ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Barrett Esophagus: Prevalence, Treatment, and the Link to Esophageal Adenocarcinoma

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G&H What is Barrett esophagus?

NS Barrett esophagus (BE) is a metaplastic change of the inner lining of the esophagus. Usually, the esophagus is lined with squamous epithelium, a tissue that is similar to the lining of the palms of the hands. With BE, the cells change to specialized columnar epithelium, which is more similar to the tissue found in the small intestine and colon.

G&H Why does this change occur?

NS We think that BE occurs as a result of chronic exposure to acid. The columnar epithelium is more resistant to acid breakdown than the original squamous cells. The condition may have been a very adaptive change in response to reflux at some point in human evolution.

G&H How are BE and esophageal adenocarcinoma connected?

NS BE predisposes people to esophageal adenocarcinoma. Most people who develop BE will not get esophageal adenocarcinoma. However, the risk of esophageal adenocarcinoma is 30 or more times higher among people with BE compared with the general population.

G&H Does an individual with BE usually know that he or she has the condition?

NS The vast majority of people who have BE do not know that they have it. Esophageal adenocarcinoma associated with this condition is difficult to prevent because most individuals do not undergo routine upper endoscopy, even if they are experiencing reflux symptoms. Most people with BE-related cancer never knew that they had BE prior to being diagnosed with cancer.

G&H Is there a different rate of occurrence in men vs women?

NS Men and women have approximately the same occurrence of reflux symptoms; the classic symptoms of heartburn and regurgitation occur in approximately the same percentage of men and women. However, men are approximately 2 to 3 times as likely to develop BE, and approximately 4 times as likely to develop esophageal adenocarcinoma, compared with women. Both conditions are far more common in men than in women.

G&H If the incidence of reflux is the same among men and women, why is BE more common among men?

NS Certain differences in the bodies of men and women may help explain this phenomenon. When men gain weight, they are more likely to have truncal obesity, meaning that the fat accrues around the waist. As a result of this change, fat occupies a greater volume of the abdominal cavity, and a hiatal hernia—part of the stomach herniating up into the chest—is more likely. In addition, the fat increases the pressure on the stomach, which leads to more reflux. This mechanical explanation may be why people who are overweight tend to have more reflux.

Another consideration is that people with obesity are more susceptible to a number of precancerous and

cancerous conditions, even in the absence of a mechanical explanation, such as the one described above. Women with obesity are more susceptible to colon cancer, for example. This increased susceptibility may be due to different hormones circulating in the body. In obesity, there is an increase in insulin and insulin-like growth factors, along with other trophic hormones that stimulate cell growth.

By contrast, women tend to get heavy in their hips and buttocks. They become more pear-shaped, whereas men become more apple-shaped. This adipose tissue in the hips and buttocks is less biologically active. Thus, in addition to not having the mechanical pressure that occurs with an apple-shaped body, the biological role of the fat itself is different. Peripheral fat is different from intra-abdominal fat.

These explanations have not been proven, but they are some current considerations as to why men and women have such different rates of BE and associated esophageal adenocarcinoma.

G&H Does the type of food consumed make a difference in the likelihood that a person will develop these conditions?

NS Researchers have studied different foods in order to discern any link to BE and other reflux-associated conditions. Although some associations between various dietary factors and the risk of BE have been reported, probably the best advice to give to a person who is looking to avoid BE (or a person with BE who is looking to avoid progression) is to eat a healthy diet in moderation and to avoid any foods that trigger reflux in the patient.

Alcohol consumption does not appear to be strongly associated with an increased risk of either BE or esophageal adenocarcinoma, unlike that seen with many cancers. Interestingly, alcohol does increase the risk of squamous cell cancer of the esophagus, which constitutes approximately one-third of all esophageal cancer diagnoses in the United States each year. In fact, alcohol is one of the strongest risk factors for this type of esophageal cancer. However, that link is not observed with esophageal adenocarcinoma, the type of cancer resulting from BE. Smoking, however, is a risk factor for BE and esophageal adenocarcinoma.

G&H Is there any indication that BE is becoming more common in women?

NS The incidence of BE is increasing for both men and women. The proportions are still the same—men experience the condition more often—but the number of both men and women who develop BE has gone up substantially in the past 40 years.

G&H Does the same hold true for esophageal adenocarcinoma?

NS Many cases of BE are diagnosed during endoscopies of people who are experiencing heartburn symptoms or who have completely unrelated symptoms. BE is incredibly common; 2 to 3 million people are diagnosed in the United States each year. Approximately 10% of people with frequent reflux symptoms have BE; the vast majority will never develop esophageal adenocarcinoma. For individuals diagnosed with BE, gastroenterology professional societies recommend undergoing an endoscopy every 3 years or so to make sure that there are no signs of cancer transformation.

G&H Which patients with BE typically develop esophageal adenocarcinoma?

NS Only a small subgroup progresses to esophageal adenocarcinoma. Those who do progress typically have what is known as dysplasia, a precancerous cellular change. In people who have BE without dysplasia, the chance of progressing to esophageal adenocarcinoma is approximately 3 per 1000. However, in individuals with dysplasia, the risk can increase dramatically. BE with high-grade dysplasia is associated with an esophageal adenocarcinoma risk of 6% or higher per year. Being diagnosed with a condition for which the chance of developing cancer is 6% per year is extremely nerve-racking. We often perform endoscopic interventions for people who have BE with dysplasia. These interventions are performed less commonly for BE patients without dysplasia.

G&H What is the goal of detecting this precancerous state? Can the progression to esophageal adenocarcinoma be prevented?

NS There are good reasons to identify dysplasia. There are effective interventions, and esophageal adenocarcinoma is a particularly deadly type of cancer. In patients diagnosed with this cancer—not with BE but as a result of symptoms stemming from the cancer itself—the 5-year survival rate is approximately 15%. In other words, that individual has an 85% chance of being dead within 5 years of the diagnosis. At the point that the cancer presents symptomatically, often not much can be done to extend survival time.

However, if a person is diagnosed with BE with dysplasia, we can perform endoscopic therapies to decrease the chance of esophageal adenocarcinoma by 90% or more. For people with BE with high-grade dysplasia, endoscopic therapy can be performed to burn or freeze the precancerous tissue, which dramatically decreases the likelihood that esophageal adenocarcinoma will develop. Two randomized

clinical trials treating patients with radiofrequency ablation for dysplastic BE have both demonstrated a marked decrease in esophageal adenocarcinoma risk compared with patients who did not receive the treatment.

The efficacy of endoscopic therapy in preventing esophageal adenocarcinoma in individuals with BE with high-grade dysplasia is very high. Clinicians such as myself spend a great deal of time identifying this precancerous state and then treating patients to avoid this deadly cancer.

G&H Which patients should be screened for BE in the first place?

NS Clinicians look for a particular profile among people with chronic reflux symptoms. Male gender, obesity, history of smoking, and white race are characteristics that would lead a clinician to do an endoscopy. These risk factors, in addition to GERD symptoms, should signal to a primary care physician or gastroenterologist that consideration of a screening endoscopy is warranted.

The primary goal of the endoscopy would be to check for BE. If the individual has had symptoms of GERD for at least 5 years and does not have BE, then the likelihood of ever developing the condition is very small, and no repeat screening endoscopy is necessary. However, if BE is present, then routine surveillance endoscopies are needed to follow the condition.

G&H Besides endoscopic therapy, are there other effective interventions?

NS Twenty or so years ago, the only intervention available was surgical esophagectomy. The esophagus would be removed, and the stomach would be pulled up into the chest and anastomosed to the esophageal remnant. That surgery was associated with many complications.

Dissatisfaction with having this procedure as the only treatment option led to the exploration of eradicating precancerous cells before they turn cancerous by treating the lining. The first attempts involved monopolar electrocoagulation and laser therapy. These techniques killed the precancerous cells, and normal tissue would replace them. However, the techniques were time-consuming, had associated complications, and did not always eradicate all of the problematic tissue.

More recently, several modalities that are more effective have become available. These approaches are less time-consuming and achieve higher rates of BE eradication. These techniques include radiofrequency ablation and cryotherapy. Studies of these modalities among patients with both high-grade and low-grade dysplasia show that for the vast majority of patients treated, the original, normal esophageal tissue regrows after treatment.

These treatments can be performed on an outpatient basis and usually eliminate the need for surgery. The advent of these techniques has transformed the care that can be provided for patients with BE because now we have interventions that are relatively easy, effective, and safe.

G&H Is it difficult to decide which patients would benefit from these procedures?

NS Determining exactly who should undergo these procedures is a focus of current research because most people with BE will not develop esophageal adenocarcinoma and the procedures are costly. Therefore, being able to risk-stratify patients beyond their dysplasia status is necessary.

However, figuring out which patients are at highest risk for esophageal adenocarcinoma is challenging. A great deal of research is currently dedicated to identifying prognostic groups and diagnosing people accordingly.

G&H Is BE reversible? Can dietary changes revert the condition?

NS Generally speaking, once an individual has this condition, in the absence of endoscopic treatment, it is there to stay. However, we have found that controlling acid exposure with the use of proton pump inhibitors may reduce the risk of progression of BE to more severe dysplasia or esophageal adenocarcinoma. For this reason, gastroenterologists generally recommend acid suppressants for people diagnosed with BE, even if reflux is minimal.

In addition, weight loss will reduce the amount of reflux. We do not know if weight loss will lower the risk of esophageal adenocarcinoma—that question has not been well studied—but I would not be surprised if it did.

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Suggested Reading

Abrams JA, Appelman HD, Beer DG, et al. Barrett's Esophagus Translational Research Network (BETRNet): the pivotal role of multi-institutional collaboration in esophageal adenocarcinoma research. *Gastroenterology*. 2014;146(7):1586-1590.

Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA*. 2014;311(12):1209-1217.

Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009;360(22):2277-2288.

Thrift AP, Cook MB, Vaughan TL, et al. Alcohol and the risk of Barrett's esophagus: a pooled analysis from the International BEACON Consortium. *Am J Gastroenterol*. 2014;109(10):1586-1594.

Thrift AP, Shaheen NJ, Gammon MD, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a mendelian randomization study. *J Natl Cancer Inst*. 2014;106(11).