

EPIDEMIOLOGIC AND PATHOLOGIC CHARACTERISTICS OF PATIENTS WITH ESOPHAGEAL CARCINOMA AT KURDISTAN CENTER FOR GASTROENTEROLOGY AND HEPATOLOGY



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ABSTRACT

Background

Esophageal carcinoma is the sixth in cancer incidence and cancer related deaths. There are marked geographic variations in the incidence of different types and etiology/risk factors for esophageal carcinoma. Better understanding of the etiology/ risk factors may suggest opportunity for its primary prevention.

Objectives

To assess the demographic characteristics, etiology and risk factors of patients with esophageal carcinoma at Kurdistan Center for Gastroenterology and Hepatology.

Materials and Methods

A cross sectional study extended from March 2014 to December 2015; during this period 100 patients with histologically diagnosed as esophageal carcinoma (EC) were included. Details about the demographic characteristics and risk factors for esophageal carcinoma had been reviewed.

Results

The mean age of the study population was 67 ± 13.27 years. The male constituted 58% and female 42%, (75%) were Squamous cell carcinoma (SCC) and (25%) were Adenocarcinoma (AC). Up to 84% of AC cases were male (P value: 0.002). There was significant association between type of esophageal cancer and tea drinking, temperature of tea and interval between tea being poured and drunken, P- value was 0.011, 0.031 and 0.001 respectively. There was no statistically significant association between types of EC and demographic characteristic, smoking and body mass index.

Conclusion

SCC was more common than AC; AC was more common in males. Drinking hot tea was associated with EC. Most patients were smoker and had low fruit and vegetable intake, with more dried and preserved foods intake.

Keywords: *Esophageal carcinoma, Epidemiology, KCGH, Sulaimani.*

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INTRODUCTION

Esophageal carcinoma is sixth in cancer incidence and cancer related deaths globally ⁽¹⁻³⁾. It is characterized by rapid development and fatal prognosis in most cases and it constitutes seven percent of all gastrointestinal cancers ^(3, 4). Worldwide, its incidence is increasing, an estimated 482,300 new EC cases and 406,800 deaths occurred in 2008 ⁽⁵⁾.

In the United States, more than 18,000 new cases of esophageal cancer and more than 15,000 deaths from esophageal cancer were recorded in 2014 ⁽⁶⁾. More than 95% of EC are either Squamous Cell Carcinomas (SCC) or Adenocarcinoma (AC) ^(7, 8).

The highest incidence of EC, with incidence rates greater than 100 per 100,000, is in the "Asian esophageal cancer belt," which is extending from Eastern Turkey through the southern former Soviet Union, Iraq, Iran, into Western and Northern China, Hong Kong and Japan. However, the incidence of esophageal cancer is largely increasing in the Western population. The incidence of esophageal cancer continues to increase faster than any other cancer in the Western world ^(9, 10).

Therefore, this suggests that specific environmental factors play a major role in the etiology of this malignancy ^(2, 5, 9, 10). Major risk factors in high risk areas are not well understood, but are thought to include poor nutritional status, low intake of fruits and vegetables, and drinking beverages at high temperatures. In contrast, in low-risk areas such as the United States and several Western countries, smoking and excessive alcohol consumption account for about 90% of the total cases of esophageal SCC ⁽¹¹⁾. Their incidence varies with geographic distribution around the world, possibly reflecting differences in exposure to specific environmental factors, individual lifestyle, socioeconomic pressures, diet and nutrition as well as genetic polymorphisms ^(2, 12-14).

Better understanding of the etiology/ risk factors may suggest opportunity for its primary prevention ^(15, 16). Because of lack of local data regarding the characteristics of patients with EC this study has been conducted to study risk factors, clinical, pathologic characteristics of patients with esophageal carcinoma.

PATIENTS AND METHODS

This is a cross sectional study, carried out at Kurdistan Center for Gastroenterology and Hepatology (KCGH) in Sulaimani city, which serves as a tertiary referral

center for the Sulaimani governorate, in addition to referrals from other governorates of Kurdistan region and Iraq. The study extended between March, 2014 and December, 2015. During this period, 100 patients whom were diagnosed as EC were included. All patients diagnosed with esophageal carcinoma agreed to be involved in the study.

The study commenced after approval of the medical and ethical committee at KCGH and Kurdistan board for medical specialties. Informed consent was taken from all patients. The clinical data included details about the demographic characteristics, clinical condition, past medical, surgical history, history of smoking, alcohol consumption and other risk factors of esophageal carcinoma. Smoking calculated by pack-year ⁽¹⁷⁾. The body mass index (BMI) was classified according to the World Health Organization classification ⁽¹⁸⁾. Regarding fruit and vegetable intake it is calculated according to international servings and serving less than five regarded as inadequate ⁽¹⁹⁾. Regarding tea drinking habit, we asked about the temperature of tea as a warm (less than 65°C), hot (65-69°C) and very hot (more than 70°C) and interval between tea being poured and drunk (minutes) divided to less than 2 minutes, 2-3 minutes and more than 4 minutes. Regarding amount of tea consumed (ml/day) divided to less than 500 ml, 500-999 ml and more than 1000 ml ⁽²⁰⁾.

History of exposure to chemical weapon, family history of esophageal carcinoma had been asked. History of dried food and preserved food intake had been involved and authors agreed on more than 3 times per week as excess intake. Analysis of data was done using (SPSS) version 22, using χ^2 test for categorical variables and T-test for numerical parameters. P-value \leq than 0.05 regarded statistically significant ⁽²¹⁾.

RESULTS

Results revealed that 75% of cases were SCC and the remaining 25% were AC. The SCC and AC are most common histologic types of EC and we have correlated different variable by relation with types of esophageal carcinoma. Demographic characteristics of patients as shown in Table 1 revealed that 92 cases were from Kurdistan region of Iraq (KRI), among those cases, 68 cases were from Sulaimani, 10 cases from Erbil, 9 cases from Kirkuk and five cases from Duhok. The remaining cases were from other parts of Iraq.

The age of patients with EC ranged between 21-95 years with the mean age of 67.37 ± 13.27 years. There

was no significant statistical association between type of cancer (SCC, AC) and the age groups, Table 2.

Regarding the EC and gender, 58% of the cases were males and 42% were females, there was a significant statistical association between the type of EC (SCC, AC) and gender. The majority (84%) of AC cases were male. Pearson Chi square test was significant as shown in Table 3.

Table 4 shows that there was a significant relationship between the type of EC and past medical history among study samples. Nearly 30 % of AC patients had history of GERD, Table 4.

Reviewing the medication history, most of the patients were receiving antisecretory drugs and medications for medically related disease.

As far as smoking habit concerned, smoking was ranging from 0-80 pack-years and the mean was 16.77 ± 22.76 , there were no statistically significant relationship between the type of EC and smoking, Table 5.

The mean body weight was 56.3 ± 8.7 kg and mean height 163.3 ± 7.5 cm. BMI of patients with EC ranged from 14-26 with mean 20.5 ± 2.4 . There was no significant relationship (P: 0.730) between the type of EC and patient's BMI.

Table 6 reveals that there was a significant relationship between the type of EC and tea drinking among participants. Ninety six percent of SCC cases were drinking tea and only four percent did not drink tea compared to 20% of patients with AC.

There was a significant statistical relationship between the type of EC (SCC, AC) and tea temperature among participants. The majority of SCC cases (81.3%) were drinking hot tea, while approximately half of patients with AC consumed hot tea. Pearson Chi square test was significant (P: 0.031). There was a significant statistical association between the type of EC (SCC, AC) and the interval (minutes) between tea being poured and drunk among participants. The majority of SCC cases (81.3%) were drinking tea in less than two minutes compared to 40% of patients with AC.

There was no significant association between the type of EC and amount of tea drunken daily, P-value: 0.062.

Regarding other factors such as fruit, vegetable intake and the use of dried and preserved food as shown in Table 7. Fruit and vegetable serving was ranging between 0-4 with the mean 2.38 ± 1.22 . There was no significant relationship between the type of EC and fruit and vegetable intake and P-value: 0.659.

As far as alcohol intake is concerned, all patients were responded as non-drinker.

Table 1. Demographic characteristics of patients with esophageal carcinoma.

Demographic characteristics	Type of cancer				Total	P Value	
	SCC		AC				
	No.	(%)	No.	(%)			
Marital status	Married	71	(94.7)	24	(96)	95	0.79
	Single	4	(5.3)	1	(4)	5	(N.S)
Ethnicity	Kurd	60	(80)	25	(100)	85	0.53
	Arab	12	(16)	0	(0)	12	(N.S)
	Turkmen	3	(4)	0	(0)	3	
Residency	Kurdistan region of Iraq (KRI)	67	(89)	25	(100)	92	0.89
	Outside KRI	8	(10.7)	0	(0)	8	(N.S)
Address	Urban	55	(73.3)	15	(60)	70	0.208
	Rural	20	(26.7)	10	(40)	30	(N.S)
Education	Illiterate	68	(90.7)	22	(88)	90	0.917
	Primary/Secondary school	5	(6.7)	2	(8)	7	(N.S)
	Postgraduate	2	(2.7)	1	(4)	3	
Occupation	Non -employee	72	(96)	22	(88)	94	0.221
	Govt. employee	2	(2.7)	1	(4)	3	(N.S)
	Private employee	1	(1.3)	2	(8)	3	

Table 2. Type of esophageal carcinoma and age groups.

Age groups (years)	Type of cancer				Total
	SCC		AC		
	No.	(%)	No.	(%)	
20-39	2	(2.7)	0	(0)	2
40-59	17	(22.7)	7	(28)	24
60-79	43	(57.3)	11	(44)	54
80-99	13	(17.3)	7	(28)	20
Total	75	(100)	25	(100)	100
P - value	0.46				

Table 3. Type of esophageal carcinoma and gender.

Gender	Type of cancer				Total
	SCC		AC		
	No.	(%)	No.	(%)	
Male	37	(49.3)	21	(84)	58
Female	38	(50.7)	4	(16)	42
Total	75	(100)	25	(100)	100
P value	0.002				

Table 4. Type of Esophageal carcinoma and past clinical history.

Past Clinical History		Type of cancer				Total	P Value
		SCC		AC			
		No.	(%)	No.	(%)		
PMH	No PMH	64	(85.3)	17	(68)	81	0.004
	GERD	2	(2.7)	7	(28)	9	
	Head & Neck Cancer	1	(1.3)	0	(0)	1	
	Celiac disease	1	(1.3)	0	(0)	1	
	Other medical disease (HT, DM, IHD)	7	(9.3)	1	(4)	8	
PSH	No PSH	57	(76)	21	(84)	78	0.615
	Cholecystectomy	4	(5.3)	0	(0)	4	
	Partial gastrectomy	2	(2.7)	1	(4)	3	
	Others	12	(16)	3	(12)	15	
Family hx. of Esophag. cancer	No	70	(93.3)	25	(100)	95	0.185
	Yes	5	(6.7)	0	(0)	5	
Exposure to chemical weapons	No	75	(100)	24	(96)	99	0.082
	Yes	0	(0)	1	(4)	1	

Table 5. Type of esophageal carcinoma and smoking habit.

Smoking	Type of cancer				Total
	SCC		AC		
	No.	(%)	No.	(%)	
Smoker	29	(38.7)	14	(56)	43
Ex-smoker	22	(29.3)	5	(20)	27
Never	24	(32)	6	(24)	30
Total	75	(100)	25	(100)	100
P Value	0.314				

Table 6. Type of esophageal carcinoma and detailed tea drinking habit.

Drinking Tea	Type of cancer				Total
	SCC		AC		
	No.	(%)	No.	(%)	
Yes	72	(96)	20	(80)	92
No	3	(4)	5	(20)	8
Total	75	(100)	25	(100)	100
P value	0.011				
Temperature of Tea					
No	3	(4)	5	(20)	8
Warm	8	(10.7)	5	(20)	13
Hot	61	(81.3)	14	(56)	75
Very hot	3	(4)	1	(4)	4
Total	75	(100)	25	(100)	100
P value	0.031				
Interval (minutes) between tea being poured and drunk among participants.					
2-3	11	(14.7)	10	(40)	21
<2	61	(81.3)	10	(40)	71
Total	75	(100)	25	(100)	100
P value	0.001				

Table 7. Type of esophageal carcinoma and fruit, vegetable, dried and preserved food intake.

Variables		Type of cancer				Total	P Value
		SCC		AC			
		No.	(%)	No.	(%)		
Fruit and vegetable intake	No	12	(16)	8	(32)	20	0.82 (N.S)
	1-2 Servings	22	(29.4)	6	(24)	28	
	3-4 Servings	41	(54.6)	11	(44)	52	
Dried and preserved food intake	No	15	(20)	9	(36)	24	0.105 (N.S)
	Yes	60	(80)	16	(64)	76	

DISCUSSION

The predominant histological type in this study was SCC (75%) and the remaining 25% was AC. Similarly, in 1975 about 75% of the cases of EC diagnosed in the United States were SCC and the remaining 25% were AC^(7, 21).

In China which is also part of esophageal cancer belt, the incidence of AC has been increased. Trends in smoking and obesity as well as unhealthy diet, such as pickled vegetables and moldy or fermented foods and the use of medications may account for some of these changes^(7, 22,23). As far as demographic characteristics of patients concerned, vast majority of patients were married and the disease increased with age, and 92% of cases were from the KRI, as KCGH is tertiary referral center and near to esophageal cancer belt. Up to 70 % of cases were from urban area as this might reflect rapid shift from rural to urban area and most of our cases were Kurdish. Over 90% of cases were illiterate and non-employee; this may explain more prevalence of esophageal carcinoma in this group of patients. There was no statistically significant association between the types of EC and demographic characteristics.

In this study, the risk of esophageal carcinoma increases with age, with a mean age at diagnosis was 67.4 years which is comparable to other study⁽⁶⁾.

Esophageal cancer incidence is greater in individuals over 50 years of age due to the prolonged action of aggressive factors⁽²⁴⁾. The youngest patient reported in this study was 21 years female with celiac disease, which is lower than reported by others, 30 and 35 years^(25, 26)

This study revealed that there was a male predominance in EC (58%) and female (42%), which is comparable to the results of others' study (54.9 % males and 45.1% females)⁽²¹⁾. However another study done in Sulaimani revealed that 68% of EC were females⁽²⁷⁾. The greater incidence of EC in men regardless of histological type has been reported by various investigators^(28, 29). The underlying causes of these trends and the marked male predominance are remaining unclear. On average worldwide, males are twice as likely to develop esophageal cancer as females⁽³⁰⁾. There is no evidence, however, to suggest that esophageal cancer is sex-linked. Epidemiological data suggests that alcohol consumption is a major cause of esophageal cancer in males, whereas women are more affected by poor diet⁽³¹⁾. In contrary to what is reported in developed areas,

none of patients in our area and minor percentage of cases in nearby countries such as Iran and Saudi Arabia had history of alcohol drinking, so other factors like life style and hot beverages drinking habit could play more role^(20,27,32). The unchangeable factors in this cancer include age, sex and hereditary background⁽³⁰⁾.

The current study revealed statistically significant association between histological type of EC and gender. The majority of AC cases were male. Similar results reported by other study in Iran⁽²¹⁾. Adenocarcinoma is three to four times more common in men as it is in women, whereas the sex distribution is more equal for SCC. Abdominal adiposity is more common in men, which has led to speculation that such adiposity explains some sex-related differences in cancer risk^(6, 31).

As far as previous clinical history concerned 81% and 78% of them had no any past medical and surgical history respectively, this might explain the role of environmental factors, food and drinking habit in causation of EC in our area . In this study, 9% of the cases reported to have GERD as it's the strongest risk factor for AC which was statistically significant, similar to other studies^(2, 31). Moreover, there was significant association between SCC and head and neck cancer and celiac disease^(2, 32).

In this study, 3% of the patients had history of gastrectomy and 4% of the patients had history of cholecystectomy. A population-based study from Sweden suggested a possible link between cholecystectomy and esophageal adenocarcinoma. They speculated that the increased risk maybe due to the toxic effect of refluxed duodenal juice containing bile on esophageal mucosa⁽²⁾.

Family history was present in 5% of cases, in various studies conducted in China, relative risk of patients with a family history of EC was around 2.9% of the cases⁽²⁸⁾. Other study concludes that no one of the patients had family history of esophageal carcinoma⁽³⁰⁾. This could be explained by more roles of environmental factors. Smoking is well known to its association with EC even in ex-smokers the risk will remain^(6, 30). The current study revealed that up to 70% of the cases had smoking history (43% current, 27% ex-smokers), there was no statistically significant association between type of cancer and smoking, also its known that smoking has stronger association with SCC than AC. Studies done with others tobacco use were found in 82% of the patients, therefore, smoking increases

SCC by 5-10 folds, AC by 2 folds^(6, 29, 33). The risk of SCC decreases substantially a decade after smoking cessation. In contrast, the risk of adenocarcinoma of the esophagus does not change appreciably, even 30 years after smoking cessation⁽⁷⁾. On the other hand, in Linxian County in China, there is no association between alcohol and/or tobacco and the development of esophageal cancer. The etiological factors of the high occurrence of esophageal cancer in Linxian County are multiple and consuming hot tea is a daily habit⁽³⁴⁾. However, in Golestan province of Iran, which has one of the highest incidence rates for esophageal SCC in the world, this cancer has relatively unique epidemiological features: smoking and alcohol consumption are not major risk factors and women are as likely to have a diagnosis of esophageal cancer as men. Earlier studies in Golestan have suggested that low intake of fresh fruits and vegetables, low socioeconomic status, and opium consumption are associated with a higher risk of esophageal cancer⁽²⁰⁾. The ingestion of tobacco condensates is thought to bring tobacco carcinogens, particularly nitrosamines in contact with the esophageal mucosa. The risk of EC correlates directly with the quantity of cigarettes smoked per day and the duration of smoking. Any factor that causes chronic irritation and inflammation of the esophageal mucosa appears to increase the incidence of SCC of the esophagus. In most studies evaluating the effect of quitting smoking, a 50% reduction in risk has been seen for ex-smokers compared with current smokers, along with an inverse effect with time since stopped smoking⁽³⁵⁾.

There was no statistically significant relationship between the type of cancer and patient's BMI, up to 84% of the cases with AC were within normal range of BMI, this could be explained by up to 88% of the cases with EC had weight loss they might be overweight or obese before development of cancer. Similar results had been reported by other study in Pakistan⁽²¹⁾. This could be explained that they were from esophageal cancer belt, in which there is difference in etiological factors in cancer causation with developed countries⁽²⁰⁻²³⁾.

Trends in obesity have increased at a similar rate in both sexes. While data are limited, it appears that obesity is a more potent risk factor for AC in men than women and this is thought to be related to visceral (abdominal) adiposity rather than subcutaneous adiposity. Visceral fat are metabolically active and releases Adipokines like Tumor Necrosis Factor α , interleukin (IL1, IL6 and IL8), which are proinflammatory factors and increases reactive oxygen species. These two distributions are

quite different in men and women, and this may explain the lower incidence trends seen among women^(2,7).

The increasing prevalence of reflux, independent of the rise in obesity rates may explain as a part of the continued rise in AC incidence^(6, 7, 31).

Regarding tea drinking habit, vast majority 92% of the patients were drinking tea, of those cases 75% of them were drinking hot tea and 4% drunk very hot tea. So, there was statistically significant association between SCC and tea drinking, in majority of cases the interval between tea being poured and drinking was less than 2 minutes, which is comparable to results by other studies^(20, 36). Drinking hot tea was more common than those reported by a study done at Golestan province in Iran which was 36.2%⁽²⁰⁾. There was no clear pattern of association between amount of tea consumed and esophageal cancer risk. In addition, studies have pointed towards the possible role of drinking very hot tea. An association between drinking hot beverages and risk of esophageal cancer has been reported in several studies from different parts of the world^(20, 24). The mechanism by which thermal injury can cause esophageal cancer is not clear but both direct and indirect effects have been suggested, and it has been proposed that inflammatory processes associated with chronic irritation of the esophageal mucosa by local hyperthermia might stimulate the endogenous formation of reactive nitrogen species, such as N-nitroso compounds^(20, 37, 38). Thermal injury can also impair the barrier function of the esophageal epithelium, which may increase the risk of damage from exposure to intraluminal carcinogens, such as polycyclic aromatic hydrocarbons⁽²⁰⁾. Whatever the mechanism by which thermal injury increases the risk of esophageal cancer, this risk can be augmented by other risk factors, such as low intake of fresh fruits and vegetables, which can impair DNA repair^(20,39).

Regarding alcohol intake all patients responded as non-drinker, this is similar to results of other studies done in Sulaimani and Saudi Arabia^(27, 32). Studies done in Iran have reported 1% and 1.3% alcohol drinking respectively^(28, 30). This is in contrary to developed countries as it is regarded as one of major risk factors of SCC^(2, 6, 7, 12, 15). Population-based studies have not shown an association between alcohol consumption and esophageal adenocarcinoma. Unlike adenocarcinoma, SCC is three to five times as likely among people who consume alcohol, and the risk increases synergistically with tobacco smoking⁽⁶⁾.

The fruit and vegetable intake was inadequate by the patients in this study. This is comparable to results of other studies in which low fresh fruit and vegetables are one of the factors that predispose to esophageal carcinoma. This could be explained by the fact that in this area (mountain part of Sulaimani) mineral deficiency like: iron, zinc and selenium could be the explanation for high incidence among low socioeconomic classes, as they live in mountain area of long winter season which makes fresh fruit and vegetables unavailable for at least six months. On the other hand, during the long winter they will depend on preserved foods which contain nitrosamines, which are carcinogenic⁽²⁷⁾. Vegetables and fruits are sources of a wide variety of micronutrients and are rich in antioxidant substances, among them, β -carotene and vitamin C have been shown to play protective role in the occurrence and development of EC⁽⁴⁰⁾. Vegetables and fruits also contain dietary fiber and other bioactive compounds, which are termed as phytochemicals, which are protective⁽⁴¹⁾. Substituting fresh fruits and vegetables for poorly preserved, high-salt foods contaminated with nitrosamine carcinogens or microbial and fungal toxins may reduce the risk of esophageal cancer by as much as half^(6,7,20). As far as dried and preserved food concerned with esophageal carcinoma, there was no significant relation between type of cancer and dried and preserved food intake. In high-risk areas of China, pickled vegetables were eaten daily for 9–12 months a year and were an integral part of the diet in some families, traditionally prepared by keeping tightly packed moist vegetables in a jar packing for a few weeks or months, allowing fermentation and growth of fungi and yeasts, that can generate potentially carcinogenic N-nitroso compounds and mycotoxins. Mutagenicity and carcinogenicity of pickled vegetables have been shown in some experimental and in vitro suggested that a two-fold higher risk of esophageal SCC associated with the intake of pickled vegetables^(20,34).

In conclusion, the most common histological type of EC is SCC followed by AC. AC was more common in males. Drinking hot tea, a habit common in our area, was strongly associated with a higher risk of esophageal carcinoma. Most patients with esophageal carcinoma were smoker, had low fruit and vegetable intake, with more dried and preserved foods intake.

Prevention of EC should be based on early detection and surveillance of precancerous lesions and attention should also focus on modification of modifiable risk factors, including tobacco smoking, ingestion of hot

and spicy food and other risk factors.

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