Risk Factors for Esophageal Cancer Development

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Adenocarcinoma of the esophagus was previously recognized as an uncommon disorder. Studies now show that the incidence of this cancer has increased by approximately six fold between 1975 and 2001, a rate greater than that of any other cancer in the United States during that time.¹ This increase has been accompanied by an increase in mortality rates from 2 to 15 deaths per million during that same time period. Similar findings are occurring elsewhere in the Western world today. The cause of this increase remains uncertain. This article explores the various risk factors for the development of esophageal adenocarcinoma (Table 1).

BARRETT’S ESOPHAGUS

Barrett’s esophagus is a clearly recognized risk factor for the development of esophageal adenocarcinoma compared with the general population.² It is an acquired condition resulting from severe esophageal mucosal injury and is typically found in or adjacent to esophageal adenocarcinoma in resection specimens.³ Cancer risk in Barrett’s esophagus appears to be limited to patients with specialized columnar epithelium, although this concept has recently been questioned.

Despite the alarming increase in the incidence of esophageal adenocarcinoma, the precise incidence of adenocarcinoma in patients with Barrett’s esophagus is uncertain, with rates varying from approximately 1/52 to 1/694 years of follow-up.⁴ It is estimated that the risk of developing cancer in a given patient with Barrett’s esophagus is approximately 0.5% to 0.7% annually with no clear evidence of geographic variation.⁴,⁵ The evolving epidemiologic data suggest that despite the alarming increase in the incidence of esophageal adenocarcinoma, the vast majority of patients with Barrett’s esophagus still will never develop cancer and will die of causes other than cancer.⁶,⁷
The marked increase in the incidence of Barrett’s esophagus was attributed by many to the increased use of diagnostic upper endoscopy combined with the change in the definition of Barrett’s esophagus to include shorter segments of columnar-lined epithelium. However, recent data from the Netherlands suggest that the incidence of Barrett’s esophagus is in fact increasing in the general population independent of the number of upper endoscopies.

A variety of characteristics of the Barrett’s mucosa is associated with an increase in the risk for cancer.

**Segment Length**

Esophageal cancer develops in both short and long segments of Barrett’s esophagus. A variety of studies have examined if the risk of developing adenocarcinoma increases with increasing length of Barrett’s epithelium. Intuitively, one would think that the greater the length, the greater the amount of mucosa at risk for cancer development. Studies to date have yielded mixed results for length as a risk factor, in part because of the low incidence of progression to cancer in cohort studies. Observational studies suggest that the prevalence of cancer and dysplasia is higher in longer lengths of Barrett’s epithelium. A prospective cohort study by Rudolph and colleagues of the Seattle Barrett’s Esophagus Research Program found that segment length was not related to subsequent risk of cancer. However, when subjects with high-grade dysplasia at index endoscopy were excluded, a nonsignificant trend for risk of cancer was noted. Weston and colleagues found that a segment length of 6 cm or greater

<table>
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<th>Risk factors for esophageal cancer and strength of association</th>
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<td><strong>Strength of Association</strong></td>
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<tr>
<td>Barrett’s esophagus</td>
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<td>Dysplasia</td>
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<td>Segment length</td>
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<td>Race</td>
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<td>Reflux symptoms</td>
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<td>Smoking</td>
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<td>Family history</td>
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<td>Diet</td>
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<td>Alcohol consumption</td>
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<td><em>H. pylori</em> infection</td>
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<td>Aspirin/NSAID consumption</td>
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<td>Drugs that relax the LES</td>
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Strength of association: + = risk factor; – = protective factor; ± = equivocal or no clear evidence for or against.

The marked increase in the incidence of Barrett’s esophagus was attributed by many to the increased use of diagnostic upper endoscopy combined with the change in the definition of Barrett’s esophagus to include shorter segments of columnar-lined epithelium. However, recent data from the Netherlands suggest that the incidence of Barrett’s esophagus is in fact increasing in the general population independent of the number of upper endoscopies.

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was associated with an increased risk for developing high-grade dysplasia or adenocarcinoma. Others have also found an increased risk of subsequent development of dysplasia or carcinoma with increased length of Barrett’s epithelium.\textsuperscript{14,16} However, a recent meta-analysis found only a trend for decreased cancer risk for short-segment Barrett’s esophagus.\textsuperscript{4} Taken together, these data suggest that the relationship between segment length and cancer risk is uncertain.

**Dysplasia**

Barrett’s esophagus patients progress through a phenotypic sequence of no dysplasia, low-grade dysplasia, high-grade dysplasia, and then adenocarcinoma, although the time course is highly variable and this stepwise sequence is not preordained.\textsuperscript{17,18} Furthermore, some patients may progress directly to cancer without prior detection of dysplasia of any grade.\textsuperscript{19} Currently, dysplasia remains the only factor useful for identifying patients at increased risk for the development of esophageal adenocarcinoma in clinical practice. Low-grade dysplasia is recognized adjacent to and distant from Barrett’s esophagus-associated adenocarcinoma in resection specimens.\textsuperscript{20,21} Furthermore, systematic esophagectomy-mapping studies demonstrate that low-grade dysplasia typically occupies a far greater surface area of the involved esophagus than does high-grade dysplasia or cancer.\textsuperscript{21}

Low-grade dysplasia is characterized histologically by preserved crypt architecture, with abnormal nuclei in the basal half of the cell.\textsuperscript{22} Despite that seemingly simple definition, the diagnosis needs to be distinguished from reactive changes caused by inflammation or ulceration. Interobserver variability, even among expert GI pathologists in the interpretation of low-grade dysplasia, is especially problematic. Montgomerie and colleagues\textsuperscript{23} found interobserver agreement to be fair for low-grade dysplasia (kappa score of 0.32), but substantial for high-grade dysplasia or adenocarcinoma (kappa score of 0.65). The inability to reproducibly diagnose low-grade dysplasia may explain the highly variable natural history of this lesion.

What do we know about the natural history of low-grade dysplasia, given the limited number of subjects studied to date? First, the diagnosis is often transient,\textsuperscript{24,25} which may be due in part to the high degree of interobserver variability in establishing this diagnosis and the variable biopsy protocols by which these subjects are followed, resulting in issues related to tissue sampling. While the majority of subjects with low-grade dysplasia do not progress to adenocarcinoma or high-grade dysplasia, a subset of these subjects do progress to a higher-grade lesion. Skacel and colleagues\textsuperscript{26} followed 25 subjects with low-grade dysplasia for a mean of 26 months and found that 28% developed high-grade dysplasia or adenocarcinoma, whereas 60% regressed and 12% had persistent low-grade dysplasia. However, a consensus agreement among the GI pathologists in that study was associated with an increased risk for progression. Weston and colleagues\textsuperscript{27} followed 48 subjects with low-grade dysplasia for a mean of 41 months and found that 10% progressed to multifocal high-grade dysplasia or adenocarcinoma, 65% regressed, and 25% had persistent low-grade dysplasia. More recently, a Veterans Affairs (VA) cohort study estimated that the risk for progressing to high-grade dysplasia or adenocarcinoma was 1.3%/year in subjects with baseline low-grade dysplasia compared with 0.36%/year in subjects without low-grade dysplasia.\textsuperscript{28} However, a multicenter cohort study by Sharma and colleagues\textsuperscript{19} identified 156 subjects with low-grade dysplasia, 13% of whom progressed to high-grade dysplasia or cancer for an incidence of 0.6%/year, a rate no different from most estimates for subjects with intestinal metaplasia without dysplasia.

Srivastava and colleagues\textsuperscript{29} recently examined the significance of the extent of low-grade dysplasia as a risk factor for progression to cancer in 77 Barrett’s esophagus
subjects. They found that 31.8% of subjects with a maximum baseline diagnosis of low-grade dysplasia progressed to cancer compared with 68.2% of subjects with baseline high-grade dysplasia. In subjects with a maximum diagnosis of low-grade dysplasia at baseline, the mean proportion of low-grade crypts/subject was higher in progressors versus nonprogressors (64.5% versus 22.1%, $P = .01$). However, there was no relationship between extent (focal or diffuse) of low-grade dysplasia and cancer risk.

Thus, the natural history of low-grade dysplasia remains highly variable: some patients clearly progress to develop high-grade dysplasia or adenocarcinoma, whereas regression is seen in the majority of these individuals. However, “regression” in many cases could be related to diagnostic accuracy and/or sampling error. Taken together, studies to date suggest that low-grade dysplasia results in an intermediate risk for the development of adenocarcinoma.

High-grade dysplasia in Barrett’s esophagus is a well-recognized risk factor for the development of adenocarcinoma. Unsuspected carcinoma is detected at esophagectomy in approximately 40% of patients with high-grade dysplasia, with a range of 0% to 73%. Several recent studies have improved our understanding of the natural history of high-grade dysplasia. Buttar and colleagues followed 100 subjects with high-grade dysplasia with continued endoscopic surveillance and found cancer at 1 and 3 years in 38% and 56% of individuals with diffuse high-grade dysplasia and 7% and 14% of individuals with focal high-grade dysplasia, respectively. Reid and colleagues followed 76 subjects for five years and encountered cancer in 59%. On the other hand, Schnell and colleagues, in a study of 79 subjects, found cancer in 5% of subjects during the first year of surveillance and in 16% of the remaining subjects followed for a mean of 7 years (20% of the total group developed cancer). Others have reported regression of high-grade dysplasia over time as well. A recent meta-analysis found that the incidence of adenocarcinoma in subjects with high-grade dysplasia was approximately 6.58% annually. Mucosal abnormalities in patients with multifocal high-grade dysplasia may also be a risk factor for adenocarcinoma. Thus, high-grade dysplasia remains a worrisome lesion, although progression to carcinoma may take many years and is not inevitable.

Unfortunately, dysplasia is an imperfect marker of increased cancer risk. It is typically not distinguishable endoscopically and is often focal in nature, thereby making targeting of biopsies problematic. Furthermore, there is considerable interobserver variability in the grading of dysplasia in both the community and academic settings, and the ability of pathologists to distinguish between intramucosal carcinoma and high-grade dysplasia is problematic even in esophagectomy specimens.

**Biomarkers**

A number of molecular markers may define patients at increased risk for the development of esophageal adenocarcinoma. Among the most frequently described molecular changes that precede the development of adenocarcinoma in Barrett’s esophagus are alterations in p53 (mutation, deletion, or loss of heterozygosity [LOH]); p16 (mutation, deletion, promoter hypermethylation, or LOH); and aneuploidy by flow cytometry. Neoplastic progression in Barrett’s esophagus is accompanied by flow cytometric abnormalities such as aneuploidy or increased G2/tetraploid DNA contents, and these abnormalities may precede the development of high-grade dysplasia or adenocarcinoma. The potential importance of flow cytometry as a prognostic biomarker was illustrated in work by Reid and colleagues, who found that for subjects with no flow cytometric abnormalities at baseline and with histology that showed no dysplasia, indefinite or low-grade dysplasia, the five-year
incidence of cancer was 0%. In contrast, aneuploidy, increased 4N fractions, or high-grade dysplasia was detected in each of the 35 subjects who went on to develop cancer within five years.

Mutations of p53 and 17p LOH have been reported in up to 92% and 100%, respectively, of esophageal adenocarcinomas. Furthermore, both abnormalities have been detected in Barrett’s epithelium before the development of carcinoma. For example, Reid and colleagues found that the prevalence of 17p (p53) LOH at baseline increased from 6% in subjects negative for dysplasia to 20% in subjects with low-grade dysplasia, and to 57% in subjects with high-grade dysplasia. More importantly, the 3-year incidence of cancer was 38% for individuals with 17p (p53) LOH compared with 3.3% for individuals with two 17p alleles. However, techniques to detect p53 mutations and 17p LOH are labor intensive and have not achieved widespread acceptance in clinical practice to date. Similarly, p16 LOH and inactivation of the p16 gene by promoter region hypermethylation have been reported frequently in esophageal adenocarcinoma. Furthermore, 9p LOH is commonly encountered in premalignant Barrett’s epithelium and can be detected over large regions of the Barrett’s mucosa. It is hypothesized that clonal expansion occurs in conjunction with p16 abnormalities, creating a field in which other genetic lesions leading to esophageal adenocarcinoma can arise.

Epigenetic changes, in the form of hypo- and hypermethylation and alteration to histone complexes have also been implicated in the progression of Barrett’s esophagus to adenocarcinoma. Hypermethylation of p16, RUNX3, and HPP1 are all independently associated with an increased risk of progression of Barrett’s esophagus to high-grade dysplasia or esophageal adenocarcinoma.

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. Two recent studies have examined just such an approach with promising results. The combination of 17p LOH, 9p LOH, and DNA-content abnormality has been shown to predict the 10-year adenocarcinoma risk better than any single biomarker alone. Subjects with a combination of these abnormalities had a markedly increased risk of developing cancer compared with those with no baseline abnormalities (relative risk 38.7; 95% CI, 10.8–138.5). In those with no abnormalities of any of these biomarkers at baseline, 12% developed adenocarcinoma at 10 years. In contrast, those with the combination of 17p LOH, 9p LOH, and DNA-content abnormality had a cumulative incidence of adenocarcinoma of 79% over the same period. A risk stratification model using a methylation index constructed from the methylation values for p16, HPP1, and RUNX3 also showed potential for prediction of progression to high-grade dysplasia or adenocarcinoma. All of these studies demonstrate the potential for biomarkers to predict risk of esophageal adenocarcinoma. Unfortunately, none of these biomarkers have been validated in large-scale clinical trials to date and as such are not yet useful for clinical decision making.

REFLUX SYMPTOMS AND ESOPHAGITIS

Two studies have examined the relationship between esophagitis and esophageal adenocarcinoma. Solaymani-Dodaran and colleagues, using the General Practice Research Database in the United Kingdom, found that the relative risk for esophageal adenocarcinoma was elevated to 4.5 (95% CI, 1.04–19.6) among esophagitis subjects compared with the general population. Subsequently, a Danish population-based cohort study found that the standardized incidence ratio for esophageal adenocarcinoma was elevated to 5.38 (95% CI, 3.01–8.87) among subjects with esophagitis.
However, 10 of the 15 subjects who developed esophageal adenocarcinoma in that study had Barrett’s esophagus diagnosed at least one year before discovery of the cancer suggesting that most of the cancers were related to Barrett’s esophagus and not esophagitis per se.

What about GERD symptoms alone? The General Practice Research Database study of Solaymani-Dodaran found no relationship between subjects with a prior diagnosis of GERD without esophagitis and subsequent risk of developing esophageal adenocarcinoma. On the other hand, the landmark case-control Swedish population-based study by Lagergren and colleagues found that the more severe, frequent, and persistent the symptoms of reflux, the greater the risk of esophageal adenocarcinoma. However, this work and that of others has shown that approximately 40% of subjects with esophageal adenocarcinoma have no history of regular reflux symptoms.

AGE

Studies consistently show that the incidence of esophageal adenocarcinoma increases with age. Data from both the Surveillance, Epidemiology, and End Results (SEER) program and the Danish Cancer Registry demonstrate that the incidence rate of esophageal adenocarcinoma increases with age until it peaks at 75–79 years of age and declines thereafter. Furthermore, El-Serag and colleagues, using the SEER database, observed that this age effect has shifted upwards with time, as there has been an increase in the incidence of esophageal adenocarcinoma among younger subjects in addition to the older age groups. This suggests a cohort effect, with higher incidence rates seen among cohorts of subjects born most recently. El-Serag calculated that the odds of developing esophageal adenocarcinoma increased by 6.6% for each 5–year increase in age. (OR 1.066, 95% CI, 1.060–1.072)

GENDER

Male gender is a well-recognized risk factor for esophageal adenocarcinoma. It is estimated that the incidence of esophageal adenocarcinoma is approximately six to eight fold greater in men than in women. That being said, the incidence of esophageal adenocarcinoma is increasing steadily in both genders.

RACE

White race has long been associated with esophageal adenocarcinoma. A recent analysis of SEER cancer registry data from 1992 through 1998 provided the most comprehensive analysis of the role of ethnicity in esophageal cancer to date. Kubo and Corley found that the average annual incidence rate for esophageal adenocarcinoma for white men was double that of Hispanic men (4.2 versus 2.0/100,000/year). This rate was also four times higher than that seen in blacks, Asians/Pacific Islanders and Native Americans. Similar patterns were seen in women, where the rates for all ethnicities were lower than that encountered among the men. Interestingly, the incidence rates for esophageal adenocarcinoma increased only for the white population between 1992 and 1998 but not for the other ethnic groups. Thus, there are clear ethnic imbalances in the risk for esophageal adenocarcinoma.

FAMILY HISTORY

Given the clear association of esophageal adenocarcinoma with male gender and white race, a possible inherited component to the risk of esophageal carcinoma has
long been hypothesized. This hypothesis has been supported by a number of reports of familial clustering of both Barrett’s esophagus and esophageal adenocarcinoma.\(^{62-66}\) These small studies suggest the possibility of an autosomal dominant inheritance pattern. Larger case-control studies come to less clear-cut conclusions. First, a population-based case-control study in the United States found no association between the risk of esophageal adenocarcinoma and a family history of digestive disease cancers either as a group or by individual sites.\(^{67}\) Two Swedish case-control studies came to different conclusions. Lagergren and colleagues\(^{68}\) found that the occurrence of esophageal cancer of any histology among first-degree relatives did not increase the risk of esophageal adenocarcinoma. In contrast, Ji and colleagues,\(^{69}\) using an updated version of the Swedish Family Cancer Database, found that the standardized incidence ratio for esophageal adenocarcinoma (observed: expected cases) was elevated to 3.52 (95% CI, 1.11–8.28) among offspring of parents with esophageal cancer of any subtype. However, if the parental proband had esophageal adenocarcinoma, the subsequent risk of adenocarcinoma in offspring was not increased. However, none of the affected parents were diagnosed with esophageal adenocarcinoma. Finally, Chak and colleagues\(^{70}\) found that a positive family history was higher among cases with Barrett’s esophagus, esophageal adenocarcinoma, or gastro-esophageal junction adenocarcinoma than among GERD controls (24% versus 5%). The familial effect was present in all three of the subgroups studied. Taken together, these studies suggest that inherited factors may represent a risk factor for the development of esophageal adenocarcinoma in a small subset of subjects. The exact magnitude of the risk and the gene(s) associated with this risk are currently under investigation.

**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. A variety of observational studies have demonstrated a relationship between obesity and esophageal adenocarcinoma. A number of studies have also demonstrated an association between increasing BMI and increased risk of esophageal adenocarcinoma.\(^{71-76}\) Several systematic reviews and meta-analyses have confirmed these observations.\(^{77,78}\) Kubo and Corley\(^{78}\) found that a BMI greater than 25 was associated with an increased risk of esophageal adenocarcinoma in both men (OR 2.2; 85% CI, 1.7–2.7) and women (OR 2.0; 95% CI, 1.4–2.9) and higher levels of BMI were associated with increased risk.

Recent studies have helped to fine tune our understanding of the association between obesity and esophageal adenocarcinoma risk. A population-based case-control study from Australia found that obesity increased the risk of esophageal adenocarcinoma in a dose-dependent fashion, with the highest risk encountered for a BMI of 40 kg/m\(^2\) or greater when compared with a healthy BMI.\(^{79}\) Furthermore, risks associated with obesity were noted to be higher in men than in women. Corley and colleagues\(^{80}\) extended these observations and examined the distribution of obesity and cancer risk in a case-control study. They found that increasing abdominal diameter was strongly associated with an increased risk of esophageal adenocarcinoma in a dose-dependent manner, which did not change when adjusted for BMI (OR 4.78; 95% CI, 1.14–20.11). The fact that abdominal obesity is more common among men could also explain the male predilection for this cancer.

Is there a mechanism that could explain the association of obesity and cancer risk? Obesity, especially central obesity, increases intragastric pressure and the
gastroesophageal pressure gradient, thereby facilitating reflux of contents into the esophagus. This increase in pressure gradient is accompanied by a predisposition for hiatal hernia, another risk factor for the development of reflux and complications such as Barrett’s esophagus. Metabolic effects of obesity, especially abdominal obesity, may also contribute to these observations. A variety of hormones, including leptin, adiponectin, insulin-like growth factors, insulin, and sex steroids are associated with increasing adiposity. These hormones modulate cellular proliferation and apoptosis, thereby providing biologic plausibility for the relationship of obesity and carcinogenesis independent of reflux.

**HELMICOBACTER 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. Thus it is natural to look for a relationship between these two opposing time trends. A number of epidemiologic studies have demonstrated a negative association between *H pylori* infection and esophageal adenocarcinoma. This association has also been described with the cagA+ strain, which is felt to result in more intense inflammation and a greater tendency to gastric atrophy. A recent meta-analysis found the pooled odds ratio for the prevalence of *H pylori* infection in esophageal adenocarcinoma to be 0.52 (95% CI, 0.37–0.73) and for the *H pylori* cagA+ strain to be 0.51 (95% CI, 0.31–0.82). The primary mechanism postulated for this protective effect centers around decreased acid secretion caused by *H pylori* induced gastric atrophy, especially with cagA+ strains. A recent population-based case-control study from Ireland found that severe gastric atrophy, as measured by pepsinogen I/II ratios, was associated with a clearly decreased risk of esophageal adenocarcinoma, giving support to this as a putative mechanism of protection from esophageal adenocarcinoma. However, that same study also found the protective effect of *H pylori* infection was also encountered in atrophy-negative subjects, suggesting that mechanisms other than gastric atrophy are involved in the potential protective effects of *H pylori* infection for esophageal adenocarcinoma, such as neutralization of acid by ammonia produced by *H pylori*, proapoptotic effects of *H pylori* on adenocarcinoma cell lines, and alterations in ghrelin secretion.

**SMOKING**

A number of studies have identified current or past smoking as a risk factor for esophageal adenocarcinoma. The risk increases with increasing intensity and duration of smoking. Interestingly, the risk associated with smoking persists with little reduction of risk observed until 30 years after smoking cessation. However, a Swedish population-based case-control study did not identify smoking as a risk factor for esophageal adenocarcinoma.

**ALCOHOL CONSUMPTION**

Most epidemiologic studies find no association between alcohol consumption and esophageal adenocarcinoma. However, several studies do find a modest association of alcohol consumption and risk of esophageal adenocarcinoma. Taken together, alcohol consumption does not appear to be a major risk factor for esophageal adenocarcinoma.
DIET

A variety of studies have examined diet and food supplements and risk of esophageal adenocarcinoma. Increased consumption of fruits and vegetables is consistently associated with a decrease in the risk for esophageal adenocarcinoma.99–102 In fact, Engel and colleagues99 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%). At the same time, higher intake of saturated fats and red meat may increase cancer risk.100,101

A diet high in carbohydrates may be linked to cancer.103 A recent ecologic study found a correlation between the rise in carbohydrate consumption with the increase in esophageal adenocarcinoma rates.103 While ecologic studies should be viewed as hypothesis generating, and are flawed by the concept of ecologic fallacy, this observation is in fact plausible. A high carbohydrate diet can lead to insulin resistance, and hence elevated levels of both insulin and insulin-like growth factor, both of which have been implicated in carcinogenesis. Despite increasing attention, there does not seem to be an association between carbonated drink consumption and risk of esophageal adenocarcinoma.104,105

Lastly, the role of dietary supplements and esophageal adenocarcinoma has also been examined by a number of investigators. Recent work from the Seattle Barrett’s Esophagus Research Program found that consumption of one or more multivitamins daily was associated with a decrease in the hazard ratio of developing esophageal adenocarcinoma (HR 0.38, 95% CI, 0.15–0.99) compared with subjects not taking multivitamins.106 Similar findings were encountered for daily use of vitamins C and E in that same study. Others have also found a reduced risk of esophageal adenocarcinoma associated with antioxidant vitamin consumption.107

NSAIDS AND ASPIRIN

A number of observational studies suggest that NSAIDs, including aspirin, may play a protective role against esophageal adenocarcinoma by inhibiting the cyclooxygenase 1 and 2 enzymes, which regulate PGE2 production.108–113 One possible mechanism that is involved in reflux-associated carcinogenesis in Barrett’s esophagus is acid and bile salt induced COX-2 activation and high levels of PGE2 production. A systematic review suggested that the protective effect of aspirin and NSAIDs was greater with more regular use, an observation supported in a recent cohort study as well.108,111 However, others could find no protective effect for esophageal cancer with long-term use of NSAIDs.114

A single clinical trial examined the effect of celecoxib at a dose of 200 mg twice daily given for 48 weeks in subjects with low-grade and high-grade dysplasia on change in proportion of biopsy samples with dysplasia between subjects treated with celecoxib compared with those treated with a placebo.115 No differences were found between the two groups. A small crossover study demonstrated that high-dose PPI therapy in conjunction with aspirin at a dose of 325 mg daily can decrease mucosal PGE-2 content in mucosal biopsies from Barrett’s esophagus subjects.116 These findings led to a large randomized clinical trial in the United Kingdom (ASPECT) and a smaller clinical trial in the United States in an effort to examine the potential for chemoprevention with aspirin in conjunction with a proton pump inhibitor as a clinical strategy in Barrett’s esophagus patients.
ACID SUPPRESSION

Because 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 VA cohort study suggested that PPI therapy, especially long-duration use, was associated with a decreased risk for the development of dysplasia. However, most of the cases of dysplasia were low-grade, a lesion with an intermediate and highly variable risk for development of cancer. Similar observational data on reduction of dysplasia risk with administration of PPIs have been obtained in Australia. However, there are no randomized controlled trials that have examined the issue of dysplasia or cancer prevention and administration of PPI therapy.

ANTIREFLUX SURGERY

Some have hypothesized that antireflux surgery provides protection from progression of Barrett’s esophagus to adenocarcinoma. 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 subjects found no protective effect for surgery. The standardized incidence ratio of esophageal adenocarcinoma in the surgically treated group was 14.1, 95% CI, 8.0–22.8 compared with 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 with medically treated GERD subjects (0.072%/year versus 0.04%/year).

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. A subsequent systematic review by Chang and colleagues found no difference in the incidence of esophageal adenocarcinoma in medically versus surgically treated subjects, and that any evidence suggesting otherwise was driven by uncontrolled case series. Thus, the best available evidence suggests that antireflux surgery does not decrease cancer risk in GERD or Barrett’s esophagus patients.

DRUGS THAT RELAX THE LOWER ESOPHAGEAL SPHINCTER

The Swedish population-based case-control study of Lagergren and colleagues found a positive association between medications that relax the lower esophageal sphincter and esophageal adenocarcinoma. However, this association disappeared after adjustment for reflux symptoms, suggesting that promotion of reflux was the cause of this observation. However, Vaughan and colleagues found no such association in a population-based case-control study in the United States.

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. It appears that the current epidemic of obesity is a major risk factor for the development of esophageal adenocarcinoma, perhaps in conjunction with both a decline in the prevalence of H pylori infection and the overall aging of the population in the Western world. A better understanding of exposures that
increase and decrease risk of esophageal adenocarcinoma is urgently needed if this disturbing trend in cancer incidence is to be reversed.

REFERENCES


