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Review Article

# Epidemiology and Risk Factors of Esophageal Cancer

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*Abstract* **Esophageal cancer is the eighth most common malignancy in the world. In general, squamous cell carcinoma is more common than adenocarcinoma, except in the USA. The etiology of the cancer is multi-factorial, involving such things as smoking, alcohol, dietary habits, viral infections, GERD, environmental carcinogens, and socioeconomic status. This review also shows factors that may protect against the development of esophageal cancer such as a diet rich in fruits and vegetables or consumption of NSAIDs or helicobactor pylori infection in adenocarcinoma.**

*Key words:* **Epidemiology, Esophageal Cancer, Risk Factor**

Esophageal cancer, the 8th most frequent cancer and the 6th most common cause of cancer death in the world,[1,2] has a greatly diverse occurrence rate in different regions around the globe. For example, in Linxian, China the occurrence rate of esophageal cancer is 100 per 100,000,[3] while the average rate of the whole country of China is 13 per 100,000.[4,5] Northern Iran, South Africa and southern Thailand are examples of regions in which a higher occurrence rate of esophageal cancer has been found. In Thailand, esophageal cancer is found more often in the south when compared with other regions of the country. Thailand statistics on the occurrence rate of cancer show that esophageal cancer was found at 8.1 per 100,000 in its male population and only 1.8 in females in Songkla Province in the south. In other regions of Thailand, such as Chiangmai Province in northern Thailand, the occurrence rate of esophageal cancer is 2.5 per100,000 in males and 0.7 in females; and 1.8 and 0.6 per 100,000 people in the male and female populations respectively of Khonkaen Province in the northeast.[6]

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Concerning specific sub-types, esophageal squamous cell carcinoma (ESCC) is generally found more frequently than esophageal adenocarcinoma (EAC) in Asia and Africa, while EAC has a higher frequency of occurrence than ESCC in the US and Europe. This is because the occurrence of gastro-esophageal reflux disease (GERD), which is related to the occurrence of Barrett's esophagus and EAC, is higher in populations in the US and Europe than in other groups. Presently, the occurrence of EAC is increasing while ESCC is gradually decreasing. Since 1990 EAC has been reported as a higher frequency of occurrence than ESCC in the United States.[7]

It is vital to differentiate between ESCC and EAC cancers because of the different risk factors between them. These risk factors concern both consumption behaviors such as cigarette smoking, alcohol drinking, general dietary habits including the use of medications, and other environmental factors such as passive intake of carcinogens, infections and so on.

### *Tobacco Smoking*

Tobacco ingestion is one of the main risk factors in esophageal cancer. Several case-controlled studies have indicated that the amount and length of time of tobacco smoking has a significant relationship with the occurrence of esophageal cancer.[8-11] The occurrence rate is 4.2 times higher in current smokers and 3.4 times in former smokers than nonsmokers. It has also been found that the length of time smoking has more effect on the occurrence of esophageal cancer than does the amount of tobacco smoked.[12] Tobacco smoking is more associated with EAC cancer than ESCC. However, the amount and length of time in tobacco smoking was found to cause more occurrence of esophageal cancer[13-15] at a rate of 1.5 to 4 times when compared with those who do not smoke.[16-18]

### *Alcohol*

Although alcohol ingestion has been found to have less effect on the occurrence of ESCC than tobacco smoking,[8,10] a study conducted in Taiwan indicated that former alcohol drinkers had a 5.5 times higher risk of ESCC, and current drinkers had a risk rate of 7.6 occurrence rate than nondrinkers. The amount of alcohol ingestion had a greater influence on the occurrence of ESCC than did the length of time.[12] However, no significant relationship was found between alcohol ingestion and EAC cancer[13,14,19]. Although no significant occurrence rate of esophageal cancer was found among those who were both drinkers and smokers,[20] a higher relative risk has been found among those who were both heavy smokers and drinkers.[8,12]

### *Dietary*

Certain types of dietary intakes such as meat, pickles and salted fish have been found in some case-controlled studies to be a relative risk for ESCC. It is of interest to note that such foods likely contain N-nitroso compounds or substrates of nitrate and amine.[21-23] Diets rich in vegetables and fruits, on the other hand, are known to help prevent the occurrence of cancer. Some studies have suggested that the higher intake of vitamin C in such diets might play a role in fighting the impact of N-nitroso compounds in the human body.[24-26] Some nutritional deficiencies such as selenium and zinc have also been found to be risk factors for esophageal cancer.[27-30]

Higher ingestion of vegetables and fruits was also found to reduce the risk of EAC. This might be due to the antioxidants in vitamins C and E and beta-carotene in those diets.[31-33] A study conducted with a large number of subjects (521,457) in European countries found that diets containing a larger amount of meat ingestion can increase the risk of getting EAC.[34]

### *Nonsteroidal Anti-inflammatory Drugs (NSAIDs)*

A 2003 meta-analysis study found that aspirin and other NSAID drugs are associated with EAC rates up to 40% less than non-NSAID users, depending on the amount of drug used,[35] and other studies have had similar findings.[36-39] It has been hypothesized that NSAID use might reduce inflammations which can lead to cancers, although in one study conducted in Linxian, China, in which celecoxib was randomly given to cases, no reduction of esophageal squamous dysplasia was found.[40]

### *Human Papilloma Virus (HPV) Infection*

It is widely known that HPV, particularly HPV16 and 18, which is the main causes of cervical cancer, including certain types of cancers in such areas as the vulva and penis.[41,42] HPV was reported as being of relative risk to esophageal cancer in only cases using polymerase chain reaction (PCR)[43] while there was no

relationship between these two variables in other techniques.[44-47] It might be possible that the finding of HPV in some esophageal cancer patients using the PCR technique was due to some sort of contamination. To date, the International Agency for Research on Cancer (IARC) has concluded that there is no proven evidence to state that HPV causes esophageal cancer.[48]

### *Epstein-Barr Virus (EBV)*

It is widely known that EBV is one of the risk factors for nasopharyngeal carcinoma.[49] It has also been found in some studies to have a relationship with the occurrence of esophageal cancer.[50,51] All studies finding the relationships between EBV and esophageal cancer, however, have been done using the PCR technique in which contamination of EBV can occur in lymphocytes of cancer tissues. In contrast when ISH (in situ hybridization) or PCR in cell lines techniques, which are free from lymphocyte contamination, were used, no significant relationship between the virus and esophageal cancer was found.[51-58]

### *Helicobacter Pylori*

*H. pylori*, a major cause of stomach cancer,[59,60] was not found to have any correlation with the occurrence of EAC. Three meta-analysis studies reported that *H. pylori* found in the stomach reduced up to 50 percent possibilities of EAC.[61-63] It has been hypothesized that H. pylori reduces the gastric acid and therefore reduces Gastro-Esophageal Reflux Disease (GERD) which is the cause of Barrett's esophagus and EAC.[64] There is no known relationship between ESCC and *H. pylori*.

### *N-Nitroso Compounds*

N-Nitroso compounds contain in animal samples have been found to be a relative risk for cancer in the nasal cavity, esophagus, and stomach.[65-68] To date there is no clear explanation on how these N-Nitroso compounds are responsible for cancers in human beings. These compounds can be taken into our body by cigarette smoking, ingestion of certain food such as pickled fish, pork sausages, salted beef, salted fish, and also from endogenous synthesis within the human body.[69,70] No biomarkers were found to detect physical changes in the human body, to date.

N-Nitroso compounds comprised of Nitrosamines and Nitrosamides are the result of a biochemical synthesis of nitrites and amines or amides. Nitrites are compounds resulting from synthesis of nitrates found in foods by certain types of bacteria in the oral cavity.[71,72]

Meta-analysis studies in esophageal cancer have shown a high level of correlation between nitrosamines and certain types of foods that contain nitrites and nitrosamines such as animal meat.[73]

### *Polycyclic Aromatic Hydrocarbons (PAH)*

PAHs are compounds resulting from the incomplete combustion of organic substances such as grilled animal meat and other substances which contribute to environmental air pollution such as cigarette smoke or smoke from burning coal.[74-76] PAHs have been recognized as a risk factor for several types of cancer including some types of skin, lungs, and urinary bladder cancers.[77] Cigarette smoke, which has a high PAH content, is known to be highly correlated to esophageal cancer. However, as with N-nitroso coupounds, there is yet no known biomarker to correlate changes in the human body with the intake of these compounds. There are, therefore, no empirical explanations for the relationships between these compounds and esophageal cancers. Chinese patients in Linxian who were found to have a high occurrence of ESCC were also found to have large quantities of urinary PAH markers reflect exposure only in the 24 to 72 hours before urine collection.[78-81]

### *Acetaldehyde*

Acetaldehyde can be taken into the human body in several ways, but the most prevalent source is alcohol. When taken into the human body, the enzyme alcohol dehydrogenase (ADH) transforms ethanol into acetaldehyde which is further transformed into acetate by acetaldehyde dehydrogenase (ALDH). Laboratory studies show that acetaldehyde causes point of mutation in human lymphocytes, cellular proliferation, and inhibits DNA repair. Acetaldehyde is also a risk factor for esophageal cancer.[82] However, the IARC has said that more empirical studies are needed before acetaldehyde is accepted as a known cause of esophageal cancer.[83]

### *Gastro-Esophageal Reflux Disease (GERD)*

GERD is widely accepted as one of the risk factors of EAC. Lagergren et al. reported a close relationship between GERD and EAC.[84] In general the occurrence rate of EAC is 8 times higher in people with GERD than

those without, while the occurrence rate has risen to 20 times in cases of acute GERD patients.[85-87] GERD changes the esophageal membrane into Barrett's esophagus and this may finally develop into EAC. There is a risk rate of 0.5-1 per cent a year for the occurrence of EAC in Barrett's esophagus patients.[88-90] However, GERD and Barrett's esophagus are not found to have any relationship to ESCC.

### *Obesity*

A high Body Mass Index (BMI) is one of the risk factors for EAC.[90-93] A meta-analysis study reported a positive relationship between EAC and overweight (BMI = 25-30 $kg/m^2$) and obese individuals (BMI >30 $kg/m^2$), at levels of 2 to 3 times respectively above the norm.[90,91] These findings corresponded with studies among Americans and Europeans which found that overweight and obese people were more susceptible to EAC. This might be because obesity increases abdominal pressures and therefore increases the occurrence rate of GERD[94] which can later develop into Barrett's esophagus and EAC, although another study also reported a higher occurrence rate of EAC in overweight people even without GERD.[95]

### *Socioeconomic Status*

Socioeconomic status is determined by earnings, education and jobs. People with lower socioeconomic status have been found to have a higher risk of esophageal cancer than those with a higher socioeconomic status. Study conducted in Sweden[96] has reported an apparent relationship between the occurrence of both ESCC and EAC and socio-economic status in which ESCC had a higher level of relationship.[97]

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