



## REVIEW

# Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China

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### ABSTRACT

Esophageal cancer is one of the most fatal diseases worldwide mainly because of its rapid progression and poor prognosis. Although the incidence of esophageal adenocarcinoma has markedly risen in North America and Europe in the past several decades, esophageal squamous cell carcinoma is still the predominant subtype of esophageal cancer, especially in China. It accounts for more than 90% of all esophageal squamous cell carcinoma cases in China. Geographical differentiation is one of the most distinctive characteristics of esophageal cancer. The progression, risk factors, and prognosis of these two subtypes of esophageal cancer differ. This study reviews the epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China, thereby providing systematic references for policy-makers who will decide on issues of esophageal cancer prevention and control.

### KEYWORDS

Epidemiology; etiology; prevention; esophageal squamous cell carcinoma; review

## Introduction

Esophageal cancer is the eighth most common cancer worldwide, with approximately 456,000 new cases in 2012 (3.2%); it is the sixth most common cause of cancer-related death, with an estimated 400,000 cases (4.9%)<sup>1</sup>. Approximately 80% of the new cases occur in less developed regions in the world, and 60% of these cases occur in China<sup>2</sup>. Esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC) are the two major histological sub-types of esophageal cancer. Esophageal adenocarcinoma has become the predominant type of esophageal cancer in North America and Europe, especially among white men<sup>3</sup>, whereas ESCC is the predominant subtype in China (more than 90% of the total number of esophageal cancer cases)<sup>4</sup>. The striking geographical variation implies that environmental and genetic factors play important roles in the development of esophageal cancer.

## The incidence and mortality of esophageal cancer in China

Esophageal cancer is the fifth most frequently diagnosed

cancer and the fourth leading cause of death from cancer in China, with estimated 286,700 new cases and 211,000 deaths in 2012, according to the National Central Cancer Registry<sup>5</sup>. In China, incidence is generally higher among males and in rural areas. Age-specific incidence and mortality increase with age. The incidence of esophageal cancer before the age of 40 is relatively low but increases rapidly after the age of 40 (**Figure 1**). The mortality of esophageal cancer before the age of 45 is also relatively low and increases rapidly after the age of 50 (**Figure 2**) and peaks between the ages of 80 and 85.

The incidence of esophageal cancer has been steady in recent decades and in most countries. The incidence among males in Asia has generally declined, whereas the incidence slightly increased in Europe. The increasing female incidence rate is lower than in males, especially among people of ages > 45 years old. Data provided by National Central Cancer Registry show that age-adjusted incidence rate decreases from 15.93/100,000 to 10.01/100,000 from 2000 to 2011 in China<sup>6</sup>, particularly in the high-risk areas<sup>7,8</sup>. From 2000 to 2011, age-adjusted mortality rate decreased from 12.69/100,000 to 7.55/100,000. Age-adjusted mortality rate has dramatically decreased across the three National Retrospective Sampling Survey of Death Causes (1973-1975, 1990-1992 and 2004-2005). Primary prevention, such as lifestyle modification, secondary prevention, such as screening, and improved medical level, may be the main cause for the decline of esophageal cancer incidence in China.

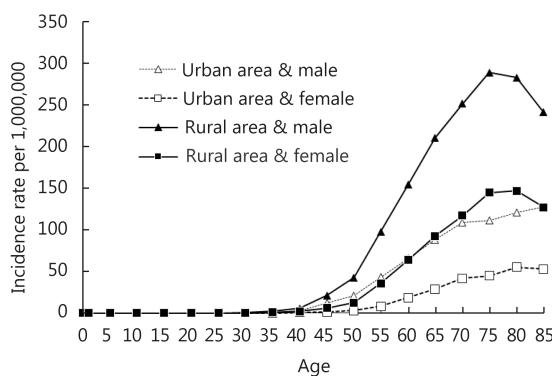
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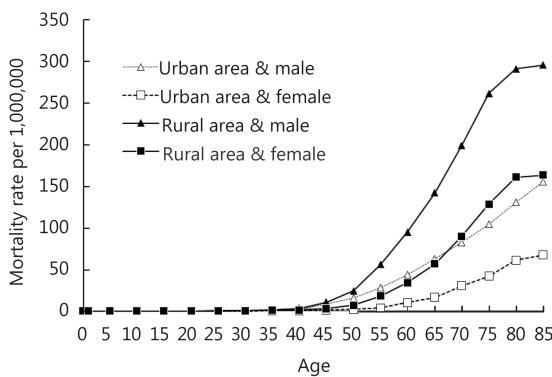
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**Figure 1** Age-adjusted incidence rates for esophageal cancer according to region and gender in China, 2012.



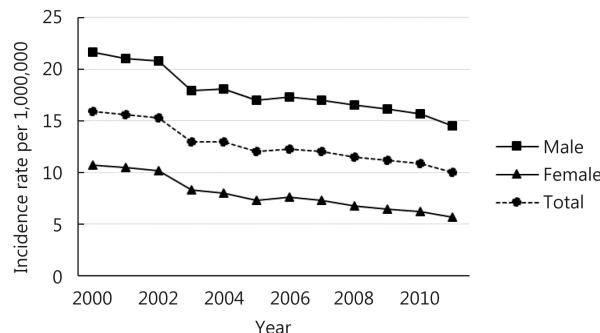
**Figure 2** Age-adjusted mortality for esophageal cancer according to regions and gender in China, 2012.

The incidence and mortality of esophageal cancer are also affected by geography. The greatest burden of ESCC occurs in the “Asian Esophageal Cancer Belt,” which extends from northern Iran, east to China, and north to Russia, presents an estimated ESCC of more than 100 cases/100,000 person-years<sup>9</sup>. The third national census of cancer shows evident regional differences in the incidence of esophageal cancer in China. Provinces with a high incidence of esophageal cancer were Hebei, Henan, Fujian, and Chongqing, followed by Xinjiang, Jiangsu, Shanxi, Gansu, and Anhui<sup>10</sup>. Provinces with higher rates, where near the Taihang Mountains, and the highest incidence of esophageal and cardiac carcinoma were in Linxian, Henan Province, where esophageal and cardiac carcinoma accounted for 81.4% of all malignant tumors in the region. More than 90% of esophageal patients in China are ESCCs; thus, we focus on ESCC in this review.

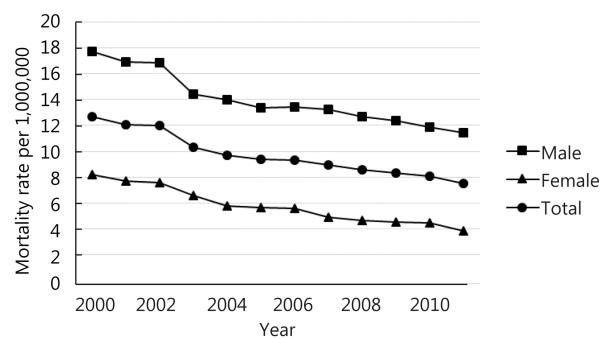
## Risk factors of ESCC

### Smoking and drinking

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**Figure 3** Trends in incidence rates (ASR) for esophageal cancer in China from 2000 to 2011.



**Figure 4** Trends in mortality rates (ASR) for esophageal cancer in China from 2000 to 2011.

Diseases (WHO, 1990), “epidemiological studies make it clear that drinking and esophageal cancer are related, and smoking can also cause esophageal cancer.” Smoking and alcohol drinking are the main risk factors for ESCC in Western countries, and the risk of ESCC increases by threefold to sevenfold for smokers compared with non-smokers<sup>11</sup>. Tobacco smoking is classified by the International Agency for Research on Cancer (IARC) as a cause of esophageal cancer<sup>12</sup>. Compared with non-alcohol drinkers, ESCC risk increases by 38%, 260%, and 550% among those who drink 1–1.5 units of alcohol per day, 1.5–6 units of alcohol per day, and 6+ units of alcohol per day, respectively<sup>13,14</sup>. In addition, reports pointed out that smoking and alcohol drinking exert a synergistic effect on ESCC risk. A meta-analysis showed that the combined effect of drinking and smoking is almost double the sum of their effects individually<sup>15</sup>. However, another meta-analysis showed that the effect of smoking on ESCC is considerably higher in Asian populations than in Western populations. In a prospective study of risk factors for ESCC in Linxian, China, smoking and alcohol drinking were not significantly associated with the more significant risk factors of long-term

ESCC risk, which is not consistent with results of previous studies in other areas in the world<sup>16</sup>.

## Diet

### **Lack of fresh fruit and vegetables**

In several observational studies, non-frequent consumption of fresh fruits and vegetables is closely associated with a higher risk of ESCC<sup>17-21</sup>. However, in that report, no distinction was made between ESCC and esophageal adenocarcinoma. A meta-analysis that included several prospective studies suggested that eating fruits and vegetables is significantly associated with reduction in ESCC risk<sup>22</sup>. A recent population-based case-control study in a rural China population showed that compared with the lowest quartile, the highest quartile of the vegetable and fruit intake was associated with a reduction of ESCC risk by 30%<sup>23</sup>.

### **Hot beverage and pickled vegetables**

Consumption of high-temperature drinks and pickled vegetables (traditional Asian style) are classified by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) as a possible cause of esophageal cancer based on limited evidence. A meta-analysis showed that the consumption of hot food and beverages is associated with an increased risk of esophageal cancer, particularly ESCC<sup>24</sup>. Several observations indicated that the consumption of hot beverages increased the burden of ESCC among Africans<sup>25</sup>. A study in China showed that consuming hot and extremely hot beverages rapidly increased the risk of ESCC significantly among the Chinese population<sup>26</sup>. Eating pickles and sauerkraut was once popular topics in esophageal cancer high-risk studies, and these foods were considered high-risk factors. In addition, another study in China showed that subjects who consumed pickled foods had a 1.76-fold increased risk of ESCC compared with subjects who did not consume pickled foods<sup>27</sup>. Fungi in pickles induce animal cancer<sup>28</sup>. However, epidemiological studies on this topic remain controversial.

### **Red meat, processed meat, and hot maté**

Based on limited evidence, consumption of red meat, processed meat, and hot maté has been classified by WCRF/AICR as a possible cause of esophageal cancer. A meta-analysis showed that ESCC risk is 57% higher in people who consume high amount of red meat and 55% higher in people who consume processed meat compared with those with low meat consumption<sup>29</sup>. A meta-analysis showed that ESCC risk is 2.6 times higher in maté drinkers versus non-drinkers<sup>30</sup>.

However, a pooled analysis of case-control studies found that the risk of ESCC only increased by 60%<sup>31</sup>.

### **Micronutrient deficiency**

Deficiency of several vitamins/minerals is proven to be closely associated with high ESCC incidence; the most pronounced effect is observed in developing countries. Several studies revealed the effect of micronutrients, such as beta-carotene, folate, vitamin C, and vitamin E, on ESCC risk<sup>32-34</sup>. Plasma riboflavin levels are significantly related to the risk and prognosis of ESCC patients, thereby suggesting that moderate supplementation of riboflavin will decrease risk, prevent recurrence of ESCC, and improve the prognosis of ESCC patients<sup>35</sup>. The Nutrition Intervention Trial that has been conducted among the general population in Linxian showed that consumption of the compound capsule of vitamin B2 and nicotinic acid decreased the incidence of esophageal cancer by 14%. Experimental results show that β-carotene, vitamin E, and selenium intake can reduce esophageal cancer mortality by 17% (RR 0.83, 95% CI: 0.71–0.98) in people less than 55 years old and can also reduce total mortality and mortality caused by stomach cancer; the main type of esophageal cancer is ESCC in this study<sup>36</sup>. Selenium and zinc nutritional statuses were also inversely related to ESCC risk in China<sup>37,38</sup>.

## Chemical factors

High doses of polycyclic aromatic hydrocarbons (PAH) and nitrosamine exposure may cause ESCC in a high-risk region. In Northeast Iran, two studies reported the urinary levels of a PAH metabolite that indicated exposure to PAH in >41% of the individuals tested<sup>39</sup>. Studies in Brazil and China presented similar results. Nitrosamine is a broad-action carcinogen, and its precursors are nitrate nitrogen, nitrite nitrogen, and secondary amines that exist in air, water, and food. The amount of nitrite amine in drinking water and food is higher in high-risk than in low-risk regions<sup>40</sup>. After the interaction of NMBzA (a common carcinogen in Linxian) with human fetal esophageal epithelium transplanted into the mesentery of nude mice, squamous cell carcinoma, (including Alu sequence in humans) appeared in the draft site. NMBzA can induce human ESCC; and result of this study is considered the most conclusive evidence of nitrite amine as a contributor to the etiology of ESCC in Linxian country<sup>41</sup>.

## Infections

The association between HPV infection and ESCC remains

controversial. A recent systematic review of the relationship between HPV infection (types 16 and 18) and esophageal cancer worldwide found that HPV is closely associated with esophageal cancer in China, and in other countries, with an integrated OR=1.62 (95% CI: 1.33–1.98)<sup>42</sup>. The highest HPV prevalence was found in Africa and Asia; notably, this result was obtained among Chinese studies from provinces with high ESCC incidence rates<sup>43</sup>. However, three consecutive studies demonstrated that HPV infections are independent of ESCC<sup>44–46</sup>. A large prospective study does not support the major role for HPV 16, HPV 18, and HPV 73 in the etiology of ESCC. In a high-risk area in China, the infection of esophageal cells with high-risk HPV types occurs in 13% of asymptomatic adults with no evidence of squamous dysplasia and a similar proportion of individuals with mild, moderate, or severe dysplasia. The relationship between ESCC and HPV still requires further validation.

## Family history of esophageal cancer

Esophageal cancer presents significant family aggregation. ESCC risk may be higher in people with a positive family history of esophageal cancer<sup>47</sup>. In a large population-based case-control study, strong association between a family history of esophageal cancer and the risk of ESCC was found. The risk of ESCC increased with increasing number of affected relatives. In particular, cases of both parents being affected render an eightfold risk of ESCC for their offspring<sup>48</sup>. Previous epidemiological studies conducted in endemic areas (including mainly Linxian and Shanxi) in China demonstrated that individuals with a family history of esophageal cancer present a higher risk of such cancer<sup>49,50</sup>. However, a multicenter population-based case-control study performed in the United States did not find any familial link for ESCC<sup>51</sup>. A Swedish case-control study also revealed no association between a history of esophageal cancer in first-degree relatives and the risk of ESCC<sup>52</sup>.

## Genetic changes

Previous epidemiological studies showed familial aggregation of the disease in families and higher frequency of allelic loss in ESCC cases with a positive family history. The genetic and environmental interactions may play a certain crucial role in ESCC progression<sup>53,54</sup>. In addition, evidence has shown that RNA expression differs by family history status and that 152 genes present different expression patterns between persons with positive versus a negative family history of upper gastrointestinal cancer<sup>55</sup>. The current etiology of esophageal

cancer genetics has made substantial achievements in molecular theory, but these findings still need validation through clinical trials. Exome sequencing has been conducted on 113 tumor-normal pairs and has yielded a mean of 82 non-silent mutations per tumor and eight cell lines. The mutational profile closely resembles those of squamous cell carcinomas of other tissues but differs from that of esophageal adenocarcinoma<sup>56</sup>. Whole-genome and whole-exome sequencing in Chinese patients with ESCC identified eight significantly mutated genes; among these genes, six are well-known tumor-associated genes (TP53, RB1, CDKN2A, PIK3CA, NOTCH1, and NFE2L2), and two are novel genes in ESCC (ADAM29 and FAM135B)<sup>57</sup>. Three genome-wide association studies examined ESCC, and two subsequent analyses used combinations of these three studies to report as many as 12 loci associated with ESCC risk. A locus in the HLA class II region at 6p21.32 (rs35597309) achieved genome-wide significance in the two populations at the highest risk for ESCC<sup>58</sup>.

## Other factors

Socioeconomic status (SES) was associated with a higher risk of ESCC in both low- and high-risk areas worldwide<sup>59</sup>. A study in Taixing, China, comparing different SES indicators and composite wealth scores found an inverse association between low SES and ESCC<sup>60</sup>. The poor nutritional status of the Linxian population in 1984, as reflected by the dietary data and the low BMI record in study<sup>16</sup>, is a serious matter. Efforts to improve diet, particularly the availability of a greater variety of affordable foods, continue to be a public health priority in Linxian. These efforts to improve the SES of the Linxian population are likely to exert substantial beneficial effects on the health of the people living in the area, and these effects may already be evident in recent reports, which suggested a decline in the rates of ESCC in this area<sup>61</sup>.

Several epidemiological studies have reported an increased risk of ESCC or its precursor lesions in those with poor oral hygiene<sup>16</sup>. Studies from China in the 1970s led to the hypothesis that high risk of ESCC could also result from poor oral health, poor oral hygiene practices, or tooth loss<sup>40</sup>. Recently, a study in China showed that toothbrushing exerts protective effects against ESCC and that tooth loss is associated with an elevated risk for ESCC<sup>62</sup>. Furthermore, in South America, Europe, and Japan, case-control studies have shown that tooth loss can increase the risk of ESCC<sup>63</sup>. However, the association between ESCC with poor oral hygiene and tooth loss can be confounded by other related factors, such as low SES, smoking, and drinking.

## Prevention and screening

ESCC is a common cancer worldwide with a poor prognosis because of the lack of symptoms at early stages. Most patients are diagnosed too late for curative treatment. In China, the survival rate is less than 10% when diagnosed at an advanced stage but can be as high as 85% if detected at an earlier stage<sup>64</sup>. The mortality of ESCC can be reduced through identifying modifiable risk factors and reducing the exposure to these factors (primary prevention) or early diagnosis of precancerous lesions and early cancer treatment (secondary prevention).

Etiological studies still cannot verify which factors play a dominant role in the pathogenesis of esophageal cancer, and the targeted prevention and control measures for primary prevention are deficient. As with other chronic diseases, for the primary prevention strategies for ESCC, we strongly recommend for people to eliminate risk factors, such as quitting alcohol, drinking, and smoking, increasing the consumption of vegetables and fruits, reducing nitrosamine and its precursor PAH intake, and changing lifestyle.

At present, no international specification or recommendation for esophageal cancer screening, early

diagnosis, and treatment is available. Countries with a high prevalence of ESCC have initiated screening programs because early detection is associated with better outcomes. Similar to all population-based screening programs, screening for the early detection of ESCC must be cost-effective. Endoscopy with iodine (Lugol's solution) staining of the esophageal mucosa, known as chromoendoscopy, is the gold standard for the diagnosis of abnormal esophageal mucosal lesions in studies from Korea, Japan, and China. However, this method may be too expensive and invasive in several high-risk communities. Therefore, Iran utilizes nonendoscopic methods. Several new endoscopic imaging modalities, such as narrow-band imaging, cannot be used appropriately at the population level because of its questionable validity and cost-effectiveness for large populations<sup>65-68</sup>.

Since the 1970s, several screening methods have been developed and tested in the high-risk areas of China, such as balloon cytology with smears<sup>69-72</sup>, liquid-based balloon cytology<sup>73</sup>, occult blood detection<sup>74,75</sup>, and endoscopic examination with iodine staining and biopsy<sup>76,77</sup>. Studies have indicated that endoscopy with iodine staining and indicative biopsy can increase the sensitivity and specificity of

**Table 1** Screening strategy of esophageal cancer in high-risk areas of China

Population	40–69 years old high risk population
Method	Endoscopy + iodine staining+ indicative biopsy
Pathologic diagnostic criteria	
Mild dysplasia	Atypical cells are distributed mainly in the basement membrane, less than 1/3 of the epithelium
Moderate dysplasia	Atypical cells are involved in the top layer of epithelium or less than 2/3 of the epithelium
SD/CIS	Precursor lesions involve the epithelium without invading the basement membrane; atypical cells are fully or almost fully distributed in the epithelium with a clear structure of the basement membrane
Intramucosal carcinoma	Lamina propria is invaded and restricted to the mucosa layer; the rate of lymph node metastasis rate ranges from 1% to 5%
Submucosal carcinoma	Submucosa is invaded; muscular layer of esophagus is not invaded; the rate of lymph node metastasis ranges from 10% to 50%
Treatment and follow-up	
Mild dysplasia/moderate dysplasia	Interventions such as nutrition or medication can be taken, affecting their differentiation in its reversal Follow-up for these patients should be conducted every 3-5 years
SD/CIS and intramucosal carcinoma	These patients should receive the treatment of EMR/APC. Follow-up should also be conducted annually
Submucosal carcinoma	These patients should receive the Esophagectomy. Esophagectomy should also be conducted for patients with SD/CIS or intramucosal carcinoma and the lesion is large than 3 cm in diameter or invasion of esophageal circumference 3/4
In advanced esophageal cancer	Standard treatments, such as surgery, radiotherapy and chemotherapy should be used according to the conditions of patients

SD: sever dysplasia; CIS: carcinoma in situ; EMA: endoscopic mucosal resection; APC: argon plasma coagulation.

esophageal cancer screening. A population-based prospective cohort study with buffer regions control in Cixian showed a reduction in cumulative incidence, the risk of further cancer, and cumulative mortality. Risk was reduced by 29.47%, 39%, 33.56%, and 55% in the intervention group versus control group after a 10-year follow-up period among > 45,000 people aged 40–69 years old<sup>78</sup>. This study is the first in the world to demonstrate that the use of endoscopic screening with iodine staining can reduce incidence and mortality of esophageal cancer in high-risk areas. This study provides scientific evidence for the early diagnosis and treatment of upper gastrointestinal disease in high-risk areas in China.

China presents a high incidence of esophageal cancer, especially in rural areas. Over the past half-century, many cancer studies have been carried out in these high-risk areas. Based on domestic and international research and transfer of “the early diagnosis and treatment of cancer” program in China, endoscopic iodine staining and biopsy have been recommended in areas with a high incidence of esophageal cancer. For patients (40–60 years old) in areas with high incidence rate of esophageal cancer, the screening and treatment of early abnormal lesions prevent progression to esophageal cancer. All lesions were diagnosed on the basis of histopathological examination (**Table 1**)<sup>79</sup>. The program of screening and the early diagnosis and treatment of esophageal cancers are effective in high-risk areas in China. In non-high risk areas, this large-scale population screening is not aligned with China's national conditions. In non-high risk urban areas, a high-risk population assessment may be carried out. Screening of high-risk groups may be more cost-effective. However, this method needs to be verified in more cohort studies.

## Conclusions

The treatment and prevention of esophageal squamous cell carcinoma are among the most important public health issues in China. During the last three decades, socioeconomic development, medical level improving, lifestyle changing and screening, and mortality from esophageal cancer decreased in China. However, the burden of this fatal disease is considerable due to the immense scale of the Chinese population. Effective preventive actions, such as health education, nutritional intervention, and screening, should be enhanced, especially in high-risk areas.

## Conflict of interest statement

No potential conflicts of interest are disclosed.

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