Epidemiology of Esophageal Adenocarcinoma

MANUEL PERA, MD, PhD,1* CARLOS MANTEROLA, MD, PhD,2 OSCAR VIDAL, MD,1 AND LUIS GRANDE, MD, PhD1
1Section of Gastrointestinal Surgery, Hospital Universitari del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain
2Department of Surgery, Universidad de La Frontera, Temuco, Chile

The incidence of esophageal adenocarcinoma has risen rapidly over the past 25 years in the United States as well as in several Western European countries. This increase had been most dramatic among white males. The majority of these cancers arise from a background of premalignant Barrett esophagus. However, less than 10% of the patients with esophageal adenocarcinoma were known to have Barrett esophagus previously. It is uncertain which risk factors contribute to the increasing incidence of esophageal adenocarcinoma, although gastroesophageal reflux disease, cigarette smoking, and obesity have been implicated. Whereas infection with Helicobacter pylori and use of non-steroidal anti-inflammatory drugs are associated with reduced risk, low intakes of fruit, vegetables, and cereal fibers seem to increase the risk of esophageal adenocarcinoma. Presently there is no evidence that strongly supports any specific strategy to screen a subgroup of the population at risk for Barrett esophagus and adenocarcinoma of the esophagus.


KEY WORDS: esophageal adenocarcinoma; Barrett esophagus; gastroesophageal reflux; obesity

INTRODUCTION

One of the most notable changes in the epidemiology of esophageal cancer is the increasing incidence of adenocarcinoma of the esophagus (ACE) and esophagogastric junction (EGJ) in the United States and western countries over the past two decades. Incidence rates of squamous cell carcinoma (SCC) of the esophagus have been steady or declining along the recent years in these geographical areas. In this review, we will discuss current trends in incidence of esophageal adenocarcinomas as well as the role of different risk factors possibly associated with this epidemiological change.

Demographics Trends of Adenocarcinoma of the Esophagus and EGJ

From 1926 to 1976, surgical series reported that ACE was uncommon, representing only 0.8–3.7% of all esophageal cancers [1–4]. In surgical series reported during the last 15 years from major referral institutions, 60–80% of the patients were diagnosed as having adenocarcinoma of the distal esophagus or EGJ compared with only 10–15% a decade earlier [5–8]. Using the Johns Hopkins tumor registry data covering four decades (1959–1994), Heitmiller and Sharma [9] found that the number of new cases of ACE increased sharply after 1978, and in 1994, for the first time since 1959, the number of patients with ACE exceeded that of patients with esophageal SCC. The changes in the yearly frequency of esophageal SCC and ACE reported in surgical series appear to be the representative of trends reported by epidemiological studies for the general population.

Several population-based studies from United States and Western Europe have now confirmed the rising incidence of ACE and EGJ [10–15]. Data from the SEER program in the United States indicated that the incidence of ACE in white males had doubled from the early 1970s to the late 1980s [15]. Blot et al. [11] showed that the increased frequency for ACE in the United States through the 1980s had been on the order of 5–10% per year. By 1990, adenocarcinomas accounted for nearly half of all the esophageal cancers among white males [10]. Based
on recent incidence trends available from the SEER program through 1998, Brown and Devesa [16] reported that among white males, the incidence of ACE increased from 0.72 per 100,000 inhabitants in 1974–1978, to 3.7 per 100,000 inhabitants in 1994–1998, an increase more than 400%.

The rate of increase in incidence for ACE over the last 25 years was greater than that of any other major malignancy in the United States (Fig. 1). With the concurrent decrease in frequency of esophageal SCC, rates of ACE among white males surpassed those of SCC of the esophagus after 1988. Rates of ACE among white females, although much lower than those among white males, increased more than 300%, from 0.11 per 100,000 inhabitants in 1974–1978, to 0.47 per 100,000 inhabitants in 1994–1998. Whereas ACE rates increased more than 100% in Afro-American males, from 0.35 per 100,000 inhabitants in 1974–1978, to 0.81 per 100,000 inhabitants in 1994–1998, the rates of esophageal SCC among this population subgroup remain significantly higher [16] (Fig. 2). In a comparison study within the U.S. using the SEER cancer registry for the years 1973–1998, Kubo and Corley [17] reported substantial regional, temporal, and ethnic differences in incidence rates between ACE and adenocarcinoma of EGJ. These authors observed higher incidences of ACE and adenocarcinoma of EGJ in Seattle than Utah (5.3 and 4.0 vs. 2.4 and 2.8 per 100,000 person year, respectively). Association with other variables was also verified (male gender and white population were of predilection in both types of adenocarcinomas in all studied regions).

Similar trends have also been seen in Denmark, UK, Switzerland, Sweden, and Norway [13,18–22]. A recent study, using the Eurocim data, found an increase in the incidence of ACE in both sexes in six European countries during the period 1973–1995 [23]. Within the European population, the incidence rates for ACE are highest in Scotland (>9 cases per 100,000 men) compared with other countries analyzed.

These epidemiologic observations for ACE are paralleled by rising rates of adenocarcinoma of the EGJ [11,20,24,25]. Zheng et al. [25] examined the incidence pattern of adenocarcinoma of the EGJ and distal esophagus in Connecticut between 1955 and 1989. For males, adenocarcinoma of the EGJ increased during the study period from 0.6 per 1,000 in 1955–1959 to 3.0 per 100,000 in 1985–1989. For females, adenocarcinoma of the EGJ was low (0.1 per 100,000) and unchanged for the time period between 1955 and 1969; however the rate increased from 0.1 per 100,000 in

---

**Fig. 1.** Relative change in incidence of esophageal adenocarcinoma and other malignancies (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age-adjustment using the 2000 U.S standard population. Baseline was the average incidence between 1973 and 1975. Solid black line, esophageal adenocarcinoma; short dashed line, melanoma; line, prostate cancer; dashed line, breast cancer; dotted line, lung cancer; dashes and dotted line, colorectal cancer. Reprinted from Pohl H et al., The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence, J Nat Cancer Inst 2005;97:142, by permission of Oxford University Press.
1965–1969 to 0.6 per 100,000 in 1985–1989. In the West Midlands (UK), Powell and McConkey [26] reported that the incidence rate of EGJ tumors increased from 0.7 to 2.0 per 100,000 between 1962 and 1981.

The causes for this alarming increase in the incidence of adenocarcinoma of the esophagus and EGJ are unclear. Several studies have confirmed that these trends are real, excluding anatomic reclassification of adenocarcinoma of the gastric cardia as a possible explanation for these increased incidence rates [12,27]. Various risk factors for ACE and EGJ adenocarcinoma have been proposed, including tobacco use, alcohol, dietary factors, medications, obesity, and H. pylori infection, and will be discussed in the following sections. However, it is generally accepted that ACE and a percentage of adenocarcinomas of the EGJ arise from long or short segments of Barrett esophagus (specialized intestinal metaplasia), a condition caused by chronic reflux of acid and duodenal contents into the esophagus [14,28].

Sex, Race, and Age Distribution

ACE and EGJ show similar epidemiologic characteristics that clearly distinguish them from SCC of the esophagus and from adenocarcinomas of the stomach. These features include very high male-to-female ratios at around 7:1 and a higher incidence among whites compared with blacks [11,21,29–31]. Yang and Davis [15] found that the incidence of ACE in the black population was 30% that of the white population. Zheng et al. [25] reported that the male:female ratio of age-adjusted incidence rates in Connecticut was approximately 5.5 for adenocarcinoma of the EGJ and approximately 2.2 for adenocarcinoma of the distal stomach. The white:black ratio for adenocarcinoma of the EGJ has been increasing, mainly reflecting a more rapid increase in the incidence of adenocarcinoma of the EGJ in whites [25]. Adenocarcinomas, either in the distal esophagus or at the EGJ, generally affect patients over 50 years of age, with the peak at around 55–65 years [15]. Devesa and colleagues [12] showed that the increasing trends for ACE and EGJ varied by age, being more predominant among older males: below 65 years, the rates for ACE doubled, whereas the rates for EGJ adenocarcinoma increased by 20%. In contrast, above the age of 65 years, there was a threefold to fourfold increase in ACE and a 60% increase in EGJ adenocarcinoma.

Survival

Sundelof and colleagues investigated the observed and relative survival among patients with ACE and SCC in Sweden, calculating survival rates by the life-table method. Comparing survival among the entire Swedish
population in the same age, sex, and calendar year strata, they verified that 5-year survival rate and 5-year relative survival rate for ACE increased from a stable figure close to 4% and 5% during 1961–1989, respectively, to 10.5% and 13.7% during 1990–1996, respectively [32]. In a more recent study, Polednak et al. [33], using a computer program that included mortality rates for the general population and relative survival rates for patients with ACE and SCC, verified an increase in relative survival rates for ACE and esophageal SCC, and for both males and females from 1975–1979 to 1995–1998, 3-year relative survival rates increased from 10.3% to 20.7% in males, and from 6.6% to 18.6% in females for ACE. These authors suggested that possible explanations for this change were related with improvements in detection from increasing use of endoscopy, improvements in surgical technique and multimodality therapy for early stage cancer.

Gastroesophageal Reflux Disease and ACE and EGJ

Chow et al. [34] compared 196 patients with ACE or EGJ adenocarcinoma with 196 matched controls. Significant twofold or greater risk for adenocarcinoma in both locations were associated with a past history of gastroesophageal reflux disease (GERD), hiatus hernia, esophagitis/ulcer, or dysphagia. The odds ratio increased with increasing number and severity of these conditions. A population-based, case-control study in Sweden found a strong association between symptomatic GERD and the risk of ACE [35]. A similar association, although weaker, was also found for adenocarcinoma of the EGJ, but not for esophageal SCC. Among patients with recurrent reflux symptoms versus those who had no such symptoms, the odds ratios were 7.7 for ACE and 2.0 for adenocarcinoma of the EGJ. In addition, the more frequent, more severe, and longer-lasting the symptoms of reflux, the greater the risk. Among those with long-standing severe reflux symptoms, the odds ratios were 45.5 for ACE and 4.4 for adenocarcinoma of the EGJ. The authors noted reflux symptoms equally often in ACE cases with or without Barrett esophagus. They questioned the role of Barrett esophagus in the carcinogenic pathway. However, 62% of their ACEs had Barrett esophagus, which would be expected in <1% of asymptomatic individuals and in 3–7% of patients with reflux symptoms and no cancer [36].

Similar to the findings of the Swedish Group, Farrow et al. [37] found that both frequent GERD symptoms and a history of hiatus hernia were associated with increased risk for ACE, whether or not the symptoms were treated with H₂ blockers or over-the-counter medications. Neither reflux symptoms nor reflux conditions (hiatus hernia, esophagitis) were associated with increased risk for adenocarcinoma of the EGJ in this multicentre study [37]. The cancer risk for an individual patient with GERD is low. GERD is highly prevalent in the general population and it is estimated that 15–20% of adults have reflux symptoms every week [38]. It has been estimated that in a population of 100,000, over 10,000 subjects would be expected to have reflux symptoms with a corresponding incidence of ACE of only about 2.3/100,000 per year [36]. Barrett esophagus is the probable intermediate stage between GERD and adenocarcinoma [39]. However, on the basis of symptoms alone, it is impossible to identify individuals with GERD who have an associated Barrett esophagus. Shaheen [40] believes that until there is a better way of stratifying cancer risk among patients with heartburn, decreasing the incidence of ACE will be difficult. It has been suggested that among 50-year-old men with symptoms of GERD, one time screening endoscopy for Barrett esophagus and adenocarcinoma of the esophagus may be cost-effective [36,41].

ACE and EGJ and Barrett Esophagus

Barrett esophagus, an acquired condition secondary to GERD, is a metaplastic change of the lining of the esophagus with replacement of the normal squamous epithelium by columnar intestinal-type epithelium [42]. It is now generally accepted that most, if not all, ACEs develop from areas of Barrett esophagus [43]. The prevalence of Barrett esophagus has been estimated at 3–7% in patients with frequent reflux symptoms undergoing endoscopic examination, compared with 1% in patients having endoscopy for any clinical indication [39]. In a population based study, Conio and Cameron found that the incidence and prevalence of clinically diagnosed Barrett esophagus have increased in parallel with increasing use of endoscopy. The rate of newly diagnosed Barrett esophagus increased 28-fold over the years in the study from 0.37 to 10.5 per 100,000 individual years. The incidence changed at a rate similar to the 22-fold increased utilization of endoscopy reported over the same time interval [44]. Prach et al. [45] in Scotland, found 1.4 cases of Barrett esophagus per 1,000 endoscopies in 1980–1981, increasing to 42.7 per 1,000 endoscopies 12 years later, concluding that a true increased incidence of Barrett esophagus had occurred [45].

BE is more common in males than in females, with a ratio of about 2.1. This male predominance increases with the development of Barrett adenocarcinoma, which has a ratio of at least 3:1. The mean age for diagnosis of Barrett esophagus in males (62.0 yrs) is lower than in females (67.5 yrs). The same trends apply to ACE, where the mean age at diagnosis is 64.7 years for males and 74.0 years for females. A recent study from the UK
suggests that the age difference of 20 years for the diagnosis of Barrett esophagus in females may explain, in part, the higher frequency of ACE in males, as many females would not survive long enough to progress to symptomatic ACE [46].

Autopsy data suggest that the majority of individuals with Barrett esophagus are undetected in the general population [47]. Cameron [48] estimates that there are about 1 million individuals with Barrett esophagus in the USA. Most (a “silent majority”) do not know they have the condition, and may not be diagnosed unless endoscopy is performed to investigate symptoms, or progression to ACE occurs. Patients with Barrett esophagus are at risk of developing dysplasia and adenocarcinoma in this metaplastic epithelium. Although the precise risk remains unclear, data from retrospective and prospective studies of patients with Barrett esophagus suggest that the risk for progression to malignancy is approximately 1% per year [49]. However, Shaheen [40] has suggested that cancer risk in Barrett esophagus may be overestimated in the literature due to publication bias, and that an esophageal cancer incidence rate of 0.5% per year might be a more reasonable estimate. Despite an increased risk of ACE, most patients with Barrett esophagus die from other causes [50]. For patients with known Barrett esophagus, endoscopic surveillance for early detection of cancer or dysplasia is probably beneficial [51]. However, optimal endoscopic surveillance intervals may change again based on current information showing a lower estimate of cancer incidence [52]. Endoscopic surveillance programs are not likely to reduce the death rate from ACE in the general population because the majority of patients with Barrett esophagus remain undiagnosed. Recent series of patients with ACE reported that less than 10% were known to have Barrett esophagus before seeking medical attention for symptoms of esophageal malignancy [53–55]. The lack of GERD symptoms in patients with Barrett esophagus may, in part, contribute to this observation [56].

Additional Risk Factors for ACE and EGJ

Tobacco smoking. Tobacco smoking has been reported as a risk factor for ACE and EGJ [57–63]. In a multicenter, population-based, case-control study conducted in 1997, definitive evidence on the effect of cigarette smoking on risk of esophageal and EGJ adenocarcinomas was reported [59]. Risk appears to be more than doubled, with a dose-response pattern among smokers. Little reduction in risk was observed until smoking cessation for more than 30 years, in contrast to the steady decrease in risk observed after quitting cigarettes for other smoking-related cancers such as the cancer of the lung and SCC of the esophagus. Gammon et al. [59] suggested that smoking may affect the induction of ACE at an early stage in carcinogenesis. Although these data support the role of tobacco as an etiologic risk factor for ACE and EGJ, it does not explain the rising incidence of these tumors at a time when SCC of the esophagus is stable or decreasing in incidence, and considering recent reductions in the prevalence of cigarette smoking in the general population [64]. More recently, Lagergren and colleagues tested the association between tobacco and the risk of ACE and EGJ in a case-control study in Sweden. Although smoking was associated with EGJ adenocarcinoma, and was dose-dependent (OR = 4.2, 95% CI = 2.5–7.0 among heavy smokers compared with never-smokers), the risk for ACE with smoking was weak or absent, and it was concluded that tobacco smoking does not play an important role in the etiology of ACE [60].

Alcohol. To date, several observational studies have failed to find a consistent association between alcohol consumption and risk of ACE and EGJ [59,61–63,65].

Obesity. Obesity has assumed epidemic proportions in the United States and Europe and is a risk factor for a number of chronic diseases as well as for a number of different types of cancer (colorectum, postmenopausal breast, endometrium, gallbladder, prostate, bladder, thyroid, and connective tissue) [66–69]. A multicenter population-based, case-control study revealed that excess weight is a strong risk factor for ACE, with risk rising with increasing body mass index (BMI) [70]. To a lesser extent, excess weight increased the risk of EGJ adenocarcinoma while no effect was seen for gastric adenocarcinoma or esophageal SCC. The positive association between risk of ACE and usual BMI was significantly modified by age, with the greatest increase in risk seen among the youngest group (ages <50 years). This observation suggests that obesity is particularly important for early-onset tumors, while other risk factors may assume a more prominent role for tumors developing in the later years [70]. The mechanism by which overweight might affect the risk of ACE and EGJ remains to be identified. One hypothesis suggests that obesity by increasing the risk of hiatal hernia and GERD would presumably increase the risk of Barrett esophagus, the precursor lesion for ACE [71]. However, two studies have shown that obesity per se is a strong risk factor for ACE and EGJ, independent of GERD [35,70]. A population-based study showed that the risk of ACE and EGJ adenocarcinoma increased in a linear manner with increasing BMI and reflux severity, and these risk factors combined in a multiplicative manner [65]. Among obese individuals (BMI > 30 kg/m²) with reflux symptoms, the odds ratio was 179.2 for ACE and 12.2 for EGJ adenocarcinoma, compared with lean individuals (BMI < 22 kg/m²) without reflux symptoms. However, the absolute risk of
developing ACE and EGJ adenocarcinoma is still very low. These authors also assessed the benefits of endoscopic screening of individuals with various combinations of BMI and GERD symptoms. Despite impressive risk estimates, they found no evidence to support general endoscopic surveillance among individuals with reflux symptoms, although in the small group of very obese men with severe GERD symptoms, surveillance might be warranted. In a recent multicenter, population-based case-control study, Engel et al. [58] confirmed that BMI above the lowest quartile was associated with a 41.1% risk for developing ACE.

**Diet and nutrition.** The potential role of dietary factors has attracted considerable attention in previous epidemiologic studies. Most of the available data, however, relate to esophageal SCC, and information about dietary factors for ACE remains sparse. At least three case-control studies identified high intake of dietary calories and fat as strong risk factors for ACE and EGJ [64,72,73]. Several studies have suggested that some nutrients could be considered as protective factors against ACE and EGJ adenocarcinoma, including fruits and fresh vegetables, lutein, niacin, β-carotene, folate, iron, zinc, and vitamins B6, B12, and C [62,64,71,74,75]. A multicentre population-based, case-control study in England and Scotland showed that high BMI in early adulthood and low consumption of fruit were important risk factors for ACE in women [76]. These authors found that these two factors accounted for 90% of the risk for ACE in this population. Antioxidants (vitamin C, β-carotene, alphatocopherol) have the potential to neutralize the harmful effects of DNA-damaging free radicals, such as those produced by smoking, and these nutrients have generally emerged as protective factors in previous studies of esophageal SCC [77,78]. Terry et al. [78] observed that higher intakes of antioxidants were associated with similarly decreased risks of ACE. These authors also suggested that the inverse association between antioxidants and risk for ACE was stronger among individuals with GERD as well as among smokers [78].

To date, four case-control studies have reported a protective effect of dietary fiber and risk of ACE [64,71,73,79]. Terry et al. [75] found a strong inverse association between fiber intake and EGJ adenocarcinoma. This inverse association was related almost entirely to the intake of cereal fiber, whereas fiber from fruit and vegetables was essentially unrelated to risk [75]. Although a protective trend for high fiber intake and ACE was observed, this was not statistically significant. These authors hypothesized that saliva and swallowed air contribute to high nitrosamine concentrations in the most proximal part of the stomach [75], and under acidic conditions, wheat fiber would act as a strong scavenger of nitrites.

Finally, recent studies implicated low serum selenium levels as a risk factor for ACE and EGJ [80,81].

![Diagram of risk and protective factors related with adenocarcinoma](image)

- **Protective factors**
  - H. Pylory
  - Selenium
  - Dietary fiber
  - Antioxidants
  - Fruits and vegetables

- **Risk factors**
  - H. Pylory
  - Relaxing LES drugs
  - Obesity
  - Fat intake
  - Alcohol
  - Tobacco
  - Dysplasia
  - Barrett
  - GERD

0 : No evidence
0.5 : It has been suggested
1 : Slight evidence
2 : Middling evidence
3 : Strong evidence

Fig. 3. Summary of the risk and protective factors related with adenocarcinoma of the esophagus and esophagogastric junction. LES, Lower esophageal sphincter; GERD, Gastroesophageal reflux disease.
speculated that selenium may act primarily during later stages of progression towards ACE. Evidence from laboratory and population-based studies suggests that some selenium-containing compounds may have anticarcinogenetic effects, and results from a cross-sectional study of individuals with Barrett esophagus suggest that higher serum selenium levels may be associated with a reduced risk of ACE [80].

Medications use. Lagergren et al. [82] investigated whether medications that promote GERD (by relaxing the lower esophageal sphincter) are associated with increased risk for ACE. It was found that daily long-term users (>5 years) of any of these medications had an increased risk (OR 3.8, 95% CI 2.2 to 6.4) compared with individuals who had never used these drugs. This association was particularly strong for anticholinergics. Adjustment for reflux symptoms almost eliminated this association, leading these investigators to suggest that such medications may promote ACE by increasing reflux. It was suggested that long-term use of drugs that promote lower esophageal sphincter relaxation might be responsible for about 10% of the ACEs. However, since ACE is still a rare disease, the absolute risk for an individual patient taking such medication is actually very low [83].

By contrast, use of aspirin and other non-steroidal anti-inflammatory drugs is reported to be associated with a 50–90% reduction in the risk of ACE [84–87].

Helicobacter pylori infection. The results of a meta-analysis have confirmed quantitatively that while H. Pylori is an important risk factor for non-cardia gastric cancer, it is not associated with increased risk for adenocarcinomas of the EGI [88]. The risk for gastric adenocarcinoma and its precursor lesion (atrophic gastritis) is associated particularly with CagA + compared with CagA – strains of H. pylori [89]. By contrast, an inverse relation between CagA + strains of H. pylori infection and risk for ACE and EGJ adenocarcinoma has been reported [90–92]. It has been suggested that the increasing incidence of ACE and EGJ is linked to declining rates of H. Pylori infection in western countries. It will be of future interest to evaluate whether variations in acidity and content of refluxate are involved in the mechanism by which H. pylori strains may affect the risk for ACE (90).

SUMMARY

The incidence of ACE is increasing rapidly in western countries, however, the reasons for this epidemiological change remain unclear. A summary of protective and risk factors for ACE and EGJ is shown in Figure 3. Barrett esophagus represents the precursor lesion for most of these tumors but the majority of individuals with this condition remain unrecognized in the general population. Identification of high-risk groups at risk for progression to ACE remains an urgent challenge for the next several years. Recent data also suggest that ACE may be preventable through dietary intervention.

REFERENCES