Advances in Barrett's Esophagus and Esophageal Adenocarcinoma

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Despite advances in diagnosis and therapy, esophageal adenocarcinoma remains an aggressive and usually lethal tumor. This review focuses on the epidemiology of esophageal adenocarcinoma and its presumed precursor lesion, Barrett's esophagus; the pathogenesis of the cancer; advances in treatment of adenocarcinoma and Barrett's esophagus; and strategies for cancer prevention. Emphasis is placed on recent literature. Although the absolute number of cases of adenocarcinoma in the United States is still small, the incidence of this cancer has increased dramatically in the last 40 years, and adenocarcinoma is now the predominant form of esophageal cancer in this country. Recent evidence suggests that Barrett's esophagus is more prevalent in asymptomatic individuals than previously appreciated. The pathogenesis of Barrett's esophagus is poorly understood. Given that some subjects will have repeated bouts of severe erosive esophagitis and never develop Barrett's esophagus, host factors must play an important role. The utility of neoadjuvant radiation and chemotherapy in those with adenocarcinoma, although they are widely practiced, is not of clear benefit, and some authorities recommend against it. Ablative therapies, as well as endoscopic mucosal resection, hold promise for those with superficial cancer or high-grade dysplasia. Most series using these modalities feature relatively short follow-up, and longer-term data will be necessary to better describe the effects of these therapies. The value of chemoprevention in subjects with dysplastic Barrett's esophagus by use of cyclooxygenase 2 inhibitors, nonsteroidal anti-inflammatory drugs, or proton pump inhibitors is unknown. Similarly, although endoscopic screening is widely practiced, its value in patients with chronic gastroesophageal reflux disease symptoms is of unproven value, and recommending bodies are divided as to its practice.

Because of its rapidly increasing incidence over the last 40 years, esophageal adenocarcinoma has gone from a somewhat esoteric disease entity to the predominant form of esophageal cancer in the United States. Although still a rare cause of cancer death internationally, esophageal adenocarcinoma has become a significant health concern in Western countries. Given the poor prognosis associated with the disease, a better understanding of the pathogenesis of the disease and the factors associated with increased risk is essential. Also, strategies for prevention of esophageal adenocarcinoma are hotly contested.

The following review will focus on new developments in the field of Barrett's esophagus (BE) and esophageal adenocarcinoma. Given the myriad aspects of these disease states, an exhaustive review of all that is known about them is beyond the scope of this article. Therefore, this work will concentrate on the epidemiology of the disease states, the pathogenesis of the cancer, advances in treatment, and strategies for cancer prevention. Special emphasis will be placed on recent data, with effort to place these data in the context of our knowledge of BE and esophageal adenocarcinoma.

Epidemiology of Barrett's Esophagus and Esophageal Adenocarcinoma

The incidence of esophageal adenocarcinoma in the United States has increased approximately 300%–500% in the last 40 years.[1–3] Although previous misclassification of some esophageal adenocarcinomas as gastric cardia tumors may be in part responsible for the noted increase, it does not likely explain the entire increase. If misclassification were to explain all of the increase, a concomitant decrease in the number of gastric cardia tumors might be expected over the same time period. The opposite is true; the incidence of gastric cardia tumors has not decreased and may have actually increased over this period.[4,5]

Less clear is the trend in the incidence of BE. Because BE is thought to be the precursor lesion to most or all cases of adenocarcinoma of the esophagus, increases in cancer might

Abbreviations used in this paper: BE, Barrett's esophagus; EMR, endoscopic mucosal resection; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia; PDT, photodynamic therapy.

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be expected to be preceded by increases in the incidence of BE. Longitudinal single-center studies do show an increase in diagnosis of BE over the past several decades.[6,7] However, this increasing trend mirrors the increasing use of upper endoscopy. It may, therefore, mean that the increased incidence of BE described in these studies is due to increased opportunity for detection, as well as the increasing appreciation of BE as a risk factor for cancer, as opposed to a true increase in prevalence.

The increasing trend in esophageal adenocarcinoma closely resembles the epidemic increase in obesity in the US population.[8,9] Additionally, obesity has been strongly associated as a risk factor for esophageal adenocarcinoma, even after controlling for the severity of reflux symptoms.[10,11] These 2 facts have led authorities to suggest a causal relationship between trends of increasing obesity and resultant esophageal adenocarcinoma in the US population.[12–14] Although such a relationship is certainly plausible, no causal chain has been definitely proven, and changes in other environmental exposures over the last 50 years may account for all or part of the observed increase.

One recent important contribution to this field has been the demonstration of the prevalence of BE in asymptomatic populations. BE has long been recognized as a possible complication of chronic reflux disease. However, 40% or more of esophageal adenocarcinoma is found in subjects without previous symptoms of reflux[15–17]—an observation that is inconsistent with the theory that BE arises from gastroesophageal reflux disease (GERD) and is the predisposing lesion to adenocarcinoma. This apparent contradiction may be at least partially explained by recent prevalence data of BE in asymptomatic populations. Gerson et al[18] performed upper endoscopy on 110 subjects with no or negligible GERD symptoms who were presenting for colorectal cancer screening. The surprising and somewhat unsettling finding in this primarily Veterans Administration Medical Center cohort was that almost 25% of those with no GERD symptoms harbored BE, and 8% of the subjects had long-segment disease (>3 cm). Other groups[19,20] have found that lesser, but still substantial, proportions of asymptomatic individuals have BE (Table 1). Currently unknown is whether these asymptomatic individuals with BE have the same increased risk of cancer that has been shown in previous, symptomatic cohorts that have been followed up longitudinally.

Also unknown is the exact risk of cancer in subjects with BE. Initial reports pegged this risk at 1% or more per year. More recent reports and a meta-analysis have suggested this risk to be approximately half that amount.[21–24] Of course, these analyses provide rough estimates based on accumulated data from cohorts for multiple years. It is quite possible (perhaps even likely) that cancer risk is unevenly spread in any given subject's "Barrett's lifetime." For instance, it may be that the initial period immediately after the development of the BE is a critical time in which a subgroup of subjects experience rapid progression through degrees of dysplasia to cancer. Conversely, perhaps nondysplastic BE of 10 years' duration is at very little, if any, risk of progression. Because the exact time of development of BE in subjects diagnosed with the condition is unknown, we have no data as to cancer risk as a function of the duration of preceding BE.

Pathogenesis of Barrett's Esophagus and Cancer

BE is thought to be a sequela of chronic reflux disease. Subjects with chronic reflux disease seem to harbor BE 5%–15% of the time.[25–27] However, it is unclear why some subjects develop severe recurrent erosive esophagitis and never develop BE, whereas others with relatively few symptoms and little or no inflammatory disease on upper endoscopy develop long segments of severely dysplastic disease. It has been suggested that a genetic predisposition to the development of BE might be a necessary prerequisite to the disease. However, to date, a "Barrett's gene" (or genes) has remained elusive. Several groups have attempted to study the heritability of BE as presumptive evidence of a genetic contribution to the disease. Family cohort studies have shown that BE occurs in family groups more frequently than would be expected by chance.[28] However, if there is a Barrett's gene, the penetrance of the phenotype must be low, because most first-degree relatives of those with BE do not have BE themselves.[29]

Table 1. Prevalence of BE in Asymptomatic Cohorts

Study	Year	Patient population	n	Prevalence of BE	Prevalence of long-segment BE
Gerson et al[18]	2002	Veterans Administration medical center	110	25%	7%
Rex et al[19]	2003	University hospital	556	5.6%	0.36%
DeVault et al[20]	2004	Academic practice	138	12.3	NR

NR, not reported.