Review

Epidemiologic differences in esophageal cancer between Asian and Western populations

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Abstract

Esophageal cancer is a common cancer worldwide and has a poor prognosis. The incidence of esophageal squamous cell cancer has been decreasing, whereas the incidence of esophageal adenocarcinoma has been increasing rapidly, particularly in Western men. Squamous cell cancer continues to be the major type of esophageal cancer in Asia, and the main risk factors include tobacco smoking, alcohol consumption, hot beverage drinking, and poor nutrition. In contrast, esophageal adenocarcinoma predominately affects the whites, and the risk factors include smoking, obesity, and gastroesophageal reflux disease. In addition, Asians and Caucasians may have different susceptibilities to esophageal cancer due to different heritage backgrounds. However, comparison studies between these two populations are limited and need to be addressed in the near future. Ethnic differences should be taken into account in preventive and clinical practices.

Key words Esophageal cancer, epidemiology, molecular epidemiology, ethnicity

Esophageal cancer is the eighth most common cancer around the world. In 2008, an estimated 482 000 new esophageal cancer cases were diagnosed and 407 000 related deaths occurred globally[1]. There is an obvious difference in esophageal cancer incidence between men and women. For men, the incidence is 2–4 times higher than that for women. Esophageal cancer incidence and mortality are also affected by geography. Eastern Asia and eastern and southern Africa have the highest rates, whereas Europe and North America show lower rates. In males, the highest incidence of esophageal cancer is observed in southern Africa [age-standard rate (ASR): 22.3 per 100 000], eastern Asia (ASR: 20.3 per 100 000), and eastern Africa (ASR: 14.9 per 100 000). Similarly, these areas are also sites of the highest incidence among females.

Epidemiology of Esophageal Cancer in Asian and Western Countries

Esophageal cancer has two main histological types:

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esophageal squamous cell carcinomas (ESCCs), which occur in the middle or upper one-third of the esophagus, and esophageal adenocarcinomas (EACs), which occur in the lower one-third of the esophagus or in the junction of the esophagus and stomach[2,3]. These two types differ in many aspects, including incidence, mortality, risk factors, clinical features, genetic susceptibility, and pathogenesis. The incidence of ESCC has been declining over the past decades, whereas the incidence of EAC continues to increase. Approximately half of esophageal cancer cases are EAC in some Western countries, such as the United States [4]. In contrast, ESCC continues to be the dominant type in other areas of the world, especially in Asia.

ESCC

Marked difference in incidence of ESCC among countries or ethnicities is an epidemiologic characteristic of ESCC. The high-risk areas for ESCC include South America and the "Asian Esophageal Cancer Belt," which extends from eastern Turkey, through Iraq, Iran, and the southern part of the former Soviet Union (Kazakhstan, Turkmenistan, Uzbekistan, Tajikistan) to Mongolia and western/northern China[5]. ESCC is the major type of esophageal cancer in Asia, especially in China. More than half of global ESCC cases occur in China, including the high-incidence areas of Linxian in Henan Province, Cixian in Hebei Province, and Huai'an in Jiangsu

Province[6-8].

ESCC incidence continues to decrease in the United States, partly because of the decrease in tobacco smoking and alcohol consumption[9]. More than 90% of ESCC cases are attributed to alcohol consumption and tobacco smoking in the United States. and other Western countries[10,11]. In Asia, ESCC incidence has declined in past decades because of socioeconomic level elevation and lifestyle modification, but ESCC is still a significant health burden[12]. Tobacco smoking and alcohol consumption are also the main risk factors for ESCC in Asia. ESCC risk has been reported to increase by 3- to 7-fold in current smokers[12]. Other risk factors include drinking hot beverage, family cancer history[13], poor nutrition such as lack of fruit and vegetables in the diet, mechanical injuries, and opium use, with estimated risk ratios (RR) or odds ratios (OR) up to 2.5[14-17]. In Linxian, China and Golestan, Iran, the incidence of ESCC is similar among males and females; however, in other regions across Asia, this trend is different: the incidence for males is higher than that for females[18,19]. In these areas, the proportions of smokers and drinkers are very low for women[20], suggesting a minor role of smoking and drinking in ESCC. It is likely that other risk factors may exist in these high-risk areas that account for the majority of ESCC cases, but the exact factors are still not well understood.

EAC

The incidence of EAC is increasing in many countries. In the United States, it is rising more rapidly than any other cancer, causing EAC to be named as "an emerging disease"[21]. The incidence of EAC increased by approximately 6-fold from 1975 to 2000[21]. EAC incidence is also increasing in other developed areas and countries around the world, including the United Kingdom and Denmark[22,23]. In China, an increasing trend was also reported in both urban and rural areas[24]. Furthermore, EAC is often diagnosed at an advanced stage and has a 5-year survival rate of less than 20%[25].

The sharp increase of EAC incidence in the United States and other Western countries is due in part to the increasing prevalence of known risk factors such as being overweight or obese[26]. A meta-analysis including 14 studies showed that EAC risk increased by more than 2-fold in overweight and obese individuals[27]. Another major risk factor for EAC is gastroesophageal reflux disease, which is also increasing in frequency, and its sequela, Barrett's esophagus. One case-control study reported that among persons with recurrent gastroesophageal reflux disease, as compared with persons without such symptoms, the OR was 7.7 [95% confidence interval (CI), 5.3 to 11.4] for EAC[27]. The increasing incidence of gastroesophageal reflux disease

may be linked to changes in lifestyle and dietary habits. In Barrett's esophagus, the squamous epithelium damaged by reflux esophagitis is replaced by a metaplastic, columnar epithelium, which has a malignant predisposition[28]. Other suggested risk factors for EAC include family cancer history (OR = 1.74)[29]. *H. pylori* infection is hypothesized to be protective against EAC because it reduces acidity in the stomach and thereby reduces esophageal damage from reflux[26]. In the past few decades in the United States, advances in sanitation and the widespread use of antibiotics have led to a decline in the prevalence of *H. pylori* colonization, which may be associated with the recent increase in EAC incidence. The increasing incidence of EAC in China may be due to increased tobacco consumption, which is another important risk factor for EAC[26]. In some areas in China, unhealthy diet, such as pickled vegetables and moldy or fermented foods, has been associated with increased risk of EAC[30].

Molecular Epidemiology of Esophageal Cancer in Asian and Western Countries

Environmental and behavioral factors may increase the risk of esophageal cancer. However, only a small fraction of individuals with risk factors ultimately develop esophageal cancer[31]. Therefore, genetic susceptibility may play an important role in esophageal cancer development. Immigrant epidemiology studies have supported that genetic factors are important components affecting esophageal cancer risk[32,33]. Single nucleotide polymorphisms (SNPs) are the most common genetic polymorphisms, accounting for a large proportion of genetic variations in the human genome[34]. SNPs may influence the risks, outcomes, and responses to particular therapeutic interventions of certain diseases. The identification of genetic markers for esophageal cancer may be useful for high-risk population screening, early detection, and predicting drug response/prognosis, thus allowing for early diagnosis and personalized medicine in the future.

Genome-wide association studies for esophageal cancer

Over last several years, genome-wide association studies have successfully identified hundreds of genetic polymorphisms reproducibly associated with diverse complex diseases and traits, including cancers[34]. Recently, four ESCC genome-wide association studies were reported, all of which were conducted in Asian populations (three in the Chinese Han population and one in a Japanese population)[35-38]. The first genome-wide association study of ESCC performed in Japanese individuals revealed two functional SNPs in alcohol

dehydrogenase 1B (*ADH1B*) (rs1229984, OR = 1.79) and aldehyde dehydrogenase 2 family (*ALDH2*) (rs671, OR = 1.67), which encode metabolic enzymes for alcohol and carcinogens associated with altered ESCC risk. This study also reported gene-environmental interactions of rs671 with alcohol drinking and smoking, and found a similar link between SNP rs1229984 and alcohol drinking[35]. In 2010, two genome-wide association studies in Chinese populations identified two additional susceptibility loci [rs2274223 in phospholipase C, epsilon 1 (*PLCE1*) and rs13042395 in chromosome 20 open reading frame (*C20orf54*)] for ESCC[36,37]. More recently, a larger genome-wide association study (2043 cases and 2063 controls) on ESCC performed in Chinese Han individuals revealed three new SNPs, rs10052657 in phosphodiesterase 4D (*PDE4D*) (OR = 0.33), rs2014300 in runt-related transcription factor 1 (*RUNX1*) (OR = 0.62), and rs10484761 near to unc-5 homolog C (C. elegans)-like (*UNC5CL*) (OR = 1.77), to be associated with ESCC risk at significant level[38]. This study reported that three variants (rs11066105, rs11066280, and rs2074356) in strong linkage disequilibrium on 12q24 conferred risk to ESCC in a gene-environmental interaction manner, with increased risk in tobacco and alcohol users[38]. Despite the increasing use of genome-wide association studies, none has been reported for esophageal cancer in Western populations or for EAC in Asian or Western populations.

Genetic susceptibility for ESCC

The tumorigenesis of esophageal squamous cells involves genes that encode regulators of diverse cellular processes, including alcohol metabolism [e.g., *ALDH2* and alcohol dehydrogenase 2 (*ADH2*)], folate metabolism [e.g., thymidylate synthase (TS) and methylenetetrahydrofolate reductase (*MTHFR*)], DNA repair [e.g., X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*), xeroderma pigmentosum, complementation group C (*XPC*), and xeroderma pigmentosum D (*XPD*)], cell cycle control [e.g., tumor protein p53 (TP53) and cyclin D1 (*CCND1*)], apoptosis (e.g., *FAS*), inflammation [e.g., cytochrome c oxidase subunit II (*COX2*)], and carcinogen metabolism. These genes also include those encoding phase I enzymes (e.g., *CYP* genes) and phase II enzymes (e.g., *GST* genes) that contribute to either carcinogen activation or detoxification[39,40]. In the past decade, dozens of genetic variants of these genes were identified via candidate gene approaches to be associated with ESCC[39,40]. Notably, the majority of these molecular epidemiologic studies have been conducted in Asian countries, such as China and Japan, because of the high ESCC incidence there. Studies in Western populations are relatively rare.

Genetic susceptibility for EAC

In contrast to ESCC, there have been only limited studies focused on EAC susceptibility. However, with the increasing incidence of EAC, epidemiologists and other researchers have started to better investigate this type of esophageal cancer, primarily in North American and European populations. In these studies, variants of genes encoding phase I and II enzymes [e.g., glutathione S-transferase theta 1 (*GSTT1*), glutathione S-transferase pi 1 (*GSTP1*), and glutathione S-transferase mu 3 (*GSTM3*)], DNA repair genes [e.g., *XRCC1*, excision repair cross-complementing rodent repair deficiency, complementation group 1 (*ERCC1*), *XPC*, and *XPD*], and cell cycle control (e.g., *TP53, TP73*, and *CCND1*)[39,40] were linked to EAC susceptibility. SNPs in other genes, such as the vascular endothelial growth factor (*VEGF*) gene[41], were also reported to be associated with susceptibility for EAC in Western populations. The association studies for EAC in Asian population are scarce. The only study conducted in an Indian population revealed that *GSTM3* polymorphism might modulate the risk of EAC [42], but the sample size was very small.

Prognosis and Survival of Patients with Esophageal Cancer

Current treatments for esophageal cancer mainly include surgery, chemotherapy, radiotherapy, or a combination of these modalities. The location and size of the tumor, presence or absence of metastases, cell type, and patient goals are all factors for formulating a treatment plan. Nevertheless, after reviewing the literature, Wong *et al.*[43] reported that the combination of chemotherapy and radiotherapy before surgery provides more benefit than radiotherapy or chemotherapy alone for localized disease.

There are substantial differences in the clinical features and prognosis of ESCC and EAC. Compared to those with ESCC, patients with EAC may have more advanced tumors, as well as a higher percentage of invaded lymph nodes, shorter time until resumption of feeding, shorter hospital stay, higher diffuse recurrence rate, and lower incidence of tobacco-related second primary tumors[44]. In addition, some studies have also reported that ESCC is less likely to have early regional lymph node dissemination and distant relapse than EAC[44-46]. For clinical therapy, radiotherapy alone has been used for inoperable squamous cell carcinomas in the past; however, it showed little effect on the relatively radioinsensitive adenocarcinomas[47]. On the contrary, patients with EAC benefit more from neoadjuvant chemotherapy than do those with ESCC. In summary, different clinical and histological characteristics between

ESCC and EAC justify a differential therapeutic approach and result in distinct clinical outcomes.

Despite the improvement of local treatments, surgery, chemotherapy, radiotherapy, and combined modalities, the overall survival rate for patients with esophageal cancer is still very low, with a range of 10% to 15%[48]. Several epidemiologic studies suggested that gender may be an intervening factor for esophageal cancer: women with esophageal cancer tend to have a better prognosis than do men[49]. However, patients with the same clinical features and treatments may have different clinical outcomes, indicating genetic variants may play an important role in esophageal cancer prognosis. Researchers sought to use personal genetic information in combination with clinical information to provide patients with esophageal cancer the best personalized supportive care and therapy. Similar to studies on esophageal cancer risk, studies on esophageal cancer prognosis can also be divided into two types by using histology and ethnicity: associations between SNPs and ESCC prognosis in Asian populations and associations between SNPs and EAC prognosis in Western populations. On one hand, SNPs from different pathways, including the xenobiotic metabolism pathway (e.g., *GSTT1* and *GSTM1*)[50,51] and the folate pathway (e.g., *TS* and *MTHFR*)[52-54], have been reported to influence the outcome of ESCC in Asian populations, such as Chinese and Japanese. Researchers also found that genetic variants in *MTHFR*, *TS*, and 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*) might contribute to ESCC

prognosis in German populations[55]. On the other hand, for EAC prognosis, DNA repair pathways (e.g., *XRCC1*) have received much attention because cisplatin is routinely used in EAC chemotherapy[56]. The association between EAC outcomes and polymorphic variants on other pathways, including the inflammatory pathway [e.g., interleukin 1 beta (*IL1B*) and interleukin 6 (*IL6*)][55] and the folate pathway (e.g., *TS* and *MTHFR*)[54,56], have also been evaluated in Western populations. However, knowledge regarding genetic variants and esophageal cancer prognosis is still limited.

Conclusions

In terms of traditional epidemiology (incidence, demographics, histology, and risk factors) and molecular epidemiology (genetic susceptibility and sensitivity to treatments), esophageal cancer has distinct characteristics in Asian and Western populations. The ethnic and histological differences should be considered in future studies and clinical practices. Hence, Asian studies should focus more attention on EAC. Future molecular epidemiologic studies would be helpful in identifying high-risk populations, performing early screening and diagnosis, and guiding clinically personalized therapy for esophageal cancer.

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