

# ESOPHAGEAL CANCER

## Epidemiology of Esophageal Squamous Cell Carcinoma

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**Esophageal squamous cell carcinoma (ESCC) accounts for about 90% of the 456,000 incident esophageal cancers each year. Regions of high incidence include Eastern to Central Asia, along the Rift Valley in East Africa, and into South Africa. There are many causes of ESCC, which vary among regions. Early studies in France associated smoking cigarettes and heavy alcohol consumption with high rates of ESCC, but these factors cannot explain the high incidence in other regions. We discuss other risk factors for ESCC, including polycyclic aromatic hydrocarbons from a variety of sources, high-temperature foods, diet, and oral health and the microbiome—all require further research. A growing list of defined genomic regions affects susceptibility, but large genome-wide association studies have been conducted with ethnic Chinese subjects only; more studies are called for in the rest of Asia and Africa. ESCC has been understudied, but growing infrastructure in more high-incidence countries will allow rapid progress in our understanding.**

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Esophageal cancer, the sixth leading cause of cancer death in the world, is a complex disease with many causes that differ by histologic type and the population in which it is found.<sup>1</sup> Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EADC), have almost completely distinct geographic patterns, time trends, and primary risk factors. Patients with either cancer have a poor prognosis because of the late stage at diagnosis for most patients. The causes of ESCC vary—the primary agents that cause ESCC in one population might not be associated with this cancer in another. We briefly review the descriptive epidemiology of ESCC and confirmed and suspected risk factors.

### Descriptive Epidemiology

The International Agency for Research on Cancer (IARC) estimates that there were about 450,000 cases of

esophageal cancer in 2012: 88% were cases of ESCC and 12% were cases of EADC.<sup>2</sup> The geographic distribution of ESCC varies greatly, with more than 10-fold differences between countries (Figure 1). The highest incidence rates stretch from Eastern to Central Asia, with another band running along the Indian Ocean coast of Africa along the Great Rift Valley. A third area with higher incidence was centralized around Uruguay in South America and encompassed the entire Gaucho Region of the continent, but lately the rates in Uruguay have decreased.

Although there are differences in rates among countries, there are also notable differences within countries. This is well documented in China—cancer mortality was mapped at the county level in the 1970s, and although rates have decreased in recent years, they vary among regions.<sup>3</sup> Within China, rates of esophageal cancer can vary 10-fold and there are sharp differences over short geographic distances (Figure 2). The most studied region of China is the North Central Taihung Mountain range. In small areas of this region, ESCC are the, or near the, leading cause of death, with incidence rates exceeding 125/100,000 per year.<sup>4</sup> The large population of China and the high rates lead to China having about half of all ESCC cases on earth. These regions often have high incidence rates of gastric cardia adenocarcinoma and ESCC; these 2 cancers account for up to 25% of deaths in some areas. High rates of ESCC and gastric cardia adenocarcinoma are also reported in northeastern Iran,<sup>5</sup> but there is no clear explanation for this phenomenon.

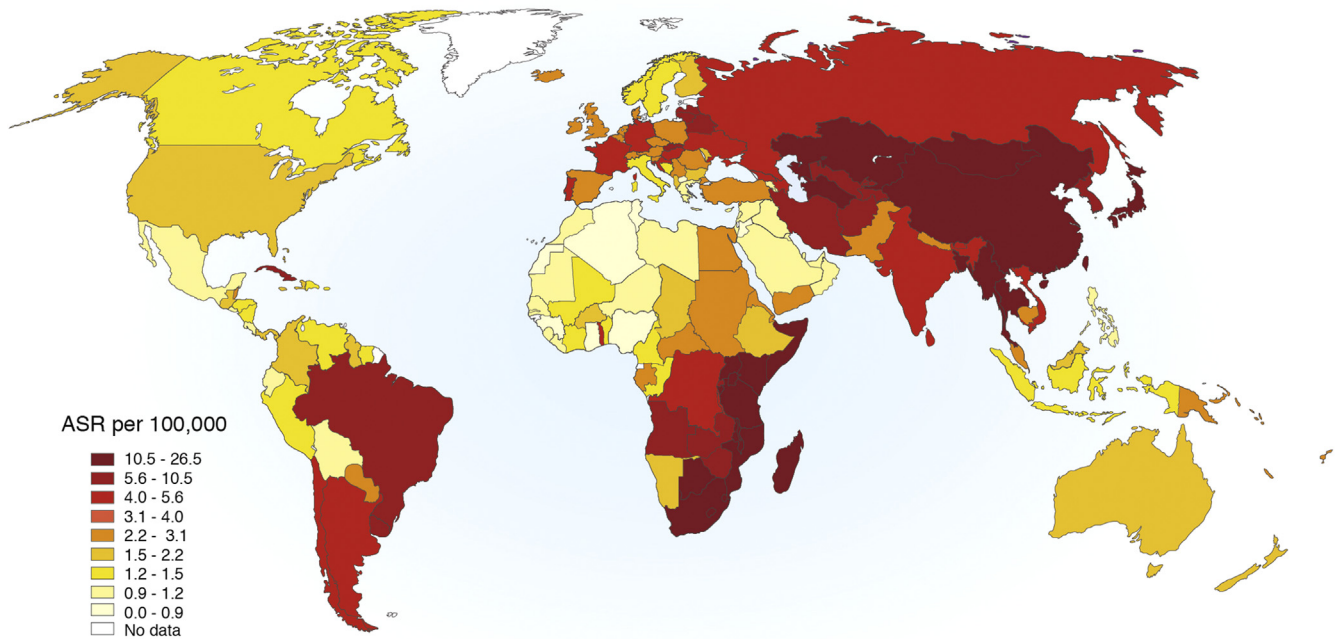
Overall, ESCC is more common in men (69%) than women (31%). However, the ratio varies among low-risk

**Abbreviations used in this paper:** BMI, body mass index; EADC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GWAS, genome-wide association studies; IARC, International Agency for Research on Cancer; PAH, polycyclic aromatic hydrocarbon; SES, socioeconomic status; SNP, single-nucleotide polymorphism.

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**Figure 1.** Incidence rates for esophageal squamous cell carcinoma in men (Reprinted with permission from Ferlay et al).<sup>1</sup> ASR, Age standardized rate.

areas, like the United States, where the ratio of men to women can reach 4:1, and high-incidence areas of China and Iran, where the ratio is lower, approaching or even exceeding 1:1.<sup>2</sup> About 12 countries are thought to have higher rates in women than men, including several in northeast Africa and the Middle East. This variation in sex ratio likely reflects etiologic factors. Early studies from France<sup>6</sup> and later studies from Western countries showed that risk for ESCC is increased by smoking tobacco and heavy consumption of alcoholic beverages. These behaviors were historically more prevalent in men than in women. In high-incidence areas, tobacco and alcohol contribute little (or not at all) to ESCC incidence because they are rarely used in the population (eg, alcoholic beverages in Iran). In these areas, key risk factors are less well described, but seem to be less sex-dependent.

During the last 40 years, there have been large changes in the incidence of different types of esophageal cancers, and these trends are region-specific. In the United States<sup>7</sup> (Figure 3), Europe,<sup>8</sup> Australia, and many other Western countries, the incidence of ESCC had been decreasing for several decades, whereas the incidence of adenocarcinoma has increased. In Eastern Europe,<sup>8</sup> Japan, and South America, ESCC still predominates.<sup>2</sup> In most of Asia and Sub-Saharan Africa, esophageal carcinomas occur almost exclusively as ESCCs. As noted, the co-occurrence of gastric cardia adenocarcinoma in populations with high incidence of ESCC<sup>5,9</sup> creates challenges to tracking EADC because there is no definitive system for separating adenocarcinomas that span the esophagogastric junction.

Within countries, the proportion of ESCC and EADC can vary greatly among population subgroups. For example, in the United States, African Americans are 7-fold more likely

to be diagnosed with ESCC than EADC, whereas US whites are about 4-fold more likely to develop EADC than ESCC.<sup>7</sup> The reasons for these large differences are not clear and cannot be fully explained by known risk factors.<sup>10</sup>

The ESCC incidence is decreasing in many Western countries, especially among men, probably due to decreased smoking prevalence. But these decreases are not universal. For example, the IARC projects almost no change in the rates of ESCC in Australian, Japanese, or UK men between now and 2030.<sup>11</sup> Incidence rates might increase in women in some of these same countries, likely due to women's later peak in cigarette smoking rates and possibly due to changing social mores regarding alcoholic beverage consumption by women. Furthermore, the number of cancer cases is unlikely to decrease even in the presence of falling rates because of the growing and aging populations in developing countries, which have most ESCC cases.

## Known and Suspected Risk Factors

The etiology of ESCC is multifactorial and strongly population-dependent. A study in the United States estimated a population-attributable risk of 89% using only cigarette smoking, alcoholic beverage consumption, and low consumption of fruits and vegetables.<sup>12</sup> In contrast, a large cohort study conducted in a high-incidence region of China found that tobacco smoking had little role in ESCC etiology and that modest alcohol consumption was associated with lower risk of the disease than in nonconsumers.<sup>13</sup> This lack of effect seems to be explained partly by lower exposure rates, but our understanding remains incomplete. Given these large differences in etiology, population-specific estimates are needed for all risk factors and we can draw few

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