Current challenges in Barrett's esophagus

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ABSTRACT

Barrett's esophagus, a risk factor for esophageal adenocarcinoma, often goes undetected because it has no defining symptoms that distinguish it from gastroesophageal reflux disease (GERD). Yet early recognition is crucial, and development of reliable, cost-effective surveillance methods must be a public health priority. Several promising techniques could lead to more effective prevention, identification, and management of this premalignant lesion.

BARRETT'S ESOPHAGUS is a well-established precursor of esophageal adenocarcinoma, which is one of the fastest-growing and most deadly cancers in the United States.

Yet the diagnosis and treatment of Barrett's esophagus, a complication of gastroesophageal reflux disease (GERD), is fraught with unresolved questions:

- When and how should we screen patients with GERD for Barrett's esophagus? An estimated 20% of the US population has GERD,[1] and Barrett's esophagus is diagnosed in about 10% of this subset.[2–4] Endoscopic screening of every patient with GERD would be prohibitively expensive.
- How should Barrett's esophagus be treated? Traditionally, the goal of treatment has been simply to control GERD symptoms with drugs or surgery. But does this actually prevent adenocarcinoma?
- How should patients with Barrett's esophagus be followed to detect adenocarcinoma at an early and potentially curable stage? Guidelines are available, but current surveillance methods are imperfect and inefficient. Furthermore, as noted, endoscopy is expensive, raising questions of cost-effectiveness.
- How common is it? Estimates differ because definitions differ and because only a minority of cases are detected.

This paper discusses what we know and what we do not know about Barrett's esophagus, with current recommendations and promising developments.

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Barrett's esophagus: Pathologic appearance

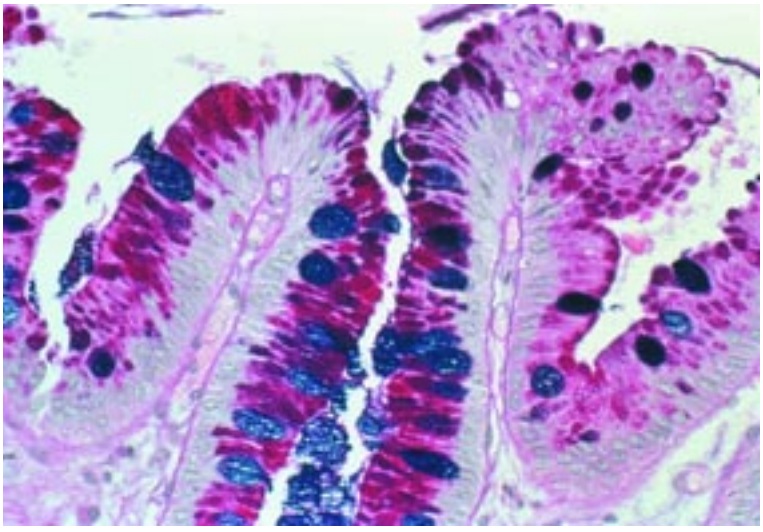

FIGURE 1. Specialized columnar epithelium characterized by acian blue-positive and mucin-containing goblet cells. This type of epithelium is diagnostic of Barrett's esophagus.

THREE TYPES, BUT ONLY ONE CARRIES SERIOUS CANCER RISK

The hallmark of Barrett's esophagus is columnar epithelium rather than the squamous epithelium that lines the normal

esophagus (FIGURE 1). Of the three histologic subtypes of Barrett's esophagus—cardiac, fundic, and intestinal metaplasia—only the last has significant premalignant potential, owing to its higher rate of cellular proliferation. This subtype is characterized by goblet cells, which stain with alcian blue PAS at a pH of 2.5.

Historically, a diagnosis of Barrett's esophagus required that the columnar mucosa extend more than 3 cm above the esophageal junction. However, the American College of Gastroenterology has changed its practice guidelines[5] to recognize that columnar mucosa that is noted at endoscopy and confirmed through biopsy to have intestinal metaplasia carries a cancer risk regardless of how far it extends. This is because epidemiologic data suggest that the length of a Barrett's segment changes little once injury occurs.

The silent precursor

It is estimated that for every patient diagnosed with Barrett's esophagus, another 20 go undetected. This was borne out by an autopsy study in Olmsted County, Minnesota.[6]

As *H pylori* has declined, esophageal carcinoma has increased

This disappointing rate of diagnosis may be the result of decreased sensitivity to acid in patients with Barrett's esophagus: they have more acid reflux but are less sensitive to it and therefore less likely to bring it to their physician's attention.[7] The lessened sensitivity may be due to either the columnar epithelium itself or to the age of most Barrett's patients, who tend to be elderly and therefore are less sensitive to acid.[8] These patients may also treat their heartburn with over-the-counter remedies, which may ameliorate their symptoms but delay a visit to the physician.

Not an equal-opportunity disease

White, middle-aged men who have long-standing GERD are at highest risk for Barrett's esophagus. Smoking increases that risk, and alcohol use has been suggested but not proved as a risk factor. A study by Cameron et al[9] showed that the mean age at development of Barrett's esophagus is 40 years, while the mean age at diagnosis is 63 years—an average lag time between development and diagnosis of more than 20 years. Patients with this condition develop reflux symptoms at an earlier age, have the symptoms for longer periods, have more severe nocturnal reflux, and tend to have complications of GERD such as ulceration, stricture, and bleeding.[10,11]

What causes the histologic changes?

The cause of the histologic changes that lead to Barrett's esophagus remains enigmatic. However, these changes are believed to be the result of abnormal healing after mucosal injury from overexposure to stomach acid. Animal studies demonstrated that removal of esophageal mucosa, surgical creation of a hiatal hernia, and histamine-induced acid hypersecretion result in reepithelialization with columnar epithelium; however, removal of the esophageal mucosa alone results in reepithelialization with squamous epithelium.[12,13]

It is widely believed that Barrett's esophagus is much more likely to develop in patients with severe GERD, probably because of increased acid exposure.[14] Compared with normal controls, these patients tend to have large hiatal hernias, ineffective lower esophageal sphincters, and inefficient esophageal clearance. The cell that begins the transformation to columnar epithelium is most likely a primordial stem cell in the esophagus, but it is unclear why the cell differentiates into columnar epithelium and why it does so in only a small subset of patients with GERD.[15] The answer likely lies in a combination of genetic predisposition, environmental factors, and reflux of duodenogastric contents.

The dysplasia-to-carcinoma sequence

It appears that columnar epithelium in Barrett's esophagus progresses to low-grade dysplasia, high-grade dysplasia, intramucosal carcinoma, and finally to invasive carcinoma.[16] Because the degree of dysplasia in the presence of inflammation is extremely difficult to establish endoscopically, staging typically is accomplished by four-quadrant biopsy of every 2 cm of the Barrett's epithelium.

However, the progression of Barrett's esophagus to cancer is unpredictable; dysplasia does not develop in most patients with Barrett's esophagus, and even if it does it sometimes disappears or does not go on to

Why adenocarcinoma of the esophagus is so malignant

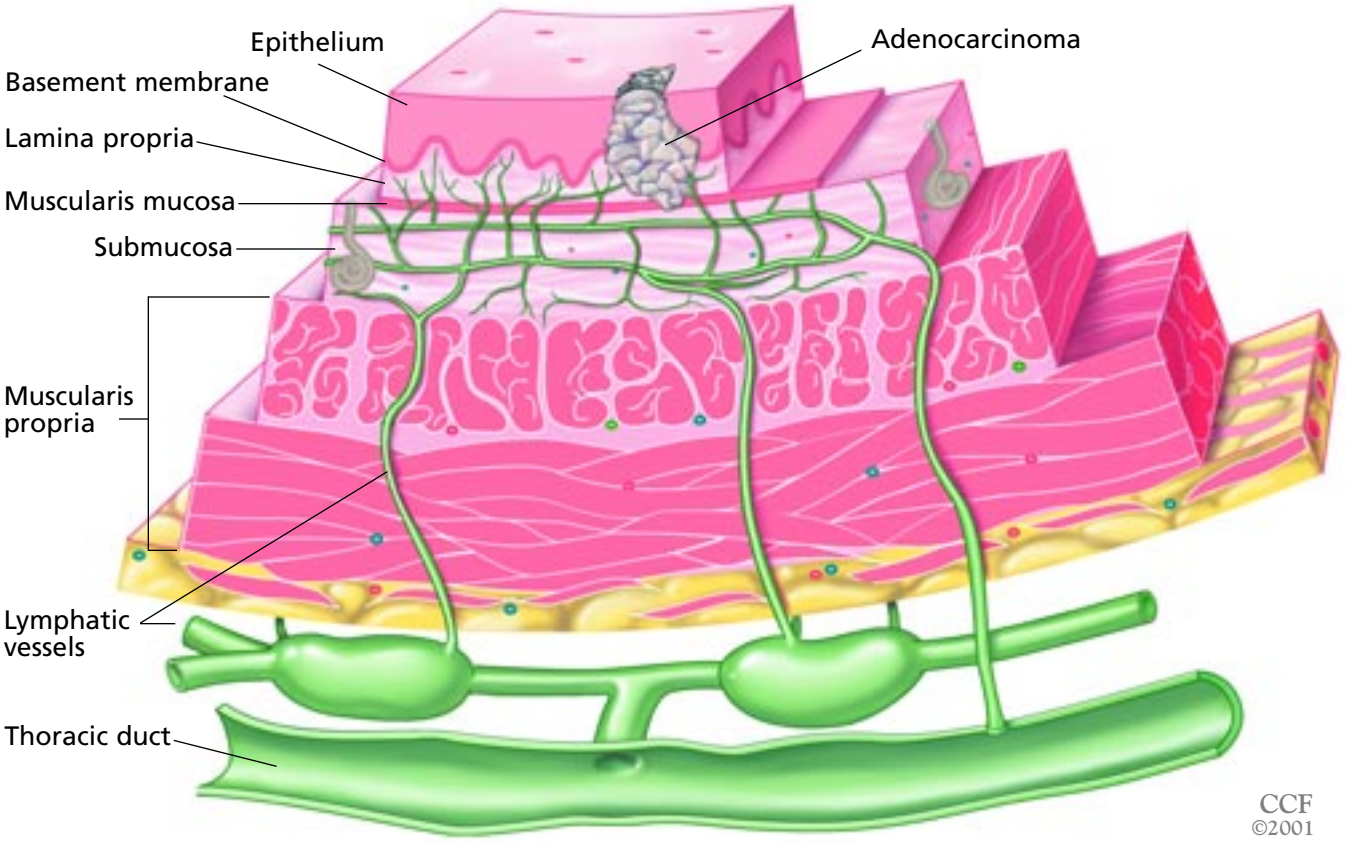

FIGURE 2. Cross-section of the esophagus. The esophageal mucosa contains lymphatic vessels even at its most superficial levels, providing any neoplasm arising there a highway by which to spread.

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become carcinoma. Patients with Barrett's esophagus are more likely than patients without intestinal metaplasia to develop esophageal adenocarcinoma, but even with this heightened risk profile, only 0.5% of patients with Barrett's esophagus develop this type of cancer each year.[17]

Why is esophageal cancer increasing?

Barrett's esophagus makes a malignant transformation in only a minority of cases, but the incidence of esophageal adenocarcinoma is on the rise, increasing 5% to 10% each year since the 1970s. This rate of increase is greater than that of any other type of cancer.

Why the increase in esophageal adenocarcinoma? There are several theories. The incidence of Barrett's esophagus itself may be on the rise because of an increase in GERD and an aging population. Then again, the increase may be an artifact of classification changes or increased use of endoscopy. An alternative hypothesis is based on the observation that as *Helicobacter pylori* infection has declined in the Western world the incidence of esophageal adenocarcinoma has risen. It is possible that *H pylori* is a protective factor against this type of cancer.

Regardless of the cause, the outlook for patients with this type of cancer has not improved appreciably in the last 20 years.[18] Overall 5-year survival has climbed only 2 percentage points to 7%; this is because even the most superficial aspect of esophageal mucosa contains lymphatic vessels, allowing for early lymph-node metastases (**FIGURE 2**).

SURVEILLANCE IS CRITICAL

Studies have demonstrated that patients who receive an early diagnosis of esophageal adenocarcinoma have less nodal involvement and a dramatically improved survival rate compared with those who do not.[19] Endoscopy and biopsy are the surveillance gold standards but are expensive.

Recommendations

Endoscopic screening of all patients who have symptomatic reflux disease is currently impractical and prohibitively expensive. Screening should now focus on individuals at highest risk: white men over age 50 with chronic symptoms of heartburn or acid regurgitation or both.

Current guidelines for endoscopy of patients with Barrett's esophagus are based on the presence and grade of dysplasia.[5] In patients with no dysplasia, endoscopy should be performed every 2 to 3 years after two negative endoscopies. Patients with low-grade dysplasia should undergo endoscopy every 6 months for 1 year, then yearly. Patients with high-grade dysplasia should receive a second confirmation followed by surgical treatment or surveillance every 3 months.

Progression of Barrett's esophagus to cancer is unpredictable

Recommendations call for four-quadrant biopsy at 2-cm intervals and at all sites of mucosal abnormalities after GERD is controlled with proton pump inhibitors (PPIs). However, the diagnosis of esophageal adenocarcinoma is challenging because mucosal changes are not always visible at endoscopy, and because this type of cancer is extremely focal in nature and sometimes subtle in presentation.[20]

OTHER SURVEILLANCE TECHNIQUES ARE BEING TESTED

Brush cytologic examination

Alternative surveillance techniques that sample broader areas of mucosa and target areas with a high probability of having dysplasia are being tested. One such method, brush cytologic examination, has the advantage of being inexpensive and able to sample a large area and preferentially exfoliate less-adhesive dysplastic cells. In addition, the cytologic specimen can be stained for expression of mutations of the p53 tumor-suppressor gene and telomerase.

Results of testing have been encouraging. In a Barrett's esophagus surveillance program at the Cleveland Clinic, brush cytologic tests were abnormal in all 11 patients with high-grade dysplasia, but abnormal in only 2 of 9 patients with low-grade dysplasia. In addition, 2 of the 39 patients without dysplasia had abnormal cells upon cytologic examination.[21]

Balloon cytologic examination

Another method, balloon cytologic examination, is six times less expensive than endoscopy and biopsy and has shown promise in mass surveillance programs in China. In a study at the Cleveland Clinic,[21] balloon cytologic tests obtained adequate columnar epithelial samples in 83% of subjects and displayed a sensitivity of 80% for high-grade dysplasia and carcinoma.

'Light' biopsy

"Light" biopsy refers to various optical techniques used during endoscopy to locate abnormal areas for sampling. Fluorescence spectroscopy,[22] light spectroscopy, optical coherence tomography, light-scattering spectroscopy, and light-induced fluorescence endoscopy are being tested for their ability to distinguish between benign and malignant tissues.

Biomarkers

Another possibility is to identify patients with Barrett's esophagus who are most at risk for esophageal adenocarcinoma on the basis of genetic markers or other risk factors. Risk stratification of patients could lead to less frequent endoscopy for patients at low risk.

TREATING BARRETT'S ESOPHAGUS

Currently available treatments for Barrett's esophagus usually control GERD symptoms and, in theory, the cellular proliferation that leads to adenocarcinoma. However, no studies have established that any of them prevents progression from dysplasia to carcinoma; in fact, treatments such as thermal ablation may mask dysplasia by fostering regrowth of squamous epithelium over intestinal metaplasia.[23]

Proton pump inhibitors

PPIs are the mainstay of treatment of Barrett's esophagus, although they typically result in little or no reversion to squamous epithelium.

A study by Ouatu-Lascar et al[24] showed that control of acid exposure in patients with Barrett's esophagus resulted in decreased cellular proliferation rates and increased cellular differentiation. This finding provides support for the idea that PPIs may protect against the development of adenocarcinoma. Most physicians do use PPIs even in patients without symptoms. Some physicians advocate the use of 24-hour pH monitoring to ensure that acid reflux is under control, but many patients find this unacceptable, and it has conferred no demonstrated advantage to date.

Surgical treatment

In patients with Barrett's esophagus, fundoplication typically relieves symptoms of GERD[25,26] but has not been proven to halt or reverse the natural history of the dysplasia-carcinoma sequence.

Thermal ablation

Thermal ablation has been proposed as a minimally invasive alternative to surgery that may be applied to broad areas of epithelium and used in combination with other therapies. Thermal ablation is based on the theory that reversal of Barrett's esophagus requires that the columnar epithelium be injured by one of several mechanisms and that acid reflux subsequently be controlled.

Photodynamic therapy

Photodynamic therapy, which appears to hold considerable promise, consists of laser activation of light-sensitive drugs that concentrate in neoplastic and preneoplastic tissue. The most common drug used in this method is porfimer sodium, which is injected intravenously and then activated by a laser, which causes it to release damaging oxygen free radicals.

Overholt et al[27] demonstrated that use of this compound in photodynamic therapy resulted in regression of 93% of low-grade dysplasias, 77% of high-grade dysplasias, and 67% of T2 cancers. However, only 43 of 100 patients experienced complete regression of Barrett's esophagus, and this technique can result in stricture formation and photosensitivity. A recent study by Gossner et al[28] evaluated the use of 5-aminolevulinic acid in photodynamic therapy; the therapy produced regression of high-grade dysplasia in 100% of the patients studied and remission of early adenocarcinoma in 77%.

THE PROMISE OF CHEMOPREVENTION

Cyclooxygenase-2 (COX-2), a mediator of inflammation, also promotes tumor development by inhibiting epithelial apoptosis. Nonsteroidal anti-inflammatory drugs (NSAIDs), and particularly COX-2 selective NSAIDs, have been discussed as possible cancer-preventing drugs. COX-2 selective NSAIDs have been used in the prevention of colon cancer,[29] and in theory they might halt the increased COX-2 expression in intestinal metaplasia, dysplasia, and adenocarcinoma associated with Barrett's esophagus. Other NSAIDs and aspirin might also decrease the risk of esophageal adenocarcinoma, as suggested by a recent epidemiologic study.[30] Further study is needed.

Photodynamic therapy has met with some success

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