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Review



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## Esophageal cancer in the world: incidence, mortality and risk factors

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## 1. Abstract

There is little about the incidence, mortality and risk factors of esophageal cancer (EC) in the world. Therefore, the purpose of this study was to determine the incidence rate, mortality and EC risk factors in the world. This review study was conducted on published English research by January 2017 with the search in by March 2018 by searching in the databases of PubMed, Scopus, and Science Direct with the keywords "esophagus cancer", "epidemiology", "incidence", "mortality", "risk factor", "world." Based on the findings of this study, the geographical distribution of the EC differs according to subtitles, as AC is more prevalent in developed countries, while SCC is more prevalent in countries in Africa and East Asia. The most important risk factors for EC are the low intake of vegetables and fruits, drinking drinks and hot liquids, reducing the intake of nutritional supplements such as selenium and zinc, smoking, excessive consumption of alcohol, past medical history, obesity and exposure to some environmental factors. According to the findings, it seems that the main cause of EC- is an undesirable lifestyle. Therefore, it is possible to improve the lifestyle and inform the community about EC risk factors and healthy lifestyle education.

## 2. Introduction

Esophageal cancer (EC) is the eighth most common cancer in the world and the sixth leading cause of death from cancer in the world [1]. An increase in the incidence of EC with its recurrence has led to massive pressures on the health care system [2]. Unfortunately, EC is often associated with an unfavorable prognosis for survival of 5 years, which varies from 4% to 40% based on the progression of the disease, with a total 5-year overall survival rate of 18% [3]. It has a very good prognosis in the case of early detection [4]. In the United States, it is estimated that 17,290 EC cases are diagnosed each year, and 15850 deaths due to the cancer are expected [5]. In the whole world, in 2012 the rate of new EC was 455800 cases, and the resulting deaths were reported to be 400200 [6]. The timing of the incidence of the two EC subtypes is different. The incidence of Esophageal adenocarcinoma (AC) in several Western countries is rising dramatically due to increased risk factors such as overweight and obesity [7]. On the contrary, the incidence of squamous cell cancer (SCC) in these countries is steadily declining due to reduced tobacco use and alcohol consumption. However, the incidence of SCC in certain Asian countries, such as Taiwan, is likely to increase due to increased tobacco and alcohol consumption [8]. Findings from studies have shown that geographical and racial distribution of BC varies from place to place; As in Asian countries is more than American countries [9]. Significant changes in the rate of incidence of EC indicates that various factors affect the increase in EC rates. On the other hand, most studies in this field focus more on clinical challenges and therapeutic approaches to EC management [10–12]. There is little about the incidence, mortality and risk factors of EC in the world. Therefore, the purpose of this study was to determine the incidence rate, mortality and EC risk factors in the world.

## 3. Methods

This review study was conducted on studies published in English by March 2018 by searching in the databases of PubMed, Scopus and Science Direct with the keywords "esophagus cancer", "epidemiology", "incidence", "mortality", "risk factors", " world". In addition, the reference lists of relevant articles were manually searched to find any other potentially eligible articles. The search strategy was tailored due to the requirements of each database. An advanced search was also carried out on cancer-related websites to access specific information for each country. We excluded reviews, commentaries, articles from overlapping samples, conference abstracts, and articles printed in languages other than English. In the initial electronic literature search, 1345 articles were obtained from, and 35 articles were obtained using manual search. After removing

duplicates using Endnote X7 (n =850), the title and abstract of the remaining 530 articles were reviewed. After this stage, 102 articles were included in the study and 428 of these articles were removed because of scientific reasons and lack of eligibility criteria or unrelated to our aim, in all, 96 full papers were reviewed.

#### 4. The incidence and mortality of EC in the world

The incidence of EC based on the geographical area is significantly different. In some countries, it is the second most common cancer, and in some others one of the few common cancers [3]. More importantly, the geographical distribution of EC differs according to subtypes; AC is more prevalent in developed countries, while SCC is more prevalent in African and East Asian countries [13,14]. In terms of regional distribution, the highest standardized incidence rate was observed in both sexes in East Asia (11 per 100,000), East Africa (9.7 per 100,000), South Africa (9.7 per 100,000), Asia (7.7 per 100,000) and Sub-Saharan Africa (4.5 per 100,000), respectively. In the continental terms have the highest incidence of EC was seen in Asia, Europe, Africa, North America, South America, and Oceania, respectively [2,15]. Ten countries with the highest age-standardized incidence rates for EC include Malawi (24.2 per 100,000) Turkmenistan (19.7 per 100,000) Mongolia (17.6 per 100,000) Kenya (17.6 per 100,000), Uganda (17.1 per 100,000), Lesotho (15.1 per 100,000), Tajikistan (14.7 per 100,000), Burundi (12.8 per 100,000), Bangladesh (12.7 per 100,000) and China (12.5 s per 100,000), respectively [16]. Racially, the incidence of ACC and SCC is different between African -Americans, and Asians as compared to Caucasians. The incidence of SCC in African American males is 4.8 times higher than in the Caucasians [17]. Conversely, the incidence of AC in Caucasian men is 5 times higher than African Americans [2].

Histologically, the two main EC subtypes are AC and SCC. While SCC has been the most common form of EC for a long time and there is a steady increase in the incidence of AC, especially in developed Western countries [4]. Regional incidence rates are low in areas such as Asia, Africa, and South America where the incidence of SCC is high. For both types of subtype, EC is higher in males than in females, with an average SCC and AC ratio of 2.5 and 4.4, respectively [18]. The highest SCC rates are in the Asian and AC regions of North America [2]. In Asia, the incidence of SCC in China is significantly higher than in other countries [19].

In terms of regional distribution, the highest age-standardized mortality rate was observed in both genders in East Asia (9.1 per 100,000), East Africa (9.1 per 100,000), South Africa (9 per 100,000), Asia (6.7 per 100,000) and Sub-Saharan Africa (5.1 per 100,000), respectively [2]. In the continental terms have the highest incidence was seen in Asia (6.7), Africa (6.2), South America (3.4), North America (2.9) and Oceania (2.9), respectively [17]. Ten countries with the highest age-standardized incidence rates for EC include Malawi (22.9 per 100,000) Turkmenistan (18.5 per 100,000), Kenya (16.5 per 100,000) Mongolia (15.9 per 100,000), Uganda (15.5 per 100,000), Lesotho (13.9 per 100,000), Tajikistan (13.6 per 100,000), Burundi (12.2 per 100,000), Bangladesh (11.7 per 100,000) and China (10.9 s per 100,000), respectively [16].

#### 5. Risk factors for BC

In developing countries, the incidence of EC is higher, because of low levels of vitamins and minerals resulting from low consumption of vegetables, and fruits [20]. The findings of a meta-analysis study on observational studies show that there is a significant relationship between the high intake of fruits and vegetables and the reduction of SCC risk [21]. High incidence of EC was found in families living in Northeastern Iran due to very little consumption of fruits and vegetables in comparison with the families living in areas with low incidence of EC [22,23].

##### (a) Hot drinks and liquids

One of the main risk factors for EC, especially in South American countries, is tea and coffee consumption. The consumption of hot drinks can also increase the risk of EC due to damage to

Table 1. Factors related to the esophageal cancer

	Factor-related to EC	Protective Risk factor	Controversial
<b>Nutrition factors</b>	Fruits and Vegetables	*	
	Hot drinks and liquids	*	
	High consumption of red meat	*	
	N-nitroso compounds	*	
	Nutritional Supplements	*	
<b>Tobacco</b>		*	
<b>Alcohol</b>		*	
<b>Previous medical history</b>	Gastroesophageal reflux disease and Barrett's esophagus	*	
	Viral agents	*	*
	Underlying esophageal disease	*	
	Previous gastrectomy and atrophic gastritis	*	
	Tylosis and Genetics	*	
	Oral and dental health Increased esophageal exposure to acid	*	
			*
<b>Drugs</b>	proton pump inhibitors (PPIs)	*	
	statins	*	
	histamine receptor antagonists (H2RAs)	*	
	aspirin and other NSAIDs bisphosphonate	*	*
<b>Obesity</b>		*	
<b>Epidermal growth factor polymorphisms</b>		*	
<b>Polycyclic aromatic hydrocarbons (PAH)</b>		*	

the esophageal mucosa [24,25]. Findings from a systematic review of 59 studies showed that more than 50% of studies found that drinking high-temperature fluids is associated with a significant increase in EC risk [24]. For tea and coffee, there is little evidence of the relationship between the rate of use (regardless of temperature) and the EC's risk. A few studies have provided separate findings for SCC and AC. The findings of a case-control study in northern Iran indicate that there is a relationship between the use of hot tea (60-64 ° C) or very hot tea (more than 65 ° C) with an increased risk of SCC [23]. Findings from a cohort study based on another population in China also showed that a high risk of EC is associated with hot tea [25].

### (b) High consumption of red meat

The results of a cohort study on Dutchmen show that high consumption of processed meat is positively correlated with SCC [26]. Findings from another prospective study also confirmed this finding [27]. Several mechanisms can cause EC and gastric cancer after consuming red meat and processed meat. Heterocyclic amines and polycyclic aromatic hydrocarbons are carcinogenic substances that form during meat cooking at high temperatures [28,29]. The N-nitroso compounds and other carcinogenic groups in processed meat contain high levels of nitrite and nitrate compounds [30]. The endogenous formation of N-nitroso compounds is influenced by

heme in meat, especially red meat [31]. The findings of the meta-analysis study in China showed that receiving foods containing nitrogen compounds would increase the incidence of SCC [4].

### (c) N-nitroso compounds

Nitrosamines and nitrosamides are both subgroups of N-nitroso compounds that are produced by the reaction of nitrates with amines or amides. N-nitroso compounds increase the incidence of nasal cavity cancers, liver esophagus in many animal models [32]. People are exposed to these chemical compounds by diet, tobacco, occupational exposure, or drinking water. Although 45%-75% of cases of exposure to these substances are due to metabolism are developed within the body [33]. Directly nitrites are found in sodium nitrite, a preservative in various prepared foods and the metabolites of nitrites digested. Vegetables are the main source of environmental nitrites. However, high levels of nitrite may also be found in water [34,35]. The conversion of nitrate to nitrite by oral bacteria is a major contributor to the formation of N-nitroso compounds, and the answer may well be why inadequate oral health is associated with a high risk of esophageal and gastric cancers [32,36]. Contact with high levels of N-nitroso compounds was more common in diets in areas with high probability compared to areas with a lower probability in China for EC [37]. A study in high-risk areas in northeastern Iran has shown that the amount of nitrosamine in the saliva of Gonbad's population is four times than the German population [22].

### (d) Nutritional Supplements

Findings Several studies have shown that there is a relationship between selenium supplementation and EC risk reduction [38-40]. Zinc deficiency increases the risk of EC due to increased carcinogens of nitrosamines and overexpression of cyclooxygenase-2 (COX) [41-44]. Lack of nutritional intakes also increases the risk of EC [45,46].

#### (i) Tobacco

One of the main risk factors for SCC is smoking. A risk of EC in smokers is 5 times more likely than non-smokers [6]. Several studies have found that TS is one of the main risk factors for EC [47-49]. Several studies have found that the risk of developing ESCC in smokers is 3 to 7 times higher than non-smokers [50,51]. In 2012, a meta-analysis study found that about 20-30% of esophageal cancer patients were addicted to cigarette smoking [52]. Over the course of decades, numerous studies have shown that the incidence of AC in the United States and Great Britain in smokers has increased at a constant rate compared to non-smokers, while this trend is relatively constant for the ESCC and even a decreasing trend [53,54]. Taking into account the prevalence of smoking in Asia, smoking is also one of the main risk factors for EC in Asia [55].

#### (ii) Alcohol

Alcohol is one of the main risk factors for ESCC. The relative risk (RR) of EC increases with increasing alcohol intake ranges from 1.8 to 7.8 based on the volume of alcohol received per week [6]. The metabolism of alcohol is regulated by specific enzymes, which their activity and expression are affected by genetic polymorphism [19]. Several ecological and retrospective studies in Europe have found that alcohol use has a positive and independent relationship with the increase in the incidence and mortality of adenocarcinoma of the esophagus (EAC). The findings of several prospective studies and meta-analysis revealed a significant and positive correlation between alcohol intake and ESCC risk.

#### (iii) Previous medical history

Gastroesophageal reflux disease and Barrett's esophagus

The prevalence of gastroesophageal reflux disease in the western population is about 10% and in the United States about 60-30 million people. GERD can cause coughing, violent voice

and a bitter taste in the mouth. Also, gastric acid can damage the esophagus and make it difficult to swallow. In more severe cases, GERD causes abnormal cells that can lead to unwanted EC cells [56]. In more severe cases, GERD causes abnormal cells that can lead to unwanted EC cells [56]. GERD symptoms are often minor and overlooked, but chronic inflammation in the esophagus can lead to irreparable complications. One of the most serious complications is Barrett's esophagus (BE) [57]. In BE, the typical cover of the esophagus changes to the membrane, which is similar to the intestinal cover. An increase in the incidence of BE over the past 30 years has been associated with an increase in AC incidence over the same period [58]. BE is a pre-cancerous lesion that develops in 6-14% of patients with GERD, and about 0.5-1.5% of these will develop AV [6]. The study findings in Spain showed that the incidence of AC in BE patients during follow-up was 48% for each year (95% CI: 0.006% -2.62%) [59].

### (e) Viral agents

The only virus known to cause esophageal cancer is the human papillomavirus (HPV). Various types of HPV, especially species 16 and 18, are known to be major risk factors for cervical cancer, as well as in vulval, anal, penicillin and oropharyngeal cancers [60]. Over the past 20 years, several studies have been conducted using various methods including isolating HPV DNA in tumor tissue and serologic methods for testing the relationship between HPV exposure and the risk of SCC [61]. However, HPV DNA research results are not compatible. Methods in which PCR was used showed evidence of HPV in tumor tissue from 0% to 67% [62,63]. Epidemiological studies have also shown similar results with serological type-restricted studies [64]. While some serological studies have found a positive relationship between SCC and HPV 16 [60,65], no cases have been found in other studies.

### (f) Underlying esophageal disease

The history of the previous disease in the esophagus, such as achalasia and caustic strictures, increases the risk of SCC [66,67]. In this regard, the findings of a population-based study of 1062 patients with achalasia showed that the risk of SCC increased more than 16-fold in the first 1 to 24-year period after diagnosis. On average, cancer has been detected in these patients 14 years after the diagnosis of achalasia [68]. Other study findings of 2414 patients with SCC showed 63 cases had a history of caustic esophageal injury due to the ingestion of lye soap during childhood. The mean time for SCC diagnosis was 41 years after soap ingestion (between 13-71 years) [69].

### (g) Previous gastrectomy and atrophic gastritis

The risk of SCC in patients who have previously undergone partial gastrectomy is more than other people. In this regard, findings from a study showed that of 115 patients with relative gastrectomy, 12 cases (10%) were affected by SCC [70]. However, other study findings indicated, the risk of SCC and AC was not affected by previous stomach surgery [71]. The risk of SCC in patients with atrophic gastritis and other conditions resulting in gastric atrophy is twice that of others [72].

### (h) Tylosis and Genetics

Tylosis is a rare disease associated with palm and heel hyperkeratosis, which increases the risk of SCC [73]. The hereditary type of Tylosis (Howell-Evans syndrome) is strongly associated with SCC [74]. The disease is the most dominant autosomal inheritance; a gene locus is mapped onto the chromosome 17Q25.1, which probably contains a tumor suppressor gene [75]. Study findings in China and Japan showed that genetic predisposition to SCC, especially in people who consume a lot of alcohol and cigarettes, is high [4]. Also, an increase in areas with a high probability of esophageal squamous cell carcinoma from China to Central Asia to Russia and northeastern Iran

and the high incidence of high esophageal cancers among people with Mongolian phenotypes may suggest a genetic involvement in this disease [76]. Studies in China and Iran have shown that the likelihood of esophageal SCC carcinoma in first-degree relatives with esophageal cancer is more than twice as likely to have no history of esophageal cancer in the family [22,77,78].

### (i) Oral and dental health

Several studies have reported the association between poor oral health and SCC infection, especially in some areas (China and Kashmar, Iran) that tobacco use and high alcohol consumption are not a major risk factor [41,79,80]. A few studies do not support this relationship [81,82]. There is a clear relationship between tooth loss and dysplasia of the esophagus, which is the precursor of SCC in esophagus [80]. Oral health may prevent dental caries, oral and gum disease, and tooth loss. It is related with a lower probability to SCC. There are several mechanisms that may increase the risk of oral squamous cell carcinoma by their poor oral health [81]. Scratch and physical damage to the epithelium of the esophagus associated with ingestion of unpeeled foods, altered food patterns due to unhealthy teeth, changes in oral flora by increasing carcinogenic microorganisms, oral mucosal infection with oral microorganisms, and genetic factors affecting the mouth. All of them are effective in squamous cell carcinoma [83]. In China [80], America [84] and Japan [48], inadequate oral and dental health has been studied as a precursor to the SCC dysplasia.

### (j) Increased esophageal exposure to acid

Findings from a study have shown that patients such as the Zollinger-Ellison syndrome, or conditions associated with gastroesophageal reflux such as surgical myotomy or sciatica scleroderma, which are prone to acid secretion, are susceptible to AC [85–87].

Also, in patients with BE due to gastroesophageal reflux, the use of proton pump inhibitors will not reduce EC risk [88].

### (k) Drugs

Findings from observational studies have shown that the use of proton pump inhibitors (PPIs) and statins in patients with BE may reduce the progression of adenocarcinoma [6]. The findings of a meta-analysis and the systematic study showed that there is a significant relationship between the use of PPIs and histamine receptor antagonists (H2RAs) and the reduction of the risk of esophageal adenocarcinoma [89]. Regular use of aspirin and other NSAIDs has chemopreventive effects on multiple cancers [90,91]. The findings of a meta-analysis study showed that regular use of aspirin and NSAID is a protective factor in esophageal cancer with odds ratios of 0.5 (95% CI: 0.38-0.66) and 0.75 (0.1-54), respectively [92]. Aspirin and NSAIDs are prostaglandin-endoperoxide synthase 1 and 2; the enzymes involved in the production of prostaglandin. However, the precise biological mechanisms involved in the antinociceptive effects of aspirin are still unknown [93]. The findings of a preliminary experimental study that examined the beneficial effect of postoperative use of aspirin on the survival rate of patients with esophageal cancer showed the 5-year survival rate of aspirin users was 51.2%, in the placebo group 41%, and in patients who did not use the pill, 42.3% ( $p = 0.04$  or  $p = 0.029$  when both groups were combined) [94]. The use of bisphosphonates is related to AC and SCC [95]. A cohort study in United Kingdom on 41,826 people treated with bisphosphonate in the years 1996 to 2006 and individually matched with a control group based on gender, age and general function regardless of the use of bisphosphate showed that after a 4-year follow-up, there was no difference in the risk of EC or stomach cancer combined with EC alone in these two groups (adjusted risk ratio [HR] 1.07, 95 % CI 0.77-1.49) [96].

## (I) Obesity

The first reports about the possible relationship between obesity and the EAC were published in the 1990s [97,98]. This finding was confirmed in studies of large populations, case studies in the United States, Europe, and Australia, and indicate a strong correlation between the increase in BMI and the risk of EA [99,100]. Findings from epidemiological studies indicate that obesity is one of the main causes of AC [101,102]. One of the main risk factors for ACE is gastroesophageal reflux disease (GER and obese people experience GER symptoms repeatedly [101]. Two main mechanisms for the development of AC in obese patients have been proposed. First, the physical mechanism involves an increase in the incidence of GERD, and the second is the mechanism of hormone-dependent, which is mainly mediated by inflammatory markers secreted by adipocytes [6].

## 6. Other factors

### (a) Gender and race

Histologically, SCC is common in blacks and white women, and AC is common in white men [4]. The incidence of Esophageal squamous-cell carcinoma (ESCC) is usually higher in males, especially in black males [6].

### (b) Epidermal growth factor polymorphisms

Specific polymorphisms of the epidermal growth factor gene are associated with higher levels of serum epidermal growth factor and increased risk of AC, especially in patients with BE [103,104].

### (c) Polycyclic aromatic hydrocarbons (PAH)

These hydrocarbons are known carcinogenic materials that are created during the incomplete burning of wood and its derivatives such as coal, coal, tobacco, and so on. Several studies have shown that PAH is an etiologic agent associated with gastrointestinal cancers, including SCC [105, 106]. In a study conducted in Lingyan, evidence of tissue pathology consistent with PAH exposure in SCC cases [105], the presence of high levels of PAH in raw and cooked foods [28] and high concentrations of hydroxypyrene glucuronide (OHPG-1), a PAH metabolite in the sample Urinary tract have been reported [107]. In studies in northeastern Iran, evidence of the potential role of PAH has been found to be an important factor in the creation of SCC [108].

## 7. Summary

This study evaluates the incidence, mortality and risk factors of EC based on a review of studies conducted in the world. Based on the findings of this study, the incidence of EC based on the geographical area is significantly different. More importantly, the geographical distribution of the EC differs according to subtitles, as AC is more prevalent in developed countries, while SCC is more prevalent in countries in Africa and East Asia. In terms of regional distribution, the highest standardized rate of incidence and mortality was found in both sexes in East Asia, Africa, South Africa, Asia, and Sub-Saharan Africa. The most important risk factors for EC are the low intake of vegetables and fruits, drinking drinks and hot liquids, reducing the intake of nutritional supplements such as selenium and zinc, smoking, excessive consumption of alcohol, past medical history, obesity and exposure to some environmental factors. According to the findings, it seems that the main cause of EC- is an undesirable lifestyle. Therefore, it is possible to improve the lifestyle and inform the community about EC risk factors and healthy lifestyle education.



## 8. Open Access

2512

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## 9. List of abbreviations

**AC:** Esophageal adenocarcinoma; **EAC:** adenocarcinoma of the esophagus; **EC:** Esophageal cancer; **ESCC:** Esophageal squamous-cell carcinoma; **GERD:** Gastroesophageal reflux disease; **H2Ras:** Histamine receptor antagonists; **HPV:** Human papillomavirus; **PAH:** Polycyclic aromatic hydrocarbons; **PPIs:** proton pump inhibitors; **RR:** Relative risk; **SCC:** Squamous cell cancer

## 10. Ethics approval and consent to participate

Not to be applied

## 11. Competing interests

The authors declare that they have no conflicts of interest.

## 12. Authors' contributions

All authors contributed to the design of the research, M.SY, MSE, NPA, MA, OO, extracted the data and summarized it. All authors drafted the first version. HSG, and HS edited the first draft. All authors reviewed, commented and approved the final version.

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