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Predictors of Progression to High-Grade Dysplasia or Adenocarcinoma in Barrett's Esophagus

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Article Synopsis

The prevalence of esophageal adenocarcinoma is increasing dramatically. Barrett's esophagus remains the most well established risk factor for the development of esophageal adenocarcinoma. There are multiple clinical, endoscopic, and pathologic factors that increase the risk of neoplastic progression to high-grade dysplasia or esophageal adenocarcinoma in Barrett's esophagus. This article will review both risk and protective factors for neoplastic progression in patients with Barrett's esophagus.

Keywords

Barrett's esophagus; esophageal adenocarcinoma; dysplasia; risk factors; neoplastic progression

Introduction

The incidence of esophageal adenocarcinoma, a disease characterized by a high mortality and an estimated 20% five year survival, has increased dramatically in recent decades.[1,2] Barrett's esophagus is the most well established risk factor for the development of esophageal adenocarcinoma.[3] The annual risk of progression from Barrett's esophagus to adenocarcinoma is approximately 0.33% per year.[4] When including both esophageal adenocarcinoma and high-grade dysplasia as a combined endpoint of progression, the incidence rate is approximately 0.9–1.0% per.[5,6] Despite this neoplastic risk, the vast majority of Barrett's esophagus patients will die of causes other than esophageal adenocarcinoma.[7] Currently, it remains unclear which Barrett's esophagus patients will progress on to neoplasia, a fact that makes current surveillance programs problematic. This chapter will examine the endoscopic, pathologic and epidemiologic risk factors for neoplastic progression in Barrett's esophagus [Table 1].

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Endoscopic Risk Factors

Segment Length

While esophageal adenocarcinoma can develop in both short and long segments of Barrett's esophagus (traditionally defined as > 3cm), our understanding of the relationship between segment length and the risk of progression has evolved in recent years. [8] A 2012 meta-analysis found a lower annual incidence of esophageal adenocarcinoma in short segment Barrett's patients (< 3cm), than in the overall Barrett's population (0.19% vs. 0.33% per year).[4] Work from the Northern Ireland Barrett's esophagus register demonstrated an increased risk for progression to adenocarcinoma/high-grade dysplasia in long segment Barrett's (HR 7.1; 95% CI 1.74–29.04).[9] A recent case control study from Berlin also found an association of segment length with progression to adenocarcinoma/high-grade dysplasia.[10] Patients with long segment Barrett's esophagus had an increased risk of progression when compared to short segment Barrett's esophagus. (OR 2.69; 95% CI 1.48–4.88).

Newer studies have examined the relationship of segment length and risk of progression not just as a binary variable of long versus short, but rather as a continuous variable. In a large multicenter study, increasing segment length was an independent risk factor for neoplastic progression in patients with non-dysplastic Barrett's esophagus.[11] Patients who progressed to adenocarcinoma/high-grade dysplasia had a longer Barrett's segment (6.1 cm vs. 3.5 cm). Perhaps more importantly, the risk for neoplastic progression increased by 28% for every 1 cm increase in length of the Barrett's segment. Similarly, a Netherlands cohort study of over 700 patients with nondysplastic Barrett's esophagus or low-grade dysplasia confirmed the concept of increasing risk with increasing segment length. [12] The relative risk of neoplastic progression to adenocarcinoma/high-grade dysplasia was 1.11 (95% CI 1.01–1.2) per 1 cm increase in segment length. The recently completed SURF trial of radiofrequency ablation in Barrett's esophagus patients with low-grade dysplasia also found segment length to be an independent predictor of neoplastic progression in the surveillance arm of the study (OR 1.35 per cm, 95% CI 1.04–1.76).[13]

However, progression does still occur in shorter segments of Barrett's esophagus and a population-based study of over 8,000 patients in Ireland found no relationship between segment length and risk of progression.[14] Taken together, it would appear that longer segments of Barrett's esophagus are associated with an increased risk of progression to adenocarcinoma/high-grade dysplasia.

Hiatal Hernia

Hiatal hernia is a well-documented risk factor for the development of Barrett's esophagus.[15] In addition, some data suggest that a larger hiatal hernia size may increase the risk of neoplastic progression in Barrett's esophagus (OR 1.20 per cm hiatal hernia, 95% CI 1.04–1.39).[16] In a cohort study of 550 patients from the Kansas City VA, a large hiatal hernia (> 6 cm) was associated with an increased risk of neoplastic progression to adenocarcinoma/high-grade dysplasia when compared to patients with no hiatal hernia.[17] However, other studies find contrary results. A 2013 case-control study of approximately 600 patients

demonstrated that while the presence of hiatal hernia increased the risk for Barrett's esophagus, it did not increase the risk of neoplastic progression to adenocarcinoma/high-grade dysplasia.[10] Overall, it is unclear if hiatal hernia size is an independent risk factor for neoplastic progression in Barrett's esophagus.

Mucosal Abnormalities

A number of mucosal changes within the Barrett's segment are associated with an increased risk of progression to adenocarcinoma/high-grade dysplasia. Erosive **e**sophagitis has emerged as a potential risk factor for esophageal adenocarcinoma. A Dutch multicenter cohort study found an increased risk of progression to adenocarcinoma/high-grade dysplasia in Barrett's esophagus patients with esophagitis at baseline endoscopy (RR 3.5; 95% CI 1.3–9.5).[12] A Danish cohort study also found an increased standardized incidence ratio for esophageal adenocarcinoma among Barrett's esophagus patients with erosive esophagitis when compared to the general population (SIR 5.2; 95% CI 4.6–5.8).[18]

Ulceration within a Barrett's segment is also associated with an increased risk of neoplastic progression to adenocarcinoma/high-grade dysplasia. The above mentioned population based case-control study from Northern Ireland also found that patients with ulceration in the Barrett's segment at diagnosis, but not elsewhere in the esophagus, were more likely to progress to cancer or high-grade dysplasia than those without (HR 1.72; 95% CI 1.08–2.76).[9]

It is unclear if mucosal abnormalities such as erosive esophagitis or ulceration are in fact risk factors for progression or rather markers of prevalent adenocarcinoma/high-grade dysplasia as shown by current endoscopic eradication studies. Overall, it appears that mucosal abnormalities are associated with an increased risk of neoplastic progression in patients with Barrett's esophagus.

Circumferential Position

Early adenocarcinoma and high-grade dysplasia appear to have a predilection to develop in the right hemisphere of the esophagus.[19,20,21,22] Work from our group found that 85% of patients with adenocarcinoma/high-grade dysplasia referred for endoscopic management had these abnormalities located in the right hemisphere of the esophagus, predominantly in the area between 12 and 3 o'clock.[20] Similar findings were described in an Australian study, where over 50% of advanced lesions were found between 2 and 5 o'clock.[19] These studies are both in line with previous data demonstrating a preference for esophagitis to be found on the right hemisphere of the esophagus, suggesting a potential inflammatory mechanism to explain this observation.[23]

Pathologic Risk Factors

Intestinal Metaplasia versus Columnar Metaplasia

Currently, there is some disagreement among GI societies as to the definition of Barrett's esophagus. The major difference is whether or not the presence of intestinal metaplasia within the columnar lined esophagus is required for the diagnosis. Early data from

Scandinavia suggested the risk of progression to adenocarcinoma/high-grade dysplasia in the columnar lined esophagus was equivalent in patients with and without intestinal metaplasia. [24] However, multiple subsequent studies have demonstrated an increased risk of neoplastic progression in patients with intestinal metaplasia.

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. 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% per year vs. 0.07% per year; HR 3.54; 95% CI 2.09–6.0).

An observational study from the University of Chicago demonstrated that in 379 patients with a columnar lined esophagus without goblet cells on pathology, none progressed to adenocarcinoma/high-grade dysplasia during an average follow up of five years.[25] In contrast, 8.9% of patients with a columnar lined esophagus with goblet cells progressed to adenocarcinoma/high-grade dysplasia.

While there are not yet enough data to definitively state that intestinal metaplasia is a necessary component to the neoplastic risk of Barrett's esophagus, it does appear there is an increased risk of neoplastic progression compared to those without intestinal metaplasia.

Dysplasia

Dysplasia remains the single best marker for risk of progression in Barrett's esophagus. For patients with nondysplastic Barrett's esophagus the risk of neoplastic progression remains low. A 2012 meta-analysis found an incidence of esophageal adenocarcinoma of 1 case per 300 patient years in patients with nondysplastic Barrett's epithelium.[4] Two large, population-based studies not included in this meta-analysis also support these findings. A cohort study from Denmark evaluated the incidence of adenocarcinoma in over 11,000 patients with Barrett's esophagus.[26] The incidence rate was 1 case per 1000 person-years in patients with nondysplastic Barrett's over a median follow-up of 5.2 years. A cohort study from Ireland also had similar low rates of progression in patients with nondysplastic Barrett's esophagus, 0.17% per year.[14]

Recent work of a large United States multicenter consortium evaluated the importance of repeated biopsy proven nondysplastic Barrett's esophagus during surveillance endoscopy.[27] Patients were found to have a lower annual risk of progressing to either adenocarcinoma or high-grade dysplasia if they had multiple endoscopies documenting persistent nondysplastic Barrett's esophagus (0.34% in patients with 5 endoscopies vs. 0.75% in patients with 1 endoscopy). Overall, the neoplastic progression risk in non-dysplastic Barrett's esophagus appears to be very low.

Low-Grade Dysplasia

Low-grade dysplasia has been extensively studied as a risk factor for progression with highly variable results. This is likely due to the interobserver variability in the diagnosis of this lesion that makes diagnosis so problematic.[28] A large, multicenter outcomes study from

the United States investigated 210 patients with low-grade dysplasia to determine the rate of neoplastic progression.[29] There was a 1.83% per year incidence of progression to adenocarcinoma/high-grade dysplasia in this cohort. While the progression to esophageal adenocarcinoma was 0.18% per year if only one of three pathologists confirmed the diagnosis of low-grade dysplasia, the incidence rate increased to 0.39% per year if all three pathologists agreed. Critics of the study point out that there was a low interobserver agreement among the two expert pathologists (Kappa 0.14).[30] In addition, approximately 1 in 4 of the original low-grade dysplasia samples were subsequently upgraded to high-grade dysplasia in this study, further calling into question the results. In a landmark study from the Netherlands, 293 patients with low-grade dysplasia were assessed. [31] Biopsy samples were confirmed by two independent pathologists with extensive experience with dysplasia within Barrett's esophagus from a panel of six pathologists. Upon expert review, almost three-quarters of patients were downstaged to either non-dysplastic Barrett's esophagus or indefinite for dysplasia. In the patients that were confirmed to have low-grade dysplasia on expert review, the risk of neoplastic progression was 9.1% per patient-year with a median follow up of over 3 years. The patients with either non-dysplastic Barrett's esophagus or indefinite for dysplasia had a significantly lower risk of neoplastic progression (0.6%–0.9% per patient-year).

These results are similar to previous reports from the AMC group in the Netherlands which put the risk of progression to adenocarcinoma/high-grade dysplasia at 13.4% per year in patients with confirmed low-grade dysplasia. [32] In the surveillance arm of the SURF study examining RFA for patients with confirmed low-grade dysplasia, 26.5% of patients progressed to adenocarcinoma/high-grade dysplasia during a median follow up of 30 months.[13] Similarly, a high progression rate was seen in the original clinical trial of radiofrequency ablation for low grade dysplasia 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.[33] Finally, in a population-based, cohort study from Denmark the standardized incidence ratio for esophageal adenocarcinoma in patients with low-grade dysplasia was 5.1 per 1000 patient years (95% CI 3.0–8.6).[26]

These rates are considerably higher than those described in the most recent meta-analysis, which found a rate of progression from low-grade dysplasia to adenocarcinoma of 0.54% per year (95% CI 0.32%–0.76%) and to adenocarcinoma/high-grade dysplasia of 1.73% per year (95% CI 0.99%–2.47%).[34] However, the authors of the meta-analysis reported significant heterogeneity between the studies and acknowledged that rates of neoplastic progression were higher in the studies when expert pathologists confirmed low-grade dysplasia.

In summary low-grade dysplasia is a challenging lesion to diagnose but appears to be a risk factor for neoplastic progression when confirmed by multiple pathologists with expertise in GI pathology.

Biomarkers of Increased Risk

Given the low rate of neoplastic progression in Barrett's esophagus and the inherent limitations of current endoscopic surveillance programs, there has long been interest in

identifying biomarkers of increased risk in Barrett's patients. While multiple biomarkers have been studied, a select few will be discussed here.

One of the best studied biomarkers is the tumor suppressor gene p53. In Barrett's esophagus patients loss of heterozygosity (LOH) for p53 (RR 16; CI 6.2–39.0) as well overexpression of p53 (OR 8.42; 95% CI 2.37–30.0) are associated with progression to adenocarcinoma/high-grade dysplasia. [35, 36] A nested case-control study demonstrated similar results; loss of p53 (RR 14.0; 95% CI 5.3–37.2) and overexpression of p53 (RR 5.6, 95% CI 3.1–10.3) were associated with a higher risk of progression to adenocarcinoma/high-grade dysplasia. [37] In addition, biopsies with both low-grade dysplasia and aberrant p53 expression appear to have higher rates of neoplastic progression.[37,38]

Other tumor suppressor genes (i.e. p16), cell cycle related proteins (i.e. Cyclin-A, Cyclin-D1), growth factor receptors (i.e. EGFR), and flow cytometry for DNA abnormalities (i.e. aneuploidy and tetraploidy) have been studied at length. Despite some promising results, none of these potential biomarkers are appropriate for clinical practice at this time.

Considerable efforts have also gone into developing panels of these biomarkers that may assist in the identification of patients at increased risk for progression. A combination of 17p LOH, 9p LOH, and aneuploidy/tetraploidy was found to have a relative risk of 38.7 (95% CI 10.8–138.5) for neoplastic progression and a 10-year cumulative incidence of adenocarcinoma of nearly 80%.[39] In patients with none of these biomarkers, only 12% progressed to adenocarcinoma. A panel of methylation biomarkers for eight different genes (including p16, RUNX3, HPP1) had sensitivity for detection of progression of less than 50%.[40] The panel of just p16, RUNX3, and HPP1 has also been studied.[41,42] Finally, a nested case-control study from the Northern Ireland Barrett's esophagus registery evaluated a combination of biomarkers and anatomic pathology.[43] The panel of low-grade dysplasia, DNA aneuploidy/tetraploidy detected by image cytometry and *Asperigillus oryzae* lectin demonstrated an increasing odds ratio for each component of the panel that was present (OR 3.73 per biomarker, 95% CI 2.43–5.79).

Biomarkers and biomarker panels may one day assist in determining who is likely to progress to adenocarcinoma/high-grade dysplasia. At the present time there are multiple limitations that need to be addressed before these biomarkers are incorporated into daily clinical practice.

Epidemiologic Risk Factors

Age

The incidence of esophageal adenocarcinoma increases with age, regardless of sex or race. [44, 45] Between the ages of 50–59, white males have an esophageal adenocarcinoma incidence rate of 8.44 per 100,000 person-years (95% CI 8.05–8.85) which increases to 26.31 per 100,000 person-years (95% CI 25.27–27.38) between ages 70–79.[44] The most recent publication of the Surveillance, Epidemiology, and End Results (SEER) registry reaffirms the increase in esophageal adenocarcinoma with age.[45] Starting at age 40 and

continuing until 79, the incidence rates of esophageal adenocarcinoma continues to rise. Beyond age 80, the incidence rate appears to level off in most groups.

In patients with Barrett's esophagus, most studies suggest an increase in the risk of neoplastic progression with increasing age. A Dutch population-based study found that the risk of progression increased with increasing age at diagnosis, with a marked increase in risk after the age of 75 (HR 12; 95% CI 8.0–18).[46] Similarly in the Danish Barrett's esophagus population-based study, the incidence of adenocarcinoma/high-grade dysplasia increased progressively with age and was greatest in patients over age 70 years of age.[26]

Race

White race is a known risk factor for esophageal adenocarcinoma.[47,48,49] There is a four-fold increase in the incidence rate of esophageal adenocarcinoma in white males compared to black males and double that of Hispanic males.[50] Similar patterns are also seen in women, although with lower incidence rates in all races. While it is unclear why this difference exists, a recent study in Barrett's esophagus patients found a higher rate of dysplasia (7% vs 0%) and of long segment Barrett's esophagus (26% vs 12%) at the time of endoscopy in Caucasians compared to black patients.[51] As both dysplasia and long segment Barrett's esophagus are independent risk factors for esophageal adenocarcinoma, this may be an avenue worthy of further study.

Sex

Male gender is another well-documented risk factor for esophageal adenocarcinoma with a 6–10 fold risk increase compared to that of women.[45, 52] However, both genders have seen a dramatic increase in the number of esophageal cancers. Newer data from the SEER registry have demonstrated the largest gender difference exists largely in the earlier age cancers (i.e. younger than 65 years).[45] Furthermore, the age adjusted incidence rate in females over 80 continues to increase while the male rate plateaus. This difference may relate to estrogen exposure. Previously, estrogen exposure has been suggested as a protective mechanism against both gastric and colon cancers, and has been demonstrated to reduce apoptosis and cell growth in esophageal adenocarcinoma.[53,54,55] As women age, there is a significant decrease in estrogen, which may explain the delayed increase in esophageal adenocarcinoma incidence as seen in the SEER database data. Studies examining how risk factors with possible male predominance, including GERD, obesity, and tobacco, may affect neoplastic progression risk have not yet provided a clear mechanistic answer to this epidemiologic difference.[56] Among Barrett's esophagus patients, male gender is also a clearly recognized risk factor for progression to esophageal adenocarcinoma.[4,10,46]

Family History/Genetic Risk

Familial aggregation of Barrett's esophagus and esophageal adenocarcinoma has suggested a potential genetic component to these disease entities. Much of the work in this area has come from Chak et al. 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%).[57] On multivariate analysis, a positive family history for Barrett's esophagus,

adenocarcinoma of the esophagus, or esophagogastric junction was associated with an increased risk of developing these lesions when compared to patients with GERD alone (OR 12.23; 95% CI 3.34–44.76).

A subsequent segregation analysis by the same group found an incomplete autosomal dominant inheritance pattern for familial aggregations of Barrett's esophagus, esophageal adenocarcinoma, and gastroesophageal junction carcinoma. [58] Finally, 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.[59] Others have found an increased prevalence of Barrett's esophagus in first degree relatives of patients with adenocarcinoma.[60]

Lastly, examination of germline mutations in patients with Barrett's esophagus and esophageal adenocarcinoma has yielded interesting results. In a model-free linkage analysis comparing both concordant sibling pairs with Barrett's and esophageal adenocarcinoma and discordant sibling pairs, three genes were identified with significant mutations (MSR1, ASCC1, and CTHRC1).[61] MSR1 was associated with the presence of both Barrett's esophagus and esophageal adenocarcinoma. A genome-wide association study from the BEACON group of over 1500 cases of esophageal adenocarcinoma and 2300 cases of Barrett's esophagus found a high genetic correlation between both Barrett's and adenocarcinoma as well as multiple shared genes underlying the development of both.[62]

Taken together, these data suggests that there a genetic component to neoplastic progression in some Barrett's patients. More data are still needed to fully characterize this risk.

Tobacco

Tobacco use is a clear risk factor for the development of both Barrett's esophagus and esophageal adenocarcinoma.[63,64] A pooled analysis evaluating approximately 3,000 cases of either esophageal adenocarcinoma or esophagogastric junctional adenocarcinoma found an odds ratio of 1.67 (95% CI 1.04–2.67) for developing esophageal adenocarcinoma in patients with tobacco use, with a significant increase with increased number of pack-years smoking.[65] Current or prior tobacco use also increases the risk of neoplastic progression in patients with Barrett's esophagus.[66,67] A population based cohort from the Northern Ireland Barrett's esophagus registry demonstrated an increased risk of neoplastic progression to adenocarcinoma/high-grade dysplasia in current smokers as compared to non-smokers (HR 2.03, 95% CI 1.29–3.17).[66] Overall tobacco is an established risk factor for progression to esophageal adenocarcinoma.

Obesity

Obesity is a well-described risk factor for esophageal adenocarcinoma.[68,69] A 2013 meta-analysis of over 8000 cancers examined the relationship between body mass index (BMI) and esophageal and gastric cardia adenocarcinoma.[69] The relative risk for developing esophageal adenocarcinoma increased with an increasing BMI; the relative risk was 1.71 (95% CI 1.50–1.96) for a BMI 25–30 and 2.34 (95% CI 1.95–2.81) for a BMI > 30. An observational study from England showed a significant increase in esophageal

adenocarcinoma with a BMI >35 (HR 4.95), but only an upward trend at lower BMIs.[70] This corresponds to earlier data suggesting the largest risk was in patients with BMI > 35.[68] It would appear that male pattern central obesity is the key component of this risk, with a 2013 meta-analysis reporting an odds ratio of 2.51 (95% CI 1.56–4.04) for developing esophageal adenocarcinoma in patients with central adiposity.[71]

The impact of obesity and abdominal adiposity specifically on neoplastic progression of Barrett's esophagus to adenocarcinoma is a bit more unclear. A small cross-sectional analysis from Seattle's Barrett's esophagus project demonstrated an increasing risk of histologic and genetic abnormalities associated with high likelihood of neoplastic progression in patients with a predominantly abdominal fat distribution.[72] However, a recent cohort study of over 400 patients with Barrett's esophagus found no relation between higher waist-hip ratios and neoplastic progression to adenocarcinoma.[67] While the role in neoplastic progression in Barrett's esophagus is not fully known, it is clear that obesity and specifically abdominal adiposity are associated with an increased overall risk of esophageal adenocarcinoma.

The exact mechanism underlying this risk is not fully known, but may involve increased IGF-1, insulin resistance, and adipokines such as leptin. [73, 74, 75] These relationships are explored at length in a separate chapter.

Protective Factors

Medications

There is emerging evidence that statins may have a protective effect for multiple cancers, including esophageal adenocarcinoma. In vitro studies of statins have demonstrated multiple potential mechanisms for chemoprevention including antiproliferation, antiangiogenesis, and proapoptotic effects.[76, 77, 78] Two studies have demonstrated that regular statin use results in decreased malignant transformation from Barrett's esophagus to esophageal adenocarcinoma/high-grade dysplasia.[79,80] A cohort study from the United Kingdom found an inverse relationship between regular statin use of any dose (10+ months) and developing esophageal adenocarcinoma (OR 0.58, 95% CI 0.39–0.87).[81] The protective effect of statins appears to become more apparent with longer-term use. Overall, it appears that statins are protective against neoplastic progression.

NSAID medications have also been investigated as potential protective agents against neoplastic progression in Barrett's esophagus. In Barrett's esophagus, there is an increase in cyclooxygenase-2 (COX-2) expression as disease progresses from non-dysplastic Barrett's esophagus to adenocarcinoma/high-grade dysplasia.[82] As such, the effect of NSAIDs, including aspirin, on PGE-2 production via the COX-2 pathways may serve as a potential protective mechanism against neoplastic progression. A pooled analysis by the BEACON group of six studies totaling 1226 patients with esophageal adenocarcinoma and 1140 patients with esophagogastric junctional adenocarcinoma examined the impact of aspirin and/or NSAID use on development of these cancers.[83] 'Anytime-users' of NSAIDs or aspirin had reduced risk of esophageal adenocarcinoma compared to 'non-users' (OR 0.68; 95% CI 0.56–0.83). The odds ratio improved further with 'daily-use' for ten or more years

(OR 0.56; 95% CI 0.43–0.73) in patients. For aspirin, the overall odds ratio for developing esophageal adenocarcinoma in 'anytime-users' was 0.77 (95% CI 0.60–0.97).

Multiple studies have examined the impact of NSAID and/or aspirin use on neoplastic progression of Barrett's esophagus. Work from the Seattle Barrett's esophagus project found a decreased hazard ratio for progression to adenocarcinoma in current NSAID users (HR 0.32; 95% CI 0.14–0.70) over an average follow up of 65 months.[84] In addition, a multi-center, prospective cohort from the Netherlands showed a reduced risk of progression to cancer in Barrett's patients taking NSAIDs (HR 0.47, 95% CI 0.24–0.93).[85] This study showed an additive benefit when both NSAIDs and statins were used (HR 0.22, 95% CI 0.06–0.85). Finally, a meta-analysis found an overall reduced risk of adenocarcinoma/high-grade dysplasia among patients with Barrett's taking COX-inhibitors (RR 0.64, 95% CI 0.53–0.77) or aspirin (RR 0.63, 95% CI 0.43–0.94) reaffirming the protective effects of NSAIDs and aspirin against neoplastic progression.[86]

The seminal work by Lagergren et al. demonstrated a striking association between more frequent, more severe, and more persistent reflux symptoms and esophageal adenocarcinoma.[87] Thus it makes sense that the effect of acid suppression on neoplastic progression in Barrett's esophagus has been studied. Multiple small studies have suggested a reduced risk of neoplastic progression in Barrett's esophagus patients who use proton pump inhibitors.[79,88] Furthermore, a 2014 meta-analysis demonstrated an adjusted OR of 0.29 (95% CI 0.12–0.79) for neoplastic progression in patients with Barrett's esophagus taking proton pump inhibitors.[89] There was no benefit noted from histamine-2 antagonists. However, a recent Danish case-control study of 140 Barrett's esophagus patients found no benefit for PPI long-term users.[90] As such, it is still unclear if proton pump inhibitors themselves reduce the risk of neoplastic progression in patients with Barrett's esophagus, though there seems to be no role for histamine-2 antagonists.

Helicobacter pylori

As treatment and eradication rates of *H. pylori* have increased, the rates of esophageal adenocarcinoma have also increased prompting investigators to examine the potential relationship between the two observations. Multiple studies have demonstrated an inverse relationship between *H. pylori* infection and development of Barrett's esophagus.[91,92] These observations have also suggested a possible protective effect of *H. pylori* infection against development of esophageal adenocarcinoma. A recent meta-analysis of 13 studies, pooling 1145 esophageal cases with 3453 controls demonstrated a protective benefit of *H pylori* against developing adenocarcinoma (OR 0.57, 95% CI 0.44–0.73).[93] This study did not specifically address patients with Barrett's esophagus.

Overall it does appear that *H pylori* infection has some protective benefit against developing both Barrett's esophagus and esophageal adenocarcinoma. However the effect of neoplastic progression in patients with Barrett's has yet to be studied.

Diet

High consumption of fruit and vegetables appears to decrease the risk of adenocarcinoma in Barrett's esophagus patients.[10,94] An NIH study examined dietary patterns in the general population, finding a decreased risk for developing esophageal adenocarcinoma in patients reporting a positive Health Eating Index, which puts a premium on vegetables/fruits (HR 0.75, 95% CI 0.57–0.98). [95] On the other hand, increased meat consumption, particularly processed red meats, appears to increase the risk of esophageal adenocarcinoma. [96, 97, 98] These studies did not address neoplastic progression in patients with Barrett's esophagus.

Multiple different vitamins and supplements have been studied as well. The most consistent data, though limited, suggests fiber may play a protective role against adenocarcinoma.[99,100] Mixed data exist regarding the potential benefit of using a daily multivitamin, folate, or vitamin B12.[100, 101,102,103,104] Overall, a healthy diet including significant consumption of fruits and vegetables likely decreases the risk of developing esophageal adenocarcinoma.

Conclusions

As the prevalence of esophageal adenocarcinoma increases, research has discovered epidemiologic, endoscopic, and pathologic factors that may help determine risk for neoplastic progression. It is hoped that algorithms can be developed to risk stratify patients in the future to tailor optimal therapy and intervention to prevent the development of adenocarcinoma.

References

1. Lepage C, Drouillard A, Jouve JL, et al. Epidemiology and risk factors for oesophageal adenocarcinoma. Dig Liver Dis. 2013; 45:625–629. [PubMed: 23453359]
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. Lancet. 2013; 381:400–412. [PubMed: 23374478]
3. Verbeek RE, Leender M, ten Kate FJW, et al. Surveillance of Barrett's esophagus and mortality from esophageal adenocarcinoma: a population-based cohort study. Am J Gastroenterol. 2014; 109:1215–1222. [PubMed: 24980881]
4. Desai TK, Krishnan K, Samala, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut. 2012; 61:970–976. [PubMed: 21997553]
5. Yousef F, Cardwell C, Cantwell MM, et al. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol. 2008; 168:237–249. [PubMed: 18550563]
6. Sikkema M, de Jonge PJ, Steyerberg EW, et al. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus; a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2010; 8:235–244. [PubMed: 19850156]
7. Milind R, Attwood SE. Natural history of Barrett's esophagus. World J Gastroenterol. 2012; 18(27): 3483–3491. [PubMed: 22826612]
8. Gatenby P, Caygill C, Wall C, et al. Lifetime risk of esophageal adenocarcinoma in patients with Barrett's esophagus. World J Gastroenterol. 2014; 20(28):9611–9617. [PubMed: 25071359]
9. Coleman HG, Bhat SK, Murray LJ, et al. Symptoms and endoscopic features at Barrett's esophagus diagnosis: implications for neoplastic progression risk. Am J Gastroenterol. 2014; 109:527–534. [PubMed: 24589668]
10. Pohl H, Wrobel K, Bojarski C, et al. Risk factors in the development of esophageal adenocarcinoma. Am J Gastroenterol. 2013; 108:200–207. [PubMed: 23247577]

11. Anaparthy R, Gaddam S, Kanakadandi V, et al. Association between length of Barrett's esophagus and risk of high-grade dysplasia or adenocarcinoma in patients without dysplasia. Clin Gastroenterol Hepatol. 2013; 11:1430–1436. [PubMed: 23707463]
12. Sikkema M, Looman CWN, Steyerberg EW, et al. Predictors of neoplastic progression in patients with Barrett's esophagus: a prospective cohort study. Am J Gastroenterol. 2011; 106:1231–1238. [PubMed: 21577245]
13. Phoa KN, van Vilsteren FGI, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia. JAMA. 2014; 311(12): 1209–1217. [PubMed: 24668102]
14. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: Results form a large population based study. J Natl Cancer Inst. 2011; 103:1049–1057. [PubMed: 21680910]
15. Andrici J, Tio M, Cox MR, et al. Hiatal hernia and the risk of Barrett's esophagus. J Gastroenterol Hepatol. 2013; 28:415–431. [PubMed: 22694245]
16. Avidan B, Sonnenberg A, Schnell TG, et al. Hiatal hernia size, Barrett's length, and severity of acid reflux are all risk factors for esophageal adenocarcinoma. Am J Gastroenterol. 2002; 97:1930–1936. [PubMed: 12190156]
17. Weston AP, Sharma P, Mathur S, et al. Risk stratification of Barrett's esophagus: Updated prospective multivariate analysis. Am J Gastroenterol. 2004; 99:1657–1666. [PubMed: 15330898]
18. Erichsen R, Robertson D, Farkas DK, et al. Erosive reflux disease increases risk for esophageal adenocarcinoma, compared with nonerosive reflux. Clin Gastroenterol Hepatol. 2012; 10:475–480. [PubMed: 22245963]
19. Kariyawasam VC, Bourke MJ, Hourigan LF, et al. Circumferential location predicts the risk of high-grade dysplasia and early adenocarcinoma in short-segment Barrett's esophagus. Gastrointest Endosc. 2012; 75:938–944. [PubMed: 22381529]
20. Enestvedt BK, Lugo R, Guarner-Argente C, et al. Location, location, location: does early cancer in Barrett's esophagus have a preference. Gastrointest Endosc. 2013; 78:462–467. [PubMed: 23622975]
21. Pech O, Gossner L, Manner H, et al. Prospective evaluation of the macroscopic types and location of early Barrett's neoplasia in 380 lesions. Endoscopy. 2007; 39:588–593. [PubMed: 17611912]
22. Cassani L, Sumner E, Slaughter JC, et al. Directional distribution of neoplasia in Barrett's esophagus is not influenced by distance from the gastroesophageal junction. Gastrointest Endosc. 2013; 77:877–882. [PubMed: 23528657]
23. Edebo A, Vieth M, Tam W, et al. Circumferential and axial distribution of esophageal mucosal damage in reflux disease. Diseases of the Esophagus. 2007; 20:232–238. [PubMed: 17509120]
24. Gatenby PA, Ramus JR, Caygill CP, et al. Relevance of the detection of intestinal metaplasia in non-dysplastic columnar-lined oesophagus. Scand J Gastroenterol. 2008; 43:524–530. [PubMed: 18415743]
25. Westerhoff M, Hovan L, Lee C, et al. Effects of dropping the requirement for goblet cells from the diagnosis of Barrett's esophagus. Clin Gastroenterol Hepatol. 2012; 10:1232–1236. [PubMed: 22642957]
26. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011; 365:1375–1383. [PubMed: 21995385]
27. Gaddam S, Singh M, Gokulakrishnan B, et al. Persistence of nondysplastic Barrett's esophagus identifies patients at lower risk for esophageal adenocarcinoma: results from a large multicenter cohort. Gastroenterology. 2013; 145:548–553. [PubMed: 23714382]
28. Montgomery E, Broner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol. 2001; 32:368–378. [PubMed: 11331953]
29. Wani S, Falk GW, Post J, et al. Risk Factors for progression of low-grade dysplasia in patients with Barrett's esophagus. Gastroenterology. 2011; 141:1179–1186. [PubMed: 21723218]
30. Bergman J, Vieth M. Let's not jump to conclusions regarding low-grade dysplasia in Barrett's esophagus. Gastroenterology. 2012; 142(5):e18–19. [PubMed: 22449581]

31. Duits L, Phoa KN, Curvers WL, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. Published online first: July 17, 2014.
32. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-Grade dysplasia in Barrett's esophagus: overdiagnosed and underused. Am J Gastroenterol. 2010; 15:1523–1530. [PubMed: 20461069]
33. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009; 360:2277–2288. [PubMed: 19474425]
34. Singh S, Manickmam P, Amin AV, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. Gastrointest Endosc. 2014; 79:897–909. [PubMed: 24556051]
35. Reid BJ, Prevo LJ, Galipeau PC, et al. Predictors of progression in Barrett's esophagus II: baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk for neoplastic progression. Am J Gastroenterol. 2001; 96:2839–2848. [PubMed: 11693316]
36. Murray L, Sedo A, Scott M, et al. TP53 and progression from Barrett's metaplasia to oesophageal adenocarcinoma in a UK population cohort. Gut. 2006; 55:1390–1397. [PubMed: 16682429]
37. Kastelein F, Biermann K, Steyerberg EW, et al. Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus. Gut. 2013; 62:1676–1683. [PubMed: 23256952]
38. Kaye PV, Haider SA, Ilyas M, et al. Barrett's dysplasia and the Vienna classification: reproducibility, prediction of progression and impact of consensus reporting and p53 immunohistochemistry. Histopathology. 2009; 54(6):699–712. [PubMed: 19438745]
39. Galipeau PC, Li X, Blount PL, et al. NSAIDs modulate cdkn2a, tp53, and DNA content risk for progression to esophageal adenocarcinoma. PLoS Med. 2007; 4(2):e67. [PubMed: 17326708]
40. Jin Z, Cheng Y, Gu W, et al. A multi-center, double-blinded validation study of methylation biomarkers for progression prediction in Barrett's esophagus. Cancer Res. 2009; 69:4112–4115. [PubMed: 19435894]
41. Sato F, Jin Z, Schulmann K, et al. Three-tiered risk stratification model to predict progression in Barrett's esophagus using epigenetic and clinical features. PLoS ONE. 2008; 101:1193–1199.
42. Schulmann K, Sterian A, Berki A, et al. Inactivation of p16, RUNX3, and HPP1 occurs early in Barrett's associated neoplastic progression and predicts progression risk. Oncogene. 2005; 24:4138–4148. [PubMed: 15824739]
43. Bird-Lieberman EL, Dunn JM, Coleman HG, et al. Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus. Gastroenterology. 2012; 143:927–935. [PubMed: 22771507]
44. Nordenstedt H, El-Serag H. The influence of age, sex, and race on the incidence of esophageal cancer in the United States (1992–2006). Scand J Gastroenterol. 2011; 46:597–602. [PubMed: 21271900]
45. Mathieu LN, Kanark NF, Tsai HL, et al. Age and sex differences in the incidence of esophageal adenocarcinoma: results from the surveillance, epidemiology, and end results (SEER) registry (1973–2008). Diseases of the Esophagus. 2014; 27:757–763. [PubMed: 24118313]
46. de Jonge PJ, van Blankenstein M, Looman CW, et al. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. Gut. 2010; 59:1030–1036. [PubMed: 20639249]
47. Coupland VH, Lagergren J, Konfortion J, et al. Ethnicity in relation to incidence of oesophageal and gastric cancer in England. Br J Cancer. 2012; 107:1908–1914. [PubMed: 23059745]
48. Ashktorab H, Nouri Z, Nouraie M, et al. Esophageal carcinoma in African Americans: a five-decade experience. Dig Dis Sci. 2011; 56:3577–3582. [PubMed: 21847566]
49. Sadler GJ, Jothiamni D, Zanetta U, et al. The effect of ethnicity on the presentation and management of oesophageal and gastric cancers: a UK perspective. Eur J Gastroenterol Hepatol. 2009; 21:996–1000. [PubMed: 19352189]
50. Kubo A, Corley DA. Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. Am J Gastroenterol. 2004; 99:582–588. [PubMed: 15089886]
51. Khoury JE, Chisholm S, Jamal MM, et al. African Americans with Barrett's esophagus are less likely to have dysplasia at biopsy. Dig Dis Sci. 2012; 57:419–423. [PubMed: 21909989]

52. El-Serag HB, Mason AC, Petersen N, et al. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut. 2002; 50:368–372. [PubMed: 11839716]
53. Camargo MC, Goto Y, Zabaleta J, et al. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012; 21:20–38. [PubMed: 22028402]
54. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med. 2004; 350:991–1004. [PubMed: 14999111]
55. Sukocheva OA, Wee C, Ansar A, et al. Effect of estrogen on growth and apoptosis in esophageal adenocarcinoma cells. Dis Esophagus. 2012; 26 (6):628–635. [PubMed: 23163347]
56. Rutegard M, Nordenstedt H, Lu Y, et al. Sex-specific exposure prevalence of established risk factors for oesophageal adenocarcinoma. British J Cancer. 2010; 103:735–740.
57. Chak A, Lee T, Kinnard MF, et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. Gut. 2002; 51:323–328. [PubMed: 12171951]
58. Sun X, Elston R, Barnholtz-Sloan J, et al. A segregation analysis of Barrett's esophagus and associated adenocarcinomas. Cancer Epidemiol Biomarkers Prev. 2010; 19:666–674. [PubMed: 20200424]
59. Chak A, Chen Y, Vengoechea J, et al. Variation in age at cancer diagnosis in familial versus nonfamilial Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. 2012; 21:376–383. [PubMed: 22178570]
60. Juhasz A, Mittal SK, Lee TH, et al. Prevalence of Barrett esophagus in first-degree relatives of patients with esophageal adenocarcinoma. J Clin Gastroenterol. 2011; 45(10):867–871. [PubMed: 21617543]
61. Orloff M, Peterson C, He X, et al. Germline mutations in MSR1, ASCC1, and CTHRC1 in patients with Barrett esophagus and esophageal adenocarcinoma. JAMA. 2011; 206(4):410–419. [PubMed: 21791690]
62. Weronica E, Levine DM, D'Amato M, et al. Germline genetic contributions to risk for esophageal adenocarcinoma, Barrett's esophagus, and gastroesophageal reflux. J Natl Cancer Inst. 2013; 105:1711–1718. [PubMed: 24168968]
63. Cook MB, Shaheen NJ, Anderson LA, et al. Cigarette smoking increases risk of Barrett's Esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. Gastroenterology. 2012 Apr; 142(4):744–753. [PubMed: 22245667]
64. Tramacere I, La Vecchia C, Negri E. Tobacco smoking and esophageal and gastric cardia adenocarcinoma. Epidemiology. 2011; 22 (3):344–349. [PubMed: 21330928]
65. Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010; 102:1344–1353. [PubMed: 20716718]
66. Coleman HG, Bhat S, Johnston BT, et al. Tobacco smoking increases the risk of high-grade dysplasia and cancer among patients with Barrett's esophagus. Gastroenterology. 2012; 142:233–240. [PubMed: 22062359]
67. Hardikar S, Onstatd L, Blount PL, et al. The role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: A prospective study of Barrett's Esophagus. PLoS One. 2013 Jan.8(1):e52192. [PubMed: 23300966]
68. Abnet CC, Freedman ND, Hollenbeck AR, et al. A prospective study of BMI and risk of oesophgaeal and gastric adenocarcinoma. Euro J Cancer. 2008; 44:465–471.
69. Turati F, Tramacere I, La Vecchia C, et al. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Annals of Oncology. 2013; 24:609–617. [PubMed: 22898040]
70. Yates M, Cheong E, Luben R, et al. Body Mass Index, smoking, and alcohol and risks of Barrett's esophagus and esophageal adenocarcinoma: A UK prospective cohort study. Dig Dis Sci. 2014; 59:1552–1559. [PubMed: 24500448]
71. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013; 11:1399–1412. [PubMed: 23707461]

72. Vaughan TL, Kristal AR, Blount PL, et al. Nonsteroidal anti-inflammatory drug use, body mass index, and anthropometry in relation to genetic and flow cytometric abnormalities in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. 2002; 11:745–752. [PubMed: 12163328]
73. Doyle SL, Donohoe CL, Finn SP, et al. IGF-1 and its receptor in esophageal cancer: association with adenocarcinoma and visceral obesity. Am J Gastroenterol. 2012; 107:196–204. [PubMed: 22146489]
74. Alexandre L, Long E, Beales ILP. Pathophysiological mechanism linking obesity and esophageal adenocarcinoma. World J Gastrointest Pathophysiol. 2014; 5(4):534–549. [PubMed: 25400997]
75. Ogunwobi O, Mutungi G, Beales IL. Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cycloxygenase-2-dependent, prostatglandin-E2-mediated transactivation of the epidermal growth factor receptor and c-Jun NH2-terminal kinase activation. Endocrinology. 2006; 147:4505–4516. [PubMed: 16740977]
76. Ogunwobi OO, Beales Il. Statins inhibit proliferation and induce apoptosis in Barrett's esophageal adenocarcinoma cells. Am J Gastroenterol. 2008; 103:825–837. [PubMed: 18371146]
77. Sadaria MR, Reppert AE, Yu JA, et al. Statin therapy attenuates growth and malignant potential of human esophageal adenocarcinoma cells. J Thorac Cardiovasc Surg. 2011; 142:1152–1160. [PubMed: 22014341]
78. Konturek PC, Burnat G, Hahn EG. Inhibition of Barrett's adenocarcinoma cell growth by simvastatin: involvement of COX-2 and apoptosis-related proteins. J Physiol Pharmacol. 2007; 58 (Suppl 3):141–148. [PubMed: 17901590]
79. Nguyen DM, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Gastroenterology. 2010; 138:2260–2266. [PubMed: 20188100]
80. Beales IL, Vardi I, Dearman L. Regular Statin and aspirin use in patients with Barrett's oesophageal adenocarcinoma. Eur J Gastroenterol Hepatol. 2012; 24:917–923. [PubMed: 22569083]
81. Alexandre L, Clark AB, Bhutta HY, et al. Statin use is associated with reduced risk of histologic subtypes of esophageal cancer: A nested case-control analysis. Gastroenterology. 2014; 146:661–668. [PubMed: 24315828]
82. Morris CD, Armstrong GR, Bigley G, et al. Cyclooxygenase-2 expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. Am J Gastroenterol. 2001; 96:990–996. [PubMed: 11316217]
83. Liao LM, Vaughan TL, Corley DA, et al. Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junction in a pooled analysis. Gastroenterology. 2012; 142:442–452. [PubMed: 22108196]
84. Vaughan TL, Dong LM, Blount PL, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. Lancet Oncol. 2005; 6:945–952. [PubMed: 16321762]
85. Kastelein F, Spaander MCW, Biermann K, et al. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. Gastroenterology. 2011; 141:2000–2008. [PubMed: 21878200]
86. Zhang S, Zhang XQ, Ding XW, et al. Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a meta-analysis. Br J Cancer. 2014; 110:2378–2388. [PubMed: 24651385]
87. Lagergren J, Bergstrom R, Lindren A, et al. Symptomatic Gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. NEJM. 1999 Mar 18; 340(11):825–831. [PubMed: 10080844]
88. Kastelein F, Spaander MCW, Steyerberg EW, et al. Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2013; 11:382–388. [PubMed: 23200977]
89. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophgael adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 2014; 63(8):1229–1237. [PubMed: 24221456]

90. Hvid-Jensen F, Pedersen L, Funch-Jensen P, et al. Proton pump inhibitor use may not prevent high-grade dysplasia and oesophageal adenocarcinoma in Barrett's oesophagus: a nationwide study of 9883 patients. Aliment Pharmacol Ther. 2014; 39:984–991. [PubMed: 24617286]

91. Rubenstein JH, Inadomi JM, Scheiman J, et al. Association between *Helicobacter pylori* and Barrett's esophagus, erosive esophagitis, and gastroesophageal reflux symptoms. Clin Gastroenterol Hepatol. 2014; 12:239–245. [PubMed: 23988686]

92. Corley DA, Kubo A, Levin TR, et al. *Helicobacter pylori* infection and the risk of Barrett's oesophagus: a community-based study. Gut. 2007; 57:727–733. [PubMed: 17895354]

93. Nie S, Chen T, Yang X, et al. Association of *Helicobacter pylori* infection with esophageal adenocarcinoma and squamous cell carcinoma: a meta-analysis. Diseases of the Esophagus. 2014; 27:645–653. [PubMed: 24635571]

94. Steevens J, Schouten LJ, Goldbohm RA, et al. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands cohort study. Int J Cancer. 2011; 129:2681–2693. [PubMed: 21960262]

95. Li WQ, Park Y, Wu JW, et al. Index-based dietary patterns and risk of esophageal and gastric cancer in a large cohort study. Clin Gastroenterol Hepatol. 2013; 11:1130–1136. [PubMed: 23591281]

96. Zhu HC, Yang X, Xu LP, et al. Meat consumption in associated with esophageal cancer risk in a meat- and cancer-histological-type dependent manner. Dig Dis Sci. 2014; 59:664–673. [PubMed: 24395380]

97. Salehi M, Moradi-Lakeh M, Salehi MH, et al. Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta analysis. Nutrition Review. 2013; 71(5):257–267.

98. O'Doherty MG, Cantwell MM, Murray LJ, et al. Dietary fat and meat intakes and risk of reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Int J Cancer. 2011; 129:1493–1502. [PubMed: 21455992]

99. Coleman HG, Murray LJ, Hicks B, et al. Dietary Fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis. Nutrition Reviews. 2013; 71(7): 474–482. [PubMed: 23815145]

100. Mayne ST, Risch HA, Dubrow R, et al. Nutrient Intake and risk of subtypes of esophageal and gastric cancer. Cancer Epi Biomark Prev. 2001; 10:1055–1062.

101. Dong LM, Sanchez CA, Rabinovitch PS, et al. Dietary supplement use and risk of neoplastic progression in esophageal adenocarcinoma: a prospective study. Nutrition and Cancer. 2008; 60(1):39–48. [PubMed: 18444134]

102. Dawsey SP, Hollenbeck A, Schatzkin A, et al. A prospective study of vitamin and mineral supplement use and the risk of upper gastrointestinal cancers. PLoS ONE. 2014; 9(2):e88774. [PubMed: 24558423]

103. Sharp L, Carsin AE, Cantwell MM, et al. Intakes of dietary folate and other B vitamins are associated with risks of esophageal adenocarcinoma, Barrett's esophagus, and reflux esophagitis. J Nutr. 2013; 143:1966–1973. [PubMed: 24132576]

104. Xiao Q, Freedman ND, Ren J, et al. Intakes of folate methionine, vitamin b6, and vitamin b12 with a risk of esophageal and gastric cancer in a large cohort study. Br J Cancer. 2014; 110:1328–1333. [PubMed: 24481406]

Key Points

1. Barrett's esophagus is the most well established risk factor for the development of esophageal adenocarcinoma
2. Risk factors for neoplastic progression in Barrett's esophagus patients include endoscopic findings (i.e. erosive esophagitis), pathologic findings (i.e. dysplasia) and clinical aspects (i.e. male sex, older age, tobacco).
3. Protective factors against neoplastic progression include medication use (i.e. statins, aspirin), dietary considerations, and *H. pylori* infection.

Table 1

Risk Factors for Neoplastic Progression to Esophageal Adenocarcinoma	
Clinical	Older Age
	White Race
	Male Sex
	Family History
	Tobacco
	Obesity
Endoscopic	Long Segment Barrett's Esophagus
	Hiatal Hernia
	Mucosal Abnormalities
	Right Hemisphere Position
Pathologic	Intestinal Metaplasia
	Dysplasia
	P53 Overexpression

Table 2

Protective Factors Against Neoplastic Progression to Esophageal Adenocarcinoma	
Dietary	Significant Fruits and Vegetables
	Fiber
Medications	Statins
	NSAIDs
	Aspirin
Acid suppression	Proton Pump Inhibitors
***H pylori* infection**	