Epidemiology and Risk Factors for Esophageal Cancer

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Introduction

Esophageal cancer has a long and fascinating history and the epidemiology is geographically dynamic with wide variation from region to region [1]. There have been several recent publications reporting the global epidemiology of esophageal cancer. The majority of these published papers have used the International Agency for Research on Cancer (IARC) databases (e.g., GLOBOCAN 2012) data as the basis for any data analysis conducted. Esophageal cancer remains the eighth most common cancer worldwide, with 455,784 new cases in 2012, and it is the sixth most common cause of death from a cancer with approximately 400,156 deaths annually [2]. Figures 1.1 and 1.2 show the breakdown of new cases and deaths associated with esophageal cancer by gender and also comparing developed and developing countries. Future predictive models estimate that by the year 2035, the number of new cases of esophageal cancer will almost double to 808,508 and the number who will die from the disease will reach 728,945 individuals in that year, making it an enormous cancer burden globally [3]. In fact, it is one of a handful of cancers for which the number of new cases in some regions of the world is actually increasing [4], with average annual increase ranging from 3.5% in Scotland to 8.1% in Hawaii [5]. It is disappointing, given the increases in rates of esophageal cancer and the continued poor prognosis for this cancer, that it receives very little attention relative to other cancers; however, there has recently been a call for a greater research focus and funding for male-dominated cancers like esophageal cancer [6]. There is an urgent need for cancer research organizations to provide increased and dedicated funding to gain a greater understanding of the dynamic epidemiology of esophageal cancer. This will be crucial to determine the causes and risk factors associated with

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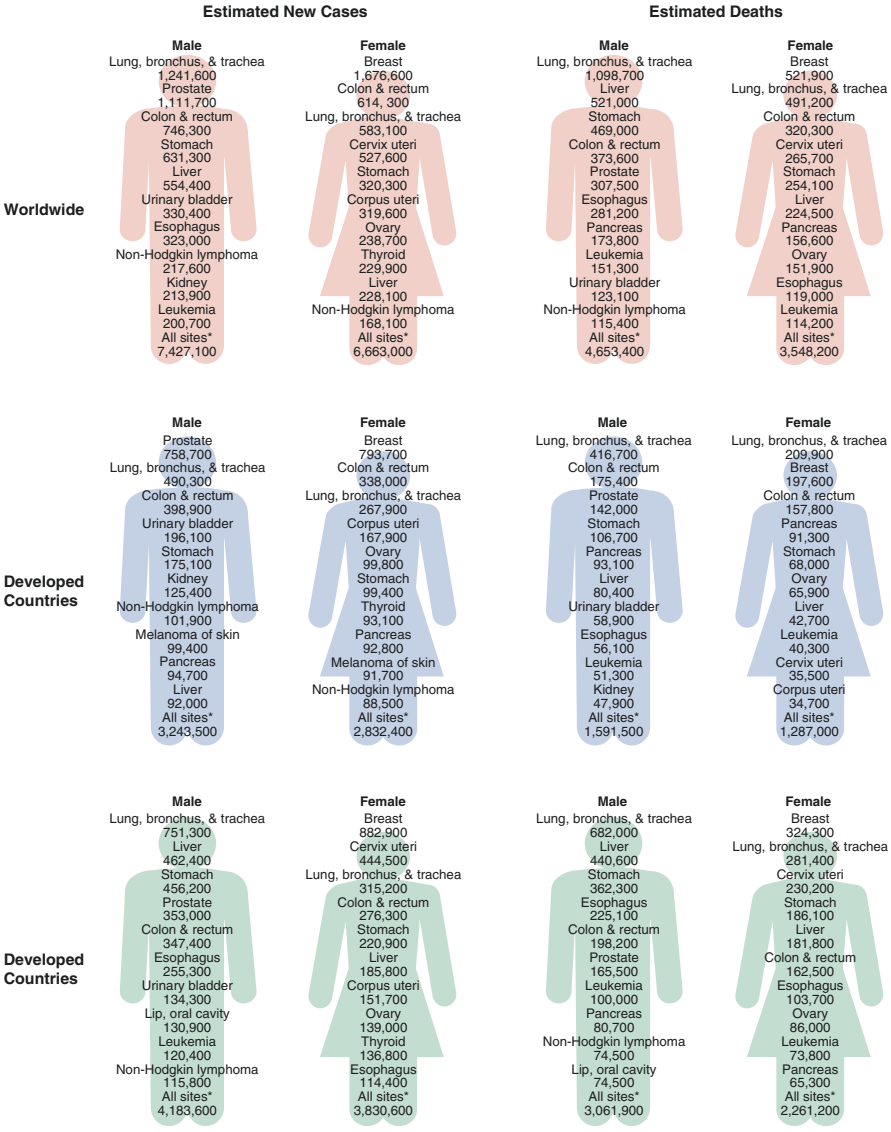

Fig. 1.1 The incidence and mortality for all cancers, note esophageal cancer

developing this lethal cancer and, more importantly, form the cornerstone of developing any prevention strategies.

There are two main histological types of esophageal cancer: adenocarcinoma and squamous cell carcinoma [7]. The epidemiology and risk factors for esophageal cancer vary substantially by these two different histological cell types. Published studies usually categorize esophageal cancer studies into either "adenocarcinoma" or "squamous cell carcinoma" histological types or a combined "esophageal cancer" grouping which contains both histological types.

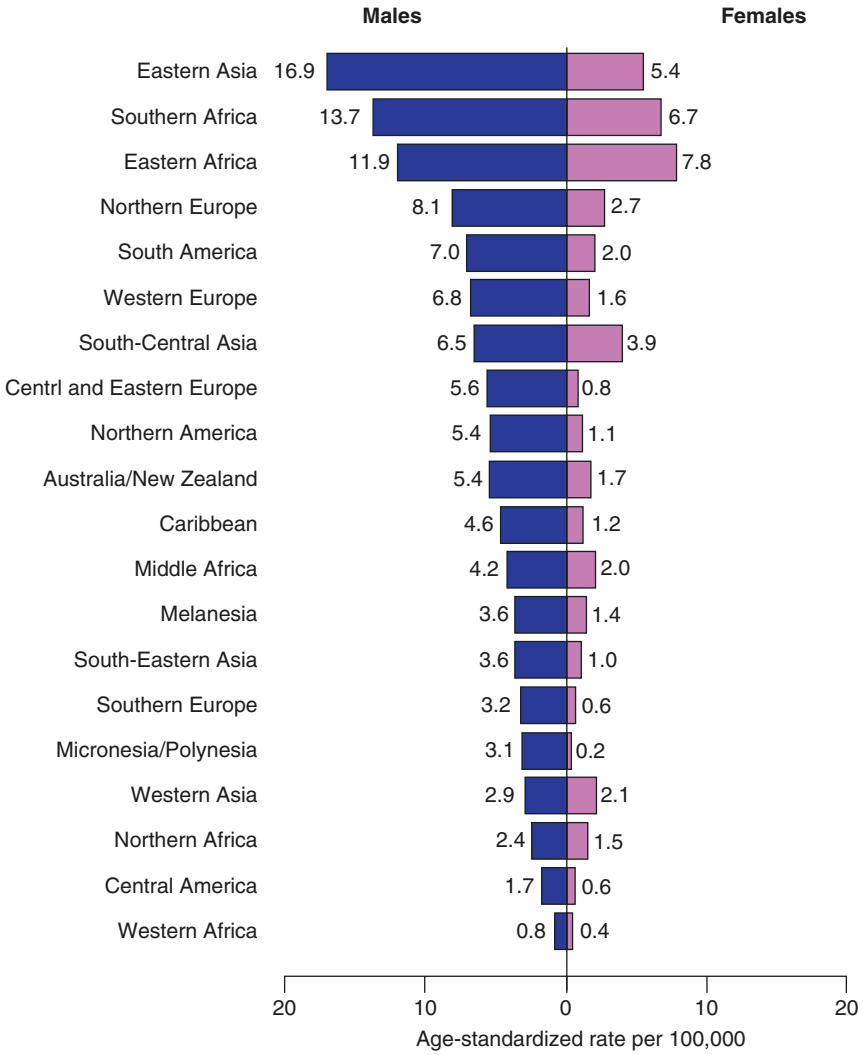

Fig. 1.2 Age-standardized incidence rates of esophageal cancer among males and females globally (GLOBOCAN 2012)

Epidemiology

Incidence

Esophageal Adenocarcinoma

The global age-standardized incidence rate of esophageal adenocarcinoma (EAC) was estimated at 0.7 per 100,000 (1.1 in men and 0.3 in women) in 2012, with 52,000 estimated cases occurring during the year [8]. The highest incidence rates

were observed in Northern and Western Europe (3.4 in men and 0.6 in women), Northern America (3.5 in men and 0.4 in women), and Oceania (3.4 in men and 0.6 in women)—contributed to mainly by Australia and New Zealand—while the lowest rates were found in Eastern/Southeastern and Central Asia (0.6 in men and 0.2 in women) and sub-Saharan Africa (0.4 in men and 0.2 in women) [8]. The highest national rates were observed in the UK (7.2 in men and 2.5 in women), the Netherlands (7.1 in men and 2.8 in women), Ireland (5.4 in men and 2.9 in women), Iceland (3.9 in men and 2.7 in women), and New Zealand (4.0 in men and 1.5 in women), while the highest absolute incidence occurred in the United States, with 10,000 cases occurring in 2012, of which 88% were in men [8].

In the United States, there has been a disturbing trend in which the number of new cases of EAC has been increasing faster than that of any other cancer, and incidence data suggests that this increase commenced sometime in the mid-1970s. The reasons for this dramatic increase in EAC are multifactorial and complex and are not explained by known risk factors. Data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database have shown an increase in the incidence of EAC from 0.40 cases per 100,000 in 1975 to 2.58 cases per 100,000 in 2009, with an average annual percentage increase in incidence of 6.1% in men and 5.9% in women during the period from 1975 to 2009 [9]. Interestingly, geographic variability was observed in the incidence of EAC across the United States, with the highest age-standardized incidence rates observed in the Northeast and Midwest and the lowest observed in the South and West [10]. Likewise, the annual percentage change over the 10-year period from 1999 to 2008 varied widely, a 3.19% annual increase for men in the Northeast, in contrast to the 0.80% annual increase observed in the West [10]. The increase in EAC incidence is predicted to continue until 2030 with a plateauing trend, reaching 8.4–10.1 cases per 100,000 person-years for males and 1.3–1.8 per 100,000 person-years for females [11].

In Europe, increasing EAC incidence trends were observed in most countries during the period from 1980 to 2002, with the steepest increases observed in the male population in Denmark, the Netherlands, England, and Scotland, where the incidence of EAC has overtaken that of esophageal squamous cell carcinoma [12]. Overall, the age-standardized incidence rate in Northern and Western Europe was 3.4 per 100,000 for men and 0.6 per 100,000 for women in 2012 [8].

Esophageal Squamous Cell Carcinoma

Globally, esophageal squamous cell carcinoma (ESCC) is the more commonly occurring of the two histological subtypes, with 398,000 estimated incident cases in 2012 and a global age-standardized incidence rate of 5.2 per 100,000 (7.7 in men and 2.8 in women). The highest incidence rates occurred in Eastern/Southeastern Asia (13.6 in men and 4.3 in women), sub-Saharan Africa (6.4 in men and 4.0 in women), and Central Asia (5.9 in men and 3.6 in women) [8]. The highest estimated national rates were calculated for Malawi, Turkmenistan, Kenya, Mongolia, and Uganda [8]. The lowest incidence regions were North America (1.7 in men and 0.7 in women), Oceania (2.0 in men and 1.2 in women), and Southern Europe (2.4 in men and 0.4 in women) [8].

Approximately 80% of ESCC cases in 2012, or 315,000 cases, occurred within what is termed the "esophageal cancer belt," an area stretching across Central to Eastern Asia from the Caspian littoral region through Iran, Iraq, and Kazakhstan to the northern provinces of China [8]. Additionally, 210,000, more than half of all ESCC cases, occurred in China in 2012 [8]. This dramatic concentration of ESCC cases to this particular geographical area is likely to reflect local risk factors.

In China, 2015 data reported that esophageal cancer (predominantly squamous cell carcinoma) was the fourth most commonly diagnosed and the leading cancer cause of death for both males and females [13]. Data analyzed between 2000 and 2011 revealed that the incidence of cancer of the esophagus had decreased for both males (annual percentage change −3.2) and females (annual percentage change −5.5). Mortality rates also decreased for both males (annual percentage change −6.1) and females (annual percentage change −6.4) during this period.

In the United States, the national age-standardized incidence rate for ESCC is 4.93 per 100,000 in men and 2.30 per 100,000 in women [10]. In contrast with the trends observed in EAC, incidence rates of ESCC in the United States have been decreasing at a rate of around 3% per year in both genders and across regions, which has generally been attributed to a decrease in the practice of smoking [10, 14]. Figure 1.3 shows that ethnic variation exists within the United States for esophageal cancer rates. An excellent graph highlights the differences between States in North America in terms of both EAC and ESCC by gender (Fig. 1.4).

This trend has been mirrored in Europe, where ESCC incidence has been decreasing or stabilizing over the last several decades in most countries [10]. The incidence

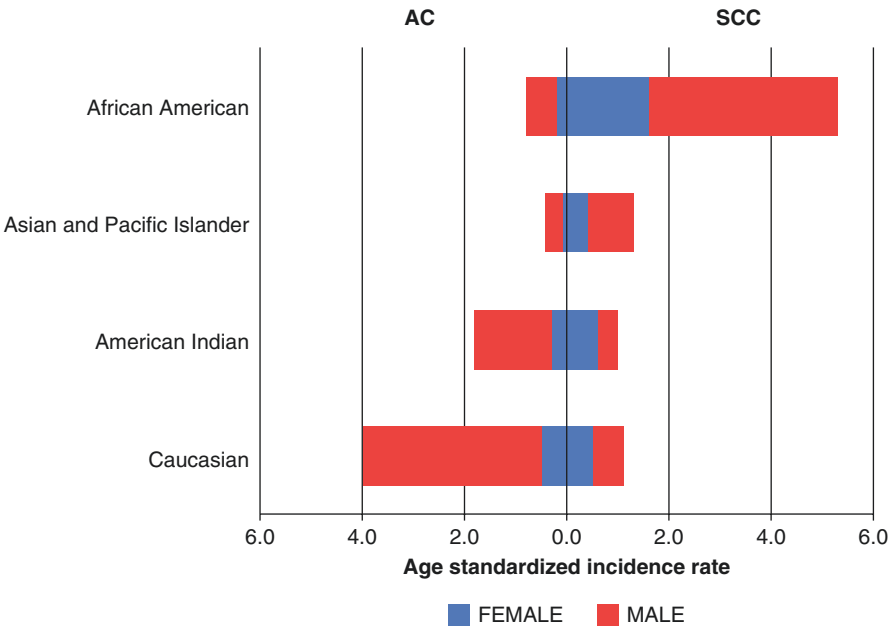

Fig. 1.3 Incidence rates of esophageal cancer in the United States by ethnic group

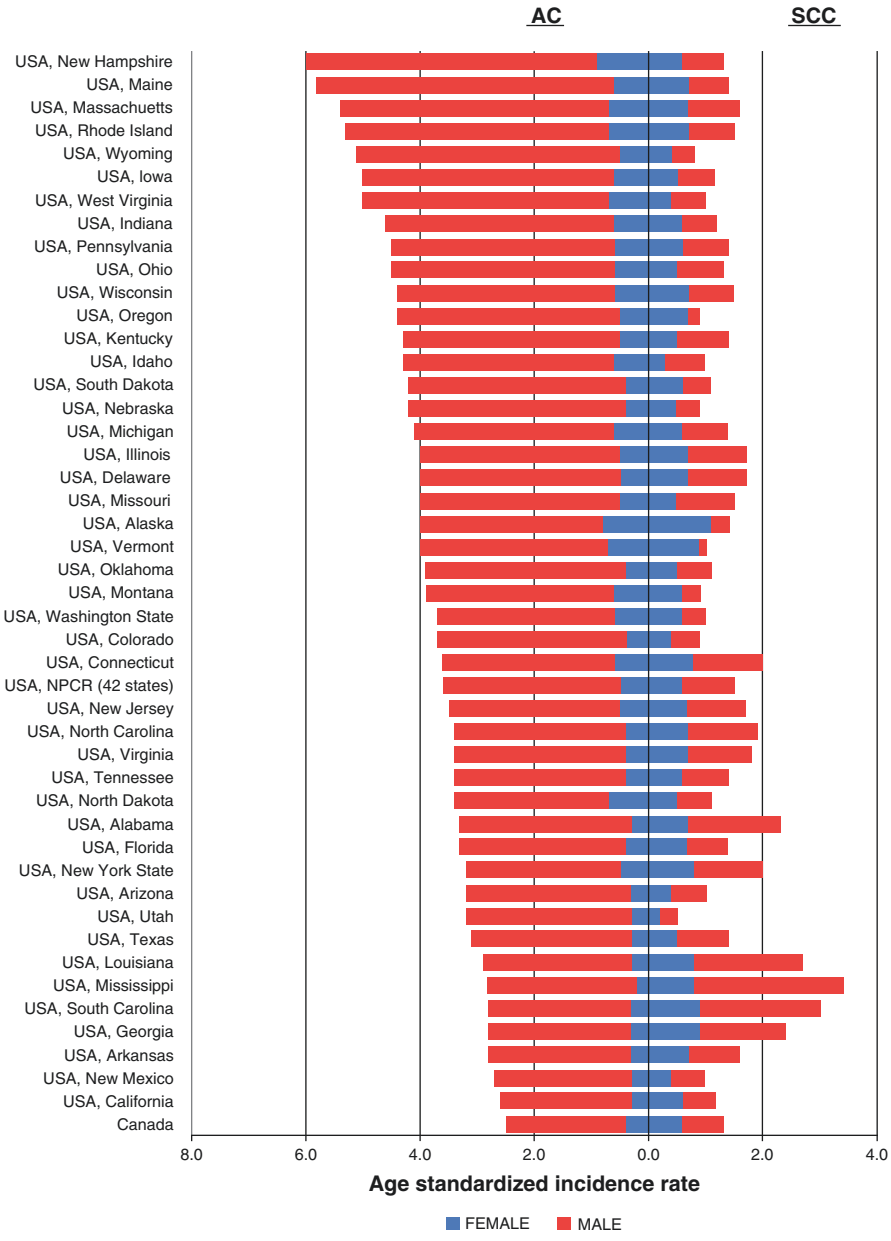

Fig. 1.4 Age-standardized incidence rates in the United States and Canada

rates in most European countries were between 2 and 4 per 100,000 in 2002, with the exceptions of France, which although experiencing a steep decrease in incidence over the last couple of decades still had an incidence rate of above 5 per 100,000, and Slovenia, which has not followed the trend and has actually seen an increase in ESCC incidence rates from just below 2 per 100,000 in 1980 to around 5 per 100,000 in 2002.

Mortality

In the United States, the estimated number of deaths from esophageal cancer in 2018 was 15,850, with a large male predominance (12,850 male deaths versus 3000 female deaths) [15]. The mortality rate from esophageal cancer increased from 4.67 to 5.44 cases per 100,000 during the period from 1993 to 2007 for white males and experienced only a minor increase from 0.76 to 0.77 in white females during the same period [16]. Esophageal cancer mortality rates are predicted to increase in the United States, with most of the deaths contributed to by EAC [11]. Cause-specific EAC deaths for years 2011–2030 are estimated to range between 142,300 and 186,298, almost double the number of deaths in the past 20 years, and EAC mortality rates are estimated to reach 5.4–7.4 cases per 100,000 person-years for males and 0.9–1.2 cases per 100,000 person-years for females by 2030 [11].

In EU, decreasing trends were observed for esophageal cancer mortality in males in a number of several southern and western European countries, and in central Europe mortality has also stabilized or declined since the mid-1990s [12]. In some northern European countries, mortality rates from esophageal cancer are still increasing, likely due to the continued increase in EAC observed in that region. Similar to the situation in the United States, the female mortality rate from esophageal cancer in Europe was comparatively low and remained stable or decreased [12]. Overall, deaths from esophageal cancer have declined in European men, from 5.34 to 4.99 per 100,000 during the period from 2000 to 2009. European women also experienced a modest decrease in mortality during this period, from 1.12 to 1.09 per 100,000 [12]. European mortality rates from esophageal cancer are predicted to decline to 4.46 per 100,000 men (resulting in approximately 22,300 deaths) and 1.07 per 100,000 women (resulting in approximately 7400 deaths) by 2015 [12]. Significantly, the predicted mortality rate for UK men is 8.51 per 100,000 by 2015, above the European average [12], which again is likely due to the expected continued increase in EAC incidence.

A recent analysis of esophageal cancer mortality data shows that Bulgaria and the Philippines have escalating rates of cancer death among females [17]. These results can be seen in Fig. 1.5, which also shows changes in incidence and mortality rates for other countries.

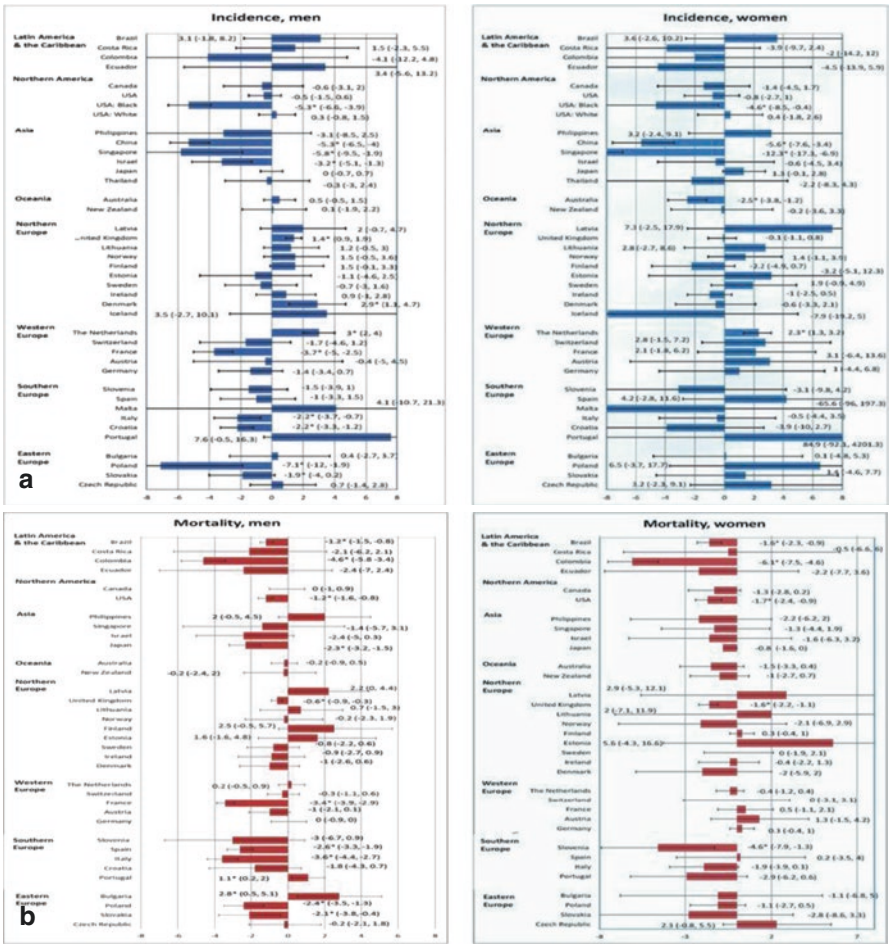

Fig. 1.5 (A) Incidence trend of esophageal cancer in males (left panel) and females (right panel). (B) Mortality trend of esophageal cancer in males (left panel) and females (right panel)

Survival

Esophageal cancer remains a rapidly fatal disease. The current 5-year survival rates are 19% in the United States [15] and 12% in Europe, with the highest European rate observed in Belgium (21.8%) and the lowest occurring in Lithuania (5.7%) [18]. There is generally no difference reported in survival between the two histological types, EAC and ESCC [18].

One study which did investigate EAC separately reported improved 5-year relative age-adjusted EAC survival rates in the United States since 1975, with the greatest improvement observed in cases with localized disease [9]. The 5-year survival rate in this group has increased from only 2.1% in 1975 to just over 50% in 2009 [9]. The 5-year survival for all stages of EAC in the United States has increased from just under 5% in 1975 to just over 20% in 2009 [9].

Risk Factors

An evidence-based approach has been taken with this section of the chapter. Where possible, meta-analyses or systematic reviews of the literature were used to summarize the current level of evidence for each risk factor.

Esophageal Adenocarcinoma

The risk factors for EAC are presented diagrammatically in Fig. 1.6 and are discussed individually below.

Age and Gender

The majority of individuals with EAC are aged 50–60 years [19]. The incidence of EAC has a strong male preponderance. Globally, the incidence of EAC was

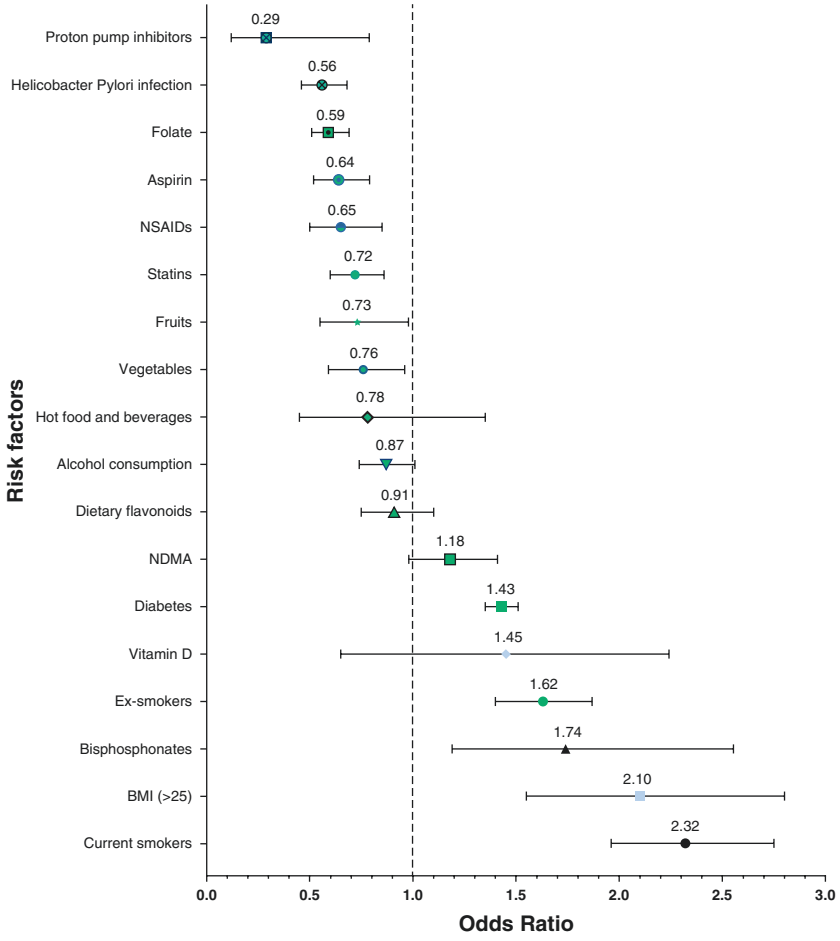

Fig. 1.6 Risk factors associated with esophageal adenocarcinoma

estimated to be 1.1 per 100,000 in men and 0.3 per 100,000 in women in 2012, a difference in incidence of over threefold [8]. The difference was most obvious in the highest incidence areas of Northern and Western Europe (3.4 in men and 0.6 in women), Northern America (3.5 in men and 0.4 in women), and Oceania (3.4 in men and 0.6 in women). Also striking are the predicted incidence rates in 2030, which are estimated at 8.4–10.1 cases per 100,000 person-years for males and 1.3–1.8 per 100,000 person-years for females [11].

Ethnicity

Several studies have found that Caucasians are more likely to develop EAC compared to ESCC. Most recently, two studies conducted in 2017 afforded further evidence that Caucasians had a higher risk of developing EAC. The first study compared Caucasian individuals to Africans, non-white Hispanics, Asians, Pacific Islanders, and Native Americans, concluding that Caucasians were more likely to develop EAC ($p < 0.002$) [20]. The second study confirmed this finding, reaffirming that the incidence rate of EAC was higher in Caucasians than in Asian and African ethnic groups upon analysis of the SEER database ($p < 0.05$) [21]. This study also suggested that molecular patterns associated with the relevant genes for EAC are similar between Asians and Caucasians (however, small differences do preside) and that these differences may be crucial in tumorigenesis and personalized treatment.

Eating Disorders

Obesity

A 2015 review found a consistent relationship in which patients with higher-than-normal BMIs had a higher risk of developing EAC compared to patients with normal BMI. Patients with BMI ≥40 kg/m^2 had a higher risk of developing this cancer (OR, 4.76, 95% CI, 2.96–7.66), compared to patients with BMI 35–39.9 kg/m^2 (OR, 2.79, 95% CI, 1.89–4.12), BMI 30–34.9 kg/m^2 (OR, 2.39, 95% CI, 1.86–3.06), and BMI 25–29.9 kg/m^2 (OR, 1.54, 95% CI, 1.26–1.88) [22].

As discussed above, there has been a dramatic increase in the incidence of EAC over the last several decades in many Western countries such as the United States, the UK, and the Netherlands. One of the contributing factors to this increase is thought to be the obesity epidemic, which has risen to prominence during a similar time period. Obesity is linked with gastroesophageal reflux disease (GERD) and Barrett's esophagus, a precursor lesion to EAC. A meta-analysis conducted in 2012 found a positive association between a body mass index (BMI) between 25 and 30 and EAC (relative risk (RR), 1.71, 95% confidence interval (CI), 1.50–1.96) [23]. The risk increased even further for BMI ≥ 30 (RR, 2.34, 95% CI, 1.95–2.81) [23]. The continuous RR for a 5-point increase in BMI was RR 1.11 and 95% CI 1.09–1.14 [23].

This is a consistent finding, with an earlier meta-analysis likewise finding an increased risk of EAC associated with a BMI of over 25 (males, OR, 2.2, 95% CI, 1.7–2.7; females, OR, 2.0, 95% CI, 1.4–2.9) [24]. A population-based study from Australia which included 367 EAC patients also reported an increased risk for BMIs of 30–35 (OR, 2.1, 95% CI, 1.4–3.1) which increased almost threefold (OR, 6.1, 95% CI, 2.7–13.6) for BMIs over 40, after adjusting for reflux [25].

Bulimia Nervosa

Historically, it has been proposed that the risk of EAC may be elevated in individuals who suffer from eating disorders like bulimia, caused by the acidic damage to esophageal mucosa in the process of self-induced vomiting [26]. A retrospective 2015 study reported seven cases that were hospitalized for anorexia nervosa, later developing ESCC (SIR, 6.1, 95% CI, 2.5–12.6), with a mean interval period of 22 years. However, this did not support the authors' hypothesis that patients with bulimia would experience higher risks of developing EAC, but the authors emphasize that it is premature to rule out an increased risk entirely due to the small sample size in their analysis [27].

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is an important risk factor for EAC. A review from 2002 reported an increased risk of EAC associated with GERD, with the risk estimates ranging from OR 2.50 and 95% CI 1.50–4.50 to OR 16.40 and 95% CI 8.30–28.40 for individuals who had experienced GERD symptoms for 5 years or more, compared with asymptomatic subjects [28]. There was a very apparent dose response, with EAC risk increasing with longer duration, as well as with increased frequency of symptoms. In one study included in the review, the risk was increased by almost eightfold (95% CI, 5.30–11.40) for those who reported at least weekly symptoms of GERD. Severity and duration of symptoms appeared to act synergistically, with individuals who had experienced severe symptoms for over 20 years being 43.5 times more likely (95% CI, 18.30–103.50) to have EAC than asymptomatic subjects. Recall bias does not seem to have influenced the results, because the study also included ESCC subjects, in whom an association was not found between reflux and the risk of cancer.

A more recent population-based case-control study from Australia published in 2008 also reported an increased risk of EAC associated with reflux (OR, 6.40, 95% CI, 4.50–9.0) [25]. There was also an apparent synergistic relationship with obesity, with the risk increasing threefold between nonobese subjects with reflux (OR, 5.60, 95% CI, 2.80–11.30) and obese patients with reflux (OR, 16.50, 95% CI, 8.9–30.6).

Barrett's Esophagus

Barrett's esophagus is defined as a change in the distal esophageal epithelium of any length that can be recognized as columnar-type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy [29]. It is recognized as the precursor lesion of EAC and patients with Barrett's esophagus are 30–125 times more likely to develop EAC compared with the general population [30]. However, despite the alarming appearance of these figures, investigators have repeatedly concluded that in relative terms, Barrett's esophagus patients remain at low risk of malignant progression and predominantly die due to causes other than EAC [30–32].

In a large meta-analysis from 2010 consisting of 51 studies, Sikkema et al. [30] reported a pooled estimate for EAC incidence of 6.3 per 1000 person-years of follow-up (95% CI, 4.7–8.4), corresponding to an annual risk of 0.6% and a pooled

incidence of fatal EAC of 3.0 per 1000 person-years of follow-up (95% CI, 2.2–3.9). The mortality rate due to causes other than EAC was 12-fold higher with an estimate of 37 deaths per 1000 person-years, as compared with the mortality rate due to EAC. Put another way, only 7% of the total number of patients died from EAC, while 93% died due to other causes.

A more recent meta-analysis from 2014 analyzed the incidence of EAC and high-grade dysplasia in Barrett's esophagus patients with low-grade dysplasia [32]. The annual incidence of EAC was 0.54% (95% CI, 0.32–0.76). A subgroup analysis looking at mortality from EAC included four studies and 318 patients with Barrett's esophagus and low-grade dysplasia. 4.4% of the patients developed EAC and 1–2.2% died due to the cancer, while 28.3% died due to causes other than esophageal disease.

Socioeconomic Status

There is very little information on the role of socioeconomic status in relation to EAC and the data is conflicting. A Swedish case-control study with 189 EAC cases and 820 control subjects aimed to determine the role of various socioeconomic factors in relation to EAC [33]. The data suggested that skilled manual workers were at an increased risk of developing EAC (OR, 3.70, 95% CI, 1.70–7.7); however after adjustment for tobacco smoking, BMI, and reflux symptoms, the result became nonsignificant (OR, 2.00, 95% CI, 0.90–4.50). There was also an increased adjusted risk for those who lived alone (OR, 2.30, 95% CI, 1.20–4.50). An earlier case-control study of 554 patients with EAC and 695 controls from the United States reported that there was an increased risk of developing EAC including junctional tumors among those with a lower level of education (<12 years); however, these findings were not statistically significant (OR, 1.3, 95% CI, 0.90–2.10; OR, 1.3, 95% CI, 0.80–2.00, respectively) [34]. The findings adjusted for age, sex, geographic center, BMI, smoking status, and alcohol consumption. A recent study which assessed sociodemographic and geographical factors in relation to esophageal cancer mortality in Sweden found that individuals with a lower education were at an increased risk (HR, 1.64, 95% CI, 1.11–2.38), as were those living in densely populated areas (HR, 1.31, 95% CI, 1.14–1.50) [35].

Occupation

A recent large cohort study found that men had higher risks of developing EAC if they were waiters (SIR, 2.58, 95% CI, 1.41–4.32), cooks and stewards (SIR, 1.72, 95% CI, 1.04–2.69), seamen (SIR, 1.52, 95% CI, 1.16–1.95), food workers (SIR, 1.51, 95% CI, 1.18–1.90), miscellaneous construction workers (SIR, 1.24, 95% CI, 1.04–1.48), and drivers (SIR, 1.16, 95% CI, 1.01–1.33). The same study found lower risks of developing EAC in men who were technical workers (SIR, 0.81, 95% CI, 0.72–0.92), physicians (SIR, 0.40, 95% CI, 0.16–0.81), teachers (SIR, 0.72, 95% CI, 0.57–0.90), religious workers (SIR, 0.75, 95% CI, 0.56–0.98), and gardeners (SIR, 0.77, 95% CI, 0.61–0.95). Among women, elevated risks for EAC were observed in food workers (SIR, 0.76, 95% CI, 0.31–1.57) and wait staff (SIR, 0.84, 95% CI, 0.40–1.55), while decreased risks were seen in teachers (SIR, 0.88, 95%

CI, 0.56–1.33), nurses (SIR, 0.79, 95% CI, 0.38–1.45), and assistant nurses (SIR, 1.02, 95% CI, 0.60–1.61). This study exemplifies that the risk for esophageal cancer varies with occupation; however the authors assert that the risk posed by most occupational categories do not differ according to histological type [36]. As such, a 1995 Swedish study found higher incidences of esophageal cancer in men that were employed in specific industries, including the food (SIR, 1.3, $p < 0.05$) and beverage and tobacco (SIR, 1.8, $p < 0.05$) industries, vulcanizing shops within the rubber industry (SIR, 4.7, $p < 0.01$), breweries (SIR, 4.2, $p < 0.01$), and butchery (SIR, 2.1, $p < 0.01$), as well as waiters, particularly employed in hotels and restaurants (SIR, 3.1, $p < 0.01$) [37]. It is important to note that some of these observations could be attributable to lifestyle factors like alcohol consumption and smoking, which are known risk factors for esophageal cancer. Occupational exposure to other risk factors of EAC could also render individuals of a certain occupation more susceptible to the development of EAC. Examining occupational exposure to smoke, an American study reported that firefighters are more likely to develop cancers of the esophagus, after adjusting for race (OR, 1.6, 95% CI, 1.2–2.1) [38].

Helicobacter pylori Infection

There has been conflicting data regarding the role of *Helicobacter pylori* infection in the development of ESCC and EAC. A meta-analysis of case-control studies reported that EAC ($n = 9$) risk was significantly reduced in patients with *H. pylori* infection (OR, 0.58, 95% CI, 0.48–0.70), which was similar for studies of *H. pylori cagA*-positive strains ($n = 6$) (OR, 0.54, 95% CI, 0.40–0.73) [39]. Another meta-analysis of case-control or nested case-control studies published in the same year assessed the relationship between *H. pylori* infection and EAC and ESCC [40]. The link between *H. pylori* infection and EAC ($n = 13$) was consistent with the previous meta-analyses (OR, 0.56, 95% CI, 0.46–0.68), as was the relationship with *H. pylori cagA*-positive studies ($n = 5$) (OR, 0.41, 95% CI, 0.28–0.62).

Diet

Hot Food and Beverage

A meta-analysis reported that hot food and beverage increases the odds of developing esophageal adenocarcinoma; however, the relationship observed was not significant (OR, 0.78, 95% CI, 0.45–1.35) [41]. A recent IARC report into the potential carcinogenic properties of very hot beverages found that there was limited evidence in humans for the carcinogenicity of drinking very hot beverages. However, there were a number of positive associations reported linking drinking very hot beverages and esophageal squamous cell carcinoma. The overall finding was that drinking very hot beverages at temperatures above 65 °C is probably carcinogenic to humans (Group 2A) [42].

Meat Consumption

Meat consumption and in particular red meat consumption is a known risk factor for colorectal cancer. A meta-analysis to determine the association between meat

consumption and risk of esophageal cancer analyzed 29 studies involving 1,208,768 individuals [43]. Any meat consumption was associated with an increased risk of developing EAC (OR, 1.53, 95% CI, 1.16–2.03), as was red meat (OR, 1.19, 95% CI, 1.08–1.33) and barbecued meat (OR, 1.23, 95% CI, 1.07–1.42). There was an increased risk associated with processed meat consumption, but it was not statistically significant (OR, 1.11, 95% CI, 1.00–1.23). Consumption of white meat (chicken) decreased the risk of EAC (OR, 0.87, 95% CI, 0.75–0.99), along with fish (OR, 0.79, 95% CI, 0.54–1.15) which was not statistically significant.

Fruit and Vegetables

Another meta-analysis of observational studies aimed to determine the association between fruit and vegetable intake and risk of EAC [44]. The analysis included 12 studies with 1572 cases of EAC and found that intake of both fruit (OR, 0.73, 95% CI, 0.55–0.98) and vegetables (OR, 0.76, 95% CI, 0.59–0.96) was associated with a decreased risk of developing EAC.

Minerals and Vitamins

Flavonoids

Flavonoids are a class of plant pigments, often responsible for the vivid colors of fruits and vegetables. Common dietary sources of flavonoid include black tea, orange and grapefruit juice, and wines. Historically, little or no consistent association was found for a possible relationship between flavonoids and esophageal adenocarcinoma. However, a 2015 study found that the intake of anthocyanidins, present in wine and fruit juice, reduced the risk of developing EAC (OR = 0.43, 95% CI, 0.29–0.66) [45]. A 2016 meta-analysis confirmed this finding, reporting that intake of dietary flavonoids reduces the risk of developing esophageal cancer, regardless of histological type (OR, 0.91, 95% CI, 0.75–1.10; $I(2)$, 0.0%) [46]. This was also reflected in another meta-analysis conducted in 2016, which compared patients of highest intake and lowest intake for total flavonoids and for each flavonoid subclass. It reported lower risks for developing esophageal cancers, regardless of histological type, in the intake of anthocyanidins (OR, 0.60, 95% CI, 0.49–0.74), flavanones (OR, 0.65, 95% CI, 0.49–0.86), flavones (OR, 0.78, 95% CI, 0.64–0.95), and total flavonoids (OR, 0.78, 95% CI, 0.59–1.04) [47].

Vitamin D

Most recently, a 2016 meta-analysis found a nonsignificant elevated risk for developing adenocarcinoma and vitamin D intake (OR, 1.45, 95% CI, 0.65–2.24). This meta-analysis also discussed the results obtained from one study that reported a decreased risk (OR, 0.49, 95% CI, 0.31–0.79) of esophageal adenocarcinoma in individuals who had a higher lifetime mean daily UV radiation exposure [48].

N-Nitrosodimethylamine (NDMA)

NDMA is a semi-volatile organic compound found in industrial waste and sometimes in very low concentrations in food, such as meats. A 2016

meta-analysis reported no significant relationship with EAC (RR, 1.18, 95% CI, 0.98–1.41) [49].

Folate

There is conflicting evidence regarding the role of folate in the development of upper gastrointestinal cancers. Evidence exists both implicating folate in carcinogenesis and suggesting that folate may reduce cancer risk. A recent meta-analysis of 9 studies and including 2574 esophageal cancer cases found high dietary folate intake to be associated with a decreased risk of any histological type of esophageal cancer (OR, 0.59, 95% CI, 0.51–0.69) [50]. The study also found a risk reduction for EAC (OR, 0.57, 95% CI, 0.43–0.76) associated with a high dietary folate intake [50]. These results are supported by findings that polymorphisms in genes involved in folate metabolism that result in lower circulating folate levels are associated with an increased risk of esophageal cancer.

Drugs

Sex Steroids

A recent study reported that higher levels of sex steroids may be linked with a decreased risk of developing EAC. As such, higher levels of dehydroepiandrosterone (DHEA) were associated with a 72% decreased risk (OR, 0.28, 95% CI, 0.13–0.64; $p = 0.001$). Similarly, estradiol was also associated with a 48% reduced risk (OR, 0.52, 95% CI, 0.29–0.93; $p = 0.03$) [51].

Proton Pump Inhibitors

Acid-suppressive medications such as proton pump inhibitors (PPIs) are commonly used in the management of GERD. It has been suggested that PPI use may decrease the risk of progression from Barrett's esophagus to EAC. A meta-analysis from 2014 based on seven observational studies investigated this possibility and found a decreased risk of EAC or high-grade dysplasia in patients with Barrett's esophagus taking PPIs (OR, 0.29, 95% CI, 0.12–0.79) [52]. There is no clinical evidence indicating that PPI therapy may increase the risk of neoplastic progression to EAC, and therefore if this finding is supported by further studies, it could warrant the use of PPI therapy in patients with Barrett's esophagus for its chemopreventive effects.

Bisphosphonates

Following a report by the US Food and Drug Administration of 23 cases of esophageal cancer between 1995 and 2008, which implicated the bisphosphonate alendronate as a possible causative agent, there has been an increase in interest and investigation into the potential for an increased carcinogenic risk associated with bisphosphonate use, particularly for esophageal cancer. However, several studies have subsequently reported conflicting results. A meta-analysis from 2012 of seven studies with 19,700 esophageal cancer cases did find an increased risk of esophageal cancer associated with any bisphosphonate use (OR, 1.74, 95% CI, 1.19–2.55) [53]. In addition, the study found the risk to be increased with longer duration of use

compared with shorter duration (OR, 2.32, 95% CI, 1.57–3.43, versus OR, 1.35, 95% CI, 0.77–2.39) [53].

Nonsteroidal Anti-inflammatory Agents and Aspirin

A number of studies have reported conflicting results on the relationship between aspirin and nonsteroidal anti-inflammatory agents (NSAIDs) and esophageal cancer, especially EAC. A prospective cohort study and meta-analysis failed to find a statistically significant association between either aspirin (OR, 1.00, 95% CI, 0.73–1.37) or NSAID (OR, 0.90, 95% CI, 0.69–1.17) use and EAC risk in the results from the cohort study [54]. The meta-analysis conducted by the same investigators did however find a decreased risk of EAC associated with both aspirin (OR, 0.64, 95% CI, 0.52–0.79) and NSAID (OR, 0.65, 95% CI, 0.50–0.85) use. A more recent meta-analysis from 2011 likewise found a decreased risk of EAC associated with both aspirin (OR, 0.73, 95% CI, 0.65–0.83) and NSAID (OR, 0.84, 95% CI, 0.72–0.98) use [55]. The meta-analysis also found a reduced risk of EAC among patients with Barrett's esophagus associated with either aspirin or NSAID use (RR, 0.64, 95% CI, 0.42–0.96) [55].

Statins

Recently, a chemopreventive role for statins in esophageal cancer has been suggested. An early meta-analysis that included seven studies (n = 6895 esophageal cancer cases) found a reduced risk of esophageal cancer associated with statin use (OR, 0.75, 95% CI, 0.67–0.84) [56]. Moreover, a greater reduction was observed for a longer duration of use (OR, 0.45, 95% CI, 0.31–0.67), with no heterogeneity ($I^2 = 0\%$, $p = 0.79$). There was also a reduction in the risk of progression to EAC in BE patients (OR, 0.56, 95% CI, 0.41–0.76), with no heterogeneity ($I^2 = 0\%$, $p = 0.93$). Only atorvastatin and simvastatin showed a statistically significant reduction in risk, with OR 0.68, 95% CI 0.55–0.86, and OR 0.76, 95% CI, 0.66–0.89, respectively; no heterogeneity was present. Subgroup analyses for prospective and retrospective studies both showed a reduced risk, with OR 0.75, 95% CI 0.67–0.86, and OR 0.68, 95% CI 0.54–0.86, respectively; heterogeneity was not present [56]. A recent meta-analysis of 20 studies included 372,206 cancer cases and 6,086,906 controls [57]. Statin use was not associated with an increased risk of esophageal cancer among patients with Barrett's esophagus (OR, 0.59, 95% CI, 0.50–0.68). In addition, statin use was associated with a lower incidence of both EAC (OR, 0.57, 95% CI, 0.43–0.76) and all esophageal cancers (OR, 0.82, 95% CI, 0.70–0.88) [57].

Alcohol Consumption and Tobacco Smoking

The lack of a relationship between alcohol consumption and EAC is consistent across studies. No relationship between alcohol consumption and EAC was found in a recent large prospective cohort study from the Netherlands [58]. In fact, the lack of relationship between alcohol consumption and EAC was confirmed by a meta-analysis which included 20 case-control and 4 cohort studies (RR, 0.87, 95% CI, 0.74–1.01) [59].

Smoking, however, has been linked with EAC. A meta-analysis of 33 studies published found that compared to never smokers, there was an increased risk of EAC among current smokers (RR, 2.32, 95% CI, 1.96–2.75), ever smokers (RR, 1.76, 95% CI, 1.54–2.01), and ex-smokers, (RR, 1.62, 95% CI, 1.40–1.87) [60]. Similarly, in a large prospective follow-up study of 474,606 participants, current smokers were at increased risk for EAC (HR, 3.70, 95% CI, 2.20–6.22), as were former smokers (HR, 2.82, 95% CI, 1.83–4.34), when compared with never smokers [61].

Another meta-analysis found that the risk of EAC increased with greater BMI. However, after adjusting for other confounding factors, it was noted that there was a significant inverse relationship with drinking-years in those drinkers that consumed <5 drinks per day, who had particularly reported no acid reflux. Conversely, no such association was found for heavier drinkers [62]. In 2017, a meta-analysis examined the effect of water pipe smoking and esophageal cancer, without classifying the histological type of the cancer [63]. Water pipe smoking is a method of tobacco smoking originating from the Middle East that involves smoking a variety of flavored tobacco using a water pipe. Some modern terms that describe this type of smoking are shisha, hookah, hubble-bubble, narghile, and qalyan. The paper collected data from five case-control studies, reporting that water pipe smoking confers a significant positive association (OR, 3.63, 95% CI, 1.39–9.44) [63].

Metabolic Disorders

A recent population-based study reported that EAC is mildly associated with metabolic syndrome in elderly patients (OR, 1.16, 95% CI, 1.06–1.26) [63]. The association in males is linked to individuals without prior diagnosis of GERD; however, it was noted that in females, the occurrence of EAC was not related to GERD status [64]. Over the last 30 years, the incidence of EAC and diabetes mellitus has been increasing steadily in the United States. Investigating a possible association to explain this trend, a recent study found that diabetes mellitus is significantly associated with EAC independent of obesity, another known risk factor for EAC (OR, 2.20, 95% CI, 1.70–2.80) [65]. This was confirmed in a meta-analysis, reporting that diabetes mellitus conferred an increased risk for EAC (RR, 1.43, 95% CI, 1.35–1.51) [66].

Esophageal Squamous Cell Carcinoma

The risk factors for ESCC are presented diagrammatically in Fig. 1.7 and are discussed individually below.

Age and Gender

The incidence of esophageal cancer increases with age. The majority of individuals with ESCC are aged between 60 and 70 years, an older age group than for EAC; however, there are some specific groups that are at much higher risk very early in life (in their 20s) [19]. As with EAC, ESCC is more common in men than in women. The global incidence was estimated at 7.7 per 100,000 in men and 2.8 per 100,000 in

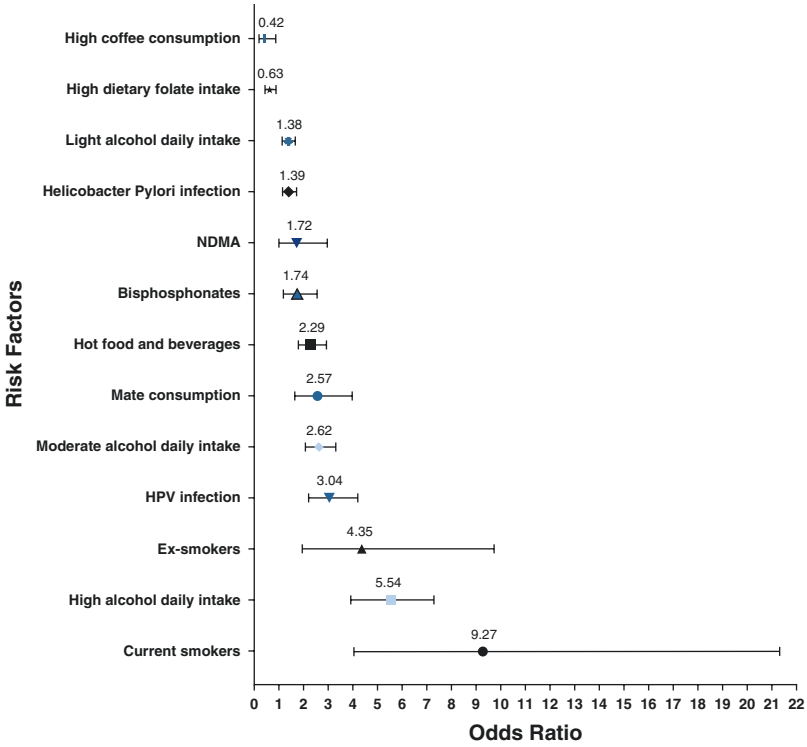

Fig. 1.7 Risk factors associated with esophageal squamous cell carcinoma

women. Again, as with EAC, the difference in incidence between the genders is most evident in the high-incidence region of Eastern and Southeastern Asia (13.6 in men and 4.3 in women) [8]. In the United States, the national age-standardized incidence rate for ESCC is 4.93 per 100,000 in men and 2.30 per 100,000 in women [10]. This difference is thought to be due to risk factors such as smoking and alcohol consumption which historically have had a larger male participation rate.

Ethnicity

A recent finding reported a higher incidence of ESCC in individuals of African descent compared to Caucasians. However, it also highlights that the racial disparities in this cancer have declined over time in the United States [67]. This observation was supported by another study that found the incidence of ESCC to be the highest among African-Americans compared with white non-Hispanics, Hispanics, or Asians, according to the SEER database. Additional analysis determined that the estimated incidence of ESCC in African-American men (at age 60) who consumed alcohol and tobacco (30/100,000) was relatively similar to the incidence of EAC in white non-Hispanic men (at age 60) with GERD (40/100,000) [68]. In another study, it was reported that ESCC rates varied in different Asian ethnic groups, but it

was far more prevalent in both foreign-born and US-born Asian-Americans. This study reported that rates of ESCC were higher in US-born Asian men (4.0 cases per 100,000) compared with foreign-born Asian men (3.2 cases per 100,000) and Caucasian men (2.2 cases per 100,000) (p = 0.03). This suggests that there are genetic and environmental factors that come to play in the incidence of ESCC [69].

Alcohol Consumption and Tobacco Smoking

The distinct risk outcomes of alcohol consumption observed in EAC and ESCC are plausibly attributable to the varying pathogeneses between the two histological types [70]. The association between alcohol consumption, smoking, and ESCC is well established, as is the synergistic increase in risk that heavy alcohol consumption and smoking have on this cancer. A large prospective cohort study from the Netherlands consisting of 120,852 participants and published in 2010 found a greatly increased risk of ESCC in consumers of >30 g of ethanol per day compared with nondrinkers (RR, 4.61, 95% CI, 2.24–9.50) [58]. The RR for current smokers who consumed between 5 and 15 g of ethanol per day was 4.48 (95% CI, 1.97–10.20), and this increased in daily drinkers of 15 g of ethanol to 8.05 (95% CI, 3.89–16.60), when compared with never smokers who consumed <5 g/day of ethanol.

A recent meta-analysis specifically analyzed the effects of alcohol consumption and tobacco use on ESCC, both alone and in combination [71]. This study found an increased risk in nonsmoking drinkers (OR, 1.21, 95% CI, 0.81–1.81), though this was statistically nonsignificant, and in nondrinking smokers (OR, 1.36, 95% CI, 1.14–1.61). This increased to OR 3.28 (95% CI, 2.11–5.08) in concurrent smokers and drinkers. Studies have reported ORs as high as 50.1 for the increased risk of ESCC in the highest smoking and highest alcohol consumption group, compared with nonsmokers and nondrinkers [72].

Recently, meta-analyses have been conducted analyzing the dose-response risk of alcohol consumption on esophageal cancer, with particular emphasis on light and moderate alcohol drinkers, nonsmokers, and, in recognition of genetic polymorphisms involved in alcohol metabolism, different racial groups. A meta-analysis which included 40 case-control and 13 cohort studies found that after adjusting for age, sex, and tobacco smoking, there was an increased risk of ESCC associated with light alcohol drinking (≤12.5 g/day) (RR, 1.38, 95% CI, 1.14–1.67), which increased for moderate drinkers (12.5–50 g/day) (RR, 2.62, 95% CI, 2.07–3.31) and for high alcohol intake (>50 g/day) (RR, 5.54, 95% CI, 3.92–7.28) [73]. The association was slightly stronger in Asian studies for light drinkers (RR, 1.52, 95% CI, 1.06–2.19), but was weaker for moderate (RR, 2.52, 95% CI, 1.69–3.74) and heavy (RR, 4.31, 95% CI, 2.46–7.55) consumption. Among never-smokers, the risk estimates were RR 0.74, 95% CI, 0.47–1.16, for light; RR 1.54, 95% CI, 1.09–2.17, for moderate; and RR 3.09, 95% CI, 1.75–5.46, for heavy drinkers.

Another meta-analysis which also examined racial effects on risks of ESCC found that compared to nondrinkers, weekly consumption of more than 200 g of alcohol was associated with an increased risk of ESCC, and the risk was greater in Asian never drinkers (OR, 5.05, 95% CI, 3.40–7.49) than for Europeans (OR, 3.42, 95% CI, 2.29–5.09) [74]. This observation could be due to the effect of

polymorphisms of genes involved in alcohol metabolism occurring more commonly in those populations.

Another meta-analysis examined the relationship between light alcohol drinking and various cancers by comparing light drinkers (defined as consuming ≤12.5 g of ethanol or ≤1 drink per day) to nondrinkers [75]. The study found a positive relationship even for light drinkers (RR, 1.30, 95% CI, 1.09–1.56) and estimated that 24,000 deaths from esophageal ESCC were attributable to light drinking in 2004 worldwide.

Tobacco smoking is also independently associated with an increased risk of ESCC. A large prospective follow-up study of 474,606 participants found that current smokers were at increased risk for ESCC (HR, 9.27, 95% CI, 4.04–21.29), as were former smokers (HR, 4.35, 95% CI, 1.95–9.72), when compared with never smokers [61]. The association was much stronger for ESCC in current smokers than the same study found for EAC.

Further evidence analyzing race-specific effects of alcohol and tobacco on the risk of ESCC also found an increased risk of ESCC, with the effect of current smoking versus never smoking being weaker among Asians (OR, 2.31, 95% CI, 1.78–2.99) than among Europeans (OR, 4.21, 95% CI, 3.13–5.66) [74].

Socioeconomic Status

The evidence for a relationship between socioeconomic status and ESCC appears to be much clearer than for EAC. In a case-control study, 347 male cases and 1354 male controls consisting of both African-Americans and Caucasians from the United States were compared in terms of social class [76]. Income was an important factor and those individuals with a low income (<$10,000 per year compared with those earning $25,000 or more annually) had a substantially increased risk of developing ESCC (African-American OR, 8.00, 95% CI, 4.30–15.00; Caucasian OR, 4.30, 95% CI, 2.10–8.70). Another case-control study from India compared 703 cases of ESCC with 1664 controls matched by age, sex, and geographic area [77]. After adjusting for ethnicity, place of residence, religion, education, fruit intake, vegetable intake, smoking status, hookah, nass, ever-use of bidi and gutka, and alcohol consumption, there was a strong relationship between occupations requiring physical activity and ESCC (OR, 5.65, 95% CI, 3.49–9.12).

Occupation

As noted previously, the risk of developing esophageal cancer based on occupational categories does not generally vary with the histological type of tumor. However, a study reported that among men, increased risks of ESCC were seen in waiters (SIR, 3.22, 95% CI, 2.30–4.38), cooks and stewards (SIR, 2.53, 95% CI, 1.94–3.25), seamen (SIR, 1.77, 95% CI, 1.53–2.05), food workers (SIR, 1.21, 95% CI, 1.03–1.42), miscellaneous construction workers (SIR, 1.39, 95% CI, 1.25–1.54), and drivers (SIR, 1.23, 95% CI, 1.13–1.34) [36]. As seen with EAC, lower risks for ESCC were observed among technical workers (SIR, 0.72, 95% CI, 0.66–0.79), physicians (SIR, 0.46, 95% CI, 0.27–0.74), teachers (SIR, 0.49, 95% CI, 0.40–0.60), religious workers (SIR, 0.59, 95% CI, 0.47–0.74), and gardeners (SIR, 0.72, 95% CI, 0.63–0.82).

Opium

This potential link was first reported in 1977 based on a 2-year clinical study undertaken in Northern Iran [78]. One potential mechanism by which opium may assist in esophageal cancer formation relates to papaverine (1% in crude opium) affecting esophageal peristalsis and causing esophageal relaxation and stasis [79]. This combined with micronutrient deficiency makes the esophageal mucosa vulnerable to carcinogenic attack. A case-control study was conducted in the Golestan Province in Northeastern Iran with 300 ESCC cases and 571 controls whose age, gender, and neighborhood of residence matched [80]. An adjusted analysis found that opium use was associated with a twofold increased risk of developing ESCC (OR, 2.12, 95% CI, 1.21–3.74).

Diet

Hot Food and Beverages

A comprehensive meta-analysis found an increased risk associated with the consumption of hot food and beverages and the development of ESCC (OR, 2.29, 95% CI, 1.79–2.93), which remained even after adjusting for the confounding variables like smoking and alcohol consumption (OR, 2.39, 95% CI, 1.71–3.33) [41].

There have been numerous studies assessing the level of risk associated with diet and nutrition in the development of esophageal cancer. Several recent evidence-based meta-analyses have determined the risk associated with various food groups and vitamins in relation to esophageal cancer.

Eggs

A risk assessment of egg consumption and esophageal cancer reported that among seven studies (n = 2223 cases), there was an increased risk (OR, 1.25, 95% CI, 0.98–1.61); however, this was not statistically significant [81].

Meat Consumption

A recent meta-analysis to determine the association between meat consumption and risk of esophageal cancer analyzed 29 studies involving 1,208,768 individuals [43]. The study found an increased risk of ESCC associated with the consumption of red meat (OR, 1.41, 95% CI, 1.24–1.61), processed meat (OR, 1.54, 95% CI, 1.06–2.23), and barbequed meat (OR, 1.33, 95% CI, 1.15–1.45). The consumption of white meat (chicken) (OR, 0.73, 95% CI, 0.65–0.83) and fish (OR, 0.66, 95% CI, 0.58–0.76) both conferred a protective effect on the development of ESCC.

Pickles

A relationship between Asian pickled vegetable consumption and ESCC has been suggested by experimental studies; however, the results of epidemiological studies have been inconsistent. A meta-analysis from 2009 sought to investigate the relationship and included 34 studies, of which 3 were prospective studies [82]. They found an increased risk of ESCC associated with the consumption of pickled vegetables (OR, 2.08, 95% CI, 1.66–2.60). The adjusted studies retained the positive

relationship (OR, 2.15, 95% CI, 1.64–2.81). However, the subgroup analysis of the three prospective studies revealed a nonstatistically significant relationship (OR, 1.52, 95% CI, 0.82–1.63), illustrating the need for more prospective studies to confirm the potential relationship.

Tea and Coffee Consumption

A number of studies have investigated whether a relationship exists between the consumption of tea and coffee and esophageal cancer. The most recent is a large European study which included 442,143 participants from nine European countries [83]. The results showed a decreased risk of esophageal cancer of any type among current smokers who consumed high levels of coffee (HR, 0.48, 95% CI, 0.28–0.83), as well as a decreased risk of ESCC among current smokers who consumed high levels of tea (HR, 0.46, 95% CI, 0.23–0.93) and coffee (HR, 0.37, 95% CI, 0.19–0.73). There was also a decreased risk of ESCC in men who consumed high levels of coffee (HR, 0.42, 95% CI, 0.20–0.88). There were no statistically significant associations with EAC.

Another large study from Norway examined the relationship between coffee intake and oral and ESCC in a follow-up of 389,624 Norwegian men and women aged 40–45 years [84]. Using 1–4 cups per day as the reference level of consumption, the study did not find a statistically significant relationship, neither protective nor harmful, linking different levels of coffee consumption and ESCC.

A large follow-up study from the United States with 481,563 subjects, including 123 ESCC and 305 EAC cases, also investigated the relationship between hot tea, iced tea, and coffee consumption and risk of upper gastrointestinal tract cancers [85]. The only statistically significant relationship observed was an inverse association between high levels of coffee drinking and EAC for the cases occurring in the last 3 years of follow-up—the risk estimate for drinking >3 cups/day compared to <1 cup/day was HR 0.54 (95% CI, 0.31–0.92).

A Cochrane review conducted in 2009 investigated the consumption of green tea (from the *Camellia sinensis* plant) for the prevention of cancer and found no evidence that green tea consumption reduces the risk of gastrointestinal cancers, including esophageal cancer [86].

In addition, a recent IARC report into the potential carcinogenic properties of very hot beverages found that there was limited evidence in humans for the carcinogenicity of drinking very hot beverages. However, there were a number of positive associations reported linking drinking very hot beverages and esophageal squamous cell carcinoma. The overall finding was that drinking very hot beverages at temperatures above 65 °C is probably carcinogenic to humans (Group 2A) [42].

Minerals and Vitamins

Toenail Mineral Concentration

A recent study examined the concentration of selenium (OR, 0.78, 95% CI, 0.41–1.49), zinc (OR, 0.80, 95% CI, 0.42–1.53), chromium (OR, 0.9, 95% CI, 0.46–1.80), and mercury (OR, 0.61, 95% CI, 0.27–1.38) in a population based study and

found no significant evidence asserting a correlation between toenail mineral concentration and SCC [87].

NDMA

Though NDMAs have not been proven to be significantly associated with EAC, evidence has been published suggesting that there is a significant positive relationship with ESCC (RR, 1.72, 95% CI, 1.01–2.96) [88].

Folate

A recent meta-analysis of 9 studies including 2574 esophageal cancer cases found high dietary folate intake to be associated with a decreased risk of any histological type of esophageal cancer (OR, 0.59, 95% CI, 0.51–0.69) [50]. The study also found a risk reduction for ESCC (OR, 0.63, 95% CI, 0.44–0.89) associated with a high dietary folate intake [50]. These results are supported by findings that polymorphisms in genes involved in folate metabolism that result in lower circulating folate levels are associated with an increased risk of esophageal cancer.

Diet-Related Inflammation

Chronic diet-related inflammation has been linked to increased risk of developing diabetes [89], heart disease [90], and obesity [91]. Several studies have detected a positive association between diet-related inflammation and ESCC. A 2015 study investigated participants with varying dietary inflammatory indices (DII), uncovering that higher DII scores (i.e., more pro-inflammatory diets) were associated with a higher risk of ESCC with the DII being used as a categorical variable (OR quintile 5 versus 1, 2.46, 95% CI, 1.40–4.36) [92]. This result was further supported by a study conducted a year later that presented significant associations for ESCC (OR quartile 4 versus 1, 4.35, 95% CI, 2.24–8.43) and EAC (OR quartile 4 versus 1, 3.59, 95% CI, 1.87–6.89) for individuals with higher recorded DIIs [93].

Maté Consumption

Maté is a tealike infusion made from the leaves of the perennial tree *Ilex paraguariensis*, which is native to Argentina, Brazil, Paraguay, and Uruguay. It is a popular drink in some parts of South America, where it is also variously also referred to as yerba maté, erva maté, chimarraõ, and cimarrón. The consumption of maté is suspected to be a risk factor for cancers of the upper aerodigestive tract, including ESCC. In a recent meta-analysis of nine studies, 1565 ESCC cases were analyzed to determine the relationship [94]. ESCC was associated with exposure to maté drink (OR, 2.57, 95% CI, 1.66–3.98). There was an increased risk of ESCC associated with a higher consumption of maté, versus low consumption (OR, 2.76, 95% CI, 1.33–5.73, versus OR, 1.84, 95% CI, 1.12–3.00).

Tooth Loss and Oral Hygiene

There is a dearth of data on the relationship between oral hygiene/tooth loss and esophageal cancer. A recent case-control study conducted in Kashmir on ESCC patients (n = 703) and matched controls (n = 1664) reported an inverse association between

never cleaning teeth and developing ESCC (OR, 0.41, 95% CI, 0.28–0.62) [95]. There was also an association made with the combined number of decayed, missing, or filled teeth (3–4) (OR, 2.44, 95% CI, 1.47–4.03). The adjusted data suggest that the greatest risk is associated with an increased number of decayed, missing, or filled teeth.

There have been a couple of other studies which have focused on tooth loss in relation to risk of developing esophageal cancer. A study from China found an increased risk of esophageal cancer associated with tooth loss (RR, 1.30, 95% CI, 1.10–1.60) [96]. An increased risk of ESCC was also found in subjects in Iran who had 32 decayed, missing, or filled teeth compared with those who had 15 or less decayed, missing, or filled teeth (OR, 2.10, 95% CI, 1.19–3.70) [97]. In addition, compared with daily toothbrushing, practicing no regular oral hygiene resulted in more than a twofold increase of ESCC risk (OR, 2.37, 95% CI, 1.42–3.97). These results were not significantly changed when the analysis was restricted to never smokers. Another study also confirmed the increased risk of ESCC associated with tooth loss in two other regions, namely, Central Europe and Latin America [98]. The study found missing 6–15 teeth was an independent risk factor for esophageal cancer in Central Europe (OR, 2.84, 95% CI, 1.26–6.41) and Latin America (OR, 2.18, 95% CI, 1.04–4.59). An increased risk of esophageal cancer associated with missing teeth was also reported in Japan (OR, 2.36, 95% CI, 1.17–4.75) [99].

By contrast, a study from Finland found no statistically significant relationship between tooth loss and ESCC [100]. Likewise, a Swedish study from 2011 which included 6156 ESCC cases found no association between oral disease and ESCC after adjustment for diseases related to alcohol consumption (OR, 1.3, 95% CI, 0.9–1.9) or tobacco smoking (OR, 1.1, 95% CI, 0.8–1.7) [101].

Oral Cancer

Oral cancer and ESCC share similar risk factors, namely, smoking and alcohol consumption. The occurrence of primary oral cancer has been reported to increase the risk of developing secondary ESCC, based on a population-based study conducted in Taiwan over 28 years [102]. The study suggested that there was a bidirectional relationship between oral cancer leading to esophageal cancer and vice versa. Primary oral cancers were ten times more likely to develop a secondary cancer of the esophagus (SIR, 10.40, 95% CI, 9.35–11.53), and those individuals with primary esophageal cancer were seven times more likely to develop a secondary oral cancer (SIR, 7.31, 95% CI, 6.11–8.67). An Iranian study found that in its analysis of a possible relationship between these two cancers, a relatively high rate of opium abuse (9%) was observed in the patients affected by oral cancer [103]. There is some correlation between opium addiction and oral and ESCC, as opium is also a proposed risk factor (OR, 1.77, 95% CI, 1.17–2.68) for ESCC [104].

Infectious Disease

Viral Disease

A 2015 study found that HIV infection was correlated with the incidence of SCC (OR, 2.30, 95% CI, 1.00–5.10); however, it also noted that there is a more prominent risk in individuals under 60 years of age (OR, 4.30, 95% CI, 1.50–13.20) [105].

Another study that investigated 51 mucosotropic HPV types detected no such association between SC and mucosal alpha-papillomaviruses [106]. A meta-analysis reported that a prior HPV infection increases the risk of ESCC by threefold (OR, 3.04, 95% CI, 2.20–4.20). The authors also indicated that studies that were conducted in countries with low to medium ESCC incidence presented a stronger relationship with HPV (OR, 4.65, 95% CI, 2.47–8.76) than that in areas of high OSCC incidence (OR, 2.65, 95% CI, 1.80–3.91) [107].

Helicobacter pylori Infection

There has been conflicting data regarding the role of *Helicobacter pylori* infection in the development of ESCC and EAC. An early meta-analysis of 18 studies reported a decreased risk for ESCC in patients with *H. pylori* infection (OR, 0.85, 95% CI, 0.55–1.33) and a nonsignificant increased risk associated with *H. pylori cagA*-positive strains (OR, 1.22, 95% CI, 0.70–2.13) [108]. In addition, there was an inverse statistically significant association with *H. pylori* infection and EAC (OR, 0.52, 95% CI, 0.37–0.73) and for *H. pylori cagA*-positive strains (OR, 0.51, 95% CI, 0.31–0.82).

A meta-analysis of case-control studies reported that the level of risk for ESCC ($n = 5$) was decreased but not statistically significant (OR, 0.80, 95% CI, 0.45–1.43), but studies of *cagA*-positive strains ($n = 2$) showed an increased nonsignificant risk (OR, 1.20, 95% CI, 0.45–3.18) [39].

Moreover, in the same year there was another meta-analysis of case-control or nested case-control studies assessing the relationship between *H. pylori* infection and esophageal adenocarcinoma and squamous cell carcinoma [40]. When assessing ESCC ($n = 9$), the risk was increased but not statistically significant (OR, 1.10, 95% CI, 0.78–1.55), and the link with *cagA* studies ($n = 4$) was null (OR, 1.01, 95% CI, 0.80–1.27).

A more recent systematic review and quantitative meta-analysis aimed to determine the relationship between *H. pylori* infection and ESCC [109]. There were 40 studies that were included in the final analysis which included 3806 cases and 15,897 controls. The relationship between *H. pylori* infection and ESCC ($n = 17$) appeared protective but not statistically significant (OR, 0.82, 95% CI, 0.63–1.06). There was no evidence of publication bias ($p = 0.53$), but there was significant heterogeneity ($I^2 = 74.00$; $p < 0.001$). However, among those with *H. pylori cagA*-positive strains ($n = 12$), there was an increased risk of developing ESCC (OR, 1.39, 95% CI, 1.14–1.71; $I^2 = 0.00$, $p = 0.88$). There was no heterogeneity among these studies ($I^2 = 0.00$). This finding was further enforced by the strong relationship demonstrated in developing countries (OR, 1.70, 95% CI, 1.25–2.32). This meta-analysis identified a statistically significant relationship between *H. pylori cagA* positivity and ESCC, which had not previously been identified.

Medications

Bisphosphonates

Following a report by the US Food and Drug Administration of 23 cases of esophageal cancer between 1995 and 2008 which implicated the bisphosphonate

alendronate as a possible causative agent, there has been an increase in interest and investigation into the potential for an increased carcinogenic risk associated with bisphosphonate use, particularly for esophageal cancer. A meta-analysis from 2012 of seven studies with 19,700 esophageal cancer cases did find an increased risk of esophageal cancer associated with any bisphosphonate use (OR, 1.74, 95% CI, 1.19–2.55) [53]. In addition, the study found the risk to be increased with longer duration of use compared with shorter duration (OR, 2.32, 95% CI, 1.57–3.43, versus OR, 1.35, 95% CI, 0.77–2.39) [53].

Conclusions

Esophageal cancer, while not a common cancer, continues to increase in incidence, with predictive models estimating cases of esophageal cancer to almost double to 808,508 by the year 2035, resulting in 728,920 deaths in that year from the disease. The two histological subtypes, esophageal adenocarcinoma and esophageal squamous cell carcinoma, differ in their epidemiology and risk factors by geographic region.

EAC has experienced a surge in incidence rates during the past few decades, most strikingly in Western countries, where incidence rates have increased up to six- to sevenfold during the period from 1975 to 2009. In Northern and Western Europe, North America, and Australia, its incidence continues to increase and is expected to plateau by 2030. ESCC is still the more common of the two histological subtypes, and in certain countries its incidence has stabilized or decreased recently. Approximately 80% of ESCC cases in 2012, or 315,000 cases, occurred within what is termed the "esophageal cancer belt," which stretches across Central and Eastern Asia, with more than half of all ESCC cases occurring in China.

Risk factors for the two subtypes vary widely. While both are more common in men, EAC is associated with GERD, Barrett's esophagus, and obesity, whereas ESCC seems to result from exposure to carcinogens and is associated with tobacco smoking, the consumption of alcohol and certain foods and beverages, poor oral hygiene, and a low socioeconomic status. Recent developments have included investigations into the effects, both protective and harmful, of different commonly used medications such as PPIs, bisphosphonates, and NSAIDs on esophageal cancer; studies looking into the impact of food and beverage subgroups such as meat, pickles, folate, and maté drink on esophageal cancer; as well as studies evaluating the effects of light to moderate alcohol drinking on esophageal cancer and how alcohol consumption affects the risk of esophageal cancer among different racial groups.

Esophageal cancer remains a rapidly fatal disease, with 5-year survival rates of 19% in the United States and 12% in Europe. Given its poor prognosis and that it is one of the few cancers which continue to increase in incidence, greater research focus and funding into this disease is urgently required.

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