Esophageal cancer and Barrett’s esophagus
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Many advances have occurred in the past few decades in the diagnosis and management of Barrett’s esophagus and early esophageal adenocarcinoma. We have attempted to capture the salient features of these lesions in several chapters written by international experts in the field.

Highlights of this book include the recognition of the lower neoplastic progression of Barrett’s esophagus (0.2–0.4 % per year), in spite of the rising incidence in younger age groups. Also, the risk factors for esophageal adenocarcinoma are detailed by epidemiology: age, gender and ethnicity. There is a complex interplay of inherited predispositions, environmental exposures and tissue responses that lead to neoplastic progression. Unfortunately, the advances in molecular biology have failed to yield a simple documented approach to the risk stratification of patients. Multiple mutations have been identified and analyzed, with sophisticated statistical techniques, without a clear clinically useful result. Histologic dysplasia remains the “standard” biomarker for the progression of Barrett’s esophagus to esophageal adenocarcinoma. Therefore, careful surveillance biopsies remain necessary. A high-quality white light endoscopy examination, using high definition endoscopes, is still the best method to target biopsy the high-risk appearing areas of Barrett’s esophagus.

Unfortunately, advanced esophageal adenocarcinoma is often found at the first recognition of BE. If nodular-appearing mucosa are identified in the Barrett’s segment, then endoscopic resection of the most abnormal appearing area is essential for proper T staging. Endoscopic ablation therapy is the primary treatment of high-grade dysplasia and T1a esophageal adenocarcinoma. Accompanying endoscopic ultrasound and body imaging are needed for disease deeper than T1a; such disease requires surgical intervention. With limited distal esophageal cancer, a local resection may be possible. For more extensive disease, chemoradiation may be appropriate, followed by definitive surgery. Medical therapy controlling gastroesophageal reflux symptoms with proton pump inhibitors is the background for the above interventions. An ideal approach to neoplasia in Barrett’s esophagus would be chemoprevention but, unfortunately, no intervention has yet been documented to be effective in a large clinical trial.

Ultimately, better risk stratification, more effective biomarker predictability of progression to neoplasia, and effective chemoprevention remain key goals for patients with esophageal cancer and Barrett’s esophagus.

As editors, we hope that you will find this book comprehensive, intellectually stimulating and helpful in the clinical care of patients with this disease.

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CHAPTER 1

Epidemiology of esophageal carcinoma

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1.1 The incidence and mortality related to esophageal cancer

Esophageal cancer is the sixth most common cancer among men and the ninth among women, affecting more than 450,000 people globally each year. Approximately 90% of cases of esophageal cancer are squamous cell carcinoma (ESCC) [1], and the rest are adenocarcinoma (EA). The highest reported incidence and mortality rates for ESCC occur in Jiashan, China, with an age-adjusted incidence rate of 14.6 cases per 100,000 (Figure 1.1). The highest age-adjusted incidence rates of EA occur in Scotland (6.6 per 100,000) and in other parts of the United Kingdom [2]. In the United States, the age-adjusted rate of esophageal cancer in 2009 was 4.1 per 100,000; EA alone had 2.7 cancers per 100,000, a sharp increase from the 1973 rate of 0.4 cancers per 100,000 [3] (Figure 1.2).

Although EA is the fastest-rising malignancy among white men in the United States, its increase may be slowing [4]. The US average annual percentage change in incidence was 8.4 (95% CI 7.7–9.1) before 1997, but it decreased to 1.6 (95% CI 0.0–3.3) from 1998 to 2009 [5]. In Scandinavia, the average annual percentage change has continued to increase [6].

In addition to geographic differences in the distribution of EA, there are remarkable variations in the demographics of persons affected by this cancer. The incidence of EA increases with age and peaks in the eighth decade of life. Independent of age, however, people born in more recent years have a higher incidence of EA [7]. EA incidence is five-fold higher among non-Hispanic whites than among blacks, while ESCC incidence rates among black men are four times higher than for white men [8]. Finally, most esophageal cancer cases (77.7%) affect men [6].

The incidence of EA is 7–10 times higher in men, while the incidence of ESCC is only 2–3 times higher in men than in women, according to numerous cancer registries around the world [9, 10]. This sex discrepancy varies among different races; for example, in the 50–59 age group, the highest male-to-female ratio was 20.5 in Hispanics, followed by 10.8 in whites and then 7.0 in blacks. With EA, male predominance is evident globally (Figure 1.1). Whether the difference in incidence rates among men and women or between whites and blacks is due to less gastroesophageal reflux disease (GERD) and/or Barrett’s Esophagus (BE) prevalence, or to a less progressive form of these diseases, is unknown. Despite an equal distribution of GERD between men and women [11, 12], men seem to have a more severe form of the disease, with a higher complication rate [13].

With ESCC, some areas (e.g. South Karachi, Pakistan; West Midlands, UK; Oman; Penang, Malaysia; South Australia; Kuwait) have a higher age-adjusted incidence rate among women than among men [2] (Figure 1.1).
The reason behind this is unknown. The main risk factors for ESCC, which show broad regional variation, include heavy alcohol consumption, tobacco smoking and human papilloma virus infection, as well as few rare disorders, such as achalasia of the cardia, and tylosis. These will not be discussed further in this review.

1.2 Mortality

Esophageal cancer is a highly fatal disease. The overall five-year relative survival for patients diagnosed with esophageal cancer in the United States was approximately 17.3% between 2003 and 2009 (Figure 1.2). The disease stage at time of diagnosis impacts survival greatly, as the age-adjusted five-year relative survival of 38.6% in localized disease declines to 3.5% in disease associated with distant spread. However, the overall survival over the past two decades has slightly, but significantly, improved. Despite the use of screening endoscopy in high-risk groups, about 35% of EA cases between 2004 and 2010 were diagnosed at an advanced stage [14]. A higher mortality rate for nonwhite Hispanics and blacks mostly has been attributed to the decreased receipt of cancer-directed surgery, indicating possible ethnic disparities in treatment application or availability [15].

1.2.1 Progression of BE to EA

A summary of published annual EA-risk data of nondysplastic BE ranges from 0.12–0.50% to 0.33–0.70% in population-based studies and meta-analyses, respectively [16]. Recent studies have indicated that the risk of progression from BE to EA is lower than previously reported [17]. The risk in a Dutch study of 42,207 patients was 0.4% [18]; in an Irish study of 8,522 patients, it was 0.22% per year (95% CI 0.19–0.26%) [19]; and in a Danish study of 11,028 patients, it was 0.12% (95% CI 0.09–0.15) [20].

1.3 Risk factors for EA

Risk factors for esophageal adenocarcinoma are outlined in Table 1.1.
**Epidemiology of esophageal carcinoma**


**Table 1.1** Summary of risk factors for the development of esophageal adenocarcinoma.

<table>
<thead>
<tr>
<th>Degree of confidence</th>
<th>Risk factor(s)</th>
</tr>
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<tbody>
<tr>
<td><strong>Definite risk</strong></td>
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<tr>
<td>Increased</td>
<td>BE</td>
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<tr>
<td></td>
<td>Obesity</td>
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<td>Central obesity</td>
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<td></td>
<td>Smoking</td>
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<td></td>
<td>GERD</td>
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<td></td>
<td>Family history of BE or EA</td>
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<td></td>
<td><em>H. pylori</em></td>
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<tr>
<td></td>
<td>Aspirin/NSAIDs</td>
</tr>
<tr>
<td>Decreased</td>
<td>Alcohol</td>
</tr>
<tr>
<td>No change</td>
<td></td>
</tr>
<tr>
<td><strong>Possible risk</strong></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Bisphosphonates</td>
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<tr>
<td>Decreased</td>
<td>PPI</td>
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<td></td>
<td>Statins</td>
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**1.3.1 GERD**

Several population-based case control studies have established a strong association, including a dose-response relationship between GERD symptoms and EA (and adenocarcinoma of the gastric cardia), but not ESCC [21, 22]. In a meta-analysis of five population-based studies, the presence of at least weekly GERD symptoms was associated with an odds ratio (OR) for developing EA of 4.92 (95% CI 3.90–6.22), which increased to 7.4 (95% CI 4.94–11.10) when the symptoms occurred on a daily basis, compared with asymptomatic controls or those with less frequent symptoms [23]. However, up to 40% of the patients with EA may not report bothersome GERD symptoms.

**1.3.2 Tobacco smoking**

A pooled analysis of individual data from ten case-control and two cohort studies from Australia, Canada, Ireland, the United Kingdom and the United States, including 1242 EA cases, 1263 gastroesophageal junction cancer (GEJ-CA) cases, 954 ESCC cases and 7053 controls without cancer [24], reported an increased risk of both types of esophageal cancer with history of tobacco smoking. The calculated OR of EA increased from 1.66 (95% CI 1.1–2.4) with 1–29 pack-years of smoking to 2.77 (95% CI 1.4–5.6) with...
>60 pack-years smoking history, with a statistically significant trend ($p < 0.01$). The same study concluded that, for equal pack-years of smoking, more cigarettes per day for shorter duration was less deleterious than fewer cigarettes per day for longer duration. For example:

Previous smokers have in EA, when comparing those with equal pack-years of smoking, patients who smoked 10–19 cigarettes/day had an increased risk compared with those who smoked more than 40 cigarettes/day ($p$ for trend = 0.40). Previous smokers have a lower risk of developing EA or ESCC than current smokers, but slightly higher than those who have never smoked [25]. Tobacco smoking does not seem to play a major role in developing BE [26]; however, in patients with established BE, the risk of EA increases with the magnitude and duration of smoking history [27]. Some studies indicate that the effect of smoking is stronger for ESCC than for EA [28]. Lastly, based on the risk estimates and the prevalence of smoking in the population, elimination of smoking would potentially prevent 39.7% of EA cases and 56.9% of ESCC cases [29].

1.3.3 Alcohol consumption
Large population-based studies consistently show a lack of association between alcohol consumption and EA [30–36]. For example, in an Irish study [34], no associations were found between total alcohol consumption in the preceding five years and reflux esophagitis, BE or EA (OR, 1.26, 95% CI 0.78–2.05; OR, 0.72, 95% CI 0.43–1.21; and OR, 0.75, 95% CI 0.46–1.22, respectively). Similarly, in a prospective evaluation of BE patients, a study found no increased risk of progressing to EA with increasing number of drinks per day or with the type of alcoholic beverage consumed [27]. However, with both alcohol consumption and current smoking, there is an eight-fold increased risk of developing ESCC [25].

The relationship between wine consumption and risk of BE or EA seems to follow a J-shaped curve, with both very low and very high intake associated with increased risk. An Australian study [36] found that those who drank modest levels of wine (<50–90 g/week) or port or spirits (<10–20 g/week) had significantly lower risks of EA, ESCC and GEJ CA than non-drinkers; higher consumption was associated with increased risks of ESCC only with a significant linear effect (OR, 1.03; 95% CI 1.02–1.05 per 10 g alcohol/week). Where to draw the cut-offs for the transitions in this curve is unclear. Although these findings are suggestive of a protective effect of modest intake of wine with regard to the risk of developing BE or EA, there are several biases that make it important to maintain a healthy skepticism [37].

1.3.4 Obesity
The association between obesity and EA has been corroborated in large and population-based case control studies conducted in the United States, Europe and Australia. These studies showed a strong association between increasing body mass index (BMI) and risk of developing this cancer [32, 38–47]. The association between BMI and EA has also been supported by prospective cohort studies [33, 48–54].

For example, a nested case control study from the UK General Practitioners Research Database (287 patients with EA and 10,000 randomly selected controls) found a positive association between BMI > 25 and EA (OR 1.7; 95% CI 1.2–2.3) [33]. In a cohort study from the Netherlands, including 120,852 participants, the relative risk of EA was 4.0 (95% CI 2.3–6.9) for obese individuals (BMI ≥ 30) compared with persons of normal weight (BMI 18.5–25.0) [50]. Abnet et al. found that, in a cohort of approximately 500,000 individuals from the United States, a BMI of 35 or more was associated with an EA hazard ratio [HR] of 2.3; (95% CI 1.4–3.6) compared with a normal BMI (18.5–25.0) [52].

Similarly, several meta-analyses confirmed the association between obesity and increased risk of EA. One calculated a pooled, adjusted OR of 1.52 in overweight patients and 2.78 in obese patients from nine case control studies (eight were population-based) [55], and another meta-analysis of 14 studies (two were cohort studies, eight were population-based studies, and four were hospital-based case control studies) calculated a pooled, adjusted OR of 1.9 for overweight patients and 2.4 for obese patients [56]. More recently, a larger meta-analysis that examined ten population-based case control and eight cohort studies found similar results for overweight (relative risk [RR] 1.87, 95% CI 1.61–2.17) and obese (RR 2.73, 95% CI 2.16–3.46) groups [57]. They also reported a summary RR for increments of five kg/m² of BMI of 1.13, 95% CI 1.11–1.16. Most data indicate that the strength of the association between obesity and EA is similar between sexes, or slightly more pronounced in men; however, data on women are limited.

The association between BMI and EA, combined with the strong male and white race predominance of
this cancer, have prompted research into the influence of body fat distribution typically found in white men (predominantly abdominal adiposity) in the development of EA (and BE). Abdominal fat distribution might promote and exacerbate GERD, the main risk factor for EA, by elevating intra-abdominal and, consequently, intragastric pressure which, in turn, promotes transient relaxation of the lower esophageal sphincter and separation of the crural diaphragm from the GE junction [58]. In addition, obese individuals are more likely to have metabolic dysfunction, and there are at least three main mechanisms via which abdominal obesity may predispose to BE. These include alterations in the levels of adipokines (both proinflammatory (leptin) and anti-inflammatory (adiponectin)), cytokines and chemokines; hyperinsulinemia and insulin resistance; and alterations in the insulin/Insulin-like Growth Factor (IGF) pathway. These reflux-independent effects of central adiposity have not been comprehensively examined [59].

That abdominal adiposity seems to confer additional increased risk of EA (to that of BMI) has some support from prospective studies [53, 54, 60, 61]. In a cohort study of 41,295 individuals in whom body fat distribution was measured using bioelectrical impedance tests, 30 patients with esophageal or gastric cardia adenocarcinomas were identified. The HR per 10 cm increase in waist circumference was 1.5 (95% CI 1.1–2.0) [60]. Steffen et al. identified 88 patients with EA in a prospective European study of 346,554 individuals and showed that, among several anthropometric measures (including BMI, waist circumference and waist-to-hip ratio [WHR]), the risk of EA correlated most strongly with waist circumference [54].

A nested case control study within a cohort of 206,974 US individuals, in which 101 patients with EA were identified, found that abdominal diameter equal to 25 cm (versus < 20 cm) was strongly associated with risk of developing EA (OR 3.5; 95% CI 1.3–9.3) [53]. Moreover, an Irish study comparing computerized tomography-measured abdominal fat composition showed that EA patients (n = 110) had greater intra-abdominal visceral adiposity than those with ESCC (n = 46), gastric adenocarcinoma (n = 38), or controls (n = 90) [62]. Similar to the findings from individual studies, a meta-analysis of five studies (one hospital, one population-based case-control and three cohort studies), examining the effect of central obesity on the risk of EA, found more than a two-fold increase in risk compared with those with normal body habitus (OR 2.51, 95% CI 1.56–4.04) [63]. This association was also present when examining BMI as the risk factor (OR 2.45, 95% CI 1.84–3.28).

It is unclear whether obesity increases the risk of BE and, consequently, EA, or increases the risk of EA in people who already have BE. Hardikar et al. found no significant increase in risk of developing EA among BE patients when evaluating BMI or WHR, in both genders [27]. Similarly, in a meta-analysis of 11 studies, BMI was borderline significant for increasing the risk of BE (OR 1.24, 95% CI 1.02–1.52) [63]. However, central obesity almost doubled the risk of BE (OR 1.98, 95% CI 1.52–2.57), and this effect persisted after adjusting for the effect of BMI (OR 1.88, 95% CI 1.20–2.95).

### 1.3.5 Diet

Non-starchy vegetables, fruits, and foods containing beta-carotene and/or vitamin C or folates probably have a protective effect against esophageal cancer [64]. A meta-analysis of mainly case control studies reported an inverse associations of vitamin C and β-carotene/vitamin A intake with EA with an OR of 0.49 (95% CI 0.39–0.62) and 0.46 (95% CI 0.36–0.59), respectively, when comparing those in the highest quartile of intake to those in the lowest quartile [65].

Three studies reported on the association between vitamin E and risk of EA, but the summary OR did not reach statistical significance (0.80, 95% CI 0.63–1.03). Most studies have found a decrease in risk of developing EA with increased dietary intake of these antioxidants, but not from vitamin supplementation [66]. Even while controlling for GERD symptoms, fruit intake was significantly associated with a decreased risk of EA (OR 0.50, 95% CI 0.30–0.86) [45]. A meta-analysis of studies assessing the association of folate intake and esophageal cancer reported a summary OR of 0.50 (95% CI 0.39–0.65) among three case control studies examining the risk of EA [67].

In a population-based case control study examining fiber intake with EA, a statistically significant inverse association, mainly driven by a higher intake of cereal fibers, was found with GEJ-CA, but not EA (OR 0.3, 95% CI 0.2–0.5 and 0.7, 95% CI 0.4–1.2, respectively) [68]. No significant association between vegetable and fruit fibers with EA or GEJ-CA was found. The authors speculated that vegetables containing high levels of
nitrates nullify the effect of the fibers and, thus, show no association with risk of EA or GEJ-CA. Interestingly, in a study comparing BE patients with GERD patients and population controls [10], total fiber intake was associated with decreased risk of developing BE (OR 0.34, 95% CI 0.15–0.76, comparing highest with lowest quartiles). However, when examining the sources of fiber, the association was found to be significant only with vegetable and fruit fibers, but not cereal fibers (OR 0.47, 95% CI 0.25–0.88 and 0.73, 95% CI 0.36–1.45, respectively). This highlights the problem of examining quartiles of dietary intake (g/day) among different studies. The Swedish study [68] used 3.3 g/day and 3.6 g/day for the highest quartiles of fruit and vegetable intake, respectively. However, in the US study [10], the highest quartile for fruits and vegetables was 13.2 g/day, about a four-fold difference.

Conflicting results regarding intake of red meat, fat, and dairy products with EA have been reported [69]. A meta-analysis of 35 studies examined the effects of fish, and red, white, and processed meat on the risk of esophageal cancer; four of these were cohort and 31 were case control studies [70]. Of these studies, 14 examined ESCC only, five focused on EA, and three reported separate results for the two cancers, while 13 did not distinguish between EA and ESCC. When stratified by type of cancer, red meat was weakly associated with increased risk of ESCC (OR 1.63, 95% CI 1.00–2.63), but not associated with EA (OR 1.19, 95% CI 0.98–1.44). However, pooling the six studies that evaluated processed meat showed a significant association with increased EA risk (OR 1.37, 95% CI 1.05–1.78), but not ESCC (OR 1.17, 95% CI 0.90–1.51). White meat, poultry, and fish did not have significant associations with risk of EA or ESCC.

In their review, Kubo et al [71] reported on six studies evaluating carbohydrate intake with risk of developing EA. All were case control studies; three reported decreased risk of EA (OR ranging from 0.34 to 0.39), while the other three reported non-significant associations.

### 1.3.6 Proton Pump Inhibitors (PPIs)

In the United States alone, 139 million prescriptions of PPIs were dispensed in 2008. This number continues to rise, and in 2012 there were 157 million dispensed prescriptions [72]. Since BE and EA are thought to develop from continued esophageal acid exposure, using PPIs to decrease this exposure may reduce risk of esophageal neoplasia. However, on the other hand, unimpeded nonacid reflux in the presence of PPIs use may increase risk of neoplasia.

Several observational, non-population-based cohort studies from the United States, Australia, and the Netherlands have reported a significant decrease in the risk of high-grade dysplasia (HGD)/EA associated with PPI use among BE patients [73–75]. A prospective cohort study done in Australia on 328 patients with BE concluded that delaying PPI therapy for more than two years after the diagnosis of BE increased the risk of HGD/EA 20-fold (adjusted for age, sex, non-steroidal anti-inflammatory drug [NSAID]/aspirin use). A retrospective cohort study of 344 US veterans with BE, with 2,620 patient-years of follow-up, of whom 67.2% were on PPI, determined that the risk of HGD/EA was significantly lower among the PPI users (HR 0.39, 95% CI 0.19–0.80, adjusting for gender, age at BE diagnosis, and BE length).

A multi-center prospective cohort study in 540 BE patients in the Netherlands, with a median follow-up of 5.2 years, in whom regular endoscopic surveillance was performed, found that PPIs were prescribed in 85% of patients at inclusion in the study, for a median duration of 4.0 years. The use of PPIs at inclusion was associated with reduced risk of neoplastic progression (HR 0.43; 95% CI 0.21–0.88); but after adjustment for age, gender, time of BE diagnosis, BE length, esophagitis, histology, and use of other medications, the risk reduction became non-significant (HR 0.47; 95% CI 0.19–1.18). In a hospital-based, case control study of 87 EA cases and 244 BE controls without dysplasia or cancer, the OR for HGD/EA in patients using PPIs for more than six months, based on information collected by questionnaires, was 0.05 (95% CI 0.02–0.1), adjusting for age, sex, educational level, smoking status, alcohol use and reflux symptoms [76].

These studies were limited by selection bias related to the referral setting; ascertainment bias, in which patients not on PPIs may undergo more frequent endoscopy; and limited adjustment for possible confounders, such as obesity or Helicobacter pylori status. Confounding by indication is also of major concern in all these studies, even after excluding patients that started on PPIs within six months or one year before diagnosis.

There is no evidence for an effect of PPI or fundoplication [77, 78] on EA development among patients...
with GERD but without BE. On the contrary, most studies show that PPI use is more common among patients who develop EA, but none of the studies found an effect for PPI independent of GERD symptoms (i.e. PPI are a marker of GERD, which is the EA risk factor). In a nested case control study done in the United Kingdom [79], in which 287 cases of EA were identified and 10,000 controls were randomly sampled from the general practice research database, current use of PPI was associated with a higher, but non-significant, risk of EA – adjusted OR 1.51 (95% CI 0.91–2.50). With inclusion of GERD, peptic ulcer disease and dyspepsia in the model, the point estimate decreased to 0.84 (95% CI 0.48–1.50). Moreover, PPI was not associated with EA among patients whose main symptoms were dyspepsia or ulcer.

1.3.7 Aspirin and NSAIDs

Several observational studies have examined the use of aspirin and/or NSAIDs and their association with esophageal cancer. A meta-analysis of nine observational studies published through 2001 [80] (two cohort and seven case control studies, of which five were population-based) evaluated this association among 1,813 cases of esophageal cancer and reported a 43% reduction in the odds of developing esophageal cancer in patients with a history of any use of aspirin/NSAIDs (adjusted OR 0.57, 95% CI 0.47–0.71). However, only four studies stratified their analysis by histologic subtype (EA vs. ESCC) and reported that patients taking aspirin/NSAIDs had a 33% (95% CI 13–49%) and 42% (95% CI 22–57%) reduction in odds of developing EA and ESCC, respectively.

In a subsequent meta-analysis of ten observational studies published through 2008 (one cohort, one hospital-based and seven population-based case-control, of which two were included in the previously mentioned meta-analysis) that looked specifically at EA risk associated with use of aspirin or NSAIDs, the summary OR for the use of aspirin was 0.64 (95% CI 0.52–0.79) and that for NSAIDs was 0.65 (95% CI 0.50–0.85) [81]. Nine of the ten studies showed significant negative associations, and only one did not.

In a pooled individual-level analysis of six studies (five population-based case control and one cohort) within the BEACON (Barrett’s and Esophageal Adenocarcinoma Consortium), with 1266 EA cases and 5314 controls, compared with nonusers, NSAIDs users had an OR of 0.68 (95% CI 0.56–0.83). Results were similar when combining aspirin or non-aspirin NSAIDs [82]. This study also reported a decreasing risk of EA with increasing frequency of overall NSAID use, with an OR of 0.66 for occasional use and 0.56 for daily or greater use (p trend < 0.001).

In conclusion, despite the different methods used or populations studied, there seems to be a consistent negative association (approximately 40–50% risk reduction) between the use of aspirin or NSAIDs and both subtypes of esophageal cancer. Less is known about the level of protection (i.e., BE prevention or BE progression) or the type, dose or duration required, or the subgroups that are more likely to benefit.

Translating the findings from observational studies into a meaningful intervention remains elusive. One randomized trial of daily celecoxib (vs. placebo) failed to show EA risk reduction among patients with BE and low- or high-grade dysplasia after 48 weeks of randomization [83]. There is an ongoing randomized, double-blinded trial to evaluate the role of esomeprazole, with or without aspirin, in preventing EA in patients with BE “AsPECT” (clinicaltrials.gov identifier NCT00357682). However, given the additional cancer-reducing benefits of aspirin and NSAIDs, there has been a recent shift toward recommending these medications for general cancer (rather than organ-specific) chemoprevention in high-risk groups [84].

1.3.8 Statins

Experimental studies have shown that statins inhibit proliferation and angiogenesis, induce apoptosis and possibly also limit metastatic potential of cancer, especially colorectal cancer [85].

A meta-analysis of human studies published through August 2012 identified 13 studies (seven case control, five cohorts and one post hoc analysis of 22 randomized controlled trials) [86]. These studies examined 9285 esophageal cancer cases among 1,132,969 patients. Pooled, adjusted OR for statin use and esophageal cancer was 0.72 (95% CI 0.60–0.86), and OR of 0.70 (95% CI 0.56–0.88) from the seven high-quality studies. Of these studies, six reported a significant inverse association between statin use and the risk of esophageal cancer (two from United States, three from Europe and one from Asia), and seven studies reported no significant association. Of the cohort studies, only one reported a significant association.
In patients with known BE (five studies, 312 EA cases among 2125 BE patients), statin use was associated with an adjusted OR for EA of 0.59 (95% CI 0.45–0.78). Three of the five studies reported a significant inverse association between the use of statins and the risk of EA and/or HGD (one cohort and two case-control studies), and the other two cohort studies reported a non-significant association. Several studies lacked adjustment for a potentially important confounder, such as smoking or BMI [87, 88].

Apart from the modest and somewhat inconsistent significant association among studies, the other aspects of a causal association between statins and EA are either weak or not examined. Only two studies reported the relationship between the duration of statin use and risk of esophageal cancer [88, 89]. There was no clear duration-response relationship. Furthermore, the effect of dose or type of statin is not clear.

1.3.9 Bisphosphonates
Bisphosphonates have been linked to esophageal injury [90]. The interest in bisphosphonates and esophageal cancer increased after reports of persistent mucosal abnormalities were noted in some patients who developed esophagitis secondary to use of these medications [91]. Twenty-three cases were submitted to the FDA’s Adverse Event Reporting System of esophageal cancer in bisphosphonate users during 1995–2008 [92]. Histological analysis showed EA in seven patients and ESCC in one patient. An additional 34 cases of esophageal cancer among bisphosphonate users were also reported from Europe and Japan. Histological analysis showed EA in six patients and ESCC in five patients. One patient from the United States and three patients from Europe and Japan concomitantly carried a diagnosis of BE. All cases reported in the United States and most cases in Europe and Japan involved alendronate as the suspect bisphosphonate.

However, subsequent population-based studies examining the association between bisphosphonate use and EA have arrived at conflicting results [93–96]. Similarly, two meta-analyses published within a few months of each other [97, 98] examined the risk of esophageal cancer in patients using bisphosphonates and reported conflicting results. One meta-analysis examined four observational studies (one prospective cohort and three nested case control studies) conducted in the United Kingdom, Denmark, Taiwan and the United States [97]. In this meta-analysis, 19,320 cases of esophageal cancer developed in 589,755 people, with a slightly elevated and significant pooled OR of 1.74 (95% CI 1.19–2.25) for exposure to any oral bisphosphonate. Only the US study examined this association among patients with BE [87]. When stratified by bisphosphonate type, alendronate use had insignificant ORs, ranging from 0.73 to 1.26, depending on which overlapping studies were included, while etidronate had a significant OR of 1.58 (95% CI 1.12–2.24) when pooling the two studies that reported on this medication.

The second meta-analysis [98] included four cohort studies and three nested case control studies. This meta-analysis included studies with overlapping study populations (two used the UK General Practice Research Database [93, 94], two used the Taiwanese National Health Insurance Research Database [99, 100] and two used the Danish national prescription and discharge registries [96, 101]). The pooled RR for development of esophageal cancer in the cohort studies was 1.23 (95% CI 0.79–1.92), while the pooled OR in the case control studies was 1.24 (95% CI 0.98–1.57). Three studies examined the duration of bisphosphonate exposure. There was increased risk in both short- and long-term use (OR 1.37 (95% CI 0.77–2.39) and 2.32 (95% CI 1.57–3.43), respectively), although long-term use had the only statistically significant association.

Given the inconsistent findings, lack of distinction between EA and ESCC, and inadequate adjustment for important confounders (such as GERD), the association between bisphosphonates and increased EA risk while possible is not definite.

1.3.10 H. pylori gastric infection
H. pylori increases the risk of gastric adenocarcinoma by about six-fold, with a population-attributable risk of 75–90% of cancer cases [102]. However, its association with EA has been studied; and results have shown a different type of relationship.

A meta-analysis of ten epidemiological studies (two cohort; two nested case control; two hospital-based and four population-based case control studies) published through 2/2007, found a two-fold reduction in risk of EA among people infected with H. pylori, with a summary OR of 0.52 (95% CI 0.31–0.82). This risk reduction was similar in cag-A positive strains [103]. The authors also looked into the association between H. pylori and BE (seven studies; one population-based
and six hospital-based case control studies) and found similar results, with a summary OR of 0.64 (95% CI 0.43–0.94) and a more protective estimate for cag-A positive strains (OR 0.39, 95% CI 0.21–0.76).

In a more recent analysis, 13 studies (seven hospital-based, four population-based, two nested case control studies), six of which were included in the previous meta-analysis, were evaluated to examine the association between EA/HGD and *H. pylori* [104]. This study reported a summary OR for *H. pylori* in EA/HGD of 0.56 (95% CI 0.46–0.68), and an even slightly lower OR for cag-A strains of 0.41 (95% CI 0.28–0.62).

Despite the heterogeneity of studies looking into *H. pylori* and its association with EA and BE, in terms of methods of *H. pylori* detection and selection of control groups, there appears to be a consistently convincing protective association between these two factors. This effect is postulated, but not proven, to be due to the decreased acid production resulting from gastric atrophy, leading to decreased esophageal exposure to these acidic contents and, thus, a decrease in risk of BE and EA [104–106].

### 1.3.11 Genetics and familial factors

There are several case reports of familial GERD, BE and EA [107, 108]. For example, EA in one report developed in three members of a family that had six men, over three generations, with BE [109]. Another report identified a patient with EA with six family members who were diagnosed with BE or EA [110]. The largest study to examine familial predisposition of BE reported 20 families with multiple family members affected with BE or EA [111]. One study found a significantly higher yield of BE (40.7%) on endoscopic screening in families with familial BE (defined by one or more family member with BE or EA) than in families with sporadic cases (5.7%), although the study was small, with only 62 family members receiving endoscopy [112]. In a similar study, family members of patients with EA or HGD were invited for screening endoscopy; and 27.7% of them had confirmed BE [113]. In probands diagnosed with long-segment BE, EA or GEJ-CA, 7.3% of their first- or second-degree family members were identified as being affected by one of these three conditions [114].

Researchers have attempted to identify genetic foci related to the development of EA (and BE). A genome-wide combined linkage-association analysis, followed by an independent genome-wide single-nucleotide polymorphism (SNP)-based case control validation, found germline mutations in 11% of BE and/or EA patients, in three candidate genes, MSR1, ASCC1 and CTHRC1 [115]. The mutation in MSR1 is associated with overexpression of cyclin D1, resulting in alteration of the cell cycle progression, which can potentially contribute to tumorigenesis [116]. The other two gene mutations involve inflammatory and tissue-repair pathways.

Several gene-association studies found associations between EA and polymorphisms of single or few genes including IL-18 [117], matrix metalloproteinase genes (MMP1 and MMP2) [118], epidermal growth factor [119], insulin-like growth factor axis [120] and vascular endothelial growth factor (VEGF) [121]. In the study evaluating MMP1 and MMP2, an increased risk of EA was found only in those who had GERD, and the study of VEGF polymorphism increased the risk only in tobacco smokers, indicating an environment-gene interaction. In a systematic review of association studies published through 2007 [122], evaluating phase I and II enzyme polymorphisms, the minor allele for GSTP1 was found to increase the risk of EA (OR 1.20, 95% CI 0.94–1.54). GSTM1 null, GSTT1 null, and CYP1A1 Val(462) SNPs did not convey an excess risk for BE and/or EA.

In conclusion, there seems to be convincing data to support a familial tendency to develop BE and EA. No single genetic mutation has been identified as the culprit for the familiality of BE and EA, but SNPs within candidate genes that might confer the increased risk have been found by several studies. It is likely that there is a component of genetic susceptibility or environment-gene interactions towards the development of EA and its precursor, BE, but the attributable risk of specific genetic factors is unclear and likely to be small.

### References

Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission.


Chapter 1


