MINI-REVIEW

Epidemiologic Risk Factors for Esophageal Cancer Development

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Abstract

In retrospective studies of esophageal cancer (EC), cigarettes and hookah smoking, nass use (a chewing tobacco product), opium consumption, hot tea drinking, poor oral health, low intake of fresh fruit and vegetables, and low socioeconomic status have been associated with a higher risk of esophageal squamous cell carcinoma. Barrett’s esophagus is clearly recognized as a risk factor for EC, and dysplasia remains the only factor useful for identifying patients at increased risk, for the development of esophageal adenocarcinoma in clinical practice. Here, we review the epidemiologic studies that have investigated the epidemiologic patterns and causes of EC.

Keywords: Esophageal cancer - SCC - adenocarcinoma - epidemiology - risk factors

Introduction

EC is the eighth most common cancer in the world and ranks sixth among all cancers in mortality (Kamangar et al., 2006). Even the progress of modern biological medicine has increased the survival rate and improved the prognosis and quality of life in cancer patients. Unfortunately, the new EC cases found often present at the stage III/IV, leading to a low 5-year survival prognosis. In 2008, 16,470 new cases of EC were diagnosed, and 14,280 patients died from this disease in the United States (Jemal et al., 2008). As described by Eslick et al. (2009) “Understanding and delineating the epidemiology of EC will be the key to elucidating the causes and risk factors for EC and thus, the cornerstone of developing any prevention strategies.” This idea has also received international recognition from experts in the EC field. Here, we review recent developments in the search for the suspected etiologic factors of EC. We searched MEDLINE, COCHRANE, OVID, POISONDEX and MICROMEDEX databases (1982–2010, especially recent 5 years) for articles published in the English language using the key words ‘EC’, ‘ESCC’, ‘EADC’, ‘epidemiology’ and ‘risk factors’.

Pathologic Considerations

EC typically involves malignancy that arises from the epithelium, or surface lining, of the esophagus. There are various subtypes of EC, primarily ESCC and EADC. ESCC arises from the cells that line the upper part of the esophagus. EADC arises from glandular cells that are present at the junction of the esophagus and stomach (Kuwano 1998). Most tumors of the esophagus are malignant, and only approximately 0.5% of them are benign. A very small proportion (under 10%) is leiomyoma (smooth muscle tumor) or gastrointestinal stromal tumor (GIST). Malignant tumors are generally EADC, ESCC, and occasionally small-cell carcinomas. The latter share many properties with small-cell lung cancer and are relatively sensitive to chemotherapy compared to other types of EC. The differences between ESCC and EADC can be seen based on their pathogenesis, epidemiology, etiology and biological behavior patterns.

The principal precursor lesion of ESCC cancer is epithelial dysplasia (Kuwano 1998). Microscopically, this lesion represents an accumulation of atypical cells. Studies have shown that ESCC develops through a progressive sequence from mild to severe dysplasia, to carcinoma in situ, and finally to invasive carcinoma (Kuwano et al., 2005). These tumors frequently present as fungating, ulcerating, or infiltrating lesions in the esophageal epithelium, while the EADC usually arises as a consequence of persistent gastro-esophageal reflux (GER) from areas with specialized intestinal metaplasia in the distal esophagus. It is now widely accepted that EADC does not develop de novo but rather along a sequence of phenotypic and genetic alterations that have been termed the metaplasia-dysplasia-neoplasia sequence (Steevens et al., 2010). Similarities between adenocarcinoma of the oesophagus and the nearby, but distinct gastric cardia have led epidemiologists to present adenocarcinoma at these sites as the same disease (Steevens et al., 2010). ESCC is similar to head and neck cancer in their appearance and association with tobacco and alcohol consumption, and EADC is often associated with a history of GERD and Barrett’s esophagus.

Epidemiology

There is a markedly higher incidence of EC in some areas of the world, such as China, Iceland, India, Japan,
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United Kingdom, as well as the region around the Caspian Sea (Chung et al., 2010). Approximately 15,560 new EC cases were diagnosed in the United States during 2007 (Claudia et al., 2005). The EC incidence and mortality rates in African-American descent have been reported to be higher than that in Caucasians (Ng and Vezeridis, 2010). The incidence of EADC, which is associated with Barrett’s esophagus, is rising in the United States. And EADC is more common in Caucasian men over the age of 60.

Time trends

It was reported that the incidence of EADC has rapidly increased over the past three decades, especially in western countries (Balbuena and Casson, 2009). The EADC age-adjusted incidence increased in New Mexico from 1973 to 2002. During the last 30 years, the increase of EADC occurred primarily in non-Hispanic whites and to a less extent in Hispanics (Vega and Mazen, 2010). It was first reported that an increased incidence of EADC was found around the same time in both the UK and the USA in the 1970s (Kubo and Corley, 2004). During that time, ESCC accounted for 90% of EC and EADC in 16% of the white males in the United States; in the mid 1980s, nearly one-third of EC was due to EADC; in the late of 1990s, this number rose to 55%-60%. The incidence rate of EADC rose to 2.5 per 10,000 persons. In contrast, the incidence rate of ESCC has not changed much, and some studies have even shown that the rate of ESCC has decreased (Trivers et al., 2008). The overall age-adjusted rates of ESCC and EADC were 1.8 per 100,000 persons and 2.6 per 100,000 persons from 1998 to 2003 in the United States, respectively. The rate of EADC fell by an average of 3.6% per year, whereas the rates of EADC rose by 2.1% per year.

The incidence of EADC in England and Wales increased rapidly and consistently in both sexes (Rachet et al., 2008). In men, the age-standardized incidence of EADC rose almost five-fold, from 0.9 per 100,000 persons per year during 1971–75 to 4.5 per 100,000 persons during 1996–2001. The incidence of EADC in women has risen almost as quickly, from 0.2 to 0.9 per 100,000 persons. The incidence of EADC increased at a similar rate in both sexes, by an average of 39.6% and 37.5% every 5 years in men and women, respectively. The causes of increase of EADC remain largely unknown. Unfortunately, no related rates have been reported in developing countries.

Geographic variation

Although EC exists in nearly every country and among every race throughout the world, the truth is that the incidence rate varies widely from one area to another. Two areas less than 100 miles apart could exhibit a 500-fold difference in the incidence rate of EC. In general, most ESCC cases occur in developing countries; however, EADC does occur in developed countries. EC is characterized by striking geographic variation throughout the world. The so-called “Asian esophageal cancer belt” (Figure 1), which stretches from Turkey through countries such as Iran, Mongolia, Kazakhstan and on to the Taihang Mountain region in northern China, is an area that exhibits such variation. High-incidence areas for ESCC include Normandy and Bretagne in Europe and Northern China, Japan, India and Iran in Asia (Bader et al., 2005; Wu et al., 2008).

ESCC is one of the most common malignancies in China. Its incidence rate is high, which accounts for 23% of cancer mortality in China, and more than 50% of the EC incidence in the world occur in China. The incidence rate of ESCC even exceeds 130 per 10,000 persons in high incidence areas such as Linxian, Henan province. Another interesting finding is that animals such as chickens living in high-risk areas seem to have a higher rate of ESCC, pointing to the role of environmental exposure in the development of ESCC. It has been reported that Singapore has a high incidence rate of EADC, which may be related to the migrants from high-risk areas in China. The highest current incidence of EADC is in Great Britain (Creed and Neugut, 2004; Lagergren, 2005).

Sex, age and race

The female to male ratio for EC is 1:2–5, with a 1:3 ratio for the occurrence of ESCC and a remarkably proportional difference between males and females. In some high-risk areas of the world, such as in Linxian, China, and Golestan Province of Iran, this ratio is 1:1. The ratio of males to females is 7–10:1 for EADC. In general, males have a higher incidence rate of EC than do females, but in some high-incidence areas, e.g., Iran, females have a slightly higher incidence rate than do men. It was reported that the male to female ratio was 3.49 (95% CI, 3.4–3.59) for EC, 2.57:1 for ESCC and 7.64:1 for EADC from 1975 to 2004 (Cook et al., 2009).

The occurrence of ESCC and EADC increases with age, with incidence rates peaking at 70 years of age. The peak age in 80% of patients with EC is over the age of 50 years. Regarding race, blacks have a greater chance of being diagnosed with ESCC, while whites are more likely to be diagnosed with EADC (Claudia et al., 2005). Additionally, blacks have demonstrated worse survival rates compared to whites, because blacks were always diagnosed at more advanced stages of disease and were less likely to undergo surgery.

Survival

The survival rates for ESCC and EADC are similar...
because most patients are diagnosed during late stages of disease. The overall 5-year survival rates are still very poor regardless of race and gender. Despite improvements in surgical and medical treatments, the 5-year survival for EC remains below 20% (Jemal et al., 2009). Trends in survival in EC have not significantly improved over the past several decades.

**Risk Factors**

Associated risk factors are well known and can vary dramatically between ESCC and EADC. Risk factors for ESCC include tobacco use, alcohol consumption, and nutritional imbalance, while EADC is associated with Barrett’s esophagus, gastroesophageal reflux and obesity.

**Nitrosamines**

Recently, nitrosamines were confirmed as one of the most powerful and stable carcinogenic factors in EC, and only a small dose can induce EC in the white rat. To date, more than 20 kinds of nitrosamines have been reported to play an important role in inducing EC in animals. N-nitro compounds and precursors are present in salted vegetables and preserved fish in high incidence areas such as Cixian, China (Morita et al., 2010).

**Tobacco and alcohol use**

Most epidemiological studies have identified tobacco smoking and alcohol drinking as the main risk factors for ESCC, displaying dose- and time- dependency (Castellsagué et al., 1999). It has been reported that smoking and drinking have synergistic effects, which may increase the relative risk over 100-fold than that induced by smoking or drinking alone. Clearly, alcohol is the major factor, but smoking may increase the carcinogenicity caused by alcohol.

Jesus et al. (2008) examined that whether the type of alcohol or tobacco consumed made any difference to the susceptibility to EC. It was found that the consumption of any combination of hard liquors was more dangerous to a person’s health than low consumption of only wine, and the black type of cigarette seemed to be more harmful than the blond, using a case-control study in Spain, which was suggested that ESCC is strongly associated with alcohol drinking, but it might not contribute to EADC.

In contrast, alcohol consumption may not be significantly associated with ESCC in high-risk rural areas. In a large prospective study comprising 1,958 ESCC cases, Tran et al. (2005) found that there was no association between alcohol drinking and the risk of ESCC by gender in Linxian, China, and suggested that alcohol consumption was likely related to socioeconomic status in the Linxian population, which was inversely related to ESCC risk. The result was inconsistent with findings in the West and previous studies in China showing that alcohol use is rare and is not a risk factor in rural, high-risk areas, whereas it does increase risk in low-risk urban areas.

As the greatest risk factors in EC, the mechanisms of tobacco smoking and alcohol drinking may include the following: 1) tobacco contains a great deal of chemical carcinogens such as polycyclic aromatic hydrocarbons, nitrosamines and aromatic amines; 2) tobacco also contains carcino-potential promoting ingredients such as aldehydes, phenols and their derivatives; 3) ethanol is a highly active solvent, especially of fat-soluble compounds. Therefore, hazardous materials in tobacco can invade the esophagus epithelium quickly (Blot et al., 2006); 4) ethanol can inhibit cell metabolic activity and detoxification functions; 5) ethanol promotes cellular oxidation (Muwonge et al., 2008), which increases DNA damage. Therefore, the presence of certain antioxidants in wine but not in liquors may explain the results of the Jesus study (2008).

**Barrett’s esophagus and gastroesophageal reflux**

Both Barrett’s esophagus and gastroesophageal reflux are strongly associated with EADC. EADC arises from Barrett’s esophagus, a metaplastic transformation of the normal stratified squamous esophageal epithelium. The risk of cancer increases slightly with an increasing length of Barrett’s esophagus, but increases significantly with progression of Barrett’s esophagus to dysplasia (Oberg et al., 2005; Gatenby et al., 2007). It was reported that patients suffering from Barrett’s esophagus were found to have a 30-fold increased risk of EADC, whereas those with reflux but without Barrett’s esophagus had only a modestly increased risk (3.1 times) compared with the general population. GERD was found to be a significant risk factor for EADC (OR 5.5, 95% CI 1.2–25) in Olmsted County and Minnesota during the period from 1971 to 2000 (Solaymani-Dodaran et al., 2004; Crane et al., 2007). Lagergren et al. (1999) reported that the odds ratio was 7.7 in their 1999 population-based study in Sweden.

**Nutritional imbalance**

Both under-nutrition and over-nutrition are considered as risk factors in EC. These conditions may be associated with socioeconomic status (SES). High SES is always associated with over-nutrition in developed countries such as the USA. In contrast, low SES is associated with under-nutrition in developing countries. As a risk factor, under-nutrition includes low intake of micronutrients such as vitamin A, C, E, riboflavin, zinc, selenium and low intake of fresh fruits and vegetables. A case control study has demonstrated a reduced risk of EC associated with regular intake of fresh fruits and vegetables in southwestern China (Yang et al., 2005). The evidence for a protective association between fruit and vegetable intake and EC are convincing and consistent, a meta-study showing fruits to be more beneficial than vegetables. Similar findings were reported by the Japan Public Health Center-based Prospective Study Group (Yamaji et al., 2008).

Over-nutrition is associated with excessive carbohydrate intake and obesity. Recently, it was found that the increase in EADC was strongly correlated with the rise in carbohydrate intake (p<0.0001). They also found a significant correlation between obesity and EADC (p < 0.0001) during the same time period (Thompson et al., 2008). Obesity, which results from high caloric consumption and energy imbalance, is a risk factor that may contribute to the development of GERD and subsequent EADC (MacInnis et al., 2006; Balbuena and...
Human papilloma virus (HPV)

It was firstly demonstrated that a relationship between human papillomavirus (HPV) infection and EC in 1982 (Syrijnen, 1982). In that study, HPV infection was found in 40% (24/60) of EC tissue, which was similar to that observed in anogenital cancer. Since then, the number of reports concerning related studies has increased. Although the role of HPV infection in EC is not as remarkable as in anogenital cancers, in Europe, high frequencies of HPV have been observed in individuals with ESCC from France and Portugal (Jemal et al., 2010). HPV was often detected in the ESCCs of patients from Asia (Japan, China, Hong Kong, India, Pakistan, and Korea), South Africa, Alaska, and Australia. According to the pooled data from these high-risk areas, the incidence of HPV in ESCC ranged from 13% to 63%, with an overall incidence of 22% (Herrera-Goeppert et al., 2009; Antonsson et al., 2010). Examination of HPV infection was made in 82 tissue samples of EC and 40 samples of normal mucosa using immunohistochemistry and in situ hybridization methods. The results showed that HPV infection was high in EC from Henan emigrants, local residents and patients at the Hubei Cancer Hospital (Yao et al., 2006). The data suggested that HPV is closely related to ESCC. HPV infection may play an important role in the carcinogenesis and development of ESCC.

On the other hand, HPV has been detected at a low frequency, or not at all, in a series of studies undertaken in regions with a low incidence of ESCC, such as in the United States and in some European countries, excluding France and Portugal.41,42 It is clear that HPV is important in the pathogenesis of ESCC in high-incidence areas; however, the overall low incidence (22%) suggests that other risk factors, which may have synergistic effects with HPV, could also be important. Thus, the exact role of HPV infection in esophageal carcinogenesis is still further study.

Genetic alterations in EC and their relevance to etiology and pathogenesis

The presence of genetic abnormalities is another important factor leading to EC (Kuwano et al., 2005; Toh et al., 2010). The affected genes include the epidermal growth factor receptor, other related growth factor receptors, cell-cycle regulatory proteins, transforming growth factor-β/Smad proteins and mismatch repair genes (Sgimoto et al., 2009; Xu, 2009). The most common alterations found in EC include allelic losses at chromosomes 3p, 5q, 9p, 9q, 13q, 17p, 17q and 18q as well as mutations in p53 (mostly missense), Rb (deletions), cyclin D1 (amplifications) and c-myc (amplifications) (Sugimoto et al., 2007; Qin et al., 2008). The sequence of these alterations with respect to histopathological tumor progression is very important. Many findings underscore the differences in the etiology and pathogenesis of ESCC vs. EADC and suggest that the genetic alterations observed may represent molecular fingerprints of the critical risk involved in the development of these two cancers.49,50

The occurrence of genetic alterations associated with the development of ESCC and Barrett’s adenocarcinoma of the esophagus is shown schematically in Figure 2.
may increase the risk of ESCC (Ye et al., 2004). On the contrary, infection with *H. pylori* may reduce the risk of EADC. Curing *H. pylori* infection in patients may provoke reflux esophagitis (Jonaitis et al., 2008; Take et al., 2009).

**Conclusions**

The precise causes of EC have not been identified. As outlined in the assessment of risk factors for EC, reducing the consumption of tobacco and alcohol must be regarded as the primary preventive method. There is no clear evidence of the benefit of diet supplementation in developing country studies. Primary prevention deserves greater efforts, and the reasons for the trend of increasing EADC in western countries remain largely unexplained. As for understanding the precise etiology and epidemiology of EC, it is essential that further research be conducted.

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