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REVIEW ARTICLE

Esophageal cancer: Risk factors, genetic association, and treatment

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Summary The poor prognosis and rising incidence of esophageal cancer highlight the need for improved detection and prediction methods that are essential prior to treatment. Esophageal cancer is one of the most fatal malignancies worldwide, with a dramatic increase in incidence in the Western world occurring over the past few decades. Despite improvements in the management and treatment of esophageal cancer patients, the general outcome remains very poor for overall 5-year survival rates (~10%) and 5-year postesophagectomy survival rates (~15–40%). Esophageal cancer is often diagnosed during its advanced stages, the main reason being the lack of early clinical symptoms. In an attempt to improve the outcome of patients after surgery, such patients are often treated with neoadjuvent concurrent chemoradiotherapy (CCRT) in order to decrease tumor size. However, CCRT may enhance toxicity levels and possibly cause a delay in surgery for patients who respond poorly to CCRT. Thus, precise biomarkers that could predict or identify patients who may or may not respond well to CCRT can assist physicians in choosing the appropriate therapy for patients. Identifying susceptible gene and biomarkers can help in predicting the treatment response of patients while improving their survival rates.

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1. Introduction

Esophageal cancer remains an integral cause of cancer-related death and has shown a drastic increase of more than 6-fold in incidence rates worldwide.[1] The incidence rate of esophageal cancer varies considerably with location.[2] Esophageal squamous cell carcinoma (ESCC) has a high prevalence in East Asia, eastern and southern Africa, and southern Europe.[2,3] However, the incidence rate of ESCC is low in North America and other parts of Europe.[4] These geographical differences show that ethnicity, genetic factors, and lifestyle all play a role in the development of ESCC. Barrett's esophagus, a metaplastic transformation from the normal squamous mucosa of the esophagus to a columnar lining, is the only known precursor for esophageal adenocarcinoma; its presence transmits a 30- to 40-fold increased risk of developing esophageal adenocarcinoma.[5,6] Identifying, exploring, and intervening on all potential risk factors could have an important impact on the incidence rates of esophageal adenocarcinoma. Currently, only about 5% of patients diagnosed with esophageal adenocarcinoma have a precancer diagnosis of Barrett's esophagus.[7] Therefore, identifying risk factors and imposing effective postdiagnosis intervention could assist in the development of models that would more efficiently screen patients for Barrett's esophagus.[8,9] There are numerous studies with various sample sizes and research designs that have been conducted in the past two decades to help better understand the etiology of and risk factors for esophageal adenocarcinoma and Barrett's esophagus. The potential risk factors one might possess for being diagnosed with esophageal adenocarcinoma, according to the results of these studies, are white race, male sex, gastroesophageal reflux disease (GERD), cigarette smoking (or a history of smoking), and obesity.

2. Risk factors of esophageal cancer

2.1. Demographics

It has been reported that there is an increased risk of esophageal adenocarcinoma diagnosis for persons older than 50 years, but no trend was found for an increased magnitude of risk beyond age 50 years.[10] Racially white individuals have a 2-fold risk of developing esophageal adenocarcinoma than Hispanics, and a 3–4-fold increased risk when compared with Blacks.[11,12] A prevalence study performed in the United States on Barrett's esophagus through the use of an endoscopy indicated that its prevalence among non-Hispanic whites was 6.1%, compared to 1.7% among Hispanics and 1.6% among Blacks. Therefore, much of the differences in cancer risk attributable to race/ethnicity may be the reason for the differences in the risk of being diagnosed with Barrett's esophagus.[13] Additionally, the male/female ratio of Barrett's esophagus patients is about 2:1.[14] However, the incidence rate of esophageal adenocarcinoma shows a 38-fold increase in males over females, which may suggest that men are not only more likely to develop Barrett's esophagus, but also once they have it, may be more likely to then have their diagnosis progress to cancer.[14,15]

In ESCC, incident rates in Black men was significantly increased compared with Black women (15.8 per 100,000 person-years and 4.7 per 100,000 person-years, respectively). White men also had a higher incident rate than White women (7.1 per 100,000 person-years and 2.0 per 100,000 person-years, respectively). The male/female incidence rate ratio for ESCC were 1.8 among Whites, 2.9 among Blacks, and >4 among Hispanics, American Indians/Alaska Natives, and Asians/Pacific Islanders. ESCC accounted for 87% of all esophageal cancer in Blacks but only for 45% in Whites.[16] The incident rates significantly upregulated in Black and men was correlated with their lifestyle such as smoking and alcohol consumption.

2.2. Smoking

Smoking is a risk factor associated with both Barrett's esophagus and esophageal adenocarcinoma. It has been reported that current smokers have an increased risk of esophageal adenocarcinoma, as compared to nonsmokers [odds ratio (OR) = 1.96; 95% confidence interval (CI), 1.64–2.34].[17] Sex and duration of smoking cessation are also associated as risk factors of esophageal adenocarcinoma. Men with a history of smoking had a slightly higher risk of esophageal adenocarcinoma (OR = 2.10; 95% CI, 1.71–2.59) than women (OR = 1.74; 95% CI, 1.21–2.51). Persons who had quit smoking cigarettes for 10 years still had an increased risk of esophageal adenocarcinoma when compared to those who had never smoked (OR = 1.72; 95% CI, 1.38–2.15). Continuing to smoke also enhances the risk of Barrett's esophagus progressing to cancer.[18]

Smoking was also a major cause in ESCC, where the OR was 2.9 (95% CI, 2.1–4.1); the OR in men was higher than in women (4.0 vs. 2.7, respectively). A current smoker has more risk than an ex-smoker. Total packs per year smoked was also correlated with increasing risk of ESCC. For those who smoked >30 packs per year, the OR was 4.1 (95% CI, 2.7–6.2), and the rate was higher in men than in women (5.5 vs. 4.0, respectively).[19]

2.3. Alcohol consumption

Ethanol was metabolized by alcohol dehydrogenase and formed acetaldehyde. Acetaldehyde interacted with DNA and produced DNA adducts to induce gene mutation. Thus, alcohol is one of the risk factors for the development of upper aerodigestive tract cancer.[20] The average weekly alcohol intake exceeded 170 g, and the OR was significantly increased in ESCC patients but not in esophageal adenocarcinoma patients. The OR was upregulated in men and women with ESCC who consumed more than 210 g and 70 g per week, respectively.[21]

2.4. Gastroesophageal reflux disease

GERD is one of the important risk factors for both Barrett's esophagus and esophageal adenocarcinoma.[22,23] Approximately 10% of patients diagnosed with GERD will develop Barrett's esophagus.[24] Patients experiencing recurrent heartburn or regurgitation have an approximately 5-fold

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