REVIEW ARTICLE

Gastroesophageal Reflux Disease, Barrett Esophagus, and Esophageal Adenocarcinoma

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The incidence of esophageal adenocarcinoma has been rising rapidly over the past few decades. The major risk factors predisposing to the development of adenocarcinoma are long-standing gastroesophageal reflux disease and Barrett esophagus, but other factors may be involved as cancer can occur in their absence. In patients with Barrett esophagus, the extent and degree of dysplasia influence the risk of esophageal adenocarcinoma. As neither medical nor surgical therapies have been proven to prevent adenocarcinoma, endoscopic screening of patients with chronic reflux and endoscopic surveillance of patients diagnosed with Barrett esophagus are usually performed in an effort to detect adenocarcinomas at earlier stages. The evidence supporting strategies in the management of patients with gastroesophageal reflux and Barrett esophagus is presented. *Arch Intern Med. 2004;164:1482-1488*

The incidence of esophageal adenocarcinoma (EAC) has risen faster than that of any malignancy in the United States, with an estimated rise of 300% to 350% since the 1970s. While the total incidence of all esophageal malignancies, which include squamous cell carcinoma and adenocarcinoma, has remained stable, the proportion of adenocarcinomas has risen dramatically. Specifically, the population incidence of esophageal squamous cell carcinoma declined from 3.4 per 100 000 between 1974 and 1976 to 2.2 per 100 000 between 1992 and 1994, whereas the incidence of EAC increased from 0.7 per 100 000 to 3.2 per 100 000 during the same period.[1] In 2002, there were an estimated 13 100 cases of esophageal cancer, approximately 60% of which were adenocarcinomas.[2] Furthermore, the increasing rates of adenocarcinoma were more pronounced in older men, with a 2-fold increase in men younger than 65 years vs a 3- to 4-fold increase in men older than 65 years. Esophageal adenocarcinoma predominantly affects white men (white-black ratio, 5:1; male-female ratio, 8:1).[1]

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There also appears to be regional variations in the increasing rates of EAC in the United States: the incidence rates recorded in the Seattle-Puget Sound registry for 1998, for example, are twice those recorded in the Utah registry for the same year.[3] The reasons for the rapidly rising incidence of EAC remain unclear.

RISK FACTORS FOR ESOPHAGEAL ADENOCARCINOMA

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is extremely common in Western countries. Its prevalence in the US population has not been studied; however, a population-based study in Minnesota found that 20% of patients reported having at least weekly symptoms of heartburn and/or regurgitation,[4] the most common manifestations of GERD, often occurring after meals. While the diagnosis can be made definitively by upper endoscopy and ambulatory 24-hour pH monitoring, patients presenting with symptoms typical of GERD are often empirically treated with either proton-pump inhibitors (PPI) or hydrogen receptor antagonists.[5] Further diagnostic evaluation is indicated when there

is no response to empiric therapy or in the presence of warning symptoms of complicated GERD, ie, dysphagia, bleeding, weight loss, and/or chest pain.[5] However, evaluating only patients with warning symptoms may miss many, if not most, patients with Barrett esophagus (BE).

Barrett Esophagus

Barrett esophagus can be defined as the replacement of the squamous epithelium that normally lines the distal esophagus with columnar-appearing epithelium on upper endoscopic examination, with histologic findings of specialized intestinal metaplasia. Traditionally, BE has been defined as columnar-appearing epithelium extending at least 3 cm above the gastroesophageal junction. However, it has become clear that shorter segments of columnar-appearing epithelium may contain specialized intestinal metaplasia, and thus have malignant potential. No standardized definitions have been established. Generally, long-segment and short-segment BE are defined, respectively, as the presence of a specialized intestinal metaplasia 3 cm or greater, or less than 3 cm—but the latter definition of short-segment BE may be problematic. As there is no gold standard of what defines an endoscopically normal-appearing squamocolumnar junction, distinguishing the intestinal metaplasia of BE from that of the proximal stomach, which is found in 18% of the healthy population,[6] can be difficult and lead to unnecessary surveillance. As a result, one must decide whether to sacrifice the sensitivity or the specificity of endoscopic criteria when determining whether longer ($\geq$3 cm) or shorter ($\leq$1 cm) segments of columnar-appearing mucosa are used to define BE morphologically.

It is estimated that 5% to 15% of patients with GERD will have BE. Patients with long-standing GERD are at greatest risk for developing BE, which is considered the precursor lesion to adenocarcinoma. The presence of BE increases an individual's relative risk of cancer 30 to 120 times compared with persons without BE.[7-9]

While the major risk factor for EAC is BE arising on the background of chronic GERD, several recent studies have shown that long-standing GERD is itself a risk factor for adenocarcinoma, even in the apparent absence of BE.[10,11] The largest of these studies, a population-based case-control study, found that the risk of EAC correlated with the frequency, severity, and duration of reflux symptoms.[10] In particular, among patients with frequent reflux symptoms, the adjusted odds ratio (OR) for EAC was 16.7 (95% confidence interval [CI], 8.7-28.3) compared with asymptomatic controls. Similarly, among patients with a symptom duration of more than 20 years, the adjusted OR was 16.4 (95% CI, 8.3-28.4). Among patients with both frequent symptoms and a symptom duration of more than 20 years, the adjusted OR was 43.5 (95% CI, 18.3-105.5). The strength of these associations was independent of the presence of BE. It should be noted, however, that the apparent absence of BE in patients with EAC may have been due to tumor overgrowth.

Genetic Factors

The predilection of EAC to affect white men has triggered interest in the possible role of genetic factors in determining susceptibility to GERD, BE, and adenocarcinoma. In one study, relatives of patients with BE were 4.8 times as likely (95% CI, 1.7-13.4) to have weekly reflux symptoms as relatives of asymptomatic control patients.[12] In another study, first-degree relatives of patients with BE completed a questionnaire to assess for reflux symptoms. Relatives with reflux symptoms who had not previously undergone endoscopy were invited to undergo endoscopy. The control group consisted of patients without a family history of either BE or EAC who were referred for endoscopy by their primary physician. Relatives of patients with BE were 1.5 times more likely to have BE than controls.[13] Although this finding did not reach statistical significance, probably because of the low number of patients ultimately found to have BE, these results are intriguing and underscore the need for additional investigation.

Development of EAC Without Known Risk Factors

Other risk factors that are less well substantiated than GERD and BE include obesity, smoking, alcohol use, use of acid-suppressing medications, and infection with *Helicobacter pylori*. Of these, obesity has been the best studied but has not been established as a definitive risk factor. For example, one study found that adenocarcinoma was 7 times more likely to develop in individuals with a body mass index (calculated as weight in kilograms divided by the square of height in meters) in the highest quartile (men $>$23.7, women $>$22.1) than in those with a body mass index in the lowest quartile (men $<$20.7, women $<$19.3).[14] However, it was unclear whether the observed effect of obesity in this study was direct, or indirect by exacerbating GERD. Thus, the major risk factors predisposing to the development of EAC are BE and long-standing symptomatic GERD. However, adenocarcinoma may develop in the absence of either. In the case-control study described above, which found a correlation between the risk of adenocarcinoma and the frequency, severity, and duration of reflux symptoms, 40% of patients diagnosed with adenocarcinoma did not have a history of reflux symptoms. Furthermore, 38% of patients with adenocarcinoma did not have BE.[10] These findings were supported by a population-based registry study which found that only 19% of patients who were diagnosed with EAC over a 5-year period had BE at subsequent endoscopic examination, surgery, or autopsy.[15] Similarly, a recent systematic review found that only 24% to 64% of patients undergoing surgery for EAC had BE.[16] It has been suggested that cancer may overgrow the Barrett segment from which it arises, thus causing to underestimate the prevalence of BE in patients with adenocarcinoma.[17] Nevertheless, taken together, these results suggest the possibility that

EAC may develop in the absence of long-standing symptomatic GERD or BE.

RISK OF EAC IN PATIENTS WITH BE

The major risk factors that predispose patients with GERD to BE relate to the frequency and duration of reflux symptoms. One case-control study found that patients with reflux symptoms so severe as to wake them from sleep were more than 3 times more likely to develop BE than those without reflux. Such patients tended to have been younger at onset of symptoms, and they tended to have a longer symptom duration.[18] Another study found that patients with reflux episodes lasting more than 5 minutes or persistent reflux symptoms lasting longer than 5 years were at higher risk for BE.[19] However, it is important to recognize that BE can occur in patients without reflux symptoms. A population-based study published in 1990 showed that the prevalence of BE found on autopsy was 21 times greater than the expected prevalence based on endoscopically diagnosed cases.[20] This study was recently updated and showed that the prevalence of BE on autopsy was now only 5 times greater than the endoscopically diagnosed prevalence, which correlated with greater use of endoscopy in recent years.[21] Another study enrolled patients undergoing sigmoidoscopy screening for colon cancer for a concurrent upper endoscopy. In this population older than 50 years and without reflux symptoms, 25% were found to have BE.[22] Thus, while a longer duration and frequency of reflux symptoms increases one's risk of BE, the disease also commonly occurs in asymptomatic individuals. The prevalence of BE, and thus the number of individuals at risk for EAC, may be much higher than previously thought.

Segment Length

The risk of adenocarcinoma in individuals with BE is 30 to 120 times that of individuals without BE. Efforts have focused on identifying characteristics that can be used to further stratify the cancer risk of those with BE. One possible risk factor is the extent of BE.

In the past, BE was defined as a segment of at least 3 cm. However, in recent years, the risk of adenocarcinoma of intestinal metaplasia involving shorter segments has been increasingly recognized. Although some studies found a lower risk of adenocarcinoma with short-segment BE,[23,24] several other studies did not find a significant difference in the risk of adenocarcinoma between patients with short-segment and long-segment BE.[25-27] This discrepancy may reflect the lack of standardization of the definition of short-segment BE, which in some studies is 2 cm or less above the esophagogastric junction and in other studies is 3 cm or less. Because there is no universally accepted definition of short-segment BE, and the natural history of short-segment BE is unclear, short-segment and long-segment BE should be considered to impart the same risk of adenocarcinoma.

Low-Grade Dysplasia

The most important predictor of cancer risk in patients with BE is the presence and degree of dysplasia. Biopsy specimens are graded as negative, indefinite for dysplasia, low-grade dysplasia (LGD), and high-grade dysplasia (HGD).[28] The progression from BE to adenocarcinoma is thought to occur in a stepwise progression from metaplasia to dysplasia to adenocarcinoma. However, the time for progression of LGD to HGD and of HGD to adenocarcinoma has not been well characterized.

A low degree of interobserver agreement makes the diagnosis of LGD difficult to reach, and thus studies of the natural history of LGD are highly variable and difficult to interpret. One study of 25 patients with LGD found that 20% of patients progressed to HGD in a median period of 11 months (range, 2-43 months).[29] Another study found that the mean time for progression from LGD to HGD was 29 months.[30] In addition, several studies have found that LGD may be a transient finding, because approximately 75% of patients with low-grade dysplasia were found to have no dysplasia on a subsequent biopsy.[23,27] However, biopsy screening may reveal progression from intestinal metaplasia directly to HGD or carcinoma, without development of LGD.[31] Furthermore, one study showed that if 3 pathologists agreed on a diagnosis of LGD, there was an 80% rate of lesion progression to HGD or carcinoma.[29]

High-Grade Dysplasia

The degree of interobserver agreement in the diagnosis of HGD is excellent, approximately 85%. Previous studies having found that a high percentage of patients with HGD progressed to adenocarcinoma in a relatively short time, the use of prophylactic esophagectomy in the management of patients with HGD seemed reasonable. However, because these studies included adenocarcinomas that developed over the first 6 months of observation, subclinical cancers already present at the time of HGD diagnosis may have been recorded as new adenocarcinomas. When these prevalent cases were excluded, the percentage of patients whose HGD progressed to adenocarcinoma was lower. In one retrospective cohort study, 32% of patients with HGD developed adenocarcinoma in an average of 3 years; however, when prevalent adenocarcinomas were excluded, the rate of progression was 13%.[32] These results are supported by a recent large study of 1099 patients with BE.[33] Of the 75 patients who had HGD without carcinoma at entry into the study, only 12 (16%) developed carcinoma over the mean 7.3 years of follow-up. Of these 12 patients, 11 had early-stage cancer. These data have called into question the standard management for HGD, ie, prophylactic esophagectomy. Proponents of this approach cite the high rate of concurrent cancer found in patients undergoing surgery for HGD, which was reported to be 13 in a series of 32 patients.[34] Furthermore, there is inherent risk in allowing a premalignant lesion to progress beyond carcinoma in situ because metastasis may occur, even at very early stages.[35] However, the risks of esoph-

agectomy are not inconsequential. These include an operative mortality rate of 3% to 12% and a perioperative morbidity rate of 30% to 50%.[34,36]

Given these controversies, investigators have tried to identify subsets of HGD that may help to further stratify cancer risk. One study found that diffuse HGD, defined as dysplastic changes in more than 1 biopsy specimen or involving 5 crypts or more, was associated with a 3.7-fold increase in the risk of adenocarcinoma compared with focal HGD, defined as dysplasia limited to a single biopsy specimen or involving fewer than 5 crypts.[23,32] Furthermore, nodules found in areas of intestinal metaplasia were associated with a 2.5-fold increase in the risk of adenocarcinoma.[32] Other markers that may impart increased risk in patients with BE are under active investigation and include cell cycle regulators such as proliferating cell nuclear antigen and Ki-67, abnormalities in the DNA content of metaplastic cells, and tumor suppressor genes such as *p53*.[30,37] Thus, the management of HGD remains controversial and should be individualized. Esophagectomy continues to be recommended in patients with HGD, particularly those who are good surgical candidates and those with diffuse and nodular HGD. Frequent surveillance can be considered for patients who are not good surgical candidates and in those with focal HGD.

PREVENTION OF EAC

With the advent of PPI, reflux symptoms can be adequately controlled in most patients. However, it has become increasingly clear that a substantial proportion of patients with GERD or BE whose symptoms are controlled by medications still have abnormal acid reflux, as documented by 24-hour ambulatory pH monitoring.[38,39] While the addition of a bedtime hydrogen receptor antagonist to a maximal PPI regimen has been shown to control nocturnal gastric acid breakthrough,[40] the crucial issue is whether such aggressive control of acid reflux can prevent the development of BE in patients with GERD, cause regression of intestinal metaplasia in patients with BE, or prevent the development of EAC in patients with GERD and/or BE.

Substantial and consistent regression of BE has not been observed, even in patients with documented normalization of pH by PPI therapy,[41] although aggressive acid control has been found to result in the replacement of columnar epithelium by macroscopic islands of squamous epithelium. This would suggest that partial regression of BE occurs; yet, in a recent study, histologic evidence of intestinal metaplasia in almost 40% of the patients with BE who had endoscopic evidence of macroscopic islands of squamous epithelium demonstrated that the development of squamous islands with aggressive acid control should not be interpreted as regression of BE or a reduction in the risk of cancer.[42]

Both modern treatments of GERD—medical (PPI) and surgical (fundoplication)—are very effective at controlling reflux symptoms. However, no study has conclusively shown that either can effectively prevent the development of BE or EAC. Whereas several small surgical series of patients followed up for a mean of 5 years have reported a decreased incidence of dysplasia and/or EAC in those who underwent antireflux surgery,[43] other studies have found no significant differences in the development of EAC in patients treated medically or surgically after a mean of 7 years of follow-up.[44,45] Furthermore, long-term follow-up findings from a prospective randomized controlled trial originally reported in 1992 were recently published.[46,47] This trial randomized patients with complicated GERD to surgical (open Nissen fundoplication) or medical treatment consisting of hydrogen receptor antagonists, antacids, metoclopramide, or sucralfate. After a mean of 9 years of follow-up, the survival rate in the surgical group was worse because of an unexplained increase in cardiovascular complications. Furthermore, although the study was not designed to answer this question, no statistically significant differences were found between the medical and surgical groups in the development of EAC. These results are supported by a large retrospective cohort study, which showed similar rates of development of EAC in patients with GERD regardless of whether they were treated medically or surgically.[48] Thus, to date, neither medical nor surgical treatments for GERD and/or BE have been convincingly shown to prevent the development of EAC.

Endoscopic ablative therapy is another strategy to prevent EAC in patients with BE, particularly those with HGD. This approach uses a laser or heat energy, with or without a cellular sensitizing agent, to ablate metaplastic or dysplastic mucosa for subsequent re-epithelialization with squamous epithelium. In one study, eradication of dysplastic mucosa was achieved in 80% of patients; of these, however, 34% developed strictures, and there was a high rate of recurrence, particularly in patients with HGD.[49] Thus, endoscopic ablative therapy may not completely eliminate dysplastic epithelium and it is associated with a relatively high rate of complications. It should not be used in patients with LGD but may be considered in patients with HGD, particularly those who are poor surgical candidates.

SURVEILLANCE AND MORTALITY

The major risk factors that predispose to the development of EAC are GERD and BE. Endoscopic screening of high-risk patients with GERD, with subsequent endoscopic surveillance of patients diagnosed with BE on screening, has been proposed as a strategy to identify patients at highest risk and detect adenocarcinoma at earlier stages, thus reducing mortality. To be effective, a screening and surveillance program must reduce mortality from the disease and be cost-effective.

Small observational studies have found that EACs developing in patients with BE followed up in a surveillance program were detected at an earlier stage than EACs detected in symptomatic patients undergoing endoscopy for symptoms only.[31,50,51] One of these studies iden-

tified 198 patients with EAC who had undergone resection.[31] From a review of medical records, it was determined that 54 of the patients had prior diagnoses of BE, and 16 had been enrolled in a surveillance program. More patients had advanced-stage EAC in the nonsurveillance group than in the surveillance group, which, presumably, resulted in a decreased mortality rate in the latter group. Similarly, a recent retrospective cohort study found that the patients with known BE and EAC detected by endoscopy in the context of a surveillance program tended to have earlier-stage disease and lower mortality rates than the patients whose EAC was diagnosed when they presented with symptoms.[52] However, these studies were subject to various methological flaws, including (1) selection bias, as younger, healthier patients more likely to survive esophagectomy may have been selected for surveillance programs, and (2) lead time bias, since EAC diagnosed earlier in the context of surveillance programs may have given the appearance of longer survival. Furthermore, several studies have found that cancer is not a common cause of death in patients with BE followed up in a surveillance program. In one, in which 409 patients with BE were followed up for 10 years, 137 patients died during follow-up but only 4 (2.9%) of the deaths occurred as a result of EAC.[53] Similarly, in a group of 155 patients with BE followed up for 9 years, 79 patients died during follow-up but only 2 (1.3%) of the deaths were due to esophageal cancer.[54] Thus, although it is clear that endoscopic surveillance programs detect adenocarcinoma at earlier stages, it is not clear whether they reduce mortality.

The cost-effectiveness of screening and surveillance endoscopy for BE has been examined.[55-58] A recent study using a decision analytic model found that screening all white men with GERD who were older than 50 years, then surveillance only for patients with BE and dysplasia, would be a cost-effective approach.[58] This approach would be associated with an incremental cost-effectiveness ratio of $10 440 per quality-adjusted life-year (QALY) compared with no screening or surveillance. However, conducting surveillance in patients with BE but no dyplasia every 5 years was associated with an incremental cost-effectiveness ratio of $596 000 per QALY saved, making that approach prohibitively expensive.[58] Similarly, another study using a model evaluating screening 55-year-old men with BE every 1 to 5 years found that surveillance every 5 years would be associated with an incremental cost-effectiveness ratio of $27 400 per QALY compared with no surveillance.[56] Decreasing the interval of surveillance to every 4 years would be more effective, but at a cost of $276 000 per QALY. These analyses suggest that screening patients with chronic GERD, with subsequent surveillance for those diagnosed with BE every 5 years, might be cost-effective; however, these analyses are based on numerous assumptions, in particular the prevalence of BE and the incidence of cancer among patients with BE.

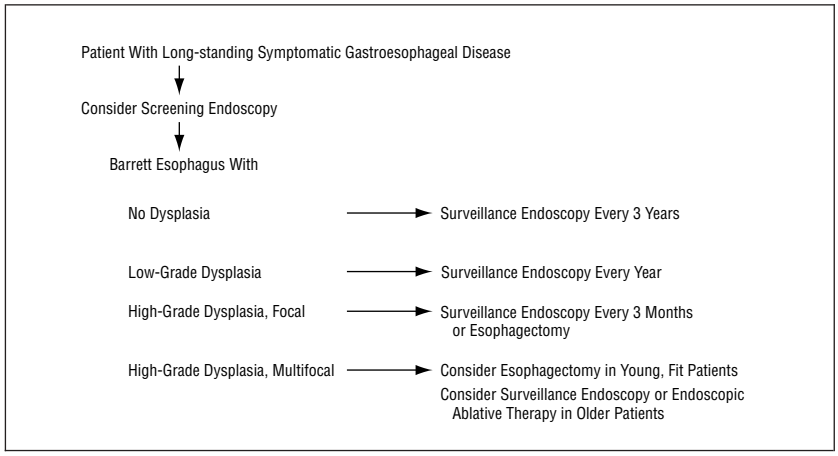
Certain caveats must be kept in mind when considering screening and surveillance programs. First, the incidence of EAC in the US population is low, with an estimated 7860 new cases in 2002, compared with 107 300 new cases of colon cancer and 169 400 new cases of lung cancer for the same year.[59] Second, while long-standing GERD and BE greatly increase an individual's relative risk of cancer, the absolute risk is low, of the order of 0.5% per year.[27,54,60,61] Third, 40% of patients with EAC have no history or symptoms of reflux; these patients would be missed, as they would not have been candidates for either screening or surveillance.

RECOMMENDATIONS

The American College of Gastroenterology has recently updated its guidelines for the management of patients with BE.[62] A screening endoscopy can be considered for patients with chronic GERD symptoms, although the duration of symptoms or the age of the patients are not specified. Proposed criteria for screening endoscopy are shown in the **Table**, although, as discussed above, there are no studies to support whether to screen or which patients to screen. Therefore, the decision to undergo screening endoscopy for chronic GERD symptoms should be individualized. Once BE has been identified, surveillance endoscopy is recommended with a frequency that is dependent on the presence and degree of dysplasia (**Figure**). A biopsy negative for dysplasia can be followed with surveillance every 3 years, and LGD can be followed up with annual endoscopy. Patients with HGD, particularly multifocal and nodular dysplasia, should be referred for esophagectomy. Patients with focal

Proposed Criteria for Screening Endoscopy

Age >50 y
White race
Male sex
Duration of reflux >5 y
Reflux symptoms at least twice per week



American College of Gastroenterology management algorithm for the diagnosis and surveillance of Barrett esophagus.[62]

HGD, particularly those who are not surgical candidates, can be followed up with intensive surveillance every 3 months.

CONCLUSIONS

The major risk factors for the development of EAC are severe and longstanding symptomatic GERD and BE. Both are associated with an increased relative risk but low absolute risk of cancer compared with patients without these conditions. White race, older age, increased severity, and longer duration of symptoms appear to further increase the risk of cancer. Aggressive acid control with either medication or surgical fundoplication has not been shown to prevent EAC. Prospective randomized clinical trials are lacking, but our recommendations at this time are to consider a screening endoscopy in white men older than 50 years who have had symptomatic GERD longer than 5 years; in those diagnosed with BE, screening should be followed by endoscopic surveillance. Patients with HGD should be managed on an individual basis, either with surgery or intensive surveillance.

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