Esophageal cancer

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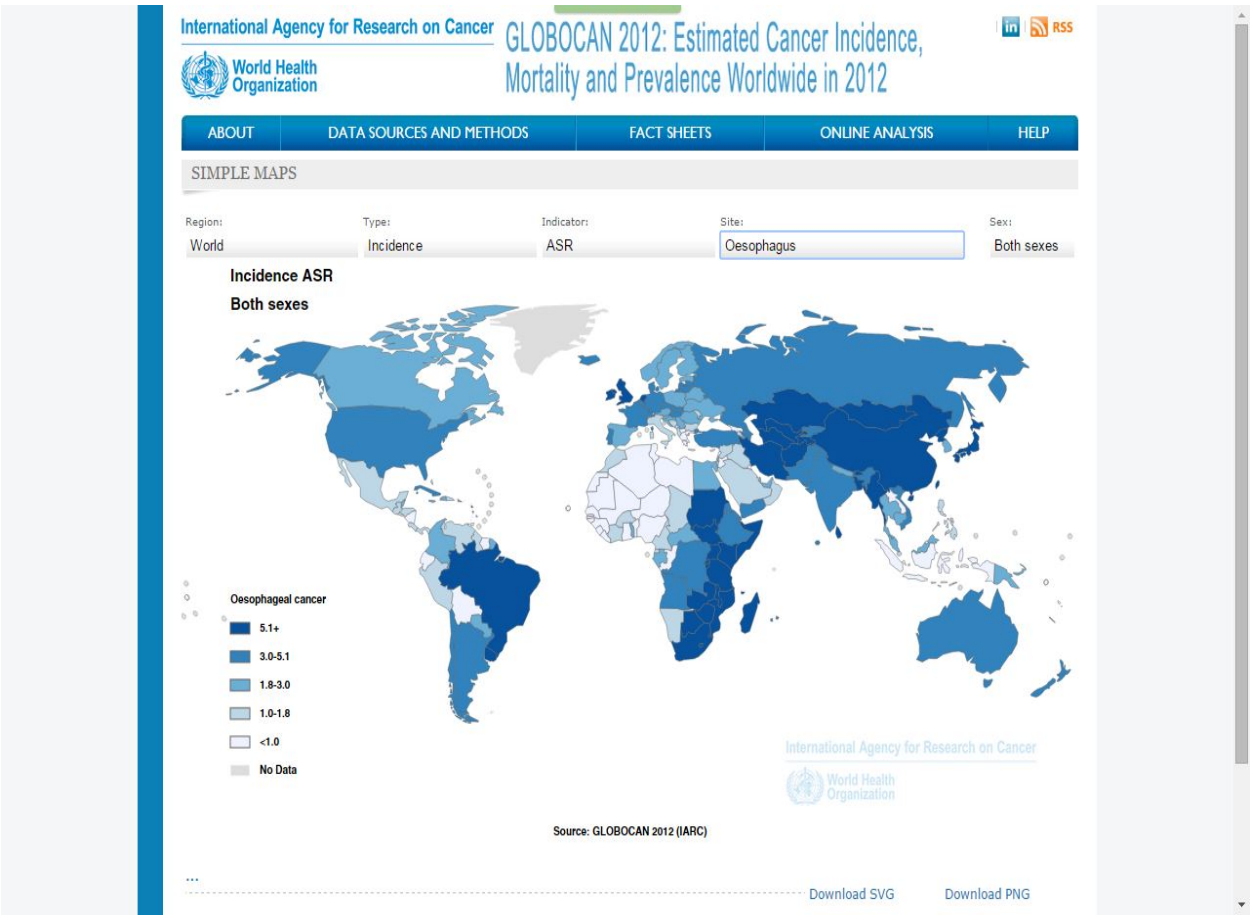
INTRODUCTION

Esophageal cancer (EsC) including squamous cell carcinoma (SCC) and adenocarcinoma is considered as a serious malignancy with respect to prognosis and a fatal outcome in the great majority of cases].
Esophageal carcinoma affects more than 450000 people worldwide and the incidence is rapidly increasing. Currently, EsC is the eighth most common incident cancer in the world because of its extremely aggressive nature and poor survival rate
EsC exhibits an epidemiologic pattern distinct from all other cancers. The incidence of esophageal adenocarcinoma has increased sharply over the past few decades, both by period and
birth cohort.
Etiological studies are required to explain the rapid increase of this lethal cancer.
Understanding the epidemiology of EsC will be the key to elucidating the causes and risk factors for esophageal cancer and thus the cornerstone of developing any prevention strategies.

INCIDENCE

Cancers arising from the esophagus, including the GE junction, are relatively uncommon in the United States. The rate of cancer of the distal esophagus is about equal to that of the more proximal two-thirds.
SCC is the predominant histologic type of esophageal cancer worldwide. The incidence of SCC increases with age as well and peaks in the seventh decade of life, which is three times higher in blacks than in whites, whereas adenocarcinomas are more common in white men.
The most important precancerous disease is Barrett’s esophagus. Patients with Barrett’s esophagus have a 50 to 100 times increase in their risk of developing cancer compared to the general population.

People with Barrett’s esophagus are much more likely to develop cancer of the esophagus.
These people require close medical follow-up in order to find cancer early.Still, although they have a higher risk, most people with Barrett’s esophagus do not go on to develop cancer of the esophagus.
In their population-based cohort study, Hvid-Jensen et al.reported an annual risk of esophageal adenocarcinoma of 0.12% among patients with Barrett’s esophagus.
For different types of esophageal cancer, the risk increases with age, with a mean age at diagnosis of 67 years. Esophageal cancer age-adjusted incidence of blacks was about twice that of whites (8.63/100000 *vs* 4.39/100000, $P < 0.05$. SCC was more commonly diagnosed in blacks and white females, whereas adenocarcinoma was more common among white males.
Although the disease is relatively uncommon in the United States, it is a major global health threat. Esophageal cancer is four times more common and slightly more lethal in men than in women. According to the National Cancer Institute (Cancer.gov) in 2012, it is estimated that17460 persons (13950 men and 3510 women) will be diagnosed with and 15070 persons will die of cancer of the esophagus in 2012.
Esophageal cancer occurs at a rate 20 to 30 times higher in China than in the United States. An esophageal “cancer belt,” primarily squamous cell cancers, extends from northeast China to the Middle East. Evidence of an association between environment and diet and esophageal cancer comes from the profound differences in incidence observed in various parts of the world.
The majority of the factors so far implicated in cancer of the esophagus appear to act directly on the
esophagus rather than systemically. Nutritional deficiencies can develop by chronic alcohol use as well as by poverty and lack of an adequate food supply, but diet does not explain the whole picture. External carcinogens are necessary to affect the end result. The association between nutrition and esophagitis may suggest methods of primary prevention of esophageal cancer and provide a chance of lowering the incidence of this deadly disease.
From 1996-2009, the annual percentage change was increased by 0.5% in all races and 0.4% in
white. However, the increase of incidence is because of the increase incidence in men. Actually,the incidence in woman dropped by 0.4% (Surveillance, Epidemiology and End Results, SEER).



MORTALITY

Figure . shows the age-adjusted esophageal cancer mortality. It is in line with the incidence rate in the world but there is no difference between men and women.

Age-adjusted mortality for blacks, although showing a declining trend, was nearly twice that of whites (7.79 *vs* 3.96, P <0.05). SCC was more commonly diagnosed in blacks and white females, whereas adenocarcinoma was more common among white males (P < 0.001.The reasons are economic
status, diet, and poor eating habits, *etc*.

SURVIVAL

Survival varied widely according to cancer site. The differences in survival related to histology were also expected. Although survival was poor for all groups, it was significantly poorer in blacks than in whites.

The overall 5-year relative survival for 2002-2008 from 18 SEER geographic areas was 16.9%. Five-year relative survival by race and sex was: 18.1% for white men; 17.0% for white women; 10.4% for black men; 12.6% for black women.

Relative survivals for esophageal cancer for all races.

The overall relative 5-year survival rates over time increase gradually in white and black, man and women. For example, the rate was below 2% in 1995 to over 10% in 2008 in black men

(SEER).

Although the overall outlook for patients diagnosed with esophageal cancer has improved in the past 30 years, most patients still present with advanced disease, and their survival remains

poor.One-third to one-half of patients treated with either chemoradiation therapy or chemoradiation therapy plus surgery are alive at 2 years, without recurrence of esophageal cancer.

The reason is because esophageal cancer is diagnosed at rather late stage. Overall, more than 30 percent of patients have metastatic disease at the time of presentation (32.15% in white and 31.83% in black).

None was found that has in situ cancer, due to the fact that it can be difficult to diagnose esophageal cancer early. Among patients who are undergoing primary surgery, 22 percent have localized disease, 30 percent have regional cancer.Stage distribution and 5-year relative survival by stage at diagnosis for 1998-2009, all races, both

Sexes

RISK FACTORS

The patterns of esophageal cancer are dramatically changing in the United States. However, the mechanisms of esophageal tumorigenesis are not fully understood. Three decades ago the large majority of these cancers were SCCs, but the incidence of esophageal adenocarcinoma has been steadily increasing.

Tobacco and alcohol consumption are the primary causes of SCCs of the esophagus. One of the strongest emerging risk factors, however, is obesity. Increases in the prevalence of obesity and the incidence of esophageal

adenocarcinoma are parallel, and several epidemiologic studies have shown upwards of threefold excess risks among overweight individuals. Further research into the causes of these usually fatal cancers may help identify other potential determinants and provide needed information to help stem their increase.

Cigarettes, red meat, alcohol 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 SCC. Barrett's esophagus is clearly recognized as a risk factor for EsC, and dysplasia remains the only factor useful for identifying patients at increased risk, for the development of esophageal adenocarcinoma in clinical practice.

Smoking increases risk of SCC and adenocarcinoma of the esophagus

Moderate to heavy smokers face an increased risk of both SCC and adenocarcinoma of the esophagus. Research suggests that when a smoker ingests tobacco condensates, it causes tobacco carcinogens, particularly nitrosamines, to come in contact with the esophageal mucosa. There is a direct correlation between the number of cigarettes a smoker smokes per day; the length of time the smoker spends smoking, and the risk of esophageal cancer.use of alcohol(3 times a day) increase the risk in addition with tobacco (RR = 0.9)

Usage of opium and SOKHTE as a product of opium in middle east countries is one of common risk factors known as a carcinogen , also chewable tobacco is another risk factor in this areas.

The effects of chronic irritation and inflammation on SCC

The incidence of SCC of the esophagus has been found to dramatically increase in the presence of any factor that causes chronic irritation and inflammation, such as excessive alcohol intake, especially in combination with smoking.This does not hold true for adenocarcinoma. This may account for more than 90 percent of all cases of SCC of the esophagus in developed countries.

Chronic esophageal irritation also occurs when food is retained and decomposed by bacteria, releasing various chemical irritants. Frequent consumption of hot beverages also appears to
increase the incidence of SCC.

Drinking hot beverage

Hot tea as one the risk factor is mentioned. The study on temperature of foods are difficult but it
is known that eating or drinking hot material is associated with cancer of esophagus .

Esophageal squamous cell carcinoma (ESCC) is clearly linked to a low socioeconomic status.
The increasing prevalence of obesity in the Western world is thought to add to the rising incidence of esophageal adenocarcinoma. More specifically, it has been postulated that obesity increases intraabdominal pressure and gastroesophageal reflux by a specific mechanism, although some studies provided contradictory results. On the other hand, adipose tissue itself influences tumor development. Adipocytes and inflammatory cells secrete adipokines and cytokines which are known to promote tumor development. The abundant availability of lipids from adipocytes in the tumor microenvironment, supports tumor progression and uncontrolled growth. Given that adipocytes are a major source of adipokines and energy for the cancer cell, understanding the mechanisms of metabolic symbiosis between cancer cells and adipocytes, should reveal new therapeutic possibilities.
Dirking and eating hot foods:
Assessment of temperature of foods is difficult but it is shown in France studies that hot tea and food is associated with cancer and drinking of 1liter hot fluid is a risk factor(OR=2.3) especially with combination of alcohol and cigarette smoking that rise OR to 7.1

Sex:
Sex is related with involving with esophagus cancer. Sex ratio in France is10 in Iran is <1 but in the world in men is 3 -5 times more than women
Nitrosamines
In studies

Nitrosamines

In studies in china on Pickled vegetable it is shown that contamination with nitrosamines is related with cancer
Fungal infection of foods is another risk factor in china that more studies are needed

socio economic factors

There are evidences in Singapore studies that low Susie economic due to diet situation of people is one of the risk factors

Genetic changes

The genetic and molecular changes underlying the development of EsC remain poorly understood. Genetic analysis of these cancers reveals frequent chromosomal losses (4q, 5q, 9p, and 18q), chromosomal gains (8q, 17q, and 20q), and occasional gene amplifications (7, 8, and17q

In the past decade, efforts have been made to use candidate gene approaches to identify genetic susceptibility factors for ESCC.
The genome-wide association studies (GWAS) has emerged as a powerful and successful tool to identify common disease alleles by using high-throughput genotyping technology to interrogate a large number of tagging single nucleotide polymorphisms
(SNPs) that serve as surrogates for untested common SNPs across the genome.
One source of bias between the two groups may lie in the different controls that were used. This may explain why the rate of G/G is different between the two groups. The second reason may be due to the detection method used.
Usually, sequencing is viewed as the gold standard, but it is
not always correct.To detect polymorphism, the PCR-RFLP that Casson's group used, might have been a better choice because PCR-RFLP tests detect the correct genotype. Direct sequencing of the PCR products, obtained with one of the primers located adjacent to a mutated nucleotide, may cause unequal amplification of alleles in heterozygous samples. This effect is even stronger when mismatched primers are used. Therefore, there is a potential pitfall in DNA
sequencing, indicating that sequencing may not always be the gold standard.
The third reason may be due to the inherent differences between the two groups. As we know, the minor allele
frequency (maf) of a SNP is different among different populations. Since it is ethnicity related,
more information is needed to know the demographic information of the patient and the control group.
CCND1 G870A polymorphism might be a low-penetrant risk factor for esophageal carcinoma, particularly among Asians. More information is needed to study large samples in relationship to pertinent demographic data.

PREVENTIVE FACTORS

The keys to prevention of esophageal cancer vary by cell type. For SCC, reduction or elimination of tobacco and alcohol consumption provide the

best means to reduce the incidence of this cancer. However, no one particular risk factor is responsible for the rising incidence of esophageal adenocarcinoma.

Several preventive strategies are under investigation using such agents as nonsteroidal anti-inflammatory drugs, selenium, alpha difluoromethylornithine, and retinoids.Vegetable intake, and fruit intake is considered to be a preventive role.

Carotene,vitamin C, and vitamin E are protective, most likely in combination with each other and other micronutrients. The role of vitamin A is not clear because of conflicting findings in the studies reviewed.When intake of raw vegetables and cooked vegetables was analyzed separately,raw vegetables were found to be more protective. Because fruits are relatively expensive in most places, increased consumption may reflect. higher socioeconomic status.

Since obesity is closely related to the incidence of the esophageal cancer, it would be interesting to follow up those patients with precancerous lesion to monitor their weight.

In patients with high-grade dysplasia, the options for preventive approaches include surveillance, endoscopic therapies, and surgical resection, but the optimum approach is debate. In an analysis of more than 15 studies, the mean incidence of occult adenocarcinoma in patients with a preoperative diagnosis of high-grade dysplasia treated with esophagectomy was 41%. This high incidence provides a rationale for use of esophagectomy, but there is concern about the risk of morbidity. Use of endoscopic treatments for high-grade dysplasia has been supported in two randomised trials. In one trial of photodynamic therapy plus proton-pump inhibitors compared with proton-pump inhibitors alone, progression to cancer was significantly decreased in the photodynamic-therapy group (13% *vs* 28%). In the other, which assessed endoscopic radiofrequency ablation in patients with Barrett's esophagus and high-grade dysplasia, radio frequency ablation was more effective in eradication of high-grade dysplasia than a proton-pump inhibitor alone, and the progression to cancer was lower (4% *vs* 22%) during short-term followup.

SCREENING AND EARLY DETECTION

Although several potential preventive measures exist, none has been proven to decrease the riskof esophageal carcinoma in prospective well-designed trial.

The relatively low incidence of esophageal cancer, the absence of early symptoms, and the rarity of a hereditary form of the disease make population-based screening untenable except in certain high-risk areas of the world.Patients who are found to have Barrett’s esophagus, however, may be candidates for regular endoscopic surveillance, since the incidence of low-grade dysplasia, high-grade dysplasia, and cancer is approximately 4 percent, 1 percent, and 0.5 percent per year,
respectively, among such patients.Whether endoscopic screening programs to detect Barrett’s esophagus in patients with chronic reflux disease symptoms are useful has been debated. Critics point out the high number of people in the general population who have reflux symptoms and the fact that at least 40% of patients with Barrett’s esophagus do not have reflux symptoms, and question the cost-effectiveness of screening. Proponents of screening for Barrett’s esophagus point to the clear associations between reflux, Barrett’s esophagus, and esophageal adenocarcinoma, and suggest that the rising incidence of esophageal adenocarcinoma justifies screening.

No definitive data are available on whether endoscopic screening for Barrett’s esophagus is associated with a reduction in cancer-related mortality and, therefore, screening is not routinely recommended. However, some experts have recommended that endoscopy be performed every three to five years in patients who have Barrett’s esophagus in the absence of epithelial dysplasia and more frequently if they are found to have low-grade dysplasia. Diagnostic endoscopy for early detection can be conducted in 2 steps: at first detection of an abnormal area through changes in relief, in color or in the course of superficial capillaries; then characterization of the morphology of the lesion.

Then treatment decision offers 3 options according to histologic prediction: abstention, endoscopic resection, surgery. The rigorous quality control of endoscopy will reduce the miss rate of lesions and the occurrence of interval cancer.