Barrett’s Esophagus and Its Progression to Adenocarcinoma

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Barrett’s esophagus, esophageal adenocarcinoma, CDKN2A, TP53, aneuploidy, NSAID, obesity

Abstract
Barrett’s esophagus (BE) is the only known precursor for esophageal adenocarcinoma (EA). Therefore, the presence of BE identifies a high-risk group of patients who may be followed-up for early detection of EA and treated to reduce the risk for its progression. The initiating event for BE is unknown, although it is associated with chronic gastric reflux. Many of the genetic lesions involved in BE neoplastic progression are known, including loss of CDKN2A (p16) and TP53 (p53) and the development of tetraploidy and aneuploidy. Intensive endoscopic surveillance has been shown to improve survival although it can be difficult to implement in practice. Several exposures may be altered to reduce the risk for progression, including weight, diet, and the use of nonsteroidal anti-inflammatory drugs. However, most of these results should be confirmed in additional cohorts before they are used to change clinical practice. (UNCCN 2006;4:367–374)

The National Comprehensive Cancer Network currently has no guidelines for the detection, prevention, or risk reduction of esophageal adenocarcinoma (EA) and its precursor Barrett’s esophagus (BE). Although EA is uncommon in the United States, with approximately 12,000 annual cases, it is a significant health concern because 5-year survival rates are around 13% and its incidence has been increasing faster than any other cancer in the western world. EA is an attractive model for both understanding progression in humans in vivo, and for cancer prevention.

BE is the only known precursor for EA. It is defined by the presence of mucinous goblet cells in an intestinalized epithelium in the esophagus. It essentially represents a transdifferentiation of the normal stratified squamous epithelium of the esophagus into a small-intestinal epithelium in the esophagus. BE is a metaplastic neoplasm in that it is typically clonal, hyperplastic, and progressive. People who have BE have more than a 30-fold risk of developing EA relative to people without BE, with approximately 0.5% to 1% of patients with BE developing EA annually.

Multiple factors make BE a good model for neoplastic progression in solid tumors. First, patients who have BE constitute a high-risk population who, once the syndrome is identified, can be followed-up in prospective cohorts. Second, unlike many other premalignant neoplasms, such as adenomatous polyps in the colon, BE is not surgically removed when detected because esophagectomies have a 3% to 23% mortality and morbidity in high- and low-volume hospitals, respectively. Given that patients with BE have a 5% to 10% lifetime rate of progression to EA, the risk for esophagectomy usually outweighs the risk for progression. Instead, endoscopic surveillance is the recommended standard of care for the early detection of EA. Third, BE can be easily visualized and biopsied safely and painlessly using standardized protocols during an upper endoscopy. Thus, changes in the neoplasm may be tracked over time for a patient. Fourth, the important genetic events in BE are among the most common events that occur in all solid tumors, including loss of CDKN2A (p16(INK4A)), loss of TP53 (p53), and development of tetraploidy and aneuploidy.

The factors that make BE a good model for solid tumor carcinogenesis also make it a good candidate for...
cancer prevention because the response to an intervention can also be tracked with neoplastic progression. Several other factors also make EA a good candidate for cancer prevention. First, because no other known precursors to EA exist, prevention of BE may serve as an intermediate endpoint for cancer prevention studies. Second, BE is estimated to take decades to progress to EA, which provides a long window of time to intervene in this high-risk group. Third, nonresectable EA is typically resistant to both chemo- and radiotherapy, highlighting the need for cancer prevention. Fourth, currently no alternatives to esophagectomy have been shown to prevent cancer. The main drawback to studying EA for cancer prevention is the relative rarity of the disease, which may require multi-institutional collaborations to build and validate cohorts with enough statistical power to determine the effects of interventions.

Etiology
Development of BE is associated with chronic gastric and duodenal reflux into the esophagus, a condition known as gastroesophageal reflux disease (GERD). The refluxate is a complicated mixture of gastric acids and duodenal bile. Patients with BE often experience a hiatal hernia and a weakened sphincter at the gastroesophageal junction. Approximately 13% of people with GERD have BE at endoscopy. Three current hypotheses may explain the initiation of BE. Reflux may cause a change in the differentiation of esophageal cells from the normal multilayered squamous epithelium to the columnar Barrett cells. Alternatively, in the abnormal environment of chronic reflux, gastric cells may migrate up into the esophagus. A further possibility is that a genetic or epigenetic lesion initiates a neoplastic clone that expands to form the Barrett segment. Environmental factors contribute to the progression of BE to EA. These include, but are not limited to, cigarette smoking, obesity, and increased body mass index. These factors are discussed below in the context of cancer prevention and risk reduction.

Progression
Only 4 genetic lesions have been thoroughly studied in a prospective cohort of patients with BE and shown to be important in BE progression: abnormalities in the tumor suppressor genes CDKN2A and TP53, tetraploidy (increased 4N fraction), and aneuploidy.

CDKN2A
The earliest known genetic and epigenetic lesion in BE progression is inactivation of CDKN2A (p16/INK4A). Inactivation of CDKN2A through loss of heterozygosity (LOH), sequence mutation, or hypermethylation of its promoter region was detected in biopsies from baseline endoscopies in more than 85% of patients with BE in one cohort. Loss of CDKN2A is associated with large clonal expansions that often fill the entire BE segment. Other Genetic Lesions
Unlike colorectal cancer, microsatellite instability associated with loss of function of hMLH1/hMSH2 has not been detected in BE and EA. However, new microsatellite alleles (shifts) have been detected at lower frequencies than classic microsatellite instability.
in both premalignant and malignant Barrett epithelium.\textsuperscript{3,10,12,33}

LOH has been detected in the adenomatous polyposis coli (APC) gene on the q arm of chromosome 5 in BE.\textsuperscript{8,34} However, LOH seems to occur after loss of TP53, and development has been observed after malignancy.\textsuperscript{8} Thus, if LOH is involved in neoplastic progression of BE, it probably occurs late in the process. The association of APC with progression to EA has not yet been tested in a prospective cohort.

**Early Detection**

**Detection of BE**

Current standard of practice requires visual identification of BE through upper endoscopy, and histologic confirmation through biopsy based on the presence of goblet cells in the intestinal epithelium. This procedure is expensive and practically excludes population-based screening strategies for the detection of BE. Unfortunately, many people with BE are asymptomatic and therefore may never undergo an upper endoscopy. The recent development of a pill camera (ESO capsule)\textsuperscript{35} may reduce costs and make screening for BE more feasible.

**Detection of Cancer**

Surveillance of BE has been shown to improve survival in patients with EA.\textsuperscript{36} However, detection of EA currently requires an intensive biopsy protocol, which may involve as many as 24 biopsies per centimeter of BE per year to effectively detect EA at an early stage when it is still easily curable. Several surveillance programs have been unable to complete this intensive protocol or clinical coordination to prevent deaths from EA.\textsuperscript{37–39} One further problem is that the squamous mucosa sometimes grows over BE, obscuring it from the endoscopist and thus preventing effective surveillance. Better technologies and protocols for early detection of EA are needed.

**Biomarkers for Risk Stratification**

Pepe et al.\textsuperscript{40} have defined 5 phases of biomarker development. Phase I is discovery science using preclinical models to identify good potential biomarkers. Phase II is an estimate of the biomarker’s receiver operating characteristic (ROC) curve for distinguishing patients who have disease from those who do not, and to explore reproducibility of the assay and the relationship of the biomarker to other factors such as exposures and disease progression. Phase III is a retrospective, longitudinal, case-control study to determine how early the biomarker can detect preclinical disease. Phase IV uses a prospective screening study to determine the number of detections and false referrals. Finally, phase V studies determine if cancer mortality is reduced by a screening test based on the biomarker. Few biomarkers have been evaluated for risk stratification in BE.

**Histology:** Histologic diagnosis of grades of dysplasia is the current gold standard of clinical practice. Despite this, dysplasia screening has been shown to fail phase II reproducibility studies.\textsuperscript{41–44} Thus, both histologic and molecular biomarkers have considerable room for improvement.

**Aneuploidy and Tetraploidy:** The molecular biomarker that has progressed furthest is detection of ploidy lesions through flow cytometry. This biomarker has shown good reproducibility among laboratories\textsuperscript{45} and has passed phase IV prospective trials.\textsuperscript{35} However, used alone, the ROC for aneuploidy or tetraploidy is not good enough to justify the risks of esophagectomy. Researchers must determine if ploidy lesions can be used as part of a panel of biomarkers to identify in which patients esophagectomy would be justified.

**TP53 LOH:** Currently, LOH in TP53 has only been used in a research context. It is based on measuring microsatellites in fresh/frozen tissue. A prospective cohort (phase IV) showed TP53 LOH to be a useful biomarker in these procedures.\textsuperscript{7} However, detection of TP53 LOH must be adapted to fixed, paraffin-embedded tissue and the assay must be simplified before TP53 LOH can be used practically as a biomarker. This must be validated in a phase II study by multiple laboratories.

**Cancer Prevention and Risk Reduction**

Two primary concerns in cancer prevention efforts impose opposing requirements on cancer prevention studies. First, the risks of intervention must not outweigh the risks of progression, suggesting that cancer prevention should generally focus on the highest-risk patients. Second, an intervention that is successful at suppressing neoplastic cells may inadvertently increase the risk for cancer in high-risk patients because a resistant clone in a genetically heterogeneous neoplasm may benefit from the suppression of its competitor clones.\textsuperscript{46,47} This suggests that cancer prevention will
be most effective on patients early in progression, before the accumulation of much genetic heterogeneity, or even before initiation. Therefore, 2 important types of cancer prevention might be attempted for preventing EA. These are prevention of BE with a very low-risk intervention and prevention of BE progression in patients who might tolerate high-risk interventions, although the intervention risks must be gauged against the likelihood of resistance.

**Acid Suppression**

Because the etiology of BE is associated with acid reflux, an important area of future study is preventing BE through acid suppression. Unfortunately, suppression of acid after initiation does not usually result in regression of BE.

**Proton Pump Inhibitors:** Most patients with BE are put on acid suppressive medications, such as proton pump inhibitors (PPIs). However, a fraction of patients continue progressing to EA. Thus, PPIs clearly do not entirely prevent cancer. A few studies have shown that many patients taking PPI medication and who are asymptomatic still have acid reflux, suggesting that higher doses may be necessary to fully control reflux. Whether increased doses of PPIs may reduce the risk for progression is unknown, although the effects of high and low doses of the PPIesomeprazole are now being tested in the AspECT trial.

**Surgery:** An alternative, and perhaps complementary, approach to acid suppression is surgical modification of the gastroesophageal junction to prevent reflux. This may include fundoplication to decrease acid reflux from the stomach to the esophagus, which is increasingly being performed laparoscopically. However, fundoplication is typically reserved for patients for whom a rigorous and complete course of PPIs failed or who have mechanical features that mitigate the efficacy of PPIs, such as a large hiatal hernia that is causing symptoms for mechanical reasons.

**Helicobacter pylori:** Studies on the effects of gastric infection with Helicobacter pylori provide further evidence for the importance of suppressing acid in the prevention of EA. Although H. pylori is an important risk factor for gastric cancer, it also raises the pH in the stomach, and infection with cagA+ strains seems to protect against progression to EA. Although entirely untested, a benign strain of H. pylori may conceivably be used in a probiotic therapy to both prevent infection with a carcinogenic or ulcer-causing strain and reduce the risk for progression to EA.

**Diet**

Obesity is a risk factor for BE, EA, and the molecular markers of progression in BE, including loss of p16, loss of TP53, and the presence of aneuploidy. This suggests that changes in diet and weight loss may be effective intervention strategies for preventing EA. A low fruit and vegetable diet has been estimated to account for 15% of EA cases. A multicenter case-control study found that nutrient intake associated with an animal diet, including fat, cholesterol, and animal proteins, was associated with EA, whereas nutrients associated with a vegetable diet, including fiber, carbohydrates, β-carotene, folate, and vitamins B<sub>6</sub> and C, seemed to be protective. Whether these dietary factors have a direct effect on BE initiation and progression or if they are surrogates for other factors associated with obesity that are driving the process of neoplastic progression is unclear.

**Nonsteroidal Anti-Inflammatory Drugs**

Various studies have shown an association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, and a reduced incidence of EA. A meta-analysis of these studies estimates that any use of NSAIDs has a protective association with EA, with an odds ratio (OR) of 0.57 (95% confidence interval [CI], 0.47–0.71). A prospective cohort study has recently corroborated the protective effects of NSAIDs. However, these studies were observational. NSAID use to prevent EA is only now being tested in the randomized, controlled AspECT trial using a combination of aspirin and high or low doses of the PPIesomeprazole.

**Selenium**

Interest in selenium for cancer prevention was sparked by a randomized controlled trial that found selenium levels were associated with statistically significant risk reduction for various cancers. The risk reduction for all types of esophageal cancer was suggestive but not statistically significant (risk ratio = 0.3; 95% CI, 0.06–1.5). A cross-sectional analysis of a BE cohort found the highest 3 quartiles of selenium levels in the participants’ blood were associated with a lower incidence of TP53 LOH (OR = 0.5; 95% CI, 0.2–0.9), tetraploidy (OR = 0.6; 95% CI, 0.3–1.2), and aneuploidy (OR = 0.4; 95% CI, 0.2–0.8).

**Smoking and Alcohol**

Smoking does not appear to be a strong risk factor for EA. Study results have been mixed, but the...
case-control studies that have found an association between smoking and EA have found only relatively weak effects, with ORs between 2.1 and 3.4. However, a large, multicenter case-control study estimated that smoking accounted for 40% of EAs. Similarly, the studies on alcohol and EA have provided mixed results, with most showing no association and the remainder having ORs ranging from 1.6 to 2.3.

Early Diagnosis

Ideally, risk stratification in the general population would facilitate screening and detection of BE. However, most patients with BE are asymptomatic and therefore screening endoscopy is likely not cost-effective. However, patients with gastroesophageal reflux that fails to respond to PPIs are candidates for upper endoscopy to exclude BE. Although uncommon, a familial predisposition to BE may exist, and although the gene locus or loci have yet to be identified, family members should also undergo screening through upper endoscopy.

When upper endoscopy indicates BE, histopathology and immunohistochemistry (if needed) are used for confirmation. BE should be defined according to its length above the gastroesophageal junction. If the length is shorter than 3 cm, it is termed short-segment Barrett, which is more common. If the length is longer than 3 cm, it is designated as long-segment Barrett. However, long-segment Barrett carries a higher risk for EA. During endoscopic screening protocols, if intestinal metaplasia is found without dysplasia, then the patient should undergo surveillance endoscopy with biopsies in 2 years. However, if low-grade dysplasia is found in the absence of surrounding esophagitis, then surveillance endoscopy with biopsies should be performed in 6 months, and annually thereafter. High-grade dysplasia (HGD) should be confirmed by another pathologist, and repeat biopsies should be performed if any doubt exists. The presence of HGD may translate into coexisting carcinoma, which requires esophagectomy or nonsurgical approaches.

Therapy

Treatment for HGD is controversial. Some guidelines recommend esophagectomy at the detection of HGD because of the possibility of coexisting carcinoma and the relative difficulty of treatment if the disease is allowed to progress to an advanced carcinoma. However, given the difficulty of diagnosing HGD, the fact that most patients with HGD do not experience progression, and that 3% to 8% (at high-volume hospitals) and 16% to 23% (at low-volume hospitals) rates of mortality and morbidity are associated with esophagectomy, other guidelines argue that esophagectomy is not warranted until carcinoma is detected. Thus, if surgery is warranted, the surgeon must be experienced in the technical and clinical aspects of esophagectomy. Patients who have medical illnesses that preclude esophagectomy can be treated with nonsurgical approaches, including endoscopic mucosal resection and photodynamic therapy. Long-term outcome data are yet to emerge.

Conclusions

The understanding of BE is both intriguingly detailed and frustratingly unconfirmed. Evidence exists that loss of TP53 and the development of ploidy lesions are important risk factors that probably drive progression to EA. The evolution of clones in BE is understood better than perhaps for any other neoplasm. Evidence even exists that NSAIDs are associated with a fivefold reduction in the risk for progressing to EA. All of these results may form the basis of improved detection and risk reduction of EA. However, only a prospective cohort has shown all of these results. Before these results can be confidently generalized to most patients with BE and used to guide clinical decisions, they must be tested in other cohorts.

References

5. Gulizia JM, Wang H, Antonioli D, et al. Proliferative characteristics of intestinalized mucosa in the distal esophagus and
43. Omsby AH, Perrus PE, Hendricks WH, et al. Interobserver variation in Barrett’s (BE) related high-grade dysplasia (HGD) and superficial adenocarcinoma: can it be improved using uniform pathologic criteria [abstract]? Gastroenterology 2000;118:A3764.
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