Incidence of esophageal cancer (EC), the tenth most common and the eighth most deadly type of cancer worldwide, is decreasing worldwide while survival rates have been rising. Men have higher rates than women due to reasons not clear. Squamous type, mainly confined to the infamous cancer belt, used to be the major type but adenocarcinoma is on the rise now, especially in the west. Southern and Eastern Africa and Eastern Asia have the highest rates with Western Africa and Central America, the lowest. The absolute risk of cancer in Barrett’s esophagus is unknown. Obesity leads to chronic gastro-esophageal reflux disease (GERD), which causes dysplasia and may lead to cancer. Role of diet and environment is only speculative with very little preventive measures. Incidence varies hugely among different populations.

**INTRODUCTION**

Esophageal cancer (EC) is the tenth most common and the eighth most deadly type of cancer worldwide with more than 80% of deaths in developing countries. The epidemiology of EC has undergone a dramatic downward shift worldwide in the last 30 years. EC is primarily of two distinct histological subtypes: squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). The major differences between ESCC and EAC are summarized in Table 1. ESCC was the dominant subtype in most areas of the world, although the dominant histologic subtype of EC in the Western world is currently EAC, attributed to an increase in the incidence of Barrett’s esophagus (dysplastic gastric epithelium in the squamous esophagus), in the last three decades. ESCC accounted for greater than 90% of all ECs in the 1970s. The incidence increases with age, EAC occurring on average 10 years earlier than ESCC. The other rare histological subtypes include small cell carcinoma,

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melanoma, carcinoid tumor, choriocarcinoma and metastatic diseases from lymphomas and sarcomas (Table 2). The aim of this review is to summarize important epidemiological data that has widespread clinical implications. The search of literature was made using PubMed and Google Scholar with the following keywords- esophagus, cancer, incidence, epidemiology- and only publications in English language, selected based on their merit, were included.

Global Epidemiological Trends

Large differences in incidence exist between Asian and Western populations, and between countries, up to 500 fold, (Figure 1) and even within a particular country. The estimated worldwide incidence of EC was 455,784 in 2012 with 400,156 deaths and is expected to be around 576,000 in 2015 with 486,000 deaths. The highest rates in both males and females were found

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in Southern and Eastern Africa and Eastern Asia with lowest rates observed in Western and Central America\(^6\) (Fig.1). West Africa and Middle Africa have very low rates, which are in sharp contrast to Eastern and Southern Africa. An esophageal cancer belt (EC belt) with the highest incidence rates for ESCC in the world\(^6\) - exists in an area that extends from the border of the Caspian Sea and Turkey through the Southern republics of the former Soviet Union and into Northern China (Fig 2). Malawi has the highest incidence and mortality in the world followed by Turkmenistan\(^6\) (Table 3). Among the developed nations, Australia and New Zealand have the highest rates followed by North America, Central and Eastern Europe.

The incidence as well as mortality has drastically decreased in China, Hong Kong, Japan, Korea and Singapore while it is increasing in Taiwan and Vietnam. Cixian county in China has one of the highest rates of incidence in China and the world.\(^7\)

**Epidemiological Determinants**

Substantial differences exist in the incidence of EC based on gender, ethnicity, country of origin, dietary habits and environmental factors.

**Gender**

In the West men develop ESCC three to four times more often and EAC six to eight times more than women.\(^4\) Interestingly there has been a large decrease in the male to female incidence rate ratio (IRR) of ESCC among all ages and particularly in age group>70.\(^8\) There is a steady and substantial decline in sex ratio with increasing age in EAC, unrelated to menopause.\(^9\) Incidence in women is 5.1 times that of men in the US.\(^6\) The rapid increase of EC, currently in the top ten by incidence from 1975-2004\(^8\) is due to the increase in men more than women,\(^8\) even though EAC is rapidly increasing among white women similar to white men.\(^10\) The highest mortality rates among both sexes are found in Eastern and Southern Africa, and in Eastern Asia. South Asian women had a higher risk than men with a six-fold difference in risk between Pakistani and Bangladeshi women, whereas there was no difference by sex in Blacks or Chinese.\(^11\)

The pathogenesis for a higher incidence of EC in men is speculative. Risk factors, like estrogen exposure, BMI and H.pylori infection, have provided no evidence of causing the sex ratio imbalance.\(^8\)

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*(continued from page 38)*

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*(continued on page 43)*
in vitro studies indicate that estrogens might inhibit esophageal carcinogenesis.14

Erosive GERD may be more prevalent in younger men compared to women.15 Other differences between the sexes that may explain the higher incidence of EAC include android obesity (abdominal or metabolic obesity), and factors that promote GERD.16,17 The epidemiological differences in the prevalence of premalignant lesions between both genders is elaborated under Barrett’s esophagus.

Esophageal Squamous Cell Cancer
Currently ESCC is predominantly a disease of the developing world (90% of EC) with a majority of cases in the cancer belt. There are also areas of high incidence of ESCC in industrialized countries, including northwestern France, Iceland, Scotland, and Finland. In the UK, Bangladeshis had a six times higher risk of ESCC compared to Pakistanis.11

The incidence of ESCC is higher in males than females and higher in black men than white men.18 Higher BMI, in sharp contrast to EAC is considered as protective factor for ESCC. Red meat, lamb, and boiled meat and higher drinking temperature19 were found to be associated with the risk of ESCC, whereas fruits and vegetables, white meat, poultry, fish, and liver were protective for unclear reasons.20 Fungal-contaminated, various nitrosamine-containing food stuffs and hot beverages, spicy food,21 deficiency of β-carotene, vitamin A, C and E and minerals zinc, selenium and molybdenum as risk factors for EC have been studied.22 Tylosis, a rare disorder associated with hyperkeratosis of the palms of the hands and soles of the feet, is associated with high incidence of ESCC.18

In the United States there is a higher incidence in coastal South Carolina and metropolitan Washington D.C./Baltimore compared to other states.18 Tobacco smoking and alcohol consumption are major risk known factors for ESCC in US, explaining over 90% of cases in men23 and to a lesser extent EAC.

Acetaldehyde, the primary metabolite of ethanol forms adducts with DNA and this adduct is responsible for the carcinogenic effect of alcoholic beverages.24 Patients with ESCC, particularly alcoholics, current smokers, and those with the ALDH2-2 allele and multiple Lugol-iodine staining lesions on endoscopy, have an increased risk of superficial head and neck squamous cell carcinoma.25 Previous history of lye ingestion is well known to cause strictures and ESCC with incidence varying from 2.6 to 7.2% in the tracheal bifurcation.26 There is a 1000- to 3000-fold increase in the incidence of EC after lye-ingestion with a latent period as long as 60 years.27

The risk of developing EC is higher in celiac disease with the age-adjusted incidence rates esophageal cancer being 50 per 100,000 person-years (normal, 3.9).28, 29 However current data shows that this risk is only short term mostly in the first year of diagnosis.30 Achalasia is associated with the development of EC, even though the risk is low.31 Brucher et al reported EC to occur in achalasia patients 140 times the rate compared to the general population.32

Esophageal Adenocarcinoma
Major risk factors for EAC are BE (a metaplastic

<table>
<thead>
<tr>
<th>Table 2. Classification of Esophageal Cancer157</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPITHELIAL</strong></td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>Ordinary Squamous Cell</td>
</tr>
<tr>
<td>Verrucous Squamous Cell</td>
</tr>
<tr>
<td>Spindle Cell (carcinosarcoma)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Ordinary</td>
</tr>
<tr>
<td>Adenoacanthoma</td>
</tr>
<tr>
<td>Mucoepidermoid</td>
</tr>
<tr>
<td>Adenoid Cystic</td>
</tr>
<tr>
<td>Small Cell Melanoma</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td><strong>METASTATIC DISEASE</strong></td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Sarcoma</td>
</tr>
</tbody>
</table>

Reproduced with permission from Abeloff’s Clinical Oncology, Ch 78. John E. Niederhuber, MD, James O. Armitage, MD, James H Doroshow, MD, Michael B. Kastan, MD, PhD and Joel E. Tepper, MD; Cancer of the Esophagus, p. 1208, Copyright Elsevier (2013).


change of the normal stratified squamous cells of the esophagus to specialized columnar epithelial cells),33 GERD, overweight and obesity among others. The growing epidemic of obesity parallels the increase in the incidence of GERD and the rise of EAC.34 The previously observed increase in EAC incidence might have slowed now35 possibly due to a change in the natural progression of Barrett’s or an increased exposure to protective factors.35 Aspirin and PPI use have been reported to decrease the risk of transition from BE to EAC36, 37 while drugs known to relax the lower esophageal sphincter (e.g., nitro-glycerin, anticholinergics, beta agonists, and benzodiazepines) increase the risk of BE and hence EAC.38

The absolute risk of EAC in Barrett’s is controversial. As the only known premalignant lesion, it is recognized as a precursor of the majority of cases of EAC39 with a 30-125 higher risk than in the general population.40 The risk for conversion from BE to EAC is 0.5% per year, and is thought to occur up to 15 years after diagnosis.10 The diagnosis and management of

(continued on page 46)
high grade dysplasia (HGD) in patients with Barrett’s esophagus is extremely controversial. Lesions in a good number of patients with high-grade dysplasia may even regress or persist and not develop cancer, the basis of recommendation for a less aggressive approach in management. Since BE is a strong risk factor for EAC, endoscopic screening of patients with Barrett’s has been advocated by many. However, the US Preventive Services Task Force has not published any guidelines for or against screening of EAC.

Earlier studies which created an alarming picture of BE and EAC appears to be exaggerated. A systematic review of 47 studies showed the overall incidence of BE to be 6.1 cases per 1000 person years. The absolute risk of EAC after a diagnosis of BE, in recent studies was several times lower, up to 4 to 5 times, than the risk reported in previous studies, which forms the basis for current surveillance guidelines. The risk of EAC among patients with BE may be small that in the absence of dysplasia, routine surveillance of such patients is of doubtful value (Table 5).

The impact of widespread use of Proton Pump Inhibitors (PPIs), on the increasing incidence of BE is contradictory. PPI treatment provides the short term benefit of symptom reduction and healing of esophagitis, and probably a long-term chemoprevention benefits of reduced progression of dysplasia and cancer. High dose of PPI therapy for up to 5 years gives variable results and benefits. In a 13 year prospective study of 188 patients on PPI treatment the incidence of EAC was 0.31%, which is among the lowest incidence recorded in patients with BE undergoing endoscopic surveillance. In contrast, patients treated with PPIs with mild or absent GERD symptoms were found to have significantly higher odds of EAC compared with severe GERD symptoms.

The incidence of EAC seems to parallel the rising epidemic of obesity since the mid-70s. The rise in obesity accounted for 6.5% increase in EAC that occurred from 1973 to 2005 and 7.6% in the year 2005. Obesity-associated EAC risk was found to be higher

Table 4. Indian Studies on Histological Type of EC

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Region</th>
<th>EAC</th>
<th>ESCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joshi et al.</td>
<td>2010</td>
<td>Uttarakhand (northern India)</td>
<td>6 (6)</td>
<td>87 (93)</td>
</tr>
<tr>
<td>Tony et al.</td>
<td>2007</td>
<td>Kerala (southern India)</td>
<td>249 (52)</td>
<td>227 (48)</td>
</tr>
<tr>
<td>Cherian et al.</td>
<td>2007</td>
<td>Tamil Nadu (southern India)</td>
<td>82 (8)</td>
<td>912 (92)</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>2001</td>
<td>Punjab (northern India)</td>
<td>69 (41)</td>
<td>100 (59)</td>
</tr>
<tr>
<td>Mehrotra et al.</td>
<td>1977</td>
<td>Uttar Pradesh (northern India)</td>
<td>3 (1)</td>
<td>193 (96)</td>
</tr>
<tr>
<td>Bhome et al.</td>
<td>2012</td>
<td>Mumbai</td>
<td>104 (23)</td>
<td>314 (71)</td>
</tr>
</tbody>
</table>

Numbers shown in bracket are in %.

among men than women. The positive association between increasing BMI and GERD in the USA is not consistently seen in other countries. BMI solely may not be a risk factor for Barrett’s pointing more towards android obesity as the risk factor. Abdominal obesity appears to increase the risk of BE whereas gluteofemoral obesity protective. Diabetes may be a risk factor for BE, independent of obesity and other risk factors.

*Helicobacter pylori* (*H. pylori*), a gram negative bacterium, has been studied worldwide and in individuals of all ages in various diseases. Conservative estimates suggest that 50 percent of the world’s population carry *H pylori*, predominantly in developing countries where water supply and sanitation are inadequate. *H. pylori* infection is a well known risk factor for gastric malignancy with a risk of up to 6 times that of the normal population. Additional data will be discussed in the next paper on gastric cancers in this series.

The recent advances in treatment of *H pylori*, a gastric carcinogen, and its effective eradication are postulated to be one major reason for the increase in EC. Chronic *H. pylori* infection results in atrophic gastritis, decreased acid production, and thus a lower likelihood for severe GERD. *H. pylori* infection is associated with lower rates of Barrett’s and EAC, in particular the more virulent CagA-positive strain of the bacteria, which are associated with a higher frequency of gastric cancer.

### Geographical Analysis

#### United States of America

The US ranks 67 in the incidence of EC in the world, which is a significant drop from 20 in 2002. It is estimated that there will be 18543 (men 14799 and women 3744) new cases of EC in 2015 with 17469 deaths (men 14055 and women 3414). According to the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) registry data, the incidence of EAC has increased 5-fold in the past 3 decades. The incidence of ESCC was the highest three decades ago, at about 21 per 100,000 and has decreased by more than 60% since then to 7.6 per 100,000 in 2002. EC represents 1.1% of all new cancer cases in the U.S. Rates for new EC cases have been falling on average 0.9% each year over the last 10 years. Death rates have been falling on average 0.6% each year over the same period. The number of new cases of EC was 4.4 per 100,000 per year with number of deaths 4.3 per 100,000 per year.

The incidence and mortality of EC has been increasing among white men, stable among white women, and decreasing in black men and women. White men have the highest incidence of EAC while black men had higher rates of ESCC which has been declining in the recent past. The incidence of EAC although low among African Americans has increased from 0.4/100,000 to 0.9/100,000 among men.

### Table 5. Dysplasia Grade and Surveillance Interval

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Documentation</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Two EGDs with biopsy within 1 year</td>
<td>Endoscopy every 3 years</td>
</tr>
<tr>
<td>Low Grade</td>
<td>• Highest grade on repeat EGD* with biopsies within 6 months</td>
<td>1 year interval until no dysplasia x 2</td>
</tr>
<tr>
<td></td>
<td>• Expert pathologist confirmation</td>
<td></td>
</tr>
<tr>
<td>High Grade</td>
<td>• Mucosal irregularity</td>
<td>ER*</td>
</tr>
<tr>
<td></td>
<td>• Repeat EGD with biopsies to rule out EAC* within 3 months</td>
<td>Continued 3 month surveillance or intervention based on results and patient</td>
</tr>
<tr>
<td></td>
<td>• Expert pathologist confirmation</td>
<td></td>
</tr>
</tbody>
</table>

*EGD – esophagogastroduodenoscopy; ER – endoscopic resection; EAC – esophageal adenocarcinoma.*

and 0.0-0.2/100,000 among women. There is a wide geographic variability in incidence rates and trends, especially for EAC in males: age standardized rates were highest in the Northeast (17.7 per 100,000) and Midwest (18.1) with both being significantly higher than the national estimate (16.0). In addition, the Northeast annual percent changes (APC) were 62% higher than the national estimate (3.19% vs. 1.97%). Lastly, incidence rate ratios (IRR) remained fairly constant across calendar time, despite changes in incidence rates.

Overall incidence of EC is higher among African Americans than Whites (8.4 vs. 8.0 cases per 100,000 persons). Among African Americans, ESCC remains the predominant subtype who have EC rates six times higher than whites. This rate is seen despite the fact that GERD is equally prevalent in blacks than whites in the United States. Survival rates by ethnicity also reveal differences, the 5-year survival rates (%) between whites and African Americans with localized lesions being 36% versus 20% and regional lesions 18% versus 11%.

Europe

UK has the highest age standardized rate (ASR) in Europe (6.5) followed by The Netherlands (6.3). The incidence rates for EC in the UK, France, Portugal, Spain, Germany, Belgium, Italy, Denmark, Netherlands, and Greece for the periods 1960 to 1964 to 1985 to 1989 and Finland had been increasing and that ESCC had been overtaken by EAC as the leading histologic subtype. A recent study of (n=43,753) which examined the incidence rates of EAC in England and Wales between 1971 and 2001 found that the age standardized rates increased rapidly by 39.6% and 37.5% for men and women, respectively. This increase was seen among different socioeconomic levels; those in the more affluent groups had a higher incidence of EAC compared to others. EC incidence in South-Asians and Blacks is lower, compared to whites, by approximately two and one third respectively. In Sweden, EC and gastric cancer have not been increasing since 2005, compared to an increase during the period 1970-2000. In UK ‘non-White’ groups had a lower incidence of esophageal, colorectal, and pancreatic cancer compared to Whites and a higher incidence of liver and gallbladder cancer. Differences in risk between Indians, Pakistanis and Bangladeshis for cancer of the esophagus, stomach, liver and gallbladder exist. Whites had the highest incidence of EC (5.8) followed by Indians and Bangladeshis. Interestingly Chinese in England had a low rate compared to whites and Indians. The lower incidence in all ethnic groups compared to Whites was largely due to their lower incidence of EAC rather than of ESCC. The rates of EC among South Asians were lower than both their countries of origin and whites in the UK.

Iran

Iran, a country with different ethnic groups, has one of the highest incidences of EC. The high incidence of the disease in particular in the north of the country provides an opportunity as well as a challenge to understand the pathogenesis of the disease and possible preventive measures. EC is now only the 6th most frequent malignancy in Iranian males, a drop from 2nd and 4th among women, a drop from 3rd. In one survey by the Iran cancer institute, 9% of all cancers and 27% of gastrointestinal cancers were esophageal. ESCC is the most common accounting for 90% of cases. Age adjusted incidence rate of ESCC in the province of Golestan and further to the East was one of the highest for any single cancer that has been reported worldwide. The infamous Asian EC belt extends to the east from the Caspian littoral area in Iran through Turkmenistan to the northern provinces of China. Other parts of Iran have variable rates of EC from 3 to 15 cases per 100,000 population. The exact etiology for this high incidence is speculative. Consumption of wheat flour, exposure to residues from opium pipes, drinking hot tea and chewing NASS (a mixture of tobacco, lime hash and other ingredients) are often suspected. A family history of EC, low socioeconomic status, and malnutrition are additional suspected factors. Investigating the association between tea drinking habits in Golestan and risk of EC, Islami and associates noted that nearly 98% of the study cohort drank black tea over 1 liter a day and 39% drank tea at temperature < 60 degree Celsius, 38.9 at 60-64 and 22% at higher temperature. Drinking very hot tea is a noted association with the increased risk of EC. The high prevalence of Human Papilloma Virus DNA in different anatomical sites of ESCC patients from Mazandaran region in north of Iran suggests a role for HPV.

Genetic factors are also suspected to play a role. Ten genes (CYP1A1, CYP2A6, CYP2E1, GSTM1, (continued on page 50)
Changing Epidemiology of Esophageal Cancers Worldwide

Epidemiology of Gastrointestinal Cancers, #2

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GSTP1, GSTT1, ADH2, ADH3, ALDH2, and O6-MGMT) are suspected to have a role in risk for EC among three Iranian ethnic groups with varying rates of EC. The high risk patients from Golestan province had higher frequency of four alleles speculated to favor carcinogenesis (CYP1A1 m1, CYP1A1 m2, CYP2A6*9, and ADH2*1).98 Despite a genetic predisposition EC rates, for reasons not clear, have decreased sharply in the recent past even in the high incidence areas.99

China

China has one of the highest incidences of EC in the world with a very high mortality rate. The age-standardized mortality decreased by 41.6% from 1973 to 2005.100 EC is the 4th most common cause of cancer death with the crude mortality rate in 2004–2005 being 15.2/100,000, which represented 11.2% of all cancer deaths.101 The age-standardized mortality of EC per 100,000 was 18.1 for men and 8.2 for women in China, compared to 8.5 and 3.4 in the world, 4.9 and 1.0 in United States, for men and women, respectively.102 China being a vast country, there is a huge geographic variation in the incidence. The six high-risk areas include Cixian and Shexian in Hebei Province, Linzhou in Henan Province, Yangcheng in Shanxi Province, Nan’ao in Guangdong Province and Yanting in Sichuan Province.103 Large cities like Shanghai and Beijing have experienced a greater decrease in EC incidence over the past several decades, when compared with rural areas such as Cixian.104 According to the Shanghai cancer registry data, the incidence of EC had significantly decreased, by 59%, between 1975 and 1988.105 The current ASR of EC in China is 6.7/100,000.6

Tobacco smoking, alcoholism, low intake of vegetables and fruits were responsible for 46% of EC mortality (87,065 deaths) and incidence in 2005.106 About 17.9% of EC deaths among men and 1.9% among women were attributable to tobacco smoking, about 15.2% of EC deaths in men and 1.3% in women to alcohol drinking, and 4.3% EC deaths in men and 4.1% in women to low vegetable intake. The fraction of EC deaths attributable to low fruit intake was 27.1% in men and 28.0% in women.106 However several other epidemiological studies done in high risk areas contradict the above and have shown that smoking and alcohol drinking play a much less significant role in the etiology of EC.107,108

In high-risk areas, with endoscopic screening and cytology, precursor lesions such as dysplasia may be detected in asymptomatic individuals with early-stage cancer.109 Squamous dysplasia was strongly associated with ESCC risk; the relative risk (RR) being 28.3 for persons with severe dysplasia as compared to normal subjects.110 A map of China is provided that highlights the high risk EC areas. In Linxian province general malnutrition, and deficiencies in selenium, zinc, folate, riboflavin, and vitamins A, C, E, and B12, were associated with an increased risk of ESCC.111 Environmental carcinogens were found in high concentrations of nitrates and nitrites, the precursors of nitrosamine, in drinking water samples, and nitrosamine in food samples was noted.112 High concentrations of nitrate nitrogen in well water correlated with ESCC incidence in two studies.113,114

There was no significant increased risk of ESCC among individuals infected with H. pylori.115 Drinking tea at a high temperature significantly increased risk of EC, after adjustment for confounding factors, including alcohol consumption and cigarette smoking.116 Human papilloma virus (HPV) infection, and especially HPV 16/18 E6/E7, with gene mutations and association with p53 overexpression, may contribute to the extremely high incidence of ESCC observed in Xingjian.117 Genetic polymorphisms, including CYP1A1, CYP2E1, and MTHFR, have been associated with ESCC risk in the Chinese population.118 Three genome-wide association studies of EC published since 2010 was consistently identified 10q23 as a susceptibility locus for ESCC.119-121

Japan

EC is the 12th most common malignancy and the ninth most common cause of cancer death in Japan, with an estimated 19683 new cases and 12440 deaths in 2012.6 ESCC remains the predominant type with no dramatic increase in EAC.122 The age-adjusted incidence rate (per 100,000 population) increased from 8.3 to 11.7 during the period 1975–2006 among men but changed little among women, who had an estimated rate of approximately 1.5 during that period.123

Alcohol consumption and cigarette smoking are two major risk factors for EC with prevalence of current drinking being 36.4% among men and 6.9% among women124 and smoking being 38.2% in men and 10.9% in women.124 Alcoholics had a 3.3-fold increased risk as compared with non-alcoholics and there is also a
The association of diet or eating habits and ESCC risk is not convincing. The Japan Public Health Center-based Prospective Study examined the relationship of fruit and vegetable intake with ESCC and showed that a 100-gram per day increase in consumption of total fruit and vegetables was associated with an 11% decrease in ESCC incidence. Interestingly the study did not show any ESCC risk with intake of pickled vegetables. An inverse association between yoghurt intake and ESCC is seen and was also shown with EAC in a previous study in Europe. A strong, positive association between gastric atrophy and ESCC has been shown in three studies. Interestingly there has been no study on the association between Helicobacter pylori and ESCC in the Japanese population.

Less Known Risk Factors- New But Not Established

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Meat</td>
<td>Established risk factor for colon cancer. Red meat, lamb, and boiled meat were directly associated with the risk of ESCC, whereas white meat, poultry, fish, and liver were protective.</td>
</tr>
<tr>
<td>Statins</td>
<td>Decreased risk of EC. 44% reduced risk of EAC.</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Inconsistent Data.</td>
</tr>
<tr>
<td>Lead</td>
<td>Possible dose–response relationship between EC and occupational lead exposure, with no biological correlation.</td>
</tr>
<tr>
<td>Oral Bisphosphonates</td>
<td>Inconsistent Data. Association vs. No Association</td>
</tr>
<tr>
<td>Lignans</td>
<td>Potent source of phytoestrogens, decreases the risk of EAC and GE junction.</td>
</tr>
<tr>
<td>Opioids</td>
<td>Postulated as promoting esophageal carcinogenesis</td>
</tr>
</tbody>
</table>
vegetarian diet on EC is controversial. Consumption of fresh fish was protective while tea consumption, was shown to be a risk factor\(^\text{141}\) probably due to thermal injury to the esophageal lining.\(^\text{139}\)

**Africa**

Limited data of incidence and mortality rates from Africa showed that ESCC is the predominant type with an estimated 27,900 new cases and 26,600 deaths in 2008.\(^\text{142}\) EC is a leading cause of cancer death among both men and women in East Africa, and among men in South Africa. Incidence and mortality rates in these two regions are more than 7 times as high as the rates in Western, Middle, or Northern Africa among men and more than 4 times as high among women.\(^\text{142}\) EC was the most common cancer in men and the third most common among women in the North Rift Valley of Kenya.\(^\text{143}\) Certain geographic locations had higher rates for women compared with men. Zimbabwe has the highest incidence of EC for both sexes, ranked fourth among men and fifth among women.\(^\text{5}\)

There has been no study explaining the reasons for this high burden of EC. The suspected risk factors include smoking, alcohol intake, poor dietary patterns such as consumption of a maize-based diet that is low in fruits and vegetables,\(^\text{144,146}\) and contamination of maize with fungi that produce fumonisins, a cancer-initiating agent in experimental animals.\(^\text{147,148}\) It was found that in Malawi, Kaposi sarcoma, cancer of the cervix and EC were the major causes of the increasing trend in cancers in the country. The increase in EC was found to be in line with the increase in Kaposi's sarcoma suggesting a link between the two.\(^\text{149}\)

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