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Barrett's Esophagus: Frequency and Prediction of Dysplasia and Cancer

Gary W. Falk, M.D., M.S. [Professor of Medicine]

Division of Gastroenterology, Hospital of the University of Pennsylvania, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Abstract

The incidence of esophageal adenocarcinoma is continuing to increase at an alarming rate in the Western world today. Barrett's esophagus is a clearly recognized risk factor for the development of esophageal adenocarcinoma, but the overwhelming majority of patients with Barrett's esophagus will never develop esophageal cancer. A number of endoscopic, histologic and epidemiologic risk factors identify Barrett's esophagus patients at increased risk for progression to high-grade dysplasia and esophageal adenocarcinoma. Endoscopic factors include segment length, mucosal abnormalities as seemingly trivial as esophagitis and the 12 to 6 o'clock hemisphere of the esophagus. Both intestinal metaplasia and low grade dysplasia, the latter only if confirmed by a pathologist with expertise in Barrett's esophagus pathologic interpretation are the histologic risk factors for progression. Epidemiologic risk factors include aging, male gender, obesity, and smoking. Factors that may protect against the development of adenocarcinoma include a diet rich in fruits and vegetables, and the use of proton pump inhibitors, aspirin/NSAIDs and statins.

Keywords

Barrett's esophagus; esophageal adenocarcinoma; dysplasia; cancer risk factors

Introduction

The incidence of esophageal adenocarcinoma continues to rise at an alarming rate in the Western world, although the pace of this increase appears to have decreased in recent years [1]. Barrett's esophagus is a clearly recognized risk factor for the development of esophageal adenocarcinoma [2,3]. This has led to widespread endoscopic surveillance of Barrett's esophagus patients in an effort to detect cancer at an earlier and potentially curable stage.

Address for Correspondence: Gary W. Falk, M.D., M.S, Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, 9 Penn Tower, One Convention Avenue, Philadelphia, Pennsylvania 19104, U.S.A., Telephone: (215) 615-4452, Fax: (215) 349-5915, gary.falk@uphs.upenn.edu.

Conflict of Interest Statement

I have no conflicts to declare

However, the overwhelming majority of Barrett's esophagus patients die of causes other than esophageal adenocarcinoma, bringing into question the value of endoscopic surveillance programs as currently practiced [4]. Thus, it is important to identify risk factors for progression to adenocarcinoma and high-grade dysplasia. This chapter will explore the various endoscopic, histologic and clinical risk factors for the development of esophageal adenocarcinoma among patients with Barrett's esophagus.

Risk of Progression to High-Grade Dysplasia & Adenocarcinoma in Barrett's Esophagus Without Dysplasia

Despite the alarming increase in the incidence of esophageal adenocarcinoma, the risk of adenocarcinoma in patients with Barrett's esophagus without dysplasia is quite low. A number of studies have examined the risk of progression of nondysplastic Barrett's esophagus to high-grade dysplasia/adenocarcinoma in recent years. Large contemporary studies clearly demonstrate a decreased risk of progression compared to earlier studies with small sample sizes [5]. Overall, the risk of progression to the endpoint of adenocarcinoma is approximately 0.12% to 0.43%/year and for the combined endpoint of high-grade dysplasia/adenocarcinoma in the range of 0.26% to 0.63%/year. [5,6,7,8,9]. Furthermore, this risk appears to be stable over time [6].

Endoscopic Features

Segment Length

Esophageal cancer develops in both short and long segments of Barrett's esophagus. However, evidence from recent observational studies suggests that increasing segment length is a risk factor for progression to high-grade dysplasia/adenocarcinoma. A recent meta-analysis found a lower annual incidence of esophageal adenocarcinoma in short segment Barrett's esophagus patients when compared to all Barrett's esophagus patients in the study (0.19% vs 0.33% per year [8]. Work from the Northern Ireland Barrett's esophagus register found the risk of progression to adenocarcinoma or high-grade dysplasia increased by seven fold in long segment compared to short segment Barrett's esophagus (hazard ratio 7.1; 95% CI 1.74–29.04) [10]. A recent case control study from Berlin also found an association of segment length with progression of Barrett's esophagus to high grade dysplasia/adenocarcinoma [11]. Compared to short segment Barrett's esophagus, patients with long segment Barrett's esophagus had an increased risk of progression (OR 2.69; 95% CI 1.48–4.88). Furthermore, for every increase in segment length by 1 cm, the risk of progression increased by 19% (OR 1.19; 95% CI 1.09–1.30). Similarly, work from a large United States multicenter cohort found that the risk for progression increased by 28% for every 1 cm increase in the length of the Barrett's segment [12]. Others have also reported an incremental increase in risk for progression with each cm increase in the segment length [13]. On the other hand, work from the Northern Ireland Barrett's esophagus register found no relationship between segment length and risk of progression [6]. Taken together, it would appear that longer segments of Barrett's esophagus are associated with an increased risk of progression to adenocarcinoma and high grade dysplasia.

Esophagitis/Mucosal Abnormalities

A number of mucosal changes within the Barrett's segment are associated with an increased risk for progression to high grade dysplasia/adenocarcinoma. A Dutch multicenter cohort study found an increased risk of progression to adenocarcinoma or high-grade dysplasia in Barrett's esophagus patients with esophagitis by the Los Angeles classification at baseline endoscopy (relative risk 3.5; 95% CI 1.3–9.5) [13]. The population based Northern Ireland Barrett's register found that patients with ulceration in the Barrett's segment but not elsewhere in the esophagus were more likely to progress to cancer or high-grade dysplasia than non-progressors (hazard ratio 1.72; 95% CI 1.08–2.76) [10]. While these studies did not determine if these abnormalities in the Barrett's segment represented prevalent disease that progressed within 6 to 12 months, these findings do suggest that mucosal abnormalities such as esophagitis in the Barrett's segment merit more intense follow up.

Directional Distribution

Several studies have now identified an apparent spatial predilection for neoplasia in the 12 to 6 o'clock hemisphere within the Barrett's segment. This was first described by Pech et al., who found that of 380 lesions removed by endoscopic mucosal resection (EMR) from 344 patients, 48% were located in the quadrant between 12 and 3 o'clock [14]. Subsequently, an Australian series of 75 patients with visible lesions who underwent EMR in Barrett's segments ≤ 5 cm demonstrated that 55% of lesions with high-grade dysplasia or adenocarcinoma were found in the area between 2 and 4 o'clock [15]. Work from Vanderbilt identified dysplasia or adenocarcinoma in 60 EMR specimens of which 62% were found in the 1 to 5 o'clock regions [16]. Finally, Enestvedt et al. found advanced histology (high-grade dysplasia or adenocarcinoma) in the right hemisphere extending from 12 to 6 o'clock in 85% of patients, with the majority of abnormalities located between 12 and 3 o'clock [17]. Taken together, these studies consistently indicate a clear predilection for lesions on the right side of the esophageal wall regardless of segment length, a region that merits more meticulous endoscopic inspection. The mechanism underlying this observation is not yet known.

Histology

Intestinal Metaplasia

While there has been considerable debate over the years, it appears that the risk of progression to both adenocarcinoma and the combined endpoint of adenocarcinoma/high-grade dysplasia are higher for individuals with intestinal metaplasia of the tubular esophagus compared to individuals without intestinal metaplasia [6]. This debate may be somewhat semantic, as it is known the yield of intestinal metaplasia increases with the number of biopsies obtained in the columnar lined segment, proximal location of biopsies and length of Barrett's esophagus.

While one study found DNA content abnormalities to be comparable in both metaplastic epithelium without goblet cells compared to metaplastic epithelium with goblet cells, other studies suggest that cancer associated genetic abnormalities are more commonly found in columnar metaplasia with goblet cells compared to columnar metaplasia without goblet

cells. [18,19]. Work from the population-based Northern Ireland Barrett's esophagus register examined the risk of progression to high-grade dysplasia and esophageal adenocarcinoma in 8,522 patients diagnosed with Barrett's esophagus defined as a columnar lined esophagus both with and without intestinal metaplasia [6]. The risk of cancer for patients with intestinal metaplasia at index endoscopy was increased compared to those without intestinal metaplasia at index endoscopy (0.38%/year vs. 0.07%/year; hazard ratio 3.54; 95% CI 2.09–6.0). On the other hand studies such as work from Sheffield in the United Kingdom suggest no difference in the risk of progression to adenocarcinoma in the two groups over a median follow up of 12 years [20]. The weight of the evidence suggests that intestinal metaplasia is a distinct risk factor for progression to neoplasia.

Dysplasia

Barrett's esophagus patients progress through a phenotypic sequence of no dysplasia, low-grade dysplasia, high-grade dysplasia and then on to adenocarcinoma, although the time course is highly variable and this step-wise sequence is not pre-ordained [21,22]. Furthermore, some patients may progress directly to cancer without prior detection of dysplasia of any grade [23]. Currently, dysplasia remains the only practical factor useful for identifying patients at increased risk for the development of esophageal adenocarcinoma in clinical practice despite the well-recognized problems with interobserver variability in the interpretation of dysplasia. Interestingly, absence of dysplasia on repeated endoscopies may identify Barrett's esophagus patients at lower risk of progression. A multicenter study by Gaddam et al. found that persistence of nondysplastic Barrett's esophagus over multiple surveillance endoscopies was associated with a decreased risk of progression to high-grade dysplasia or esophageal adenocarcinoma [24].

There are a paucity of data on the implications of progression for indefinite for dysplasia, which is to say epithelial changes not sufficient to diagnose dysplasia but with abnormalities that are of uncertain significance due to sampling or inflammation [25]. Work from a multicenter study by Montgomery et al. found that indefinite for dysplasia was associated with a similar risk for progression to cancer as was low-grade dysplasia: 14% vs. 20% [26]. More recent data suggest an especially high risk of progression to higher grades of dysplasia within the first year of diagnosis but a risk of progression comparable to nondysplastic Barrett's esophagus after the first year [27]. The risk for progression is more pronounced in multifocal indefinite for dysplasia (defined as indefinite for dysplasia in biopsies from more than one level of the esophagus) than in focal indefinite for dysplasia as well as in longer segments with indefinite for dysplasia [27,28].

Interpretation of low-grade dysplasia is characterized by considerable interobserver variability, even amongst expert GI pathologists making studies of this pathologic abnormality especially challenging [29]. While the majority of patients with low-grade dysplasia do not progress to adenocarcinoma or high-grade dysplasia, a subset of these patients do progress to a higher-grade lesion. A meta-analysis by Singh et al found the pooled incidence of progression to adenocarcinoma was 0.54%/year and for the combined endpoint of high-grade dysplasia and cancer, the rate was 1.73%/year [30]. However, there was considerable heterogeneity in these results and when stratified by the low-grade

dysplasia/Barrett's esophagus ratio as a surrogate for pathology quality, the incidence rate for adenocarcinoma was 0.76%/year for a ratio of < 0.15 and 0.32%/year for a ratio > 0.15. This finding suggests that in settings where the diagnosis of low-grade dysplasia is made more liberally, hence overcalled, there is a lower risk of progression. The importance of the confirmation of the diagnosis of low grade dysplasia comes from a series of studies from the Netherlands. Review by two gastrointestinal pathologists, with extensive experience in the diagnosis of Barrett's esophagus related neoplasia, found that of 147 patients diagnosed with low-grade dysplasia in the community, 85% of the patients were downgraded to a diagnosis of no dysplasia or indefinite for dysplasia [31]. The progression rate to the combined endpoint of high-grade dysplasia/adenocarcinoma was 13.5%/pt/year in the confirmed patients compared to 0.49%/pt/year in those where the diagnosis was downgraded. Further work by that group examined 293 additional patients with low-grade dysplasia diagnosed in the community who had biopsies reviewed by at least two gastrointestinal pathologists with experience in Barrett's associated dysplasia and 73% of these cases were downgraded to indefinite for dysplasia or nondysplastic Barrett's esophagus [32]. Risk for progression to high-grade dysplasia/esophageal adenocarcinoma was 9.1%/patient-year in the confirmed low-grade dysplasia group compared to 0.6%/patient-year in the downstaged group. Finally, results from the recent clinical trial of endoscopic ablation for Barrett's esophagus with low-grade dysplasia found a progression rate of 11.8%/pt-year using this expert panel of gastrointestinal pathologists [33]. A similar high progression rate was seen in the original clinical trial of radiofrequency ablation for dysplastic Barrett's esophagus where expert gastrointestinal pathologist confirmation was required: 14% of patients in the sham treatment arm developed high-grade dysplasia at one year of follow up [34]. Furthermore, older studies also suggested that community based pathologists had difficulties in the interpretation of both nondysplastic Barrett's esophagus and dysplasia [35]. Therefore, current evidence supports the importance of having all readings of dysplasia confirmed by a second pathologist with extensive experience in the interpretation of Barrett's associated neoplasia, and that if confirmed, these patients may indeed have a higher risk of progression to higher grades of neoplasia.

Biomarkers of Increased Risk

Given the limitations of endoscopic surveillance, a number of molecular markers to identify patients at increased risk for the development of esophageal adenocarcinoma have been studied in an effort to improve upon current surveillance algorithms. Recent technologic advances have accelerated the pace of discovery of potential biomarkers of increased risk. Abnormalities including DNA content abnormalities, chromosomal abnormalities, gene mutations, methylation changes and clonal diversity measurements define patients at increased risk for progression to cancer [36,37,38,39,40,41,42]. These genetic abnormalities appear to occur early in disease development [43]. Recent promising work in a case control study suggested that aberrant p53 expression, defined as absent or increased expression by immunohistochemistry was associated with an increased risk of neoplastic progression [44].

However, it appears that no single biomarker is adequate as a risk stratification tool. Given the complexity and diversity of alterations observed to date in the metaplasia, dysplasia, carcinoma sequence, it appears that a panel of biomarkers may be required for risk

stratification. Multiple studies have demonstrated the promise of biomarker panels including a recent population-based study using the Northern Ireland Barrett's esophagus register which identified a panel of markers consisting of expert pathologist confirmed low-grade dysplasia, abnormal DNA ploidy as detected by image cytometry, and *Aspergillus oryzae* lectin immunostaining that could distinguish progressors from nonprogressors to adenocarcinoma or high-grade dysplasia [45]. At the present time, no biomarkers or panels of biomarkers are ready for clinical practice. In order to become part of the clinical armamentarium, biomarkers will have to be validated in large prospective cohorts. Such studies will be challenging given the low overall progression of Barrett's esophagus to high-grade dysplasia/adenocarcinoma, need for assay standardization, cost, validation and financial investment for such trials. In the future, it is likely that the best predictor for the development of high-grade dysplasia or adenocarcinoma will be a combination of clinical, demographic, histologic, genetic and epigenetic data.

Epidemiologic Factors

Age

Studies consistently show that the incidence of esophageal adenocarcinoma increases with increasing age [46,47]. Among patients with Barrett's esophagus, most studies suggest that increased age is associated with an increase in the risk of progression. For example, a Dutch population based study found that the risk of progression was increased with increasing age at diagnosis with a marked increase in risk after age 75 years (hazard ratio 12; 95% CI 8.0–18) [9]. Similarly in the landmark Danish Barrett's esophagus population based study by Hvid-Jensen, the incidence of high-grade dysplasia/adenocarcinoma increased progressively with age and was greatest in patients over age 70 years of age [7]. However, smaller studies do not find a relation between patient age and risk of progression in Barrett's esophagus [11].

Gender

Male gender is a well recognized risk factor for both Barrett's esophagus and esophageal adenocarcinoma [46,47,48]. However, the incidence of esophageal adenocarcinoma is increasing steadily in both genders. Among Barrett's esophagus patients, male gender is also a clearly recognized risk factor for progression to esophageal adenocarcinoma [6,7,9,10,11].

Race

Barrett's esophagus is typically found in Caucasians and is uncommon in blacks and Asians [49,50]. Similarly, white race has long been associated with esophageal adenocarcinoma[51,52,53]. Kubo et al., in an analysis of SEER data, found that the average annual incidence rate of esophageal adenocarcinoma for Caucasian males was double that of Hispanic males (4.2 vs 2.0/100,000/yr) [54]. This rate was also four times higher than that seen in blacks, Asians/Pacific Islanders and Native Americans. Thus, there are clear ethnic imbalances in the risk for both Barrett's esophagus and esophageal adenocarcinoma.

Family History

Given the clear association of esophageal adenocarcinoma with male gender and Caucasian race, a possible inherited component to the risk of esophageal carcinoma has long been

hypothesized. This has been supported by a number of reports of familial clustering of both Barrett's esophagus and esophageal adenocarcinoma [55,56,57,58,59]. These small studies suggested the possibility of an autosomal dominant inheritance pattern. Much of the subsequent work in this area has been done by the Chak group in Cleveland, who initially found that a positive family history (first or second degree relative with Barrett's esophagus, esophageal adenocarcinoma or esophagogastric junction carcinoma) was higher among case subjects than among GERD controls (24% vs. 5%) [60]. The familial effect was present in all three of the subgroups studied. Subsequently, a segregation analysis study found that there was an incomplete autosomal dominant inheritance pattern for familial aggregations of Barrett's esophagus, esophageal adenocarcinoma and gastroesophageal junction carcinoma [61]. Furthermore, in multiplex aggregations characterized by three or more members of a family with Barrett's esophagus and/or esophageal adenocarcinoma, the median age for the diagnosis of adenocarcinoma was approximately five years younger than in duplex families or sporadic cases [62]. Efforts are now underway to identify genetic susceptibility loci for this risk. Three germ line mutations have been described in patients with Barrett's esophagus and esophageal adenocarcinoma: MSR1, ASCC1 and CTHRC1 [63].

Obesity

The rapid increase in the incidence of esophageal adenocarcinoma has paralleled the rise of obesity in the Western world. As such, obesity has emerged as a leading candidate risk factor for esophageal adenocarcinoma. Obesity has been implicated as a risk factor for both Barrett's esophagus and esophageal adenocarcinoma. Multiple observational studies demonstrate a relationship between increasing BMI and risk for esophageal adenocarcinoma [64,65,66]. The relationship between obesity and Barrett's esophagus is, however, less clear cut. It appears that increased risk is not simply related to obesity but rather to male pattern central obesity, predominantly of the visceral adipose tissue compartment [67,68]. A recent meta-analysis found that central obesity was associated with both Barrett's esophagus (OR 1.98; 95% CI 1.52–2.57) and esophageal adenocarcinoma (OR 2.51; 95% CI 1.54–2.06) after adjusting for BMI [69]. However, there was insufficient information to determine the effect of central adiposity on risk of progression of Barrett's esophagus to dysplasia or adenocarcinoma. Similarly, work from the Seattle Barrett's project found no association between BMI and progression of Barrett's esophagus to adenocarcinoma [70]. Finally, the Seattle Barrett's esophagus study was used to assess the potential role of obesity-induced hyperglycemia, and adipokine regulation on the risk of progression to adenocarcinoma [71]. Both increased levels of leptin and insulin resistance were associated with an increase in the risk of progression to adenocarcinoma whereas increased levels of adiponectin were inversely associated with cancer risk. Clarification of the best marker(s) of obesity as a risk for progression should assist risk stratification in the future.

Helicobacter pylori

The prevalence of *H. pylori* infection has been falling in the Western world at the same time that the incidence of esophageal carcinoma has been increasing. This has suggested a potential relationship between these two opposing time trends. The most recent meta-analysis to examine the association between *H. pylori* infection and esophageal adenocarcinoma found an inverse relationship between *H. pylori* infection and esophageal

adenocarcinoma (OR 0.57; 95% CI 0.44–0.73) [72]. A similar inverse relationship is seen in Barrett's esophagus [73,74]. That being said, there are no studies that have examined the relationship between *H. pylori* infection and the risk of progression of Barrett's esophagus to esophageal adenocarcinoma.

Tobacco Smoking

A number of observational studies have identified current or past tobacco smoking as a risk factor for esophageal adenocarcinoma [75,76,77,78,79]. In patients with Barrett's esophagus, both current and past smoking history increases the risk for adenocarcinoma [80]. A recent large population based cohort study from the Northern Ireland Barrett's esophagus registry examined this issue in more detail and found that current tobacco smoking increased the risk of progression to high grade dysplasia or cancer twofold compared to never smoking [81]. Furthermore, the increase in risk of progression remained elevated regardless of number of cigarettes smoked, duration of smoking, and in current as well as past smokers. The mechanism for tobacco increasing the risk for adenocarcinoma may be related to the increase in DNA damage encountered in Barrett's mucosa in smokers compared to nonsmokers [82].

Alcohol Consumption

Most epidemiologic studies find no association between alcohol consumption and either Barrett's esophagus or esophageal adenocarcinoma [83]. However studies from Northern California, Australia and Northern Ireland demonstrate a somewhat lower risk of both conditions with modest wine consumption [84,85,86]. A meta-analysis found no association between alcohol consumption and risk of progression of Barrett's esophagus to esophageal adenocarcinoma [87].

Diet

A variety of studies have examined diet and food supplements and risk of esophageal adenocarcinoma but little is known about the effect of diet on progression to cancer in patients with Barrett's esophagus. Increased consumption of fruits and vegetables, especially raw fruits and dark green leafy and cruciferous vegetables is consistently associated with a decrease in the risk for esophageal adenocarcinoma [88,89,90,91]. In fact Engel et al. found that the population attributable risk, defined as the proportion of a disease in the population attributable to a given risk factor, associated with low consumption of fruits and vegetables was 15.3% (95% CI 5.8%–34.6%) [91]. Similarly, a recent systematic review found an inverse association between highest intake versus lowest intake of dietary fiber and risk of esophageal adenocarcinoma (OR 0.66; 95% CI 0.44–0.98) [92]. In an Australian case control study, intake of the dietary antioxidants including Vitamin E and β-carotene were associated with a decreased risk of esophageal adenocarcinoma and dysplastic Barrett's esophagus respectively [93]. Similar inverse associations are seen between increasing intake of folate and Vitamin B-6 and risk of esophageal adenocarcinoma [94]. On the other hand, a diet high in red meat and fat is associated with an increase in the risk of esophageal adenocarcinoma [90,95].

However, little is known about dietary factors and risk of progression in patients with Barrett's esophagus. A cohort study of 339 patients in the Seattle Barrett's esophagus program found that consumption of ≥ 1 multivitamin daily was associated with a decrease in the hazard ratio of developing esophageal adenocarcinoma (HR 0.38, 95% CI 0.15–0.99) compared to individuals not taking multivitamins [96]. Similar findings were encountered for daily use of vitamins C and E in that same study.

Acid Suppression

Since Barrett's esophagus has the most severe pathophysiologic abnormalities of GERD, it should come as no surprise that proton pump inhibitors (PPIs) are the cornerstone of medical therapy for Barrett's esophagus. A recent meta-analysis of seven observational studies that examined the association between PPI usage and risk of high-grade dysplasia/adenocarcinoma found that PPIs resulted in a 71% reduction in the risk of high-grade dysplasia/adenocarcinoma (OR 0.29; 95% CI 0.12–0.79) [97]. This study also found a trend towards an increased protective effect with dosage duration greater than two to three years. On the other hand, a Danish population-based case control study found that PPI use resulted in no difference in the risk for high-grade dysplasia/adenocarcinoma over a median 10 year follow up [98]. Additional data are awaited from the ASPECT study in the United Kingdom. That being said, PPI therapy is warranted for symptom control and healing of erosive esophagitis in Barrett's patients so this class of drug will continue to be widely used for therapy of Barrett's esophagus. PPIs also have the theoretical benefit of decreasing epithelial proliferation and increasing cell differentiation in Barrett's esophagus [99].

Antireflux Surgery

Some have hypothesized that antireflux surgery provides protection from progression of Barrett's esophagus to adenocarcinoma [100]. However, two lines of evidence suggest that antireflux surgery does not protect patients from developing esophageal adenocarcinoma. A large population-based cohort study from Sweden of GERD patients found no protective effect for surgery [101]. The standardized incidence ratio of esophageal adenocarcinoma in the surgically treated group was 14.1 (95% CI 8.0–22.8) compared to 6.3 (95% CI 4.5–8.7) in the medically treated group. A VA cohort study also found no attenuation of the risk for developing esophageal adenocarcinoma in surgically treated compared to medically treated GERD patients (0.072%.year vs. 0.04% /year) [102].

Similar findings are seen in Barrett's esophagus patients. A meta-analysis of surgical versus medical therapy of Barrett's esophagus found no difference in the risk of esophageal adenocarcinoma between the two groups [103]. A subsequent systematic review by Chang et al. found no difference in the incidence of esophageal adenocarcinoma in medically vs. surgically treated patients with Barrett's esophagus, and that any evidence suggesting otherwise was driven by uncontrolled case series [104]. Thus, the best available evidence suggests that antireflux surgery does not decrease cancer risk in GERD or Barrett's esophagus patients.

NSAIDs and Aspirin

Multiple observational studies suggest that NSAIDs, including aspirin, may play a protective role against esophageal adenocarcinoma by inhibiting the cycloxygenase 1 and 2 enzymes, which regulate PGE_2 production. [105] A recent pooled analysis of 6 population based studies in the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) group examined the association between NSAID use and risk of esophageal adenocarcinoma [106]. They found that when compared to nonusers, NSAID users had a reduced risk of esophageal adenocarcinoma (OR 0.68; 95% CI 0.56–0.83). Almost identical effects were seen for both aspirin and non-aspirin NSAIDs. Furthermore, higher frequency and longer duration use were associated with a decreased risk of cancer in this study. However, this study did not specifically examine patients with Barrett's esophagus. An earlier cohort study from the Seattle Barrett's esophagus project found that regular users of aspirin or NSAIDs had a lower incidence of esophageal adenocarcinoma than nonusers [107]. Two recent observational studies have also addressed this issue. In a cohort study of 570 Barrett's esophagus patients from the Netherlands, NSAID use was associated with a decreased risk for progression to high-grade dysplasia/adenocarcinoma (hazard ration 0.47; 95% CI 0.24–0.93), although no effect was seen for low dose aspirin [108]. Finally, a nested case control study from the VA data base found that filled prescriptions for NSAIDs or aspirin in Barrett's esophagus patients was associated with a decreased risk of developing esophageal adenocarcinoma (incidence density ratio 0.64; 95% CI 0.42–0.97) [109].

Despite the consistent evidence from observational studies, limited clinical trial data are available to address this issue. A single clinical trial has examined the effect of celecoxib at a dose of 200 mg twice daily given for 48 weeks in patients with low-grade and high-grade dysplasia on change in proportion of biopsy samples with dysplasia between patients treated with celecoxib compared to those treated with a placebo [110]. No differences were found between the two groups. A clinical trial of esomeprazole in conjunction with low and high dose aspirin found that only high dose aspirin (325 mg daily) was able to decrease mucosal PGE_2 content in mucosal biopsies from Barrett's esophagus patients [111]. The results of a large randomized clinical trial in the United Kingdom (ASPECT) are awaited to see if chemoprevention with aspirin in conjunction with a proton pump inhibitor is a useful clinical strategy in Barrett's esophagus patients. Currently, it is premature to use aspirin for chemoprevention in Barrett's esophagus patients.

Statins

Statins are a class of drugs well known for cholesterol lowering effects which has led to extensive use for primary and secondary prevention of cardiac disease. Statins also have anitproliferative, proapoptotic, antiangiogenesis and immunomodulatory effects which could provide chemoprevention potential in Barrett's esophagus [112]. A case control study from the Houston VA suggested that statin use was associated with a reduced risk of Barrett's esophagus [113]. Furthermore, a population based study using the UK General Practice Research Database found that regular statin use was associated with a 42% decrease in the risk of esophageal adenocarcinoma (OR 0.58; 95% CI 0.39–0.87) [114]. This observation was also notable for a significant dose-response and duration-response effect. However, neither of these studies addressed the specific chemoprevention effect of statins in

individuals with known Barrett's esophagus. This was, however, addressed in a recent systematic review and meta-analysis of five studies of Barrett's patients [112]. This demonstrated a 43% reduction in the risk of progressing to the combined endpoints of high-grade dysplasia/adenocarcinoma after adjustment for potential confounders (OR 0.57; 95% CI 0-44–0.75). Taken together, these data suggest the potential for statins in chemoprevention of Barrett's esophagus, but this has not yet been addressed in clinical trials.

Drugs That Relax the Lower Esophageal Sphincter

Given that medications that relax the lower esophageal sphincter may increase the propensity to gastroesophageal reflux disease, it has been hypothesized that drugs in this class may increase the risk for esophageal adenocarcinoma. However, a recent meta-analysis of case control studies found that only theophylline (OR 1.55; 95% CI 1.05–2.28) and anticholinergics (OR 1.66; 95% CI 1.13–2.44) were associated with an increased risk of esophageal adenocarcinoma [115]. No other classes of drugs impacted the risk of esophageal adenocarcinoma and these findings are subject to all of the limitations of case control studies. Furthermore, these findings did not break out the effect of this class of drugs on risk of adenocarcinoma in Barrett's esophagus patients.

Biphosphonates

A meta-analysis has demonstrated an association between exposure to biphosphonates and risk of esophageal carcinoma (OR 1.74; 95% CI 1.19–2.55) although no mention is made of the type of esophageal carcinoma [116]. However, a VA case control study examined the association of oral biphosphonate exposure and risk of esophageal adenocarcinoma in Barrett's esophagus patients and found no increase in risk [117].

Summary

The increase in the incidence of esophageal adenocarcinoma is alarming. It is clear that Barrett's esophagus is the single best identified risk factor for the development of esophageal adenocarcinoma, yet the overwhelming majority of Barrett's patients will never develop this cancer. There are clear epidemiologic factors that patients should be informed of to potentially decrease risk including smoking cessation, a diet high in fruits and vegetables, weight loss, and routine use of proton pump inhibitors. Endoscopists need to make certain to carefully examine the 12 to 6 o'clock hemisphere of the Barrett's segment and to be especially mindful of increasing risk with increasing segment length and decreasing risk with increasing number of negative endoscopies. It is critical that all patients diagnosed with low-grade dysplasia have their slides reviewed by pathologists with expertise in Barrett's esophagus given the clear importance of expert confirmation. While biomarkers of increased risk are not yet ready for clinical application, the pace of discovery has accelerated and the need to identify biomarker panels has clearly been embraced. In the future, risk stratification of patients will likely use a multiplex profile of epidemiologic, histologic, endoscopic and molecular markers of increased risk to meet the promise of personalized medicine for Barrett's esophagus patients

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Practice Points

- The risk of progression to high-grade dysplasia/adenocarcinoma is low in the overwhelming majority of Barrett's esophagus patients
- At the time of endoscopy careful attention to the 12 to 6 o'clock hemisphere of the Barrett's segment is critical given the propensity for lesions to develop at that location
- The correct diagnosis of low-grade dysplasia requires expertise in GI pathology and has implications for progression. Most community diagnosis of low grade dysplasia is downgraded by expert GI pathologists
- Risk of progression is increased in smokers and may be increased in obese patients. Counseling for healthy lifestyle including tobacco avoidance, weight loss and a diet high in fruits and vegetables may have practical risk modification implications
- No putative molecular biomarkers of increased risk are ready for clinical application

Research Agenda

- Determine why the 12 to 6 o'clock hemisphere of the Barrett's segment is at increased risk for progression
- Develop computer assisted tools to standardize the interpretation of dysplasia
- Increase utilization of pathology slide scanning to facilitate access to expert pathologists
- Utilize the power of multicenter collaborations to identify and validate both histologic and blood-based biomarkers of increased risk
- Develop a risk stratification score to identify progressors to high-grade dysplasia/adenocarcinoma
- Identify what factors in obese patients promote progression to high-grade dysplasia/adenocarcinoma
- Commence chemoprevention trials with statins