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Mechanisms of esophageal adenocarcinoma formation and approaches to chemopreventive intervention

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ABSTRACT

The incidence of esophageal adenocarcinoma (EAC), a debilitating and highly lethal malignancy, has risen dramatically over the past 40 years in the United States and other Western countries. To reverse this trend, EAC prevention and early detection efforts by clinicians, academic researchers and endoscope manufacturers have targeted Barrett's esophagus (BE), the widely accepted EAC precursor lesion. Data from surgical, endoscopic and pre-clinical investigations strongly support the malignant potential of BE. For patients with BE, the risk of developing EAC has been estimated at 11- to 125-fold greater than that of the individual at average risk. Nevertheless, screening for BE in symptomatic patients (ie, with symptoms of reflux) and surveillance in patients diagnosed with BE have not had a substantial impact on the incidence, morbidity or mortality of EAC; the overwhelming majority of EAC patients are diagnosed without a pre-operative diagnosis of BE. This article will discuss the current state of the science of esophageal adenocarcinoma prevention, including ideas about carcinogenesis and its underlying genomic and molecular level mechanisms, and suggest strategies for a systems approach to targeted preventive management.

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1. Introduction

The incidence of esophageal adenocarcinoma (EAC), a debilitating and highly lethal malignancy, has risen dramatically over the past 40 years in the United States and other Western countries [1]. To reverse this trend, EAC prevention and early detection efforts by clinicians, academic researchers and endoscope manufacturers have targeted Barrett's esophagus (BE), the widely accepted EAC precursor lesion. Data from surgical, endoscopic and pre-clinical investigations strongly support the malignant potential of BE. For patients with BE, the risk of developing EAC has been at 11-fold [2] to 125-fold [3–5] greater than that of the individual at average risk. Nevertheless, screening for BE in symptomatic patients (ie, with symptoms of reflux) and surveillance in patients diagnosed with BE have not had a substantial impact on the incidence, morbidity or mortality of EAC; the overwhelming majority of EAC patients are diagnosed without a pre-operative diagnosis of BE. This article will discuss the current state of the science of esophageal adenocarcinoma prevention, including ideas about carcinogenesis and its underlying genomic and molecular level mechanisms, and suggest strategies for more selectively targeted preventive management.

1.1. Background: Barrett's esophagus and esophageal adenocarcinoma

Although EAC is a relatively rare disease, it represents a major public health problem in Western countries where, unlike most other cancer types, it has dramatically increased in incidence and incidence-based mortality over the past 40 years [6,7]. In the United States, incidence has increased from 0.4 cases per 100,000 in 1975 to 2.6 cases per 100,000 in 2009 [7]. EAC is a highly morbid disease with a 5-year survival of less than 20%, largely attributable to initial diagnosis at advanced stages, when current medical and surgical measures are not curative and often debilitating [8]. Hence, much clinical effort has focused on endoscopic detection, surveillance and treatment of BE, the only known precursor of EAC, to prevent the onset of invasive disease.

BE refers to an acquired condition that is characterized by the presence of specialized columnar epithelium (also called specialized intestinal metaplasia [SIM]) [9] instead of the usual stratified squamous epithelium in the distal esophagus. It develops in response to long-term exposure to gastric acid and bile refluxate leading to oxidative DNA damage in up to 10% of patients with gastro-esophageal reflux disease (GERD) [10,11]. Epidemiological

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studies have shown a 11-fold to 125-fold greater than average risk of developing EAC in individuals with BE [2–5]. However, a recent nationwide population-based study demonstrated that notwithstanding the relative risk of EAC in individuals with BE, which they found to be 11.3 (95% confidence interval [CI], 8.8–14.4), the annual risk of EAC in patients with BE was 0.12% (95% CI, 0.09–0.15), substantially lower than earlier estimates which were in the range of 0.5% [2].

BE has been the subject of a rapidly growing body of research in the cancer prevention research community since it was first described in the mid-20th century [12]. Research interest in BE was increased further in the 1970s when its clinical significance was established through its association with EAC and the (still) unexplained radical rise in EAC cases began [13,14]. Other conspicuous long-term patterns in EAC incidence, accompanied by etiologic implications, have emerged as well. In developed (Western) countries a shift in prevalence of histologic subtypes from squamous cell carcinoma (SCC) to adenocarcinoma has coincided with the increase in EAC. Whereas adenocarcinoma accounted for less than 15% of all esophageal cancers in the United States in the early 1970s, this cell type is now found in more than half of cases [15]. Unlike SCC, EAC is more common in Caucasians (over the age of 60) than it is in African Americans. Hispanics also have a lower incidence than non-Hispanic whites, but higher than African Americans. The gender disparity among EA patients is also extreme, with 6–10 times higher incidence in males than females [2]. Epidemiological studies have consistently shown that GERD, obesity and smoking are modifiable factors that are linked with an increased risk of BE and EAC. Of note, recent studies have shown an inverse relationship between the use of non-steroidal anti-inflammatory drugs and EAC (discussed below). Finally, observational evidence of infection with *Helicobacter pylori* has been consistently found to have inverse association with EAC [16,17]. Such long-term trends and associations in disease incidence often serve as the keys to underlying etiology and identification of individuals at risk. However, molecular mechanisms that explain these striking associations continue to elude researchers. As yet, neither identified risk factors nor biological insights have led to a validated set of biologically plausible factors that can account for the rise in EA and thus inform subsequent translation into widely-effective prevention, risk stratification or early detection strategies.

1.2. Barrett's management controversy

In 2015, Barrett's esophagus cases are typically identified by endoscopic evaluation and esophageal biopsy after patients are clinically diagnosed with chronic GERD. (Table 1) Current management of BE for the purpose of EAC prevention includes careful endoscopic monitoring of the lower esophagus at intervals determined by the degree of dysplasia. However, data supporting the value of endoscopic screening and surveillance of BE are inconsistent. Supportive data have shown that prior identification of BE [18] and surveillance-detected EAC [15,19] is associated with an improvement in survival. However, this finding has not been borne out in several other observational studies that found no association with a decrease in death rates [20,21]. In addition, no randomized controlled trial has been conducted to examine if surveillance strategies reduce EAC incidence [18]. Perhaps most disturbing are the undisputed estimates that more than 90% of EAC cases occur in patients with no prior diagnosis of BE, many of whom had no pre-EAC endoscopic examination [18,20]. In essence, the identification of BE in symptomatic patients has resulted in overdiagnosis of indolent but symptomatic BE (ie, Barrett's metaplasia as opposed to Barrett's dysplasia) and under-diagnosis of aggressive asymptomatic Barrett's lesions with clinically significant malignant potential. Ironically, the natural course of the specialized intestinal metaplasia that characterizes BE in the distal esophagus has been associated with a survival adaptation that provides mucosal defense against refluxed content [22–28].

Given the minimal impact that the singular emphasis on identifying and monitoring BE has had on EAC incidence at the population level, the clinical need for new approaches to EAC prevention and early detection is clear. Still, the contention that adenocarcinoma of the esophagus arises in endoscopically detectable specialized intestinal metaplastic epithelium has been accepted by investigators and has been the basis of clinical management of Barrett's patients since the 1980s. Two clinical observations have contributed to this conclusion: (1) residual BE is found in a majority of EAC esophagectomy specimens; and (2) when BE is not detected in esophagectomy, the tumors are usually large and tumor overgrowth of the intestinal metaplasia from which it evolved may explain its absence [13,29,30]. Regardless of one's perspective on the direct patient impact of endoscopy at regular intervals to detect neoplastic disease, these serial biopsies of esophageal tissue in individuals with BE have been invaluable to cancer prevention research, providing unique opportunities to observe and study the progression of benign to malignant tissue. Here we will discuss the mechanisms and conditions that underlie carcinogenesis and potential chemopreventive strategies from which they may be inferred.

2. Mechanisms underlying the GERD-BE-EA transition

2.1. BE as survival adaptation

BE has historically been thought of as an early phase of a decades long, multi-step process of carcinogenesis. The prevailing hypothesis is that malignant transformation begins with long-term GERD that leads to chronic inflammation of the esophageal squamous epithelium which converts to specialized intestinal metaplasia (SIM, ie, BE), which then progresses to low-grade dysplasia, to high-grade dysplasia and finally to invasive EAC.

Table 1
American Society for Gastrointestinal Endoscopy recommendations for Barrett's esophagus and associated pre-malignant conditions of the esophagus [93]

Histology	Intervention recommendation	Endoscopic management strategies for Barrett's esophagus
No dysplasia	3–5 years	Consider no surveillance. If surveillance is elected, perform EGD every 3–5 years with 4-quadrant biopsies every 2 cm.Consider endoscopic ablation in select cases.
Indeterminate for dysplasia	Additional evaluation to clarify diagnosis, 12 months	Clarify presence and grade of dysplasia with expert GI pathologist. Increase anti-secretory therapy to eliminate esophageal inflammation. Repeat EGD and biopsy to clarify dysplasia status.
Low-grade dysplasia	6–12 months	Confirm with expert GI pathologist. Repeat EGD in 6 months to confirm LGD. Surveillance EGD every year, 4-quadrant biopsies every 1 to 2 cm. Consider endoscopic resection or ablation.
High-grade dysplasia in the absence of eradication therapy:	3 months	Confirm with expert GI pathologist. Consider surveillance EGD every 3 months in select patients, 4-quadrant biopsies every 1 cm. Consider endoscopic resection or RFA ablation. Consider EUS for local staging and lymphadenopathy. Consider surgical consultation.