

# Barrett's Esophagus: Introduction

Barrett's esophagus is a condition in which **columnar cells** replace the usual **squamous cell** in the **mucosa** of the esophagus. The condition is recognized as a complication of gastroesophageal reflux disease. Its importance lies in its predisposition to evolve into esophageal **cancer**.

Barrett's esophagus develops in about 10–20% of patients with **chronic gastroesophageal reflux disease** or **inflammatory** of the esophagus. It occurs more often in men than in women (3:1 ratio) and is more common in Caucasian Americans than African Americans. The prevalence of this disorder increases with age — the average age at diagnosis is 55 years.

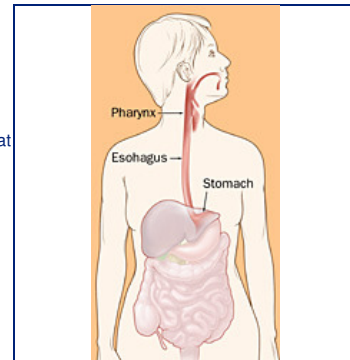


Figure 1. Location of the esophagus in the body.

## What is Barrett's Esophagus?

The mucosa of the normal esophagus is composed of squamous cells similar to those of the skin or mouth. The normal squamous mucosal surface appears whitish-pink in color, contrasting sharply with the salmon pink to red appearance of the gastric mucosa, which is composed of columnar cells. A demarcation line, the squamocolumnar (SC) junction or "Z-line", represents the normal esophagogastric junction where the squamous mucosa of the esophagus and columnar mucosa of the stomach meet (Figure 2).

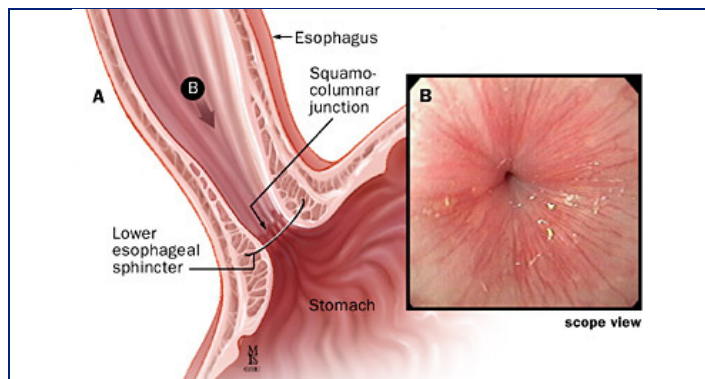


Figure 2. A, Lower esophageal sphincter and squamocolumnar junction; B, endoscopic view.

In Barrett's esophagus, columnar mucosa covers a variable length of distal esophagus (Figure 3).

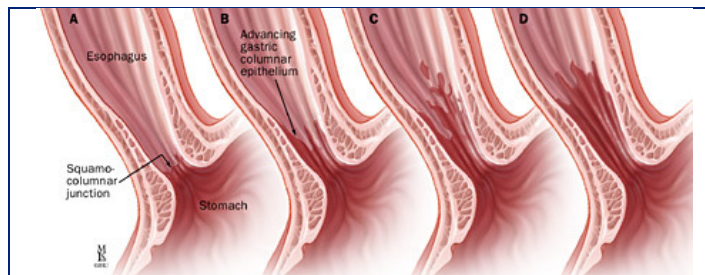


Figure 3. A, Normal esophageal epithelium; B-D, variants of Barrett's esophagus.

The squamocolumnar junction is therefore displaced into the esophagus and no longer marks the esophagogastric junction. Barrett's mucosa may extend upward in a continuous pattern in which the entire circumference of the distal esophagus is covered by columnar mucosa. At its proximal margin, there are often short extensions of the Barrett's mucosa, referred to as mucosal tongues. There can be skip areas in which islands of columnar mucosa are separated from the main area of Barrett's mucosa.

A distinction is drawn between patients with more than 3 cm of Barrett's esophagus ("long-segment Barrett's esophagus") and those with less than 3 cm of Barrett's esophagus ("short-segment Barrett's esophagus") (Figure 4).

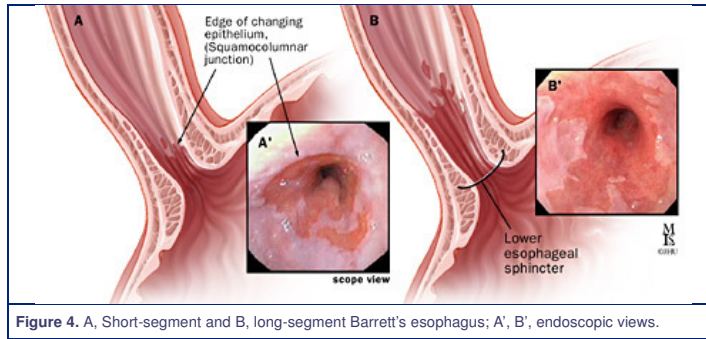


Figure 4. A, Short-segment and B, long-segment Barrett's esophagus; A', B', endoscopic views.

Although it would be logical to assume that patients with long-segment Barrett's esophagus would be at greater risk for developing Barrett's-related cancer, cancer can occur in patients with short lengths of Barrett's mucosa. Because it is not always easy to identify the exact level of transition between the esophagus and stomach in patients with Barrett's esophagus, measuring the length of Barrett's esophagus is imprecise. In some patients, there may be disagreement among endoscopists whether Barrett's is actually present.

### Symptoms

Barrett's esophagus does not produce symptoms distinct from gastroesophageal reflux disease (GERD) or esophageal inflammation. Most patients complain of heartburn pain, indigestion, blood in vomit or stool, difficulty in swallowing solid foods, or nocturnal regurgitation.

### Pathology

As previously mentioned, Barrett's esophagus is characterized by variable segments of the distal esophagus lined by columnar mucosa. Recently published guidelines suggest that a diagnosis of Barrett's esophagus should be reserved for patients with a special type of columnar mucosa. This mucosa — referred to as either "specialized columnar epithelium" or "distinctive-type Barrett's epithelium" — includes a mixture of gastric mucin-containing cells and intestinal goblet cells on microscopic examination. Most patients with extensive segments of columnar mucosa in the distal esophagus have a mixture of gastric-type mucosal cells and specialized columnar mucosa. It is the specialized columnar mucosa that appears to be at risk for malignant degeneration.

Dysplasia refers to a microscopic finding in which large and irregular nuclei develop within cells and become displaced from their normal position near the basement membrane. The more dysplastic the cells, the greater the risk of cancer. In the most extreme cases, referred to as "high-grade dysplasia," the cellular appearance may be indistinguishable from that of adenocarcinoma. In fact, the distinction between high-grade dysplasia and early cancer cannot be made on the basis of superficial biopsies obtained at endoscopy. Invasive adenocarcinoma may be found during esophagectomy even when only high-grade dysplasia has been found on previous endoscopic biopsies. Figure 5 illustrates the microscopic appearance of goblet cells, low-grade, and high-grade dysplasia found in Barrett's esophagus.

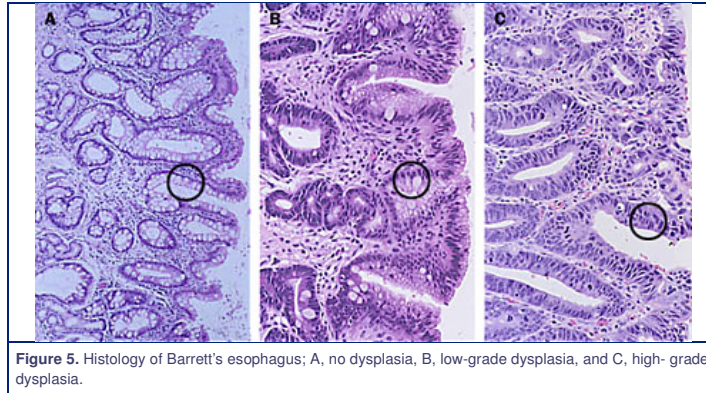
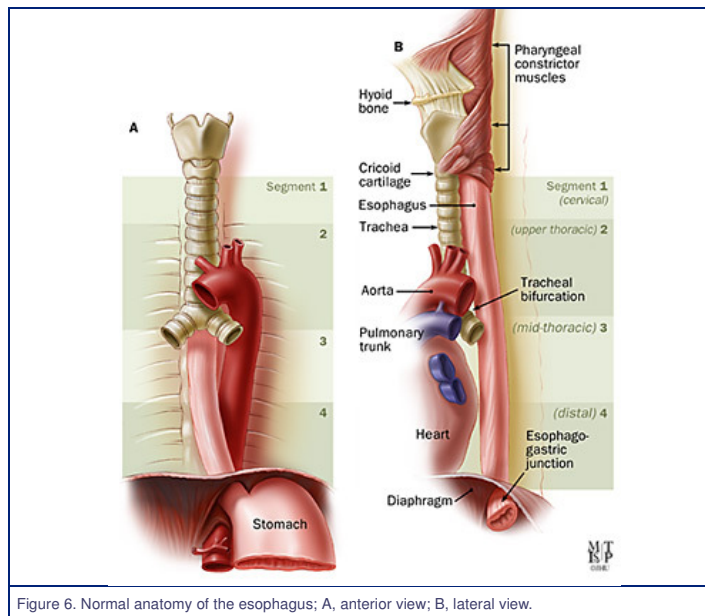


Figure 5. Histology of Barrett's esophagus; A, no dysplasia, B, low-grade dysplasia, and C, high-grade dysplasia.

## Barrett's Esophagus: Anatomy

The esophagus serves as a conduit between the pharynx and the stomach. The body of the esophagus is approximately 18–25 cm in length extending from the upper esophageal sphincter (C5-C6 vertebral space) to the lower esophageal sphincter (T10 level). The length of the esophagus correlates with an individual's height and is usually longer in men than in women.

The esophagus transports food from the mouth to the stomach in a caudad direction and prevents the retrograde movement of gastric or esophageal contents. It is a hollow tube closed at the upper end by the upper esophageal sphincter and at the lower end by the lower esophageal sphincter. The lumen is normally lined with nonkeratinizing stratified squamous epithelium. Underneath this is a supporting layer of connective tissue called the lamina propria and a longitudinally oriented, thin layer of muscle fiber (muscularis mucosae). These three layers compose the mucosal layer. This submucosa consists of loose connective tissue, blood vessels, lymphatics, and nerves. The muscularis propria has two layers, an inner circular muscle layer with circumferential fibers and an outer longitudinal layer with fibers oriented along the axis. The muscle in the muscularis mucosae is smooth throughout the length of the esophagus, whereas the muscularis propria is composed of striated muscle in the most proximal portion. Smooth and striated muscle meet in the middle third of the esophagus. A rich network of intrinsic neurons is found in the submucosa and between the circular and longitudinal muscle layers and is capable of producing secondary peristalsis. This network communicates to the central nervous system by means of the vagi, the adrenergic ganglia, and the celiac ganglia (Figure 6).



The esophagus is divided into four regions. The cervical esophagus extends from the lower border of the cricoid cartilage to the thoracic inlet (suprasternal notch) or from the cricopharyngeus to approximately 18 cm from the gums. The trachea, vertebral column, and thyroid and carotid sheaths surround this portion of the esophagus. The upper thoracic esophagus extends from the thoracic inlet to the level of the tracheal bifurcation (18–24 cm from the gums). The midthoracic esophagus includes the proximal half of the esophagus from the tracheal bifurcation to the esophagogastric junction (24–32 cm from the gums). The thoracic esophagus passes posterior to the tracheal wall and posterior to the aortic arch and the bifurcation of the trachea and left bronchus. Finally, the distal thoracic esophagus includes the distal half of the esophagus from the tracheal bifurcation to the esophagogastric junction (32–40 cm from the gums). The esophagus crosses anterior to the aorta and through the muscular diaphragm at the T10 level and enters the stomach. The abdominal portion of the esophagus is variable in length (0.5–2.5 cm). The esophagus is surrounded by collagen and elastic fibers at the level of the diaphragm.

## Barrett's Esophagus: Causes

Although initially considered a congenital abnormality, it is now recognized that Barrett's esophagus occurs as a consequence of gastroesophageal reflux disease (GERD). Gastroesophageal reflux refers to the regurgitation of gastric contents into the esophagus. Although GERD often causes symptoms without esophagitis, severe GERD can cause erosions or ulcers. During healing, erosions are usually re-epithelialized with normal squamous mucosa. However, in patients with Barrett's esophagus, the area of the healed erosion is covered by columnar instead of squamous cells.

The reason for this abnormal healing process is not completely understood. As a group, patients with Barrett's esophagus have more severe reflux as measured by pH monitor testing; however, there is considerable overlap between patients with erosive esophagitis alone and those with Barrett's esophagus. The severity of bile reflux, (reflux of gastric contents that contain bile from the duodenum as well as the usual gastric secretions), has been proposed as another factor responsible for Barrett's esophagus.

# Barrett's Esophagus: Diagnosis

## Radiographic Diagnosis

Barium contrast radiography is one of the common diagnostic tests for the evaluation of Barrett's. Although endoscopy is considerably more sensitive for the detection of esophageal cancer, double-contrast barium esophagrams can detect a ruffling of the distal esophageal mucosa (cobblestone effect) as well as peptic strictures or a solitary ulcer. The diagnostic accuracy of the double contrast barium esophagram is 70%.

## Endoscopic Diagnosis

Barrett's esophagus is primarily diagnosed by endoscopy with biopsy. Visual examination alone, however, is not a reliable option as this condition may be missed in many patients. Multiple biopsies should be taken to map out the extent of columnarized epithelium and to assess the presence of dysplasia.

Upper endoscopy involves the examination of the lining of the esophagus, stomach, and first part of the small intestine with a flexible endoscope. Gastrointestinal endoscopy allows the physician to visualize and biopsy the mucosa of the upper gastrointestinal tract. During the procedure, the patient may be given a pharyngeal topical anesthetic to help prevent gagging. Pain medication and a sedative may also be administered prior to the procedure. The patient is placed in the left lateral position and an endoscope — a thin, flexible, lighted tube — is passed through the mouth and pharynx and into the esophagus (Figures 7 and 8).

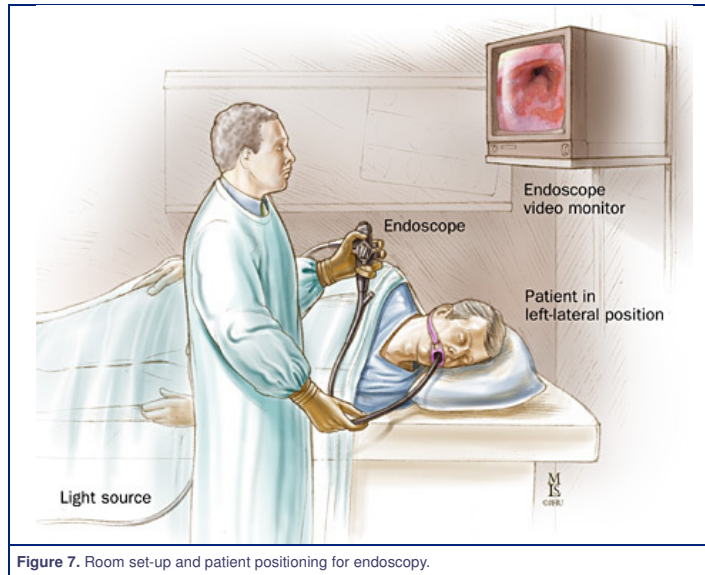


Figure 7. Room set-up and patient positioning for endoscopy.

The forward-viewing scope transmits an image of the esophagus, stomach, and duodenum to a monitor that is visible to the physician. Biopsy forceps are introduced through the auxiliary channel of the endoscope and used to obtain tissue samples along the esophagus. These biopsies may be directed to abnormal-appearing areas for sampling and subsequent tissue diagnosis.

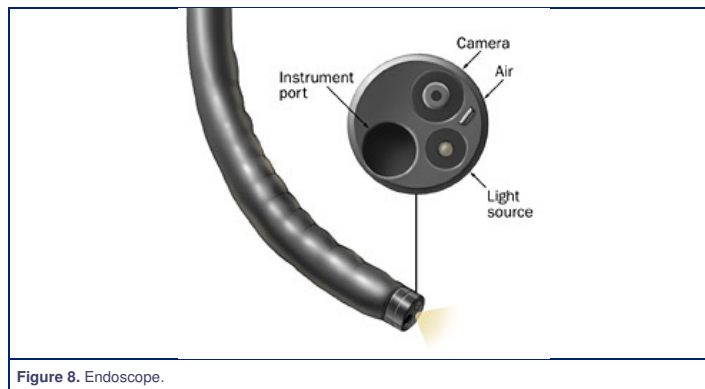


Figure 8. Endoscope.

## Screening Endoscopy

Some physicians advocate the use of screening endoscopy to diagnose Barrett's esophagus and to detect early adenocarcinoma in high-risk, asymptomatic, middle-aged, white males with a history of gastroesophageal reflux disease (GERD). However, this strategy has not proven cost-effective and currently is not recommended as standard of care in all patients with a history of GERD.

On the other hand, patients with a diagnosis of Barrett's esophagus are at increased risk for esophageal cancer and the majority of physicians in the United States perform endoscopic surveillance in this group. Published guidelines from the American College of Gastroenterology (1998) exist for the management of Barrett's esophagus and include recommendations on endoscopic surveillance. In patients with no or low-grade dysplasia on prior endoscopic biopsy, the guidelines recommend increasing surveillance from once a year to 3–6 month intervals.

The optimal endoscopic technique for surveillance has not yet been proven. There is controversy regarding the type of biopsy forceps (standard versus large particle or "jumbo" biopsy forceps), the technique (biopsy from 4 quadrants at standard intervals within the esophagus or purely at random), and the intervals between 4-quadrant biopsy (every 1 or 2 cm).

### Chromoendoscopy

Chromoendoscopy (vital staining and upper endoscopy) refers to the use of vital stains to identify abnormal mucosa. This procedure has been used as a means of esophageal cancer screening for many years. In patients who are at increased risk for squamous cell carcinoma, vital staining with Lugol's solution is performed at the time of upper endoscopy to aid in cancer detection. Lugol's staining involves the application of a solution that contains potassium iodide and iodine through a spray catheter. The dye stains the glycogen in normal squamous epithelium a dark brown color. Areas that are unstained, particularly those that are larger than 5 mm in size, are likely to be dysplastic or malignant and can be readily targeted for endoscopic biopsy. Smaller unstained areas (less than 5 mm) may result from inflammatory change. The staining procedure is quick, technically easy to perform, and inexpensive. It has been shown to be very effective in diagnosing early squamous cell cancers that are not endoscopically evident in high-risk patients with a history of head and neck cancer or heavy alcohol and/or smoking exposure (Figure 9).

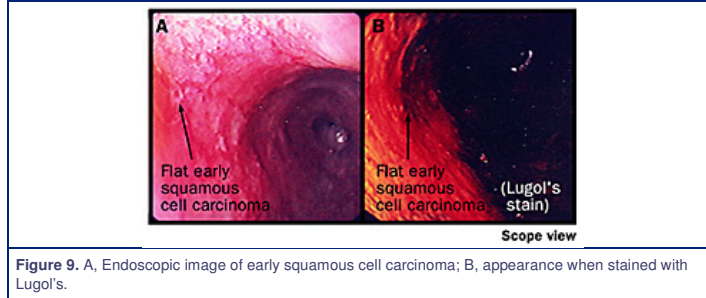


Figure 9. A, Endoscopic image of early squamous cell carcinoma; B, appearance when stained with Lugol's.

Chromoendoscopy using methylene blue staining has not been studied as a screening method for patients with Barrett's esophagus. However, methylene blue-directed jumbo biopsy has been shown in a prospective, randomized, sequential study to be more cost-effective than four-quadrant jumbo biopsy in the diagnosis of dysplasia and cancer in Barrett's esophagus. In-vivo and in-vitro studies have demonstrated that the finding of a moderate to marked heterozygous staining pattern and/or focal lack of blue stain within a diffusely stained Barrett's esophagus are highly suggestive of high-grade dysplasia or early invasive adenocarcinoma (Figure 10).

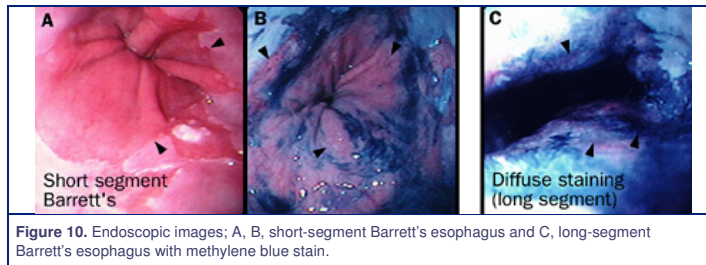


Figure 10. Endoscopic images; A, B, short-segment Barrett's esophagus and C, long-segment Barrett's esophagus with methylene blue stain.

### Future Screening/Surveillance Techniques

Flow cytometry, molecular biomarkers, and laser-induced fluorescence spectroscopy and endoscopy may demonstrate the accuracy of endoscopic surveillance for adenocarcinoma in Barrett's esophagus.



# Barrett's Esophagus: Therapy

## Medical Therapy

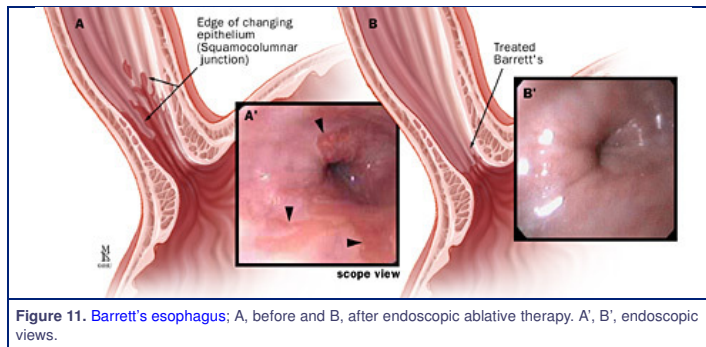
Because Barrett's esophagus is a complication of reflux-related erosive esophagitis, patients with Barrett's esophagus should be treated for GERD. The minimal goal of reflux therapy in patients with Barrett's esophagus is the healing of erosions, a step necessary to prevent extension of the Barrett's esophagus. Occasionally, patients with erosions but no Barrett's on initial endoscopy are found to have Barrett's in the area of healed erosions at follow-up endoscopy. Whether the Barrett's was missed on earlier examination or developed after effective reflux treatment permitted healing to occur is impossible to know. However, once healing does occur, extension of the length of Barrett's esophagus is rare.

For more information see the Gastroesophageal Reflux Disease Section.

## Surveillance

Endoscopic surveillance in Barrett's esophagus refers to periodic endoscopic examinations intended to uncover evidence of progression to adenocarcinoma. Because Barrett's usually evolves into cancer through increasing degrees of dysplasia, biopsies are routinely taken to look for dysplasia. The presence and severity of dysplasia generally dictates the frequency of examination. Most gastroenterologists recommend endoscopic examination every 1-2 years for Barrett's without dysplasia. With low-grade dysplasia, the interval between endoscopies may range from 3-6 months. With high-grade dysplasia, some authorities recommend esophagectomy because of the increased risk of adenocarcinoma, whereas others continue to follow patients with frequent endoscopic examinations as long as no visible growths are noted.

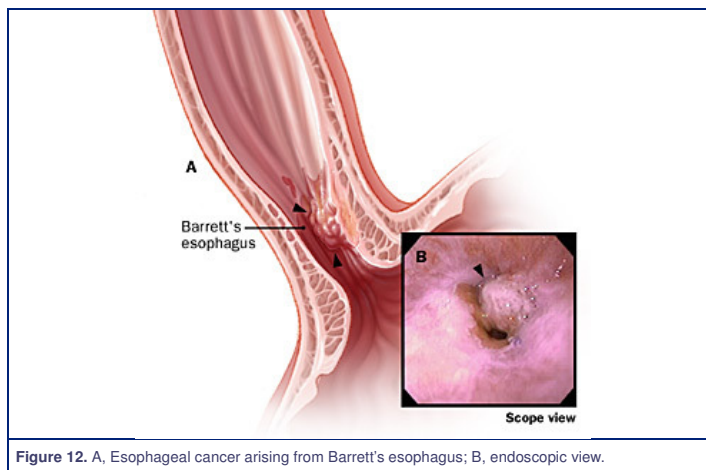
Recent studies have demonstrated that under the right conditions, Barrett's esophagus can be made to regress (Figure 11).



This process, referred to as ablation therapy, requires suppression of stomach acid in combination with thermal injury to the Barrett's mucosa that is intentionally produced during an endoscopy. Often requiring a number of treatment sessions, even long segments of Barrett's mucosa can be made to regress. However, patchy residual Barrett's mucosa may persist and it is unknown whether ablation of the mucosa reduces the risk of cancer.

## Barrett's Esophagus and Barrett's Cancer

There may be a theoretical advantage to repairing the reflux damaged squamous mucosa with columnar cells. Columnar mucosa is more acid resistant than squamous mucosa. However, this form of healing comes at a price. The columnar mucosa is a premalignant condition. In other words, Barrett's mucosa is at risk to develop into esophageal adenocarcinoma (Figure 12).



The risk of progression to cancer in Barrett's esophagus is uncertain. It may be as much as 40-50 times greater than when the esophagus is covered by normal squamous mucosa. Studies suggest that the risk of progression to cancer might be about 10%, in patients with long-segment Barrett's esophagus. The cancer risk is related to the presence and severity of dysplasia on microscopic examination of biopsy specimens taken at endoscopy. In patients followed with periodic endoscopies, those who develop esophageal adenocarcinoma usually have had dysplasia of increasing severity in the years before the diagnosis of cancer is made.

For more information see the Esophageal Cancer Section.