Esophageal Squamous Cell Cancer: Pathogenesis and Epidemiology

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Abstract

Esophageal cancer is a highly lethal disease. Despite an increasing incidence of adenocarcinoma in last decades, squamous cell carcinoma remains the predominant cell type worldwide. The majority of squamous cell cancers are from the East. Risk factors for the development of esophageal squamous cell carcinoma differ between high- and low-incidence regions. Tobacco and alcohol intake are the two major risks factors for esophageal squamous cell carcinoma. They also have a synergistic effect; the mechanism of which is now better understood. Other dietary factors include lack of certain micronutrients, consumption of food with carcinogenic ingredients, eating habits and food preservation methods. Genetic factors, viral infection and other premalignant conditions also play a role. Studying epidemiology and pathogenesis of the disease allows policymakers to enact public health policies to prevent the disease through health education and risk factors avoidance. Screening for early disease detection in high-risk populations could improve overall outcome.

Keywords

Squamous cell cancer · Esophageal cancer · Epidemiology · Pathogenesis · Tobacco · Alcohol

Introduction

Esophageal cancer is a disease of dismal prognosis. The two major histologic types of tumors, squamous cell carcinoma and adenocarcinoma, differ substantially in epidemiology, and pathogenesis. Squamous cell carcinoma remains the main cell type worldwide and most are found in Eastern populations. The cancer is characterized by late presentation and rapidly fatal course. This makes study on modifiable risk factors for esophageal cancer particularly important in the context of disease prevention. The present chapter addresses the epidemiology and pathogenesis with emphasis on esophageal squamous cell carcinoma (ESCC).

Epidemiology

Esophageal cancer is the 8th most common cancer globally and the 6th most common cause of cancer-related deaths [1]. Despite advances in diagnostic methods and multimodal therapy in high-income countries, survival rate at 5 years

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from esophageal cancer remains low. The reported five-year survival rates for esophageal cancer are 21% in China [2], 20% in the United States [3], 9.8% in Europe [4], and < 5% in places where resources are limited [5, 6]. There were an estimated 512,500 new cases of ESCC in 2020, representing 85% of all esophageal cancers [7, 8]. Although there has been a decline in the incidence of ESCC in certain parts of the world, probably related to improvement in living standard and lifestyle habits, ESCC remains the predominant histologic type worldwide.

ESCC is a male-predominant disease and is the most common histological type for both men and women. There is significant variation of incidence among different geographic regions and various ethnic groups. The incidence rates of ESCC are highest in Eastern and South-Central Asia and South Africa. In Asian countries, it is commonly found in the "*Asian esophageal cancer belt*", bounded by eastern Turkey and east of Caspian Sea through northern Iran, northern Afghanistan, and southern areas of the former Soviet Union, such as Turkmenistan, Uzbekistan, and Tajikistan, to northern China and India. In high-incidence areas worldwide, including Linxian province in China, Golestan province in Iran, Western Kenya south to Malawi, the Eastern Cape province of South Africa, Calvados in France, Southern Brazil and Uruguay, the occurrence of esophageal cancer is 50–100-fold higher than that in the rest of the world.

In China, ESCC is the 4th most frequently diagnosed cancer and the 4th leading cause of cancer deaths. The age-standardized incidence rate of ESCC in China is 12.5 per 100,000 person-years, compared to 5.6 in the rest of the Eastern Asia, 1.8 in Northern Europe, 2.3 in Western Europe, 0.9 in North America, and 1.2 in Australia/New Zealand. The crude age-adjusted mortality is up to 12.7 per 100,000 person-years [1]. Incidence is generally higher in rural areas, of which provinces like Henan, Hebei and Shanxi have the highest incidence rates in the world. Esophageal cancer most commonly presents in the sixth and seventh decades of life and is rare before the fourth decade. About 70% of the patients in Japan are in their 60 s and 70 s at the time of diagnosis according to the Population-Based Cancer Registry. Similarly, the incidence of ESCC peaks at 70–80 years of age according to National Central Cancer Registry of China [9, 10].

Pathogenesis

Several etiological factors are in association with ESCC, of which, consumption of tobacco, alcohol, hot beverages and nitrosamines, genetic factors, and personal history of squamous cell carcinoma in the head and neck region and the esophagus are most studied (Table 1).

Alcohol and Smoking

Tobacco and alcohol consumption are the two major risks factors for ESCC. Smoking is regarded by the International Agency for Research on Cancer (IARC) as a cause of esophageal cancer [11]. Compared to non-alcohol drinkers, the risk of ESCC increases by 38%, 260% and 550% among those who drink alcohol 1–1.5 L/day, 1.5–6 L/day and > 6L/day, respectively [12, 13]. Alcohol and smoking have synergistic effect on the risk of ESCC. The mechanism is well studied. Alcohol damages cellular DNA by decreasing metabolic activity within cells, thereby reduces detoxification function and promotes oxidation [14]. It acts as a solvent for fat-soluble carcinogens such as aromatic amines, nitrosamines, polycyclic aromatic hydrocarbons, phenols, and aldehyde. Therefore, these substances from tobacco can easily diffuse to the esophageal tissue. A meta-analysis showed that the combined effect of drinking and smoking doubled the sum of their effects individually [15]. In low- or medium-incidence populations like in Europe and the United States, ESCC is largely attributed to

Table 1 Etiology factors for esophageal squamous cell cancer

Factor	Contribution
Alcohol	+++
Smoking	+++
Diet related	
Deficiencies of fresh green vegetables, fruits and vitamins	+
N-nitroso containing food (e.g. pickled vegetables)	+
Chewing betel nut and mate drinking	+
Hot beverages	+
Fungal toxin	+
Infection	
Human papilloma virus	±
Pre-malignant conditions	
History of aerodigestive malignancy	+++
History of radiation to mediastinum	+
Achalasia	+
Lye corrosive stricture	+
Genetic factors	
Aldehyde dehydrogenase deficiency	++
Tylosis	+
Plummer-Vinson syndrome	+
Others	
Low socioeconomic class	+

smoking and alcohol [16, 17]. In the United States, United Kingdom, and France, population attributable risks of 57–73% have been reported for squamous cell carcinoma, based on reduction of smoking and alcohol use, and consumption of fruits and vegetables [17–20]. Similarly, studies in high incidence countries in Asia such as China estimated that 48.5% of esophageal cancers were attributable to the combined effect of alcohol, smoking and low fruit and vegetable intake [21].

Genetic Factors

Genetic predisposition may be related to the pathogenesis of ESCC. Genome-wide association studies have demonstrated a high heritability of ESCC when compared to other cancers [22], and there is an increased risk of ESCC in people who have a positive family history [23–25]. Mitochondrial studies have proved historical population migrations from central / northern to southern-eastern China; the two regions share the same high risk of ESCC and yet environmentally they are quite different [26].

Tylosis, characterized by hyperkeratosis of palms and soles, is a familial esophageal cancer syndrome inherited as an autosomal dominant trait. It has been reported to be associated with genetic mutations in RHBDF2 [27].

Genetic polymorphism is important in individuals with chronic alcohol consumption. Polymorphisms in alcohol dehydrogenase 1B (ADH1B), alcohol dehydrogenase (ADH7), and aldehyde dehydrogenase 2 (ALDH2) are known to alter ethanol metabolism. Approximately 36% of East Asians show a physiologic response to drinking that includes facial flushing, nausea, and tachycardia [28]. This facial flushing response is predominantly related to an inherited deficiency in the enzyme ALDH2. Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase and the acetaldehyde is in turn metabolized by ALDH2 to acetate. Two main variants for ALDH2 exist, resulting from the replacement of glutamate with lysine at position 487. Only individuals homozygous with the glutamate allele have normal catalytic activity. Homozygotes with the lysine alleles have no detectable activity, while heterozygotes with Glu/Lys alleles have much reduced ALDH2 activity. The inability to fully metabolize acetaldehyde results in its accumulation in the body leading to the facial flushing and unpleasant side effects. Lys/Lys homozygotes cannot tolerate much alcohol because of the intensity of the side effects, and so paradoxically they do not have increased risk because they simply would not consume a significant amount of alcohol. Individuals who are Glu/Lys heterozygotes may become habitual drinkers because they could become tolerant to the side effects of alcohol and yet they had suboptimal catalytic activity and thus the acetaldehyde accumulates. These are the individuals most susceptible to the

carcinogenic effects of alcohol consumption, which is related to acetaldehyde causing DNA damage and other cancer-promoting effects [29]. A simple questionnaire that elicits the history of a flushing response can be useful in identifying at-risk individuals, who could be advised against drinking or to undergo screening endoscopy. The risk of developing cancer may be reduced, or an earlier diagnosis could be possible [30].

Diet and Environment

In Asian countries, dietary and environmental factors certainly play a role in the development of ESCC. Studies have investigated the effects of dietary patterns, specific food and nutrients on the disease [31, 32]. Nitrosamines and their precursors such as nitrate, nitrite, and secondary amines, are found in pickled vegetables, which in turn have been shown to increase risk [33]. Nutritional depletion of certain micronutrients, particularly vitamins A, C, E, niacin, riboflavin, molybdenum, manganese, zinc, magnesium selenium, as well as fresh fruits and vegetables, together with an inadequate protein intake, predisposes the esophageal epithelium to neoplastic transformation [34]. While the lack of fresh fruit and vegetables is associated with increased risk of ESCC [35], meta-analyses showed that eating fruits and vegetables significantly reduced ESCC risk [36, 37]. The Nutrition Intervention Trial conducted in Linxian county in China showed that consumption of vitamin B2 and nicotinic acid decreased the incidence of esophageal cancer by 14%, while beta-carotene, vitamin E, and selenium intake could reduce esophageal cancer mortality by 17% in patients less than 55 years old [38].

Consumption of red meat, processed meat, and hot mate were shown to be associated with increased risk of ESCC [39, 40]. A meta-analysis showed that the cancer risk was 57% higher in people who consumed a large amount of red meat and 55% higher in people who took a large amount of processed meat [40]. Mate drinkers have a 60–260% increased ESCC risk compared to non-drinkers in South American countries [41, 42].

Change in specific dietary habits, such as replacing traditional methods of food preservation and storage with refrigeration, together with consumption of vitamin-rich food, may have produced a reduction in incidence rates in certain areas of China, especially in urban cities such as Shanghai [43, 44]. Consumption of hot food and beverages is associated with an increased risk of esophageal cancer, particularly squamous cell cancer [45, 46].

Infection

Infective pathogens including human papillomavirus (HPV), *Fusarium, Alternaria, Geotrichum, Aspergillus, Cladosporium, and Penicillium* species are found to be associated with esophageal cancer in some studies. The role of HPV, debated in more recent studies, is now controversial. Therefore, HPV vaccines may not be beneficial in ESCC prevention [47–51].

Premalignant/Neoplastic Condition

Patients with other aerodigestive malignancies have a particularly high risk of developing ESCC, presumably because of exposure to similar environmental carcinogens and "field cancerization". This concept was introduced by Slaughter and colleagues. It was postulated that clonal expansion develops in mucosa adjacent to an initial area of genetic and epigenetic alternations. This results in a proliferating field of early genetic changes that is at risk of future cancer development [52–54]. Using esophageal cancer as the index tumor, multiple primary cancers were found in 9.5% of patients, of whom 70% were in the aerodigestive tract [55]. The overall incidence of synchronous or metachronous esophageal cancer in patients with primary head and neck cancer is estimated to be 3–6% [56, 57].

Diseases that are known to predispose to esophageal cancer are few. The risk from

achalasia is estimated to be 7- to 33-fold, but symptoms of achalasia are present for an average of 15–20 years before the emergence of cancer [58]. Other diseases include lye corrosive strictures, Plummer-Vinson syndrome, tylosis, and celiac disease.

Other Factors

Low socioeconomic status is associated with increased risk of ESCC. It is believed to be an interplay of many factors including poorer nutritional status, lacking of fresh food and produce, poor oral hygiene and tooth loss. Studies showed that tooth brushing exerts protective effects against ESCC and that tooth loss is associated with increased risk of ESCC [59–61]. These findings, however, should be interpreted carefully as poor oral hygiene may also be confounded by other lifestyle habits like smoking and drinking.

Prevention

ESCC is notorious for its poor prognosis. Being asymptomatic at an early stage, the majority of patients are diagnosed at an advanced stage. The disease tends to spread early compared to other gastrointestinal tract cancers at an equivalent depth of invasion. Identifying modifiable risk factors allows potential prevention and screening at high-incidence regions. This will facilitate early diagnosis and improve prognosis.

ESCC as aforementioned has been demonstrated to be linked with several environmental risk factors. To reduce the risk of ESCC, it is advisable to abstain from smoking and excessive alcohol drinking, consume more fresh vegetables and fruits, and minimize exposure to food carcinogens like nitrites or nitrosamine.

Early detection potentially improves survival outcome. Screening strategies and prediction models have been developed and reported [62]. Currently there is no international consensus on ESCC screening, probably because of the substantial geographic variations in prevalence and concerns on cost-effectiveness. Chromoendoscopic examination using Lugol's iodine solution has been shown to be effective in Korea, Japan and China for screening of esophageal cancer. Magnifying endoscopy with narrow-band imaging (NBI) enables detection of superficial, early-stage cancers with high sensitivity but requires specialized training [63, 64]. These screening strategies and techniques are less applicable in low incidence regions.

Conclusion

ESCC is a fatal disease and a significant burden to the healthcare system especially in regions of high prevalence. Public health education, nutritional intervention and risk-stratified screening potentially reduce incidence rate and cancer-related deaths in high-incidence areas. Understanding of the epidemiology and pathogenesis of ESCC is essential for policymakers and stakeholders of healthcare systems to implement appropriate measures to improve the outlook of this lethal disease.

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