Epidemiology and pathobiology of esophageal cancer

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INTRODUCTION

The majority of esophageal cancers (EC) are squamous cell or adenocarcinomas. Although the incidence of squamous cell carcinoma (SCC) is decreasing in the United States, the incidence of adenocarcinoma (AC) arising out of Barrett's esophagus (BE) is rising dramatically, although less so in the last few years [1]. When stratified according to anatomic location, most of the increased incidence involves tumors at the esophagogastric junction (EGJ) and gastric cardia (figure 1) [2].

The epidemiology, etiologic factors, and pathobiology of AC and SCC of the esophagus will be reviewed here. Small cell carcinoma, sarcomas, and other rare tumors that arise in the esophagus and EGJ, as well as the clinical manifestations, diagnosis, and staging of EC, are discussed separately. (See "Extrapulmonary small cell cancer" and "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'Esophagus' and "Clinical manifestations, diagnosis, and staging of esophageal cancer".)

EPIDEMIOLOGY

Esophageal cancer (EC) is the eighth-most common cancer and the sixth-most common cause of death worldwide [3]. For most of the 20th century, squamous cell cancer (SCC) comprised the vast majority of esophageal cancers globally. For the past three decades, however, the

frequency of adenocarcinoma of the esophagus and esophagogastric junction (EGJ) and of gastric cardia cancers has increased dramatically, a finding initially observed in Western countries and more recently in some Eastern countries as well.

In the United States, over 21,000 cases of esophageal cancer are diagnosed annually, with over 16,000 deaths from the disease [4]. Worldwide data on incidence and mortality in different countries is available from the GLOBOCAN database. The majority of cases worldwide are SCC histology. However, the incidence and histology vary by location.

Incidence rates vary internationally by nearly 16-fold, with the highest rates found in Southern, Northern, and Eastern Africa (including Malawi and Swaziland), Eastern Asia, and Greenland, and the lowest rates in Western and Middle Africa and Central America in both males and females [5,6]. In the highest-risk area, stretching from Northern Iran through the central Asian republics to North-Central China (often referred to as the "esophageal cancer belt"), 90 percent of cases are SCC [7,8].

Major risk factors in these areas are not well understood, but are thought to include poor nutritional status, low intake of fruits and vegetables, and drinking beverages at high temperatures. In contrast, in low-risk areas for SCC, such as the United States and several Western countries, smoking and excessive alcohol consumption account for approximately 90 percent of the total cases of SCC [9]. Country-specific rates of incidence and mortality are available in the World Health Organization GLOBOCAN database. (See 'Smoking and alcohol' below.)

Temporal trends in incidence vary for the two major histologic types of EC. Incidence rates for AC of the esophagus have increased dramatically in several Western countries, in part due to increases in known risk factors such as higher BMI [1]. When stratified according to anatomic location, most of the increased incidence involves tumors at the EGJ and gastric cardia (figure 1) [10].

In contrast, rates for SCC are steadily decreasing in these same countries because of long-term reductions in tobacco use and alcohol consumption. However, SCC remains the most common histology worldwide and is increasing in certain Asian countries such as Taiwan, probably as a result of increases in tobacco and alcohol consumption [11].

ETIOLOGIC FACTORS

Hereditary factors — Familial aggregation of esophageal cancer (EC) is present in regions with a high incidence of squamous cell carcinoma (SCC), such as China [12,13]. Familial aggregation

of Barrett's esophagus (BE) is also described [14-16]. Whether this represents common environmental risk factors or inherited predisposition is unknown. Discordant data regarding familial clustering is published in reports from other regions including Sweden and the United States [17-20]. Thus, the extent to which hereditary factors are involved in the pathogenesis of EC remains uncertain.

An increased risk of EC is reported in the following hereditary conditions:

- Peutz-Jeghers syndrome (PJS) is an autosomal-dominant syndrome characterized by multiple hamartomatous polyps in the gastrointestinal tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal (including EGJ) and non-gastrointestinal cancer. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management", section on 'Gastrointestinal cancers'.)

- Germline mutations in the *PTEN* tumor suppressor gene cause autosomal-dominant conditions, such as Cowden syndrome, with variable phenotypic presentations, including hamartomatous gastrointestinal tumors, dermatologic abnormalities, neurologic symptoms, and elevated cancer risk (including rare cases of esophageal cancer) [21]. (See "PTEN hamartoma tumor syndromes, including Cowden syndrome", section on 'Gastrointestinal'.)

Squamous cell carcinoma — The incidence of esophageal SCC varies considerably among geographic regions. The highest rates are in Northern Iran, Central Asia, and North-Central China (the so-called "esophageal cancer belt") [5,22,23]. Geographic variation is also reported within individual countries [24]. Within China, for example, rates of esophageal cancer range from 1.4 to 140 per 100,000 in the Hebi and Hunyuan counties, respectively [25].

Several studies describe risk factors associated with SCC. Their relative importance (from a public health perspective) was estimated in a study that determined the population attributable risk for several of the major risk factors [9]. The authors estimated that a history of smoking, alcohol consumption, and diets low in fruits and vegetables accounted for almost 90 percent of SCC in the United States. The relative importance of specific risk factors may be substantially different in other parts of the world [26]. As noted above, the major risk factors for SCC in the EC belt of Iran and Asia are not well understood, but are thought to include poor nutritional status, low intake of fruits and vegetables, and drinking beverages at high temperatures. (See 'Dietary factors' below.)

Infection with human papillomavirus (HPV) may also contribute to SCC. (See 'Human papillomavirus (HPV)' below.)

Demographic and socioeconomic factors — Worldwide differences in the rates of SCC provide insight into risk factors associated with the disease. The importance of specific risk factors varies within different geographic regions.

- In high incidence regions, the disease has no sex specificity. In contrast, SCC is more common in males in low incidence regions.
- The incidence is higher in urban areas (compared with rural areas) of the United States, particularly among African-American men. In one report, the incidence among African-American males in Washington D.C. was 28.6 per 100,000 [27]. This compares to an overall incidence of approximately 3 to 4 per 100,000 in other parts of the United States.
- Lower socioeconomic status was associated with SCC in a large population-based study [28].

Smoking and alcohol — A nearly unifying cause of SCC worldwide is cigarette smoking and alcohol consumption, although the relative contribution of these and other factors varies geographically [29-34].

An increase in risk of SCC is associated with cigar and pipe smoking, although the magnitude of risk is less than with cigarettes [35,36]. Tobacco and alcohol synergistically increase risk [37]. Smoking and alcohol are also risk factors for other aerodigestive cancers (head and neck and lung), as a result of field cancerization. Patients with one aerodigestive malignancy have an increased risk of synchronous and second primary tumors of the aerodigestive tract compared with the age-matched general population. (See "Epidemiology and risk factors for head and neck cancer" and "Second primary malignancies in patients with head and neck cancers".)

The type and quantity of alcoholic beverages consumed may affect the risk of SCC. Hard liquor may have a higher risk than wine or beer; however, the cumulative amount of alcohol rather than the type is probably more important [38,39]. Individual susceptibility to alcohol may also be involved [40-42]. In one report, for example, variations in the alcohol dehydrogenase genes modulated the risk for aerodigestive cancers [41].

Excessive alcohol consumption is an established, potentially modifiable risk factor for several other malignancies in addition to EC. Associated comorbidities complicate treatment and treatment outcomes by contributing to longer hospitalizations, prolonged recovery, higher health care costs, and greater overall and cancer-related mortality. The American Society of Clinical Oncology (ASCO) issued a statement on the association between alcohol consumption and multiple cancers. It outlines proposals for promoting awareness of the association between alcohol use and cancer, supports evidence-based strategies to reduce the risk of cancer, and

provides education to oncology providers about cancer risk and treatment complications related to alcohol use [43].

Dietary factors — There are several dietary associations with SCC uncovered by studies in Asia. Foods containing N-nitroso compounds are carcinogenic by exerting their mutagenic potential via inducing alkyl adducts in DNA [44]. Certain types of pickled vegetables and other food products consumed in high-risk endemic areas are rich in N-nitroso compounds [45,46]. Toxin-producing fungi (eg, aflatoxin) present in food sources within endemic areas may, in part, exert their mutagenic potential by reducing nitrates to nitroso compounds [47].

Chewing of areca nuts or betel quid (areca nuts wrapped in betel leaves), which is widespread in regions of Asia, is implicated in the development of SCC [48,49]. The mechanism may involve the release of copper, with a resulting induction of collagen synthesis by fibroblasts [50].

High-temperature beverages and foods may increase the risk of EC by generating thermal injury to the esophageal mucosa [51-54]. In a systematic review of 59 studies, more than 50 percent of the studies found that intake of higher-temperature fluids was associated with a statistically significant increase in EC. Few studies reported the results for SCC and AC separately.

An association of SCC with hot tea was noted in a prospective cohort study from Northern Iran. The intake of hot tea (60 to 64°C) or very hot tea, drinking tea within two minutes of pouring (versus after >6 minutes), and drinking ≥700 mL per day of tea at ≥60°C were significantly associated with the development of SCC [54]. In a second cohort study from China, the excess risk of EC associated with consumption of hot tea was highest in those who also smoked and consumed excess alcohol [55].

Several other dietary factors affect the risk of EC; most of these studies come from regions with a high frequency of SCC. These include:

- A positive association between red meat intake and risk of SCC [56,57].
- Low selenium levels increase risk [58,59], while selenium supplementation reduces risk [60-64].
- Zinc deficiency increases risk [65]. It may act by enhancing the carcinogenic effects of nitrosamines [66-68] and by overexpression of cyclooxygenase (COX)-2 [69].
- Low intake of dietary folate increases risk [70,71].
- A meta-analysis of observational studies showed a significant association between higher intake of fruits and vegetables and reduced risk of SCC [72].

Underlying esophageal disease — The presence of specific preexisting esophageal diseases (such as achalasia and caustic strictures) increases the risk of SCC.

- In a population-based study including 1062 patients with achalasia, the risk of SCC was increased more than 16-fold during the first 1 to 24 years following diagnosis. Cancer was detected an average of 14 years after the diagnosis of achalasia [73]. (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Natural history and prognosis'.)

- In a review of 2414 patients with SCC, 63 had a history of caustic esophageal injury due to ingestion of lye during childhood. The average time to diagnosis of SCC was 41 years (range 13 to 71 years) following the ingestion [74]. (See "Caustic esophageal injury in adults", section on 'Screening for esophageal cancer'.)

Prior gastrectomy — Patients with a prior partial gastrectomy may be at increased risk of SCC. One series found that 12 of 115 patients with SCC (10 percent) had a prior partial gastrectomy [75]. This may represent co-existence of common risk factors for disorders predisposing to SCC and partial gastrectomy such as smoking or alcohol. However, another report found that the risk of SCC and AC was not affected by prior gastric surgery [76].

Atrophic gastritis — Atrophic gastritis and other conditions that cause gastric atrophy are associated with an approximately twofold increased risk of SCC (but not AC) [77]. (See "Metaplastic (chronic) atrophic gastritis".)

Human papillomavirus (HPV) — HPV infections (particularly serotypes 16 and 18) are implicated in the pathogenesis of SCC. (See "Human papillomavirus infections: Epidemiology and disease associations", section on 'Disease associations'.)

Several meta-analyses addressed the association between HPV and SCC [78-80].

- An early systematic review and meta-analysis of 66 case-control studies concluded that there was a significant association between HPV infection and SCC (summary odds ratio 3.32, 95% CI 2.26-4.87) [78]. However, HPV prevalence in esophageal SCC was only 22.4 percent, and that of HPV-16, the most frequently observed subtype, was only 11.4 percent. In addition, significant heterogeneity was observed between the included studies. This might be explained, at least in part, by differences in study populations and variability in HPV DNA detection methods. Furthermore, the association was not as strong as that observed for cervical and oropharyngeal cancers. The authors concluded that further studies were needed to clarify the relation between HPV and SCC. (See "Epidemiology, staging, and clinical presentation of human papillomavirus associated head and neck

cancer" and "Human papillomavirus infections: Epidemiology and disease associations", section on 'Oropharyngeal cancer' and "Human papillomavirus infections: Epidemiology and disease associations", section on 'Cervical cancer'.)

- The most recent analysis included 145 prospective or retrospective studies (16,484 patients) evaluating the incidence, risk, and prognosis of HPV 16/18-related esophageal SCCs in adults [80]. HPV detection utilized a variety of techniques that were all DNA-based, mostly polymerase chain reaction. There was a significantly increased risk of esophageal SCC associated with HPV infection (odds ratio [OR] 3.81, 95% CI 2.84-5.11). However, the pooled HPV 16/18 prevalence in individuals diagnosed with esophageal SCC was only 18.2 percent (95% CI 15.2-21.6). Given concerns as to the limited techniques for HPV testing, race of the populations included (mainly Asiatic countries), and lack of adjustment for other factors, the authors concluded that further epidemiologic studies are needed to confirm the association.

While there is evidence of HPV infection based upon antibody testing in a significant subset of patients with SCC esophageal cancers, it is not clear whether the association is etiologic.

Tylosis — Tylosis is a rare disease associated with hyperkeratosis of the palms of the hands and soles of the feet, and an increased incidence of esophageal SCC (picture 1) [81]. The inherited type (Howel-Evans syndrome) is most strongly linked to SCC. It is due to a mutation in the *RHBDF2* gene and is inherited in an autosomal dominant pattern [82,83].

Deletions in this gene are also implicated in sporadic forms of SCC, occurring in 70 percent of patients with SCC in one series [82]. (See "Cutaneous manifestations of internal malignancy".)

A guideline issued by the American Society for Gastrointestinal Endoscopy recommends that affected patients begin endoscopic surveillance at age 30 [84]. The time interval of endoscopic surveillance is not yet established. Generally, endoscopic examination should not be conducted more frequently than every one to three years.

Bisphosphonates — Use of oral bisphosphonates has been linked to esophageal cancer in postmarketing surveillance [85]; however, the results of cohort studies and meta-analyses to evaluate this potential association have been conflicting. Mechanistically, the finding of crystalline material similar to alendronate in biopsies of patients with drug-related erosive esophagitis and the persistence of the abnormalities after healing of the esophagitis suggested the potential for carcinogenicity [86,87]. As a result of these observations, the US Food and Drug Administration (FDA) has recommended that oral bisphosphonates not be used in patients with BE [85].

This subject is discussed elsewhere. (See "Risks of bisphosphonate therapy in patients with osteoporosis", section on 'Esophageal cancer'.)

Upper aerodigestive tract cancer — Several studies describe an association between a current or past history of SCC of the head and neck (ie, oral cavity, oropharynx, hypopharynx, or larynx), lung, or esophagus with synchronous or metachronous SCC of the esophagus [84,88-95]. This probably reflects similar risk factors such as smoking or alcohol. In prospective studies of males with head and neck cancer, the incidence of synchronous or metachronous esophageal cancer ranged from 3 to 14 percent [90-93,95,96]. Metachronous lesions appeared at varying time intervals, and there was no clear decrease in risk with time.

These observations led some authorities to recommend periodic screening endoscopy, but the benefits of this are not established. A guideline issued by the American Society of Gastrointestinal Endoscopy states that there are insufficient data to support routine endoscopic surveillance for patients with previous aerodigestive SCC [84]. However, a single endoscopy may be indicated to identify synchronous EC.

Panendoscopy (with laryngoscopy, bronchoscopy and endoscopy) was also proposed for surveillance; however, guidelines from the American Head and Neck Society do not specifically recommend routine panendoscopy in this setting. (See "Posttreatment surveillance of squamous cell carcinoma of the head and neck".)

Poor oral hygiene — Several studies suggest an association between poor oral hygiene and SCC, particularly in areas (China, Iran, Kashmir) where tobacco smoking and alcohol consumption are not major risk factors [97-101]; a few studies did not support this association [102,103].

Adenocarcinoma — For most of the twentieth century, SCC comprised the vast majority of ECs globally [104]. For the past three decades, however, the frequency of AC and EGJ and gastric cardia cancers has increased dramatically, a finding initially observed in Western countries and more recently in some Eastern countries as well [104-110]. In many epidemiologic series, the incidence of EAC has overtaken that of the previously more common SCC [111-114]. As an example, a cancer registry in the United States estimated that the age-adjusted incidence rates of AC rose progressively from 1.8 per 100,000 in 1987 to 1991 to 2.5 per 100,000 during 1992 to 1996 [115]. White Americans were affected five times more often than Black Americans, and males eight times more often than women, although the incidence among White females is also increasing (see below). A significant increase in the incidence was observed among persons aged 45 to 65.

A later registry study found that in 2009, the incidence among White males was 4.87 per 100,000 and among White females was 0.68 per 100,000 [116]. Compared with 1975, this represented an increase of 685 percent among males and 261 percent among women. Since approximately 1997, overall rate of increase in incidence appears to have slowed.

In contrast, the incidence of gastric cardia AC reached its highest level of 3.3 per 100,000 between 1987 and 1991, subsequently declining to 3.1 per 100,000 between 1992 and 1996. White Americans were affected twice as often as Black Americans, and males five times as often as women. Most patients were older than 60 with no increase among younger cohorts.

Estimates from registries of the incidence of these tumors may be limited by problems related to tumor classification. This was illustrated for gastric cardia AC in a study in which incidence was estimated from a cancer registry in Sweden. The results were compared with a gold-standard population in which classification was based upon detailed review of patient records [117]. It was estimated that the true gastric cardia incidence could be up to 45 percent higher or 15 percent lower than estimates provided by analysis of the cancer registry. The degree to which this observation accounts for the changing epidemiology of gastric cardia AC requires further clarification. A large database study in the United States concluded that the rising incidence of esophageal AC represented a real increase in disease burden and not a reclassification of SCC or adjacent gastric cardia or an overdiagnosis of esophageal AC [118].

Several studies describe risk factors associated with EAC, which will be described below. Their relative importance (from a public health perspective) was estimated in a study that determined the population attributable risk for several of the major risk factors that are known [9]. The authors estimated that a history of smoking, a body mass index higher than the lowest quartile, gastroesophageal reflux disease, and a diet that was low in fruits and vegetables accounted for almost 80 percent of cases of EAC in the United States.

At least some data suggest that interactions between risk factors may be more important than individual risk factors. In a study of 305 patients with esophageal AC and 339 age- and sex-matched controls, reflux was the strongest individual risk factor [119]. However, overall risk was substantially associated with gene-environment interactions (smoking, body mass index, and genetic polymorphisms in five apoptotic genes) that differed in individuals with and without reflux symptoms [119]. Others suggest that age modifies other risk factors. In one study, early-onset esophageal AC was more strongly associated with recurrent reflux and high body mass index (BMI) relative to older age groups [120].

GERD and other causes of esophageal acid exposure — Patients with acid hypersecretory states (such as Zollinger-Ellison syndrome) or other conditions that are associated with

gastroesophageal reflux disease (GERD; such as surgical myotomy, balloon dilation of the lower esophageal sphincter, or scleroderma), may be at increased risk for esophageal AC. Most, if not all, esophageal ACs arise from a region of Barrett's metaplasia, which is due to chronic GERD. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis" and "Barrett's esophagus: Pathogenesis and malignant transformation".)

The role of chronic reflux as an independent risk factor for esophageal AC is not well defined because more than 50 percent of patients have no history of symptomatic GERD. However, reflux symptoms were associated with esophageal AC (odds ratio 7.7) and GC (odds ratio 2.0) in a large case control study from Sweden [121]. The risk was greatest among patients with long-standing (>20 years) and severe symptoms (odds ratio 43.5 and 4.4 for esophageal and gastric cardia AC, respectively). A meta-analysis concluded that at least weekly symptoms of GERD increased the odds of esophageal AC fivefold, whereas daily symptoms increased the odds sevenfold [122]. The increased risk of developing AC of the esophagus and gastric cardia persisted even after anti-reflux surgery [123,124].

Among patients who have BE, the risk of developing EC is increased at least 30-fold above that of the general population, but the absolute risk of developing cancer in patients with Barrett's metaplasia is low (estimated annual cancer incidence 0.12 percent in one population-based Danish study [125]). It is higher in the presence of high-grade dysplasia. There are conflicting reports as to whether the use of proton pump inhibitors reduces the risk of cancer in patients who have BE as a result of chronic GERD [126,127]. (See "Barrett's esophagus: Surveillance and management", section on 'Cancer risk'.)

Endoscopic screening to detect dysplasia is recommended for patients with BE. Specific recommendations for surveillance and issues related to screening for Barrett's metaplasia in patients with GERD are addressed elsewhere. (See "Barrett's esophagus: Surveillance and management", section on 'Surveillance' and "Barrett's esophagus: Epidemiology, clinical manifestations, and diagnosis", section on 'Screening patients for Barrett's esophagus'.)

Smoking — Smoking increases the risk of AC, particularly in patients with BE [128,129]:

As an example, in a pooled analysis of 10 population-based case-control studies and two cohort studies from the International BEACON (Barrett's Esophagus and Esophageal Adenocarcinoma) Consortium, the risk of AC of the esophagus or EGJ was 2.08 times greater in smokers than in a control group [128]. The risk rose with total dose (pack-years of smoking), and it was reduced after smoking cessation, although not to the level of never-smokers.

However, a subsequent meta-analysis specifically examining the risk of EC by histologic type after smoking cessation concluded that risk did not decrease over time for AC [130]. In contrast

to SCC, in which there was a strong risk reduction after five or more years (risk ratio 0.59, 95% CI 0.47-0.75) when compared with current smokers, there was no clear reduction in the risk of esophageal AC over time, with a risk ratio of 0.72 (95% CI 0.52-1.01) 20 or more years after smoking cessation.

Alcohol — A meta-analysis of 20 case-control and four cohort studies including a total of 5500 cases concluded that there was no association between alcohol drinking and esophageal AC risk, even at higher levels of consumption [131].

Obesity and metabolic syndrome — Obesity is linked to a higher risk for esophageal and gastric cardia AC [132] and to BE [133]. A meta-analysis of case control and cohort studies identified a relative risk for esophageal or gastric cardia AC of 1.71 (95% CI 1.5-1.96) for BMI between 25 and 30 kg/m^2, and 2.34 (95% CI 1.95-2.81) for BMI ≥30 kg/m^2 [134]. Obesity did not appear to increase the risk of SCC [132,135].

Obesity may represent an indirect risk factor for both esophageal AC and BE because it increases the risk of GERD by a "mechanical" mechanism (amplified intragastric pressure, disrupted normal esophageal sphincter function, and increased risk of a hiatal hernia) [136,137]. Another possibility is a proinflammatory effect of obesity caused by the secretion of multiple proinflammatory cytokines. A proxy for these obesogenic effects is metabolic syndrome, a constellation of metabolic disorders that includes obesity, impaired fasting glucose, high blood pressure, and dyslipidemia. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)".)

This possibility is supported by the following data:

- A genome-wide association study using data from the Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study suggests that the effects of BMI on esophageal AC and BE risk are independent of GERD [133].
- In an analysis of the linked SEER-Medicare database, metabolic syndrome was associated with the risk of esophageal AC in males without GERD and in females regardless of GERD status [138].

Epidermal growth factor polymorphisms — Certain polymorphisms of the epidermal growth factor gene are associated with higher serum levels of epidermal growth factor, an increased risk of esophageal AC [139], particularly in patients with BE [139].

Helicobacter pylori infection — The observation that *Helicobacter pylori* colonizes areas of gastric metaplasia in the esophagus suggested a potential role in the pathogenesis of

esophageal AC. However, several studies demonstrated that *H. pylori* is not more common and does not have a different distribution in patients with BE than in controls [140-142].

In contrast, *H. pylori* may be a significant factor for cardia inflammation and intestinal metaplasia, a precursor lesion for gastric cardia AC [143]. Cardiac AC may be difficult to distinguish from cancers arising in the distal esophagus, particularly when the disease is advanced. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy".)

The absence of *H. pylori* may be a risk factor for the development of esophageal AC, although disparate data exist [144-147]. A meta-analysis found a significant inverse relationship between the prevalence of *H. pylori* infection and esophageal AC (odds ratio [OR] 0.52, 95% CI 0.37-0.73) but not SCC [148]. In a subsequent case control study, this inverse relationship was independent of environmental and genetic modifiers [149]. A significant inverse association was also observed for BE (OR 0.64, 95% CI 0.43-0.94) [148]. (See "Helicobacter pylori and gastroesophageal reflux disease".)

Use of drugs that decrease lower esophageal sphincter pressure — The association of chronic reflux with the development of esophageal AC suggests that drugs known to decrease the pressure of the lower esophageal sphincter (LES), and hence predispose to reflux, may be a risk factor for BE and possibly AC. However, the strength of this association remains uncertain.

A case-control trial involving 189 patients with newly diagnosed EC who were compared with 262 patients with AC of the gastric cardia, 167 patients with SCC, and 820 population-based controls [150] showed that past use of drugs known to relax the LES (such as nitroglycerin, anticholinergics, beta adrenergic agonists, aminophylline, and benzodiazepines) was positively associated with the risk of esophageal AC (odds ratio 3.8 [95% CI 2.2-6.4] for use >5 years). Assuming a causal relationship, it was estimated that approximately 10 percent of esophageal ACs occurring in males older than age 60 may be attributable to intake of these drugs.

By contrast, in another case control study, an association was detected only between asthma medications (xanthines and beta agonists and not nitrates, calcium channel blockers or benzodiazepines) and BE among persons younger than age 70 [151].

Human papillomavirus (HPV) — The contribution of HPV to the development of esophageal AC is uncertain. Transcriptionally active high-risk HPV infection has been associated with Barrett's dysplasia and AC in some studies [78,152,153]. However, its etiologic significance is unclear [154].

The available data from epidemiologic studies are too limited to confirm an association [78,155,156], and the prevalence of viral infection in EAC appears to be low (13 to 35 percent) compared with other virus-associated cancers [78,152]. (See "Barrett's esophagus: Epidemiology, clinical manifestations, and diagnosis".)

Cholecystectomy — A population-based study from Sweden suggested a possible link between cholecystectomy and esophageal AC (standardized incidence ratio 1.3, 95% CI 1.0-1.8) [157]. The authors speculated that the increased risk may be due to the toxic effect of refluxed duodenal juice containing bile on esophageal mucosa.

Nitrosative stress — As noted above, exposure to nitroso compounds derived from dietary sources is associated with carcinogenesis. The mechanisms by which this might occur are not well understood. A novel mechanism of nitrosative stress from dietary nitrate for the development of AC of the EGJ was proposed based upon preliminary human data and in vitro models [158-160]. High luminal concentrations of nitric oxide are generated at the EGJ and within BE by the reduction of salivary nitrite to nitric oxide by acidic gastric juice. A laboratory model demonstrated nitric oxide production and diffusion into the epithelial compartment where potentially carcinogenic N-nitroso products were generated [160].

Possible protective effect of cereal fiber and other nutrients

- A population-based study from Sweden found an inverse relationship between total dietary cereal fiber intake and the risk of gastric cardia AC (odds ratio 0.3 for the highest versus lowest quartile of fiber intake) [161]. "Highest" was defined as ≥14.7 g/day of cereal fiber from whole-grain bread, crisp bread, oats, muesli, and other cold and hot breakfast cereals, pasta, and rice. High intake of cereal fiber was also associated with a moderately decreased risk of esophageal AC, but not SCC. The authors hypothesized that the protective effects may be due to the ability of wheat fiber to neutralized mutagen formation from the conversion of salivary nitrites to nitrosamines. These data require confirmation before any specific recommendations can be made.

- Other reports found that diets high in fiber, beta-carotene, folate, and vitamins C and B6 were protective while diets high in dietary cholesterol, animal protein and vitamin B12 were associated with an increased risk [162,163]. A meta-analysis found a protective effect from diets high in folate [70].

- Dietary antioxidants, fruits, and vegetables were protective against BE in a case-control study of a United States population [164].

Possible protective effect of NSAIDs — Epidemiologic data suggest that aspirin and other NSAIDs, which inhibit cyclooxygenase (COX), might protect against development of EC, particularly in the setting of BE. In a pooled analysis of individual data from five case-control studies and one cohort study derived from the BEACON Consortium, NSAID users had a significantly reduced risk of EAC (odds ratio [OR] 0.68, 95% CI 0.56-0.82), and there was a trend toward reduced risk of OGJ AC (OR 0.84, 95% CI 0.68-1.02) [165]. The highest frequency (daily or more) and duration of use (≥10 years) were associated with an approximately 40 percent reduction in both esophageal (OR 0.56, 95% CI 0.43-0.73) and EGJ AC (OR 0.63, 95% CI 0.45-0.90). A similar protective effect of NSAIDs was observed among individuals with and without symptomatic GERD.

Despite these data, at least one trial failed to support the benefit for COX2 inhibitors as chemopreventive agents in patients with BE [166]. (See "Barrett's esophagus: Surveillance and management", section on 'Other chemoprevention'.)

PATHOBIOLOGIC DIFFERENCES

The difference in the risk factors for adenocarcinoma (AC), principally Barrett's esophagus (BE) and chronic reflux, suggests a different pathogenesis from squamous cell carcinoma (SCC):

- AC is largely a disease of people who are White and male, with males outnumbering females by as much as 6 to 1 in incidence [167]. One of the largest population-based studies in the United States to examine ethnic differences in the incidence of esophageal and gastric cardia cancer found that the incidence of esophageal AC in non-Hispanic White males was 4.2 per 100,000 per year, double that of Hispanic males and fourfold higher than those of Black and Asian males [168]. By contrast, SCC incidence rates were highest in Black(8.8 per 100,000 per year) and Asian subjects (3.9 per 100,000 per year). The incidence of gastric cardia adenocarcinoma was also increased in non-Hispanic White males (3.4 per 100,000 per year). However, the ethnic differences were less and the sex ratio was comparable for all ethnicities.

- Alcohol is not an important risk factor for AC, and consumption of wine may even be protective. This was illustrated in a population-based study that included 554 patients with newly diagnosed esophageal or gastric cardia adenocarcinomas, 589 patients with newly diagnosed SCC, and 695 control subjects [28]. The risk of esophageal AC was unrelated to beer or liquor consumption and was significantly lessened with wine consumption (odds ratio 0.6).

- Obesity is associated with esophageal AC but not SCC.

Differences in clinical appearance and natural history

Squamous cell carcinoma — The majority of SCCs are located in the mid-esophagus. In general, SCC arises from small polypoid excrescences, denuded epithelium, or plaques [169]. These early lesions are usually subtle, and are easily missed on endoscopy. In a series from Linxian China (where SCC is endemic), biopsy specimens in 25 of 31 patients that contained moderately dysplastic changes or cancer were obtained from sites classified as having either "friability, a focal red area, erosion, plaque, or nodule" [170]. Furthermore, 15 of 16 patients (94 percent) with moderate dysplasia or SCC could be identified in biopsies restricted to only these visibly abnormal areas.

Tissue staining after topical application of stains or pigments such as Lugol's iodide solution (table 1) during endoscopy (chromo-endoscopy) may facilitate diagnosis of early lesions, although the chromoendoscopy technique is uncommonly used in clinical practice (picture 2) [171]. Of the available agents, Lugol's solution is most commonly used in the esophagus. (See "Chromoendoscopy".)

More advanced lesions are characterized by infiltrating and ulcerated masses, which may be circumferential (picture 3). SCC invades the submucosa at an early stage and extends along the wall of the esophagus usually in a cephalad direction [172]. Local lymph node invasion occurs early because the lymphatics in the esophagus are located in the lamina propria. This is in contrast to the rest of the gastrointestinal tract, in which they are located beneath the muscularis mucosa. The tumor spreads to regional lymph nodes along the esophagus, the celiac area, and adjacent to the aorta. Invasion of local structures may result in fistula formation (such as to the trachea). Erosion into the aorta can be associated with massive upper gastrointestinal hemorrhage.

Distant metastases to the liver, bone, and lung are seen in nearly 30 percent of patients. In addition, bone marrow invasion is detected in 40 percent when monoclonal antibodies are used to stain for malignant cells [173].

Adenocarcinoma — Much more is known about the early pathology of esophageal AC because of recognition of early cancer during surveillance of patients with BE [174]. (See "Barrett's esophagus: Surveillance and management".)

The majority of cancers are located near the esophagogastric junction (EGJ) and are associated with endoscopic evidence of BE. Adenocarcinoma arising in BE may present as an ulcer, a

nodule, an altered mucosal pattern, or no visible endoscopic abnormality [175]. Early AC not associated with BE arises from an ulcer, plaque, or nodule near the EGJ [176].

Similar to SCC, lymph node metastases occur early. Involvement of celiac and perihepatic nodes is more common with AC because of the common location of the tumor at the EGJ [177].

Differences in chemotherapy responsiveness — The treatment of advanced esophagogastric cancer has evolved over time. The majority of clinical trials conducted since the mid-1990s included patients with gastric, esophageal, and EGJ cancer, regardless of histology. Although SCCs have come to represent a small minority of patients enrolled in most clinical trials, histologic subtype did not appear to play a major role in response rate or survival duration in patients treated with a variety of cytotoxic chemotherapy regimens for metastatic esophagogastric cancer. (See "Initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer", section on 'Histology, anatomic distribution, and evolution of chemotherapy strategy'.)

However, this has changed as differences in genomic alterations in biologic pathways between SCC and adenocarcinomas are beginning to be elucidated [178]. Treatment for SCC and adenocarcinoma has now diverged with the introduction of molecularly directed therapy for adenocarcinomas of the stomach and EGJ. Therapies targeting human epidermal growth factor receptor 2 (*HER2*; eg, trastuzumab) and vascular endothelial growth factor (*VEGF*; eg, ramucirumab) are applicable only to adenocarcinomas. (See "Progressive, locally advanced unresectable, and metastatic esophageal and gastric cancer: Approach to later lines of systemic therapy", section on 'Ramucirumab with or without paclitaxel' and "Initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer", section on 'HER2-overexpressing adenocarcinomas'.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Esophageal cancer (The Basics)")

SUMMARY

- Esophageal cancer (EC) is the eighth-most common cancer and the sixth-most common cause of death worldwide. For most of the 20th century, squamous cell cancer (SCC) comprised the vast majority of esophageal cancers globally. For the past three decades, however, the frequency of adenocarcinoma (AC) of the esophagus and esophagogastric junction (EGJ) and of gastric cardia cancers has increased dramatically, a finding initially observed in Western countries and more recently in some Eastern countries as well. (See 'Epidemiology' above.)

- Familial aggregation of esophageal cancer has been described in regions with a high incidence of SCC, such as China. Familial aggregation of Barrett's esophagus (BE) has also been described. Whether this represents common environmental risk factors or inherited predisposition is unknown. Thus, the extent to which hereditary factors are involved in the pathogenesis of esophageal cancer remains uncertain. (See 'Hereditary factors' above.)

- The major risk factors for SCC in the United States are smoking and alcohol consumption, but other risk factors, including infection with the human papillomavirus (HPV), may be important in specific regions of the world. The major risk factors for SCC in the "esophageal cancer belt" of Iran and Asia are not well understood, but are thought to include poor nutritional status, low intake of fruits and vegetables, and drinking beverages at high temperatures. (See 'Squamous cell carcinoma' above.)

- The major risk factors for adenocarcinoma of the esophagus are BE, gastroesophageal reflux disease (GERD), smoking, and a high body mass index. A possible protective effect of fiber intake and NSAID use is described. (See 'Adenocarcinoma' above and 'Possible protective effect of cereal fiber and other nutrients' above and 'Possible protective effect of NSAIDs' above.)

- The difference in the risk factors for AC and SCC suggest different pathobiologies. (See 'Pathobiologic differences' above.)

  Clinical appearance, and natural history also differ:

- The majority of SCCs are located in the mid-esophagus. SCC arises from small polypoid excrescences, denuded epithelium, or plaques [169]. These early lesions are usually subtle, and are easily missed on endoscopy. More advanced lesions are characterized by infiltrating and ulcerated masses, which may be circumferential.

- The majority of adenocarcinomas are located near the EGJ and are associated with endoscopic evidence of BE. Adenocarcinoma arising in BE may present as an ulcer, a nodule, an altered mucosal pattern, or no visible endoscopic abnormality. Early AC not associated with BE arises from an ulcer, plaque, or nodule near the EGJ. More advanced lesions are characterized by infiltrating and ulcerated masses, which may be circumferential. Involvement of celiac and perihepatic nodes is more common with adenocarcinomas because of the common location of the tumor at the EGJ.

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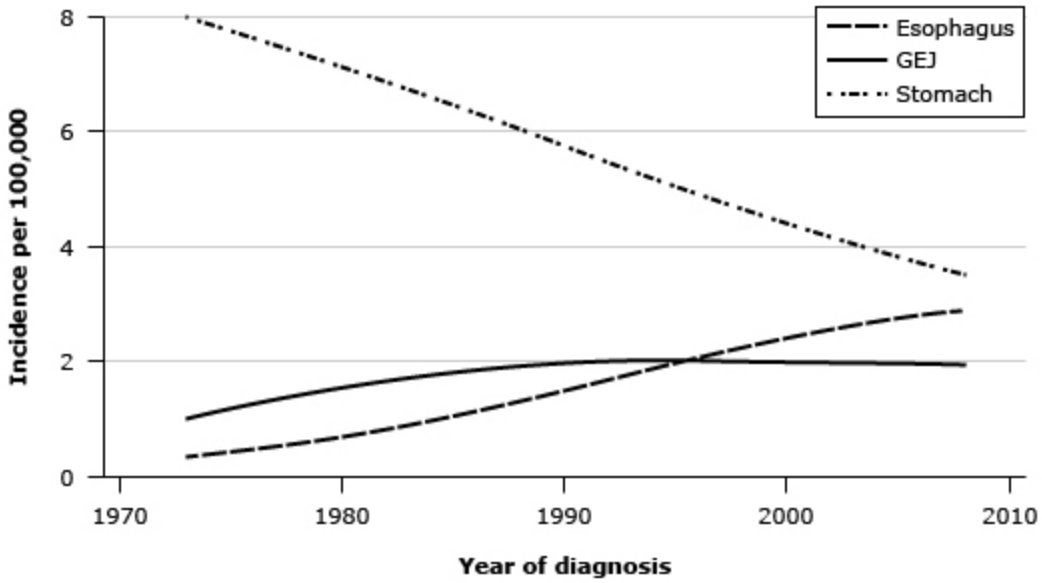
Topic 2274 Version 76.0

GRAPHICS

Incidence of adenocarcinoma of the stomach, esophagus, and GEJ, 1973-2008, United States



GEJ: gastroesophageal junction

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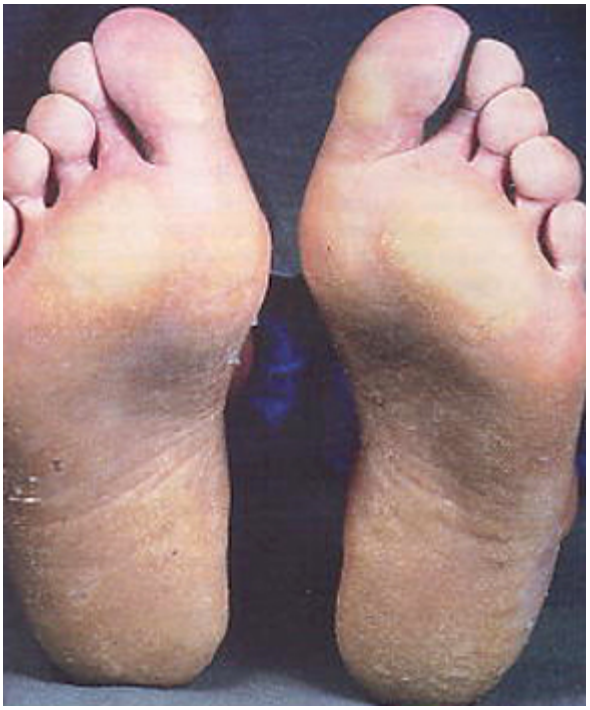
Graphic 103615 Version 1.0

Tylosis



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Tissue stains used during gastrointestinal endoscopy

Stain type	What is stained	Mechanism of staining	Positive staining	Clinical uses in GI
Vital stains				
Lugol's solution (iodine + potassium iodide)	Normal glycogen containing squamous cells	Binds iodine in non-keratinized cells	Dark brown	1) Squamous cell esophageal cancer (non-staining)
				2) Columnar epithelium in the esophagus, including residual Barrett's esophagus following mucosal ablation (non-staining)
				3) Reflux esophagitis (non-staining)
Methylene blue (methylthionine chloride)	Small or large intestinal cells or intestinal metaplasia	Active absorption into cells	Blue	1) Specialized epithelium (intestinal metaplasia) in Barrett's esophagus*
				2) Intestinal metaplasia in the stomach
				3) Early gastric cancer¶
				4) Gastric metaplasia in the duodenum (non-staining)
				5) Celiac and tropical sprue
Toluidine blue (tolonium chloride or dimethylamino-toluphenazothioni-chloride)	Nuclei of columnar (gastric and intestinal-type) cells	Diffuses into cell	Blue	1) Squamous cell carcinoma of the esophagus
				2) Gastric or intestinal metaplasia in Barrett's esophagus
Reactive stains				
Congo red (biphenylene-napthadene sulfornic acid)	Acid-containing gastric cells	Acid pH <3.0 results in color change	Turns red to dark blue or black	1) Acid-secreting gastric mucosa (including ectopic locations)
				2) Gastric cancer (nonstaining); (may be

				combined with methylene blue to outline intestinal metaplasia)
Phenol red (phenolsulfonphthalein)	H. pylori-infected gastric cells	Alkaline pH (from hydrolysis of urea to NH_3 and CO_2 by urease) results in color change	Turns yellow to red	Diagnose Helicobacter pylori infection (positive color change) and map its distribution in the stomach
Contrast stain				
Indigo carmine[Δ]	Cells are not stained	Pools in crevices and valleys between mucosal projections	Blue (indigo)	1) Colon, gastric, duodenal, esophageal lesions
				2) Barrett's esophagus

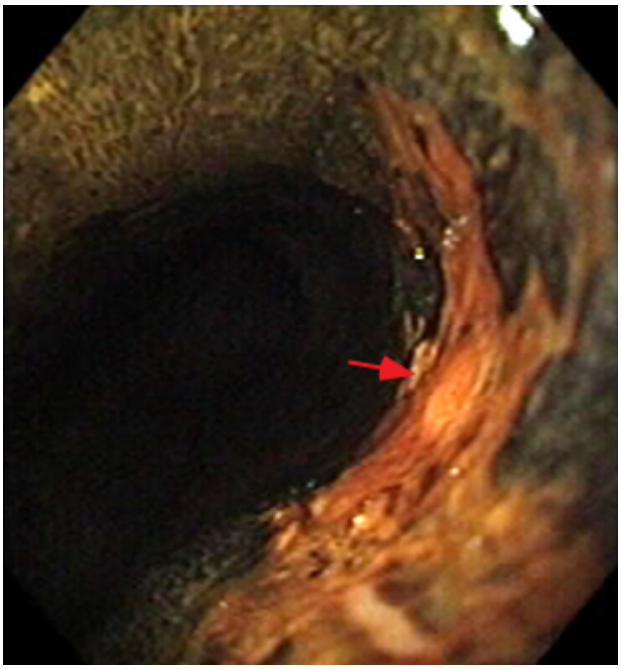
* Methylene blue does not stain non-specialized or gastric metaplasia; specialized columnar epithelium stains blue, but highly dysplastic or malignant specialized columnar epithelium in Barrett's esophagus generally takes up little to no dye; low grade dysplasia in Barrett's esophagus may or may not take up stain.

¶ With or without Congo red.

Δ Also used in combination with high resolution or high magnification endoscopy; may be used with or without crystal violet (for early colorectal cancers).

Graphic 68885 Version 9.0

Chromoendoscopy of esophageal squamous cell carcinoma

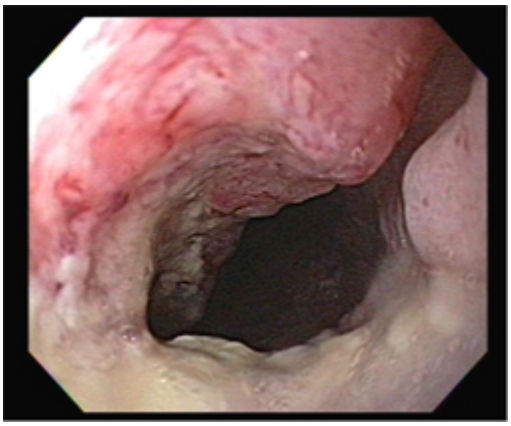


Endoscopic view of the esophagus following staining with Lugol's iodine solution showing squamous cell carcinoma, which appears as an unstained plaque (arrow). The dark brown areas are normal squamous mucosa.

Courtesy of Marcia I Canto, MD, MHS.

Graphic 71269 Version 2.0

Endoscopic appearance of a squamous cell carcinoma of the distal esophagus



Endoscopic view of the distal esophagus showing an infiltrating and ulcerated circumferential lesion.

Courtesy of Andres Gelrud MD.

Graphic 82670 Version 3.0

Contributor Disclosures

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