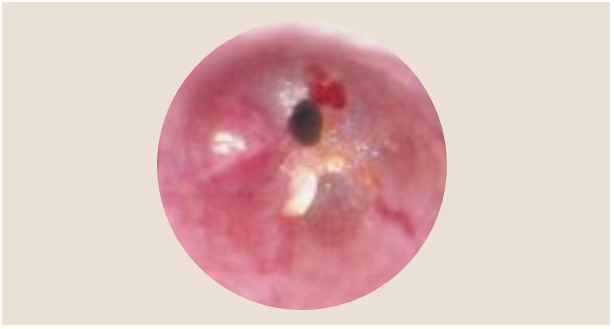

FIGURE 16. Endoscopic view of short-segment Barrett's esophagus present with Los Angeles grade B erosive esophagitis.

Research findings indicate some risk of esophageal adenocarcinoma developing in segments of Barrett's esophagus of less than 3 cm (short-segment Barrett's esophagus), but the results are inconclusive in patients with specialized intestinal metaplasia of the gastric cardia. As a result, controversy has arisen over the exact parameters of Barrett's esophagus. Some researchers narrow the definition based on length of segment and location of intestinal metaplasia. Long-segment Barrett's is used to denote the presence of columnar epithelium of greater than 3 cm; short-segment Barrett's is used when the segments of columnar epithelium extend up from the esophagogastric junction less than 3 cm into the distal esophagus. The term "intestinal metaplasia of the cardia" (or CIM) is used when the metaplasia is confined to the gastric cardia.[32]

Guidelines for diagnosis. The American College of Gastroenterology published guidelines for the diagnosis, surveillance, and management of Barrett's esophagus in 1998.[34] In these guidelines, the traditional definition of Barrett's esophagus, which restricted the length of the segment of abnormal cells to 3 cm or greater, was replaced by a definition **(Table 3)** with two key points:

- The change in the esophageal epithelium, regardless of how far the segment extends up from the esophagogastric junction into the distal esophagus, can be recognized on endoscopy
- Histologic examination confirms the presence of intestinal metaplasia.

Endoscopic examination is recommended for patients with chronic GERD symptoms, particularly patients who are aged 50 years or older, as Barrett's esophagus is most common in this age

TABLE 3
Evolving definition of Barrett's esophagus*

Old definition	New definition
"≥ 3 cm of columnar lining or intestinal metaplasia in the esophagus"	"A change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia by biopsy"

* According to the American College of Gastroenterology guidelines for diagnosis.[34]

group. The guidelines also point out the high prevalence of Barrett's esophagus in asymptomatic persons and recommend close examination of the distal esophagus for all patients undergoing endoscopy for any indication.[34]

A definitive diagnosis of Barrett's esophagus requires histologic confirmation. Numerous biopsy samples should be taken from the suspect areas to detect intestinal metaplasia. To rule out the presence of dysplasia, four-quadrant biopsies of the columnar epithelium should be taken at 1-cm to 2-cm intervals.[32] Various methods, including jumbo biopsy and balloon and brush cytology,[25] have been advocated for obtaining optimal results. Currently, the guidelines include only standard biopsy sampling.[34]

Development of dysplasia in Barrett's esophagus

Although the presence of intestinal metaplasia alone is a precancerous condition, the chances of a patient developing esophageal adenocarcinoma are even greater if high-grade dysplasia is present. Barrett's esophagus without dysplasia progresses to high-grade dysplasia in 5% of patients at 5 years. In contrast, low-grade dysplasia progresses to high-grade dysplasia in 25% of patients at 5 years.[35]

Not every patient with Barrett's esophagus goes on to develop adenocarcinoma, but for those who do, neoplastic progression in Barrett's esophagus follows a multiple-step process. As exposure to refluxed material continues to irritate the metaplastic columnar epithelium, low-grade dysplasia can develop, progressing to high-grade dysplasia, and finally to adenocarcinoma.[32]

In nondysplastic columnar metaplasia, the cells are mucus-producing with uniform-size nuclei close to the basement membrane. In high-grade dysplasia, the cells produce little or no mucus; have enlarged, pleomorphic nuclei; are stratified on the basement membrane; and have irregular-shaped glands. (In the case of adenocarcinoma, the cells penetrate the basement membrane into the wall of the esophagus.)[36] The natural history of high-grade dysplasia in Barrett's esophagus is uncertain. In many cases, high-grade dysplasia rapidly progresses to carcinoma. However, in some cases, it does not progress and can actually regress. For intermediate grades of dysplasia, progression to adenocarcinoma is less frequent.[35]

There are problems inherent in grading dysplasia, including the subjectivity of the assessment method and lack of correlation between biologic behavior of the lesion and the grade of dysplasia.[22] Low-grade dysplasia also can be confused with inflammatory atypia.[26] Furthermore, interobserver agreement, at 85% when differentiating high-grade dysplasia and carcinoma from low-grade, indefinite, and negative dysplasia, falls to 72% when diagnosing low-grade dysplasia and to 58% when diagnosing indefinite dysplasia.[25,34]

Any segment of metaplasia is capable of developing into dysplasia.[32] However, a study by Weston and colleagues[37] conducted in 152 patients with either short-segment or long-segment Barrett's esophagus found that dysplasia was more common in the latter group. The incidence of dysplasia at diagnosis was 8.1% in patients with short-segment Barrett's esophagus, compared with 24.4% ($P < 0.007$) in patients with long-segment Barrett's esophagus. Dysplasia also developed at a significantly faster rate in patients with the long-segment form, with two cases developing in patients with short-segment Barrett's esophagus compared with six cases in patients with the long-segment form ($P < 0.05$). Cameron and Carpenter[38] found that dysplasia occurs in patches and in varying degrees of severity in Barrett's esophagus and develops in many areas at the same time. Large patches form when smaller patches converge, instead of spreading out from one site.

ESOPHAGEAL ADENOCARCINOMA

Once a rare condition and still relatively uncommon in the general population, the incidence of esophageal adenocarcinoma is rising in the United States and Europe.[39] Barrett's esophagus is the only recognized risk factor for this type of esophageal cancer. Barrett's esophagus, unfortunately, has no symptoms to distinguish it from GERD, and as many as 25% of patients with long-segment Barrett's esophagus have no esophageal symptoms.[21]

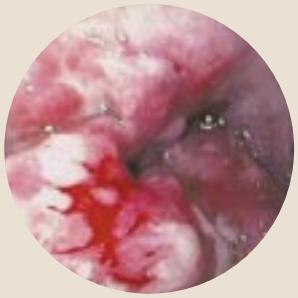

FIGURE 17. Endoscopic view of esophageal adenocarcinoma.

As a result, esophageal adenocarcinoma **(Figure 17)** is often detected when patients with the cancer present with dysphagia and weight loss. Cancer in patients presenting with these symptoms is usually incurable. Median survival is 2 years, and fewer than 10% of these patients survive for 5 years.[2]

Strong associations have been drawn between GERD and a patient's risk of developing esophageal adenocarcinoma. This section discusses these associations, the growing prevalence of this type of esophageal cancer, and the cellular process by which adenocarcinoma develops from Barrett's esophagus.

Prevalence and increasing incidence

In the mid-20th century, the overwhelming majority of cancers of the esophagus were squamous cell carcinomas. In fact, esophageal adenocarcinoma occurred so rarely that experts questioned its existence.[21] Over the past 20 years, however, while the incidence of squamous cell carcinoma has stayed constant, the incidence of adenocarcinoma of the esophagus and esophagogastric junction has risen fivefold—a growth rate exceeding that of any other cancer.[40] Esophageal cancer (both adenocarcinoma and squamous cell cancer) occurs at a rate of 3.3 per 100,000 individuals in the population.[39] Adenocarcinoma currently accounts for about half of all esophageal cancers in the United States.[21]

Esophageal adenocarcinoma is most prevalent in white males. In 1975, the incidence of adenocarcinoma per 100,000 person-years in the United States was 0.7 for white males and 0.4 for black males. However, by 1995, the incidence had risen to 3.2 for white males but only to 0.6 for black males. **Table 4** breaks down ratios of esophageal adenocarcinoma incidence rates among different age groups of white males over a recent 20-year period. For men aged less than 65 years, the rate of adenocarcinoma doubled over this period; for men aged 65 years or older, the rate increased approximately threefold to fourfold.[41]

TABLE 4
Ratios of esophageal adenocarcinoma incidence rates in white males, by age

Age (yr)	1974 to 1980*	1981 to 1987	1988 to 1994
< 55	1.0	1.4	2.3
55–64	1.0	1.3	2.3
65–74	1.0	2.4	4.5
≥ 75	1.0	1.9	3.8

* Baseline incidence.

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A comparison of the incidence of esophageal adenocarcinoma with the incidence of colon cancer in white and black males in the United States helps to put these figures in perspective. According to the Surveillance, Epidemiology, and End Results Cancer Statistics Review, the colon cancer rate for the years 1975 to 1995 was fairly steady, averaging 58.48 per 100,000 person-years for white males and a comparable 57.67 per 100,000 person-years for black males.[42]

The reasons underlying the increased incidence of esophageal adenocarcinoma in the general population are largely unknown and are under investigation. Lagergren and colleagues[43] compared the use of drugs that relax LESP, thus promoting reflux, such as anticholinergics, with the incidence of adenocarcinoma. In patients who had used these types of drugs for 5 or more years, the incidence rate ratio of adenocarcinoma was 3.8 when compared with patients who had never taken these types of drugs. The authors estimated that, assuming a causal relationship, approximately 10% of all cases of esophageal adenocarcinoma occurring in the population could be attributed to drugs that relax LESP.

Other researchers have suggested that adenocarcinoma incidence is increasing as a result of the declining rates of *H pylori* infection. They suggest that *H pylori* has a protective effect against patients developing Barrett's esophagus, esophageal adenocarcinoma, or both.[40]

Symptoms and association with GERD

Daly and colleagues[44] recently conducted a multicenter US study of 3,466 patients diagnosed with esophageal cancer to evaluate which symptoms

TABLE 5
Symptoms at diagnosis of esophageal cancer

Symptom	Number of patients	Percentage of patients*
Cervical adenopathy	190	5.5
Chronic cough	375	10.8
Dysphagia	2,566	74.0
Heartburn	712	20.5
Hematemesis	195	5.6
Hemoptysis	126	3.6
Odynophagia	574	16.6
Shortness of breath	418	12.1
Weight loss	1,974	57.3
Other	1,046	30.2

* Among all patients reported from diagnosing institutions (n = 3,466).

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these patients presented with, as well as cancer stage distribution and treatment modalities. Patients were mostly men (74.2%) and mostly white (76.8%). Approximately 30% had used tobacco previously, and 53% currently either smoked cigarettes or used tobacco in other forms. More than half of the patients reported that they did not drink alcohol, and the large majority of patients averaged fewer than two drinks per day. **Table 5** lists the symptoms with which patients presented. Most patients reported dysphagia (74%), followed by weight loss (57.3%) and GERD (20.5%). In this study, the 1-year disease-specific overall survival rate for esophageal cancer was 43%.

Chronic reflux has been identified as the main cause of Barrett's esophagus. Because Barrett's esophagus is significantly linked to esophageal adenocarcinoma, it seems logical that chronic GERD has the potential to play an important role in the pathogenesis of esophageal adenocarcinoma.

Lagergren and colleagues[39] conducted a case-control population-based investigation of the connection between GERD and adenocarcinoma of the esophagus and gastric cardia in 1,438 patients in Sweden. The 451 patients with adenocarcinoma represented 85% of all eligible cases of adenocarcinoma in Sweden. Among participants who experienced heartburn and reflux symptoms at least once per week, the risk for developing adenocarcinoma was nearly eight times that in participants who did not experience these symptoms. The authors also found that increased severity and duration of symptoms correlated with increased risk of adenocarcinoma **(Table 6)**. For example, a person with a reflux-symptom score (a measure of symptom severity) of 1 to 2 points had an odds ratio of 1.4 for adenocarcinoma. However, a person with a reflux-symptom score of 4.5 to 6.5 points had an odds ratio of 20.0.

Another investigation of the relationship between adenocarcinoma and GERD symptoms, conducted by Chow and colleagues,[45] yielded comparable results. The investigators collected data from the medical records of 196 patients with adenocarcinoma matched with 196 controls. Patients with a history of GERD symptoms for 1 year to 5 years had an odds ratio for developing adenocarcinoma of 1.2. However, patients who had symptoms for 5 years or more had an odds ratio of 2.5.

Pathophysiology from Barrett's esophagus

In patients with Barrett's esophagus in the United States, esophageal adenocarcinoma incidence rates range from 1 case in 100 patient-years to 1 case in 200 patient-years—a 30-fold to 125-fold increase in risk from that of the general population.[2] These estimates are obviously very wide ranges. In an attempt to more precisely fix the incidence rates, Drewitz and colleagues[46] conducted a study in all patients undergoing endoscopy at a Veterans Affairs Medical Center between January 1982 and April 1995. They calculated an incidence rate of 1 case per 208 patient-years. Although this study population was 98% male, these findings are similar to those from a study by O'Connor and colleagues[47] conducted in 91 male and 45 female patients from The Cleveland Clinic's Barrett's esophagus registry. The incidence rate in this study was 1 case per 285 patient-years, a slightly lower but similar figure.

Nevertheless, the risk of developing esophageal adenocarcinoma from Barrett's esophagus does seem to vary with gender. Menke-Pluymers and colleagues[48] studied characteristics of patients with benign Barrett's esophagus and patients with esophageal adenocarcinoma arising from Barrett's esophagus. In the former group, the male-to-female ratio was 1.2:1, whereas it was 3.1:1 in the group with malignant disease.

Esophageal adenocarcinoma incidence and

TABLE 6
Risk of esophageal adenocarcinoma according to the frequency, severity, and duration of GERD symptoms

	Number of controls (%)	Number of pts with adenocarcinoma (%)	Adjusted odds ratio (95% CI)
Frequency of reflux symptoms			
No symptoms	685 (84)	76 (40)	1.0
1 time per week	95 (12)	37 (20)	5.1 (2.8–9.4)
2–3 times per week	16 (2)	35 (19)	6.3 (3.8–10.3)
>3 times per week	24 (3)	41 (22)	16.7 (8.7–28.3)
Reflux-symptom score			
No symptoms	685 (84)	76 (40)	1.0
1–2 points	58 (7)	10 (5)	1.4 (0.7–3.0)
2.5–4 points	43 (5)	39 (21)	8.1 (4.7–16.1)
4.5–6.5 points	34 (4)	64 (34)	20.0 (11.6–34.6)
Duration of reflux symptoms			
No symptoms	685 (84)	76 (40)	1.0
<12 years	41 (5)	31 (16)	7.5 (4.2–13.5)
12–20 years	67 (8)	42 (22)	5.2 (3.1–8.6)
>20 years	27 (3)	40 (21)	16.4 (8.3–28.4)

prevalence rates vary depending on the length of the Barrett's esophagus segment. For patients with endoscopically obvious (long-segment) Barrett's esophagus, esophageal adenocarcinoma develops at rates ranging from 1 case per 46 patient-years of follow-up to 1 case per 441 patient-years of follow-up. For patients with short-segment Barrett's esophagus, the risk is not clearly defined. However, a study conducted by Hamilton and colleagues[49] found that, of 39 patients with esophageal adenocarcinoma that developed from Barrett's esophagus, 19 (49%) had short-segment Barrett's esophagus.

Weston and colleagues[50] conducted a prospective, multivariate analysis of the factors that predicted the development of multifocal high-grade dysplasia and esophageal adenocarcinoma in 108 patients with Barrett's esophagus. Patients newly diagnosed with Barrett's esophagus were followed for a mean of 39.9 months (range, 12 to 101 months). Five patients developed multifocal high-grade dysplasia, and 5 patients developed esophageal adenocarcinoma. The incidence for both of these conditions was 1 per 71.9 patient-years. Chi-square analysis revealed that progression from Barrett's esophagus to multifocal high-grade dysplasia and esophageal adenocarcinoma was associated with the presence of hiatal hernia ($P = 0.02$), the length of the Barrett's esophagus segment ($P = 0.001$), and the presence of dysplasia at diagnosis or at any time during the follow-up period ($P < 0.001$). Logistic regression analysis supported these associations. Progression from Barrett's esophagus to multifocal high-grade dysplasia and esophageal adenocarcinoma was associated with hiatal hernia size ($P < 0.02$ for hernias 3 cm or greater), the length of the Barrett's esophagus segment ($P = 0.009$ for segments 2 cm or greater), and the presence of dysplasia at diagnosis ($P < 0.0001$) or at any time during follow-up ($P < 0.03$).

Barrett's esophagus with or without dysplasia is a premalignant condition. Cameron and Carpenter,[38] in their study of dysplasia in Barrett's esophagus, noted that cancer can develop anywhere esophageal intestinal metaplasia occurs. This finding contrasts with the idea that cancer develops only near the squamocolumnar junction at the most proximal extent of the Barrett's epithelium. **Figure 18** roughly outlines the proposed developmental process of esophageal adenocarcinoma in Barrett's esophagus. This process begins with genetic changes that can activate proto-oncogenes, impair tumor-suppressor genes, or both. Abnormal cells begin to grow, and, after more genetic changes, autonomous cell growth, or neoplasia, occurs. Accumulating DNA abnormalities lead to malignancy and invasion of

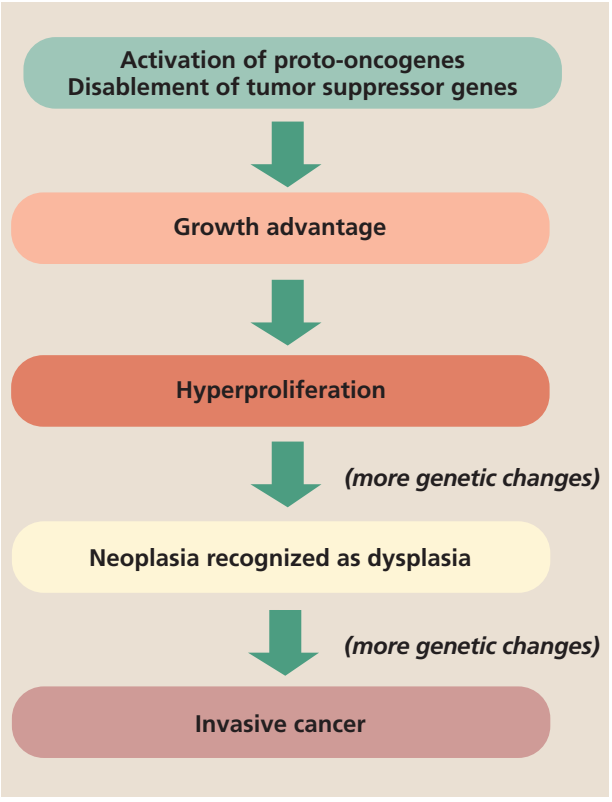

FIGURE 18. Possible sequence of genetic changes resulting in adenocarcinoma from Barrett's esophagus. Reprinted from reference 21 with permission from Elsevier.

surrounding tissue. Dysplasia occurs before this final malignant stage and can be recognized histologically.[21] Numerous studies have focused on the genetic changes that are markers for predicting and preventing the development of esophageal adenocarcinoma, including p53 alterations, cyclin D1 overexpression, and DNA ploidy.

p53 Alterations. The protein product related to this gene helps to inhibit cellular proliferation and is involved in cell cycle regulation, DNA repair, and apoptosis. As Barrett's esophagus progresses to esophageal adenocarcinoma, p53 alterations become more pronounced. In one study, 5% of patients with intestinal metaplasia had p53 alterations. For indefinite or low-grade dysplasia, 15% of patients had alterations; for high-grade dysplasia, 45% of patients had alterations; and for adenocarcinoma, 53% had p53 alterations.[40] From these data, one would assume that p53 could be a biomarker to help predict a patient's risk of developing esophageal adenocarcinoma from Barrett's esophagus. However, in a prospective study by Bani-Hani and colleagues[51] of 307 patients with Barrett's esophagus, p53 positivity was not a statistically significant marker for increased risk of esophageal adenocarcinoma (odds ratio = 2.99; $P = 0.197$).

Cyclin D1 overexpression. In other cancers, modification of messenger ribonucleic acid stability, disruption of promoter structure, and amplification of a special chromosomal region cause cyclin D1 overexpression. However, the relationship between this gene's overexpression and esophageal adenocarcinoma has not been clarified. The above-mentioned study by Bani-Hani et al[51] also investigated the link between cyclin D1 overexpression and the pathology of esophageal adenocarcinoma in Barrett's esophagus. Of the 307 patients with Barrett's esophagus, 12 developed adenocarcinoma. Of these patients, 8 (67%) had biopsy specimens that stained positive for cyclin D1 before carcinoma development. The odds ratio for this group was 6.85 ($P = 0.0106$). Comparatively, in patients with Barrett's esophagus that did not progress to adenocarcinoma, only 14 of 49 biopsy specimens (29%) stained positive for cyclin D1. The study authors noted the distinct possibility that some of these "control" patients could go on to develop esophageal adenocarcinoma. One patient who tested positive for cyclin D1, but who did not develop esophageal adenocarcinoma during the 9 years of the study, did go on to develop adenocarcinoma at a later date.

DNA ploidy. With neoplastic proliferation, the DNA ploidy of the cell changes. Cells are normally diploid (with the exception of germline cells); however, aneuploidy is observed in 63% of high-grade dysplasia in Barrett's esophagus.[40] Reid and colleagues[52] found that, among 13 patients with two cellular ploidy abnormalities (aneuploidy and increased G2-cell population), 9 developed high-grade dysplasia or adenocarcinoma. These proliferative changes were absent in patients who did not have high-grade dysplasia or esophageal adenocarcinoma. These data suggest that abnormal nuclear DNA content is an important part of the progression of adenocarcinoma from intestinal metaplasia.

Summary and implications

Esophageal adenocarcinoma is one of the most lethal cancers. One reason the prognosis is usually poor is that the cancer is often not detected until widespread metastases are already present. This poor prognosis underlies the need for further research into the developmental process of

esophageal adenocarcinoma and the need for vigilant, aggressive monitoring of patients with Barrett's esophagus and chronic GERD.

CONCLUSIONS

The sometimes tenuous relationship between GERD symptoms and complications presents interesting diagnostic challenges. Patients with daily heartburn may have no esophageal injury from refluxed material. However, patients with infrequent heartburn can present with severe GERD complications, including Barrett's esophagus. Furthermore, Barrett's esophagus, an important risk factor for esophageal adenocarcinoma, has no symptoms to differentiate it from uncomplicated GERD. These issues make diagnosis difficult, but not impossible. Ongoing research may enable investigators to draw stronger connections between GERD symptoms and GERD complications, and between one GERD complication and another. New studies may also make it easier to assess a patient's risk of developing serious GERD complications, such as Barrett's esophagus and esophageal adenocarcinoma. Until then, patients and physicians must learn to view heartburn as a symptom of a potentially serious condition and treat it accordingly.[53]

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