Review
Middle East Journal of Cancer 2010; 1(1): 5-14

Esophageal Cancer in Iran: A Review

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Abstract

Esophageal cancer is the second and third most common malignancy in Iranian males and females, respectively, claiming lives of approximately 5800 Iranians each year. Squamous cell carcinoma (SCC) is presently the most common type accounting for about 90% of all esophageal cancers in Iran. Recent studies have shown that there is a gradual increase in the incidence of adenocarcinoma of the distal esophagus along with gastric cardia adenocarcinoma.

Thirty-five years ago, the age standardizied rate (ASR) of esophageal SCC in the city of Gonbad (Golestan Province, northeast of Iran) was found to be one of the highest rates for any single cancer that had been reported worldwide (ASR >100/10^5/year). Recent studies have shown that the incidence of SCC in Gonbad has declined to less than half of what it was in the past. This decline in the incidence of esophageal SCC parallels an improvement in the socioeconomic situation of people living in this region. According to recent cancer registry data in Iran there is still an obvious intracountry variability between the incidence of esophageal cancer in the south with an ASR of 3 for males and 2 for females in Kerman and 43 and 36 in the northeastern province of Golestan. The reasons for this very high rate of SCC in northeastern Iran have been the subject of several studies during the past 35 years. According to results of these studies the suspected risk factors are: low intake of fruits and vegetables, drinking hot tea, consumption of opium products and tobacco, *H.pylori* infection in the stomach, using unhealthy drinking water from cisterns and genetic susceptibility. The main suspected mutagens are polycyclic aromatic hydrocarbons (PAH) and N-nitroso compounds. In order to embark primary and secondary prevention of this fatal cancer, further prospective studies are presently underway in the region. The Golestan esophageal cancer cohort study which follows of 50,000 subjects is on going. We expect simple and feasible evidence based preventive strategies to be implemented in the future according to the results of this study.

Keywords: Esophageal cancer, Iran, Squamous cell carcinoma, Adenocarcinoma, Cohort

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Received: October 10, 2009; Accepted: November 23, 2009

Introduction

Cancers are among the most common causes of death throughout the world. It is estimated that the overall incidence of various types of cancers will increase by 45% in developed countries by 2030. Recent reports indicate that cancers are the second most common cause of non-accidental deaths in Iran, following cardiovascular deaths.[1-3] An estimated 51,000 cases of new cancers are diagnosed each year in Iran. About 38% of these cancers arise from the gastro-intestinal (GI) tract with 6,500 of them resting in the esophagus.[4] Both histological subtypes of esophageal malignancies, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are highly lethal with a current five year survival of less than 10%.[5] Of the approximately 35,000 yearly cancer deaths in Iran, about 5,800 are due to esophageal cancers.[4] The incidence of this deadly cancer is variable in different parts of the country. Table 1 compares the age standardized rates (ASR) for esophageal cancers in Iran and other parts of the world and Table 2 compares the ASR for different provinces in Iran.[4,6-9]

In the past, SCC comprised more than 90% of esophageal cancer cases. However, over the past two decades, ADC has increased and currently represents about 60% of esophageal cancers in western countries.[3,10,11] In developing countries, including Iran and China, SCC is still the most prevalent form accounting for over 90% of cases.[12] Recent epidemiologic evidence from Iran shows an increase in ADC prevalence (Table 3).[8, 13] This has occurred two to three decades after the improvement of sanitary and public health conditions and is associated with an epidemic of obesity and gastro-esophageal reflux disease (GERD). [14, 15]

Table 1. Comparison of age standardized rates (ASR) of esophageal cancer in Iran and other parts of the world.

Geographical area	ASR/100000
High risk areas	
China (Linxian)	>100
Iran (Gonbad)	>100
Medium risk areas	
South Africa (Transkei)	33
USA (black)	29
France (Calvados)	24
Low risk areas	
USA (white)	4
Iran (Kerman)	3

Epidemiology

In the USA and other western countries tobacco, excessive alcohol ingestion, diets poor in fresh fruits and vegetables, and low socio-economic class have been associated with SCC.[16,17] In Iran and China, alcohol and tobacco are not considered as risk factors.[18-28] Table 4 compares risk factors for esophageal SCC between western, developing and developed countries. Table 5 summarizes the findings of several studies performed in Golestan province, Iran by the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences.[18-20]

As mentioned, esophageal ADC is still uncommon in Iran (<5% of all esophageal cancers), but recent data show an increasing trend for this cancer.[13] Table 6 summarizes factors associated with esophageal ADC in northwest Iran (Ardabil province).[29] As is depicted there, *H. pylori* infection and atrophic gastritis are negatively associated with ADC of the esophagus, while cigarette smoking and severe GERD symptoms are associated with an increased chance of developing esophageal ADC. Being overweight or obese has also been shown to be associated with esophageal ADC. Considering the increasing prevalence of GERD and obesity in Iran, alongside with decreased rates of *H. pylori* infection, an increase in esophageal ADC can be expected in the next decades. Unlike esophageal SCC which affects both sexes equally, in Iran, esophageal ADC is three times more common in men.[29]

Hypotheses regarding esophageal SCC in Iran

Studies from thirty-five years ago reported an ASR of 20 and 10 per 100,000 men and women respectively in Rasht, south-west of the Caspian Sea.[30] The ASRs as well as sex distribution were similar to western countries. On the other hand, the same investigators reported an unusually high

Table 2. Comparison of the age standardized rates (ASR) for different provinces in Iran.

Province	ASR for Male/100000	ASR for Female/ 100000
Golestan	43.3	36.3
Ardabil	15.4	14.4
Semnan	11.7	8.8
Kerman	3	2.1
Iran (overall)	17.6	14.4

ASR of over 100 per 100,000 population for esophageal SCC in the south-western Caspian littoral with no sex difference.[30] Such a high prevalence of esophageal SCC is rare, being seen only in Linxian, China where esophageal SCC has similar high prevalence rates.[9,10] The alarmingly high ASR and almost equal sex distribution point to a very strong environmental factor being the main culprit. In addition to northeastern Iran, esophageal SCC is common in other parts of eastern and central Asia such as Turkmenistan, Uzbekistan,[31] Kazakistan,[32] and parts of China.[18] These countries extend along the ancient Silk Road and are collectively called the Asian esophageal cancer belt. This special form of distribution among Mongol and Turk ethnicities living along the route of the Silk Road can be due to a special genetic background or environmental factors, including the climatic conditions as well as the botanical construct of this specific area.[12] Older epidemiologic studies have failed to reveal these factors.[11] Recent reports from the Gonbad area in Golestan indicate an almost equal male to female ratio as well a high prevalence for esophageal SCC in the region.[22] This prevalence, although still much higher than other parts of the world, has shown a decreasing trend over the past three decades.[8] This is most probably due to dramatic improvement in living conditions and the socio-economic status of the Gonbad area over this period of time.[8] Older studies in northwest Iran which examined the risk factors for esophageal SCC were incompletely abandoned at the beginning of the Islamic Revolution and very limited data are available regarding the genetic background of this disease.

Table 3. Age standardized rates (ASR) of esophageal cancer in different studies in Iran.

Date of study-Authors	ASR for Male/100000		ASR for Female/ 100000	
	ASR	TASR	ASR	TASR
1970- Mahboubi et al	80	165	80	180
2003- Semnani et al	43	76	36	72

Changes in living conditions as well as risk factors over the past thirty years have led to a significant decrease in esophageal cancer incidence in Gonbad. Recent studies have shown that 60% of the rural and urban population have a BMI of more than 25 kg/m^2 and 25% have a BMI greater than 30 kg/m^2. In 1970 less than 5% of the population owned a refrigerator at home while currently over 90% possess a refrigerator at home. Increased income, improved transportation, and availability of electricity, hygienic water and natural gas to 98% of the urban and over 90% of the rural population in the area has dramatically changed their living conditions. As mentioned, Linxian, China is another high prevalence area for esophageal SCC. Studies from Linxian show little change in prevalence of the disease over the past three decades.[33] Interestingly, living conditions of these people have not changed significantly in this period of time.[34] This is good evidence that living conditions can affect the prevalence of esophageal SCC, although which factor(s) are specifically responsible for this is not clear.[8,22]

Another confounding factor for accurate determination of the incidence and prevalence of esophageal SCC is that in older days the diagnosis depended mostly on history and X-ray imaging. Therefore distinguishing between esophageal SCC and cardia cancer was rather inaccurate as both diseases have similar clinical manifestations (i.e. dysphagia as the presenting symptom) and difficult to differentiate on X-ray findings. Hence misclassification of these two diseases could affect the changing epidemiology witnessed today. Despite this, esophageal SCC has decreased in Gonbad and esophageal ADC is on the rise.

Important identified or presumed risk factors for SCC in northeastern Iran are described below.

Table 4. Comparison of risk factors for esophageal SCC between developing and developed countries.

High risk area (China, Iran)	Low risk area (USA, Europe)
Food habit	Food habit
Hot tea	Alcohol
Opium	Smoking (tobacco)
Poverty	Poverty
Oral hygiene	*Helicobacter pylori*
PAH*	
Nitrosamine	
Family history of cancer	
Helicobacter pylori	
Smoking (tobacco)	

*Polyaromatic hydrocarbons

Drug abuse

The role for opium abuse in esophageal SCC was first suggested by an ecologic study performed jointly by the International Agency for Research on Cancer (IARC) and the Iranian Public Health Research Institute (IPHR), known as the IARC-IPHR study.[35] This study revealed a high urinary excretion of morphine metabolites in patients with esophageal SCC in high prevalence areas.[35] Opium abuse is common among men in rural areas of the high prevalence regions of Golestan and may have a role in development of esophageal SCC.[22] The way that opium is smoked in Iran is unique and differs from the method used in China. Pure, high quality opium is rather expensive and it is usually admixed with impurities, or its physical derivatives (e.g. "Sookhteh", remnants of smoked opium and "Shireh", another physical derivative of opium) are used. It seems that these derivatives are more associated with esophageal SCC than opium itself.[36] Sookhteh is mutagenic in *Salmonella typhimurium*, can cause morphologic changes in hamster embryos and induces lymphocytic changes in humans.[37] Pure opium does not have such properties.[37,38] Another potential cause of carcinogenicity of opiate derivatives is the presence of polyaromatic hydrocarbons (PAH) resulting from pyrolysis of opium.[7] Despite these explanations, the role of opium and its derivatives in development of esophageal SCC is not yet clear. In Kerman province, southern Iran, opium use is widespread, but esophageal SCC is uncommon. Recent studies from Golestan also indicate that only one-third of the patients diagnosed with esophageal SCC use opium.[19, 20, 22] Therefore, if opiates have any role in development of this disease, it acts in a subgroup of patients and not in the majority.[12]

Hot beverages

In some parts of South and Central America, using hot alcoholic beverages has been associated with esophageal SCC.[39-41] The proposed mechanism for possible carcinogenicity of hot beverages is continuous thermal injury to the esophageal mucosa and the resultant mucosal inflammation. In addition these beverages contain high amounts of PAHs.[42] Ecologic and case-control studies in northeast Iran have associated consumption of hot tea with the development of esophageal SCC.[43,44] Similar results have also been reported from Singapore.[45] A recently published case-control study from Golestan reported a relative risk of ten for consumption of hot tea for the development of esophageal SCC (Table 7). The inherent recall bias in obtaining the information regarding tea temperature in case-control studies makes one to consider these associations with caution. An ongoing cohort study of over 50,000 people in Golestan is currently objectively measuring consumed tea temperature. These results may help to unravel this association more clearly.[46]

Malnutrition

Malnutrition is clearly associated with development of esophageal SCC.[47-54] A low intake

Table 5. Risk factors of esophageal cancer in Golestan province, Iran.

Risk factor	Adjusted odds ratio
Hot tea	10
Non hygienic water	10
Fried & grilled meat	8
Family history of EC*	2.3
Opium consumption	2.2
Helicobacter pylori	2
Nass usage	2
Smoking (tobacco)	1.8

*Esophageal cancer

Table 6. Factors associated with esophageal adenocarcinoma in northwest of Iran (Ardabil province).

Risk factor	Adjusted odds ratio	*P* value
Low serum pepsinogen (atrophic gastritis)	0.26	0.1
Helicobacter pylori	0.25	0.02
Weekly GERD* symptoms	28	0.001
Smoking	4.7	0.007

*Gasteroesophageal reflux disease

of fresh fruits and vegetables is an important risk factor for this disease. The World Cancer Research Federation (WCRF) and the American Institute for Cancer Research (AICR) have declared that, according to current evidence, regular consumption of fresh fruits and vegetables can decrease the incidence of esophageal SCC.[52] Similar results have been obtained from studies in northeast Iran.[53, 54]

Selenium deficiency

Studies from Linxian, China have shown that serum selenium levels are very low in this region and are about one-fourth of that found in the average American diet. Selenium deficiency has been associated with a high prevalence of esophageal SCC in that region.[55] Studies performed in northeastern Iran have detected serum selenium levels higher than the average for Americans. [28] Table 8 depicts serum selenium levels in different regions of Iran with a high and low incidence of esophageal SCC. According to these studies, serum selenium does not seem to be associated with esophageal SCC in Iran.[28]

Polycyclic aromatic hydrocarbons (PAHs)

PAHs are proven carcinogens. They are derived from incomplete combustion of wood, coal and tobacco. Several lines of evidence have associated PAHs with GI tract malignancies including esophageal SCC.[56,57] Studies from Linxian have shown histopathologic changes compatible with PAH exposure in esophageal SCCs.[56] In addition, a high content of PAH in raw and cooked food[57] has been shown in this area, as well as high urinary excretion of 1-hydroxypyrine glucuronide (1-OHPG), a metabolite of PAHs.[12,24] Recent studies from Gonbad, Iran have shown much higher concentrations of PAH in raw and cooked food as compared to a low prevalence area for esophageal SCC such as Shiraz in central south Iran.[12, 24] Urine samples from both urban and rural areas of Gonbad have high 1-OHPG contents regardless of sex and cigarette smoking status.[58] Age, sex, cigarette smoking, nass consumption and drug addiction explain only 15% of the high PAH exposure in this region.[24]

N-nitroso compounds

Nitrosamines and nitrosamides are called N-nitroso compounds and are produced from the reaction of nitrates with amides and amines. N-nitroso compounds have been linked to increased incidence of nasal cavity, esophageal and hepatic cancers in animal models. Humans are exposed to N-nitroso compounds through dietary and water intake as well as smoking tobacco and through occupational exposures. Most (45-75%) of the N-nitroso compounds in the body are produced locally in the stomach.[59] Sodium nitrite, a major source of nitrites and nitrates, is used as a preservative in processed food. Vegetables and water are also good sources for nitrates.[59,60] Nitrates are transformed to nitrites by oral bacteria. This may partially explain the association of poor dental hygiene and esophageal SCC.[61, 62] In

Table 7. Distribution of tea drinking habits and corresponding odds ratio in Golestan province, Iran.

Tea Temperature	No. of SCC* patients (%)	No. of Controls (%)	Adjusted odds ratio
Warm	127 (42.6)	394 (69.6)	1
Hot	108 (36.2)	155 (27.3)	2.07
Very hot	63 (21.1)	19 (3.3)	8.16

*Squamous cell carcinoma

Table 8. Serum selenium levels in different regions of Iran.

Province	Annual incidence of EC* /10^5	Median serum selenium (IQR, mg/L)
Golestan	40	155 (141-173)
Mazandaran	19	123 (111-132)
Ardabil	15	82 (75-94)
Kerman	3	119 (110-128)

*Esophageal cancer

China, esophageal SCC is more common in areas where the general population is exposed to high nitrate containing food.[62] In a study performed in Gonbad, it has been shown that the nitrosamine concentration of saliva in Gonbad inhabitants is four times that of German people.[12] In addition, the concentration of nitrates in old water reservoirs in Gonbad has been reported to be much higher than the allowable recommendations. Therefore, access to sanitary water which is widespread now in Gonbad has most probably contributed to the significant decrease in esophageal SCC prevalence in the region.[8]

Viral agents

Human papilloma virus (HPV) is the only viral agent associated with esophageal cancer thus far. HPV, especially serotypes 16 and 18, is the major culprit in uterine cervical carcinoma and has a strong association with cancers of the vulva, anus, penis and oropharynx.[63] Serologic studies as well as studies looking at HPV-DNA[64] are inconsistent and have found evidence of exposure to HPV in 0-67% of cases.[64,65] Serologic studies have reported an association between HPV 16 and esophageal SCC[66, 67], while molecular biology studies using PCR methods have failed to detect such an association.[68] In the only Iranian study addressing this issue, esophageal SCC was associated with HPV 16 but not HPV 18.[69]

Poor oral hygiene

Poor oral and dental hygiene has been shown to be associated with esophageal SCC.[61] There is a strong association between tooth loss and squamous dysplasia of the esophagus, while good oral hygiene has been negatively associated with this condition.[7] Several mechanisms have been proposed for this observation. Poorly chewed food can mechanically injure the esophageal mucosa.[7] In addition, dietary change in edentulous people, the change in oral microflora with an increased presence of carcinogenic bacterial species, esophageal mucosal infestation by oral microflora, and genetic factors have been proposed as possible mechanisms. In Linxian,[61] increased nitrosamine production due to a change in the oral microflora has been considered as the major culprit. Esophageal dysplastic lesions have been shown to be five times more common among people with poor oral hygiene in Golestan province. Similar results have been reported from Japan, Latin America, Eastern Europe and China.[26] In addition to esophageal SCC, poor oral and dental hygiene have also been associated with gastric and oral malignancies.[7]

Genetic factors

As mentioned previously, the Asian esophageal cancer belt extends along the Silk Road. This is also the route where Mongol tribes used to invade different parts of the near east. These ethnic groups settled along this route and became the ancestors of people now living in these areas. Therefore, genetic predisposition may potentially be important in the development of esophageal SCC. Studies from Iran and China have shown that the incidence of esophageal SCC among the first degree relatives of patients with esophageal SCC is twice that of those lacking such a family history.[22] A newly published study from Gonbad has shown mutations in the BRCA-2 gene in patients with esophageal SCC.[26] Somatic mutations in TP 53 and other tumor suppressor genes have also been reported in esophageal SCC. In a study from Tehran, Iran, 50% of esophageal SCCs contained TP-53 mutations, mostly seen

in men.[70] The most common mutations are C: T displacement in the CpG and A: T displacement. Such mutations may promote inflammatory processes predisposing one to esophageal SCC. These mutations may occur with cigarette smoking. Gene polymorphism has also been studied.[71] In a study from Iran, gene polymorphism of ten genes considered to be associated with esophageal SCC have been assessed in three ethnic populations (Golestan Turkmans with a high risk for esophageal SCC, Ardabil inhabitants with moderate risk and Zoroastrians with a low risk). Turkmans had a fourfold increase in mutation rates of alleles highly associated with esophageal SCC (namely CYP1A1m1, CYP1A1m2, CYP2A6*6, and ADH 2*1) as compared to Zoroastrians.[72]

Conclusion

Our current knowledge about the etiology of esophageal SCC still has a long way to go. We hope that the results of the Golestan cohort study which is currently following over 50,000 people in the high risk area of northeastern Iran will help clarify some aspects of this deadly disease. This cohort is being undertaken by the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences in collaboration with the IARC, National Cancer Institute (NCI) of the USA and Cambridge University (UK). For the time being it can be concluded that esophageal SCC develops in genetically predisposed individuals who are exposed to environmental factors such as poverty, malnutrition, and consumption of hot beverages. PAHS, N-nitrosamines, and unknown viruses may have a role in development of this disease.

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