

Original Article

Rising Incidence of Adenocarcinoma of the Esophagus in Kerman, Iran

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Background: The fall in the incidence of esophageal squamous cell cancer and noncardia gastric cancers in western countries parallels a concomitant rise in the incidence of gastric cardia cancer and distal adenocarcinoma of the esophagus. We aimed to investigate the incidence trend of different gastric and esophageal cancers in Kerman, southeast Iran.

Methods: The information of all newly diagnosed patients with gastric and esophageal cancers were collected actively from all histopathology departments around the Kerman Province during 1991 – 2002 retrospectively.

Results: The annual age standardized incidence risks of esophageal and gastric cancers in Kerman were 1.9 and 6.9 per 100,000 populations. In average, the risks of gastric and esophageal squamous cell cancers were more or less constant, while the risk of adenocarcinoma of the esophagus increased around 11% annually.

Conclusion: The risks of upper gastrointestinal cancers in Kerman Province were quite lower than the average risks in the whole country. The rising incidence of adenocarcinoma of the esophagus in Kerman parallels its temporal pattern in western countries.

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Introduction

In many western countries an increase in the incidence of adenocarcinoma of the esophagus (ACE) and gastric cardia cancer (GCC) has been reported over the past 30 years.¹⁻² The increase in the incidence of ACE ranged from 4 – 10% per year, compared with a relatively stable incidence of squamous cell carcinoma and a slight decrease in adenocarcinoma of the distal stomach in the same period.³ In the 1970s, ACE constituted 16% of all esophageal cancers in white males in the USA. It increased to 33% by the mid-1980s,

and approached to 50% by 1990 and surpassed esophageal squamous cell cancer (ESCC) in 1995.⁴ Thus, within two decades, esophageal and gastric cardia adenocarcinomas have risen from being a rare tumor to one of the top 15 cancers among white males.

Upper gastrointestinal (GI) cancer is the etiology of 55% of all cancer-related deaths in Iran. Gastric cancer stands as the most common and accounting for 50% of all GI cancers.⁵ The incidence of squamous cancer of the esophagus and cancer of the stomach is also very high compared with western countries.⁶ There is an obvious variability in the rates of GI cancers within Iran.⁷⁻¹² The age standardized rate (ASR) for esophageal and gastric cancers in males is less than 10 in southern Iran. The lowest rate is in the coast of Persian Gulf while it gradually increases as we move from south to north of the country. It approaches 50 for gastric cancer in northwestern Iran (Ardabil) and 44 for esophageal cancer in

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northeastern Iran (Gonbad).^{7,8,10} Kerman in southeast Iran is a low-incidence area for gastric cancer (ASR=10) and esophageal cancer (ASR=3).¹²

The main risk factors for increasing the incidence of ACE in western countries are thought to be obesity and gastroesophageal reflux disease (GERD).¹³ Recent studies have shown that the incidence of both obesity and GERD are increasing in Iran similar to western countries.^{6,14,15} A case-control study in Ardabil also revealed that the main risk factors for ACE in Iran were also GERD and obesity.¹⁶

The aim of this study was to evaluate the prevalence of gastric and esophageal adenocarcinomas within a 12-year period in Kerman Province, and to find whether the incidence of ACE is increasing in Kerman compared with western countries.

Materials and Methods

Study area

Kerman in the southeast Iran with arid and semiarid climate is the largest province of Iran and constitutes 11% of the total area of the country. The province has a population of about 2.5 million, all Persians in ethnicity. The socioeconomic status of people is around the average of the country except for southern part of the province, which the status is below average.

Data source

The information of all newly diagnosed cases of upper GI neoplasias was collected actively from all of the 18 histopathology departments around the Kerman Province retrospectively. These departments have received nearly all of pathology specimens from private and public hospitals and clinics throughout the whole province. Because of availability of diagnostic endoscopy and pathology laboratory almost in all major cities of the province and coverage of insurance for most of urban and rural population, we assumed that most of the patients with cancer were diagnosed in the province and were included in our study. To maximize the accuracy of data, we also actively reviewed the records of departments and did not rely on their routine reports that were sent to the center of province as part of the national cancer registry program.

The case definition was done according to the WHO/ICD9.¹⁷ All newly proven malignant tumors

among Kerman residents during 1991 – 2002 were enrolled in the analysis. For this analysis, all primary gastric and esophageal cancers were extracted from the whole dataset.

In order to compute ASR, the population pyramid of Kerman Province was extracted from the national census in 1996. The annual populations of the Kerman Province during 1991 – 2001 were interpolated based on the census data in 1986 and 1996.

Data analysis

The crude and age- and sex-standardized incidence rates of malignant tumors were computed, classified by the anatomic site, and expressed per 100,000 person-years. Using direct method, the incidences were standardized based on the standard world population. The relative risks for sex and age group as well as the temporal variation of esophageal and gastric cancers were estimated using negative binomial models because of the over-dispersion of the distributions of risks and low goodness of fit of Poisson models.

Stata version 8 was used for these analyses and 95% confidence intervals (CIs) for incidences and risk ratios were computed.

Results

Esophageal cancer

We found 285 newly diagnosed patients with esophageal cancer during 1991 – 2002 (60.7% males). This represented 2.8% of all newly diagnosed cancers (3% in males and 2.5% in females). Risks of esophageal and also all cancers were slightly greater in males (for esophageal cancer: RR=1.21, 95%CI 1.11 – 1.33; for all types of cancers: RR=1.11, 95%CI 1.09 – 1.13). Esophageal cancer was the 10th most common cancer in males and the 11th in females (Table 1).

ASR of esophageal cancer in males and females were 2.3 and 1.3 cases per 100,000 populations per year, respectively (Table 2).

Histologically, most of esophageal cancers (72.6%) were ESCC. Around 10% of ACE was diffuse type (signet ring carcinoma, papillary carcinoma, mucinous carcinoma, and undifferentiated carcinoma).

The temporal variations of patients with gastric cancers are illustrated in Figure 1. Using negative binomial model, the variations in the annual incidence of esophageal cancers was statistically significant. The estimated risk ratio for the linear

Table 1. Relative frequency of malignancies by site in Kerman Province during 1991 – 2001 classified by sex.

Order	Female		Male	
	Location	n (%)	Location	n (%)
1	Skin	814 (19.9)	Skin	1118 (19.6)
2	Breast	822 (18.0)	Stomach	753 (13.2)
3	Stomach	357 (7.8)	Lymph node	548 (9.6)
4	Lymphoma	308 (6.7)	Bladder	527 (9.3)
5	Uterus	303 (6.6)	Prostate	305 (5.4)
6	Colo-rectal	273 (6.0)	Brain	273 (4.8)
7	Brain	192 (4.2)	Lung	264 (4.6)
8	Thyroid	170 (3.7)	Larynx	252 (4.4)
9	Bladder	137 (3.0)	Colo-rectal	240 (4.2)
10	Esophagus	113 (2.5)	Bone and cartilage	186 (3.3)
11	Gallbladder	104 (2.3)	Esophagus	169 (3.0)
12	Ovary	98 (2.1)	Hep. & cholang.*	108 (1.9)
13	Hep. and cholang.*	97 (2.1)	Connective tissue	104 (1.8)
14	Bone and cartilage	92 (2.0)	Lung	80 (1.4)

*Hep. and cholang. = Hepatic and cholangiocarcinoma.

effect of year was 1.05 (95% CI: 1.014 – 1.09), which implies that on average the risk of diagnosed esophageal cancer increased around 5% per year (Table 3). However, this raise was much more prominent in ACE (11%, $P < 0.005$) than in SCC (3%, $P = 0.14$).

The mean and median age of the patients were 60.3 and 62.0 years, respectively (range: 25 to 86 years). Twenty-one point six percent of malignant

tumors occurred in ≤ 40 -year-old patients and 50.9% in ≥ 60 -year-old patients. The incidence risk increased with age and the highest incidence risk was in more than 60-year olds (Table 4). Esophageal cancer was much more common in males than females in all age groups (Figure 2).

Gastric cancer

We found 1,112 newly diagnosed patients with

Table 2. Crude and age standardized annual incidence risk of gastric and esophageal cancers in Kerman Province during 1991 – 2001, classified by sex and histopathologic types. Risks are reported per 100,000 populations.

Site	Sex	Crude incidence	Standardized incidence (95%CI)
Gastric	Adenocarcinoma		
	Male	6.1	8.7(8.0 – 9.3)
	Female	2.6	4.1(3.6 – 4.6)
	Both	4.4	6.6(6.1 – 7)
	Lymphoma		
	Male	0.2	0.3(0.2 – 0.5)
	Female	0.1	0.2(0.1 – 0.3)
	Both	0.2	0.3(0.2 – 0.4)
	Sarcoma		
	Male	0.1	0.1(0 – 0.2)
	Female	0.1	0.1(0 – 0.2)
	Both	0.1	0.1(0 – 0.2)
	All		
Male	6.4	9.1(8.4 – 9.8)	
Female	2.8	4.4(3.9 – 4.9)	
Both	4.6	6.9(6.5 – 7.4)	
Esophageal	SCC		
	Male	1	1.5(1.2 – 1.7)
	Female	0.9	1.3(1.0 – 1.6)
	Both	0.9	1.4(1.2 – 1.6)
	Adenocarcinoma		
	Male	0.5	0.8(0.6 – 1.0)
	Female	0.2	0.3(0.1 – 0.4)
	Both	0.4	0.5(0.4 – 0.7)
	All		
	Male	1.5	2.3(1.9 – 2.6)
	Female	1	1.6(1.3 – 1.9)
Both	1.3	1.9(1.7 – 2.2)	

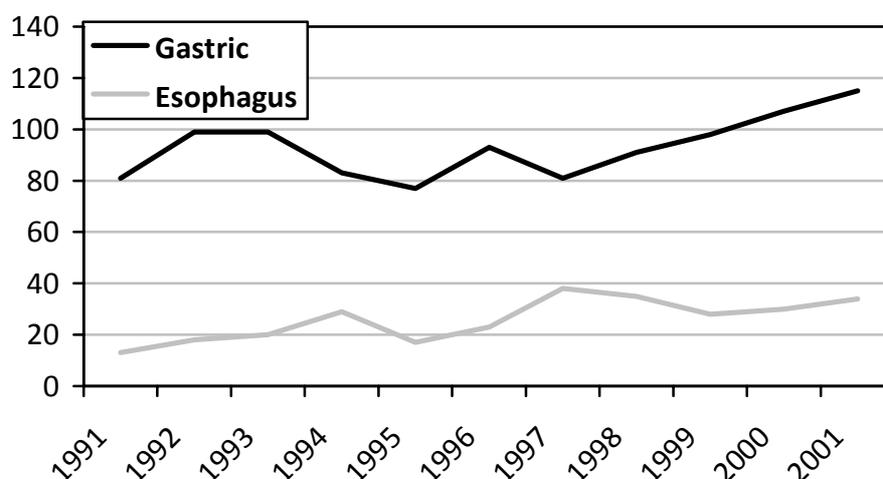


Figure 1. The annual crude numbers of gastric and esophageal cancers reported in Kerman Province during 1991 – 2001.

gastric cancer (67.8% males), representing 10.8% of all newly diagnosed cancers (13.2% in males and 7.8% in females). Risk of gastric cancers was greater in males (RR=1.36, 95%CI: 1.3 – 1.41), which was well above the corresponding RR in esophageal cancer (1.21) and in all types of cancers (1.11).

On the whole, gastric cancer was the second most common cancer in males and the third in females (Table 1). Unfortunately we did not have more information about the location of gastric cancers to classify them as noncardia gastric cancers (NCGC) versus GCC.

The crude and standardized incidence rates of gastric cancers were 4.6 and 6.9 cases per 100,000 populations per year, respectively (Table 2).

Histologically, most of gastric malignancies were adenocarcinoma (94.3%), followed by lymphoma (3.8%), sarcoma (1.5%), and others (0.4%).

Using negative binomial model, the variations in the annual incidence of gastric cancers was not

statistically significant. The estimated risk ratio for the linear effect of year was 1.00 (95%CI: 0.98 – 1.02, Table 3). This variation was not significant in any histologic types of gastric cancers.

The mean and median age of the patients were 60.8 and 63.0 years, respectively (range: 23.0 to 95.0 years). Eleven point three percent of malignant tumors occurred in ≤ 40 and 65.3% in ≥ 60 -year olds. The incidence rate increased with age and the highest incidence rate was in more than 60-year olds (Table 4). Gastric cancer in all age groups was much more common in males than females (Figure 3).

Discussion

The risks of gastric and esophageal cancers are relatively high in northern Iran, but they decline as we move toward the southern part of the country. A recent population-based cancer registry in Kerman Province showed that the ASRs of gastric cancer in males and females were 10.2 and 5.9,

Table 3. Temporal variations of gastric and esophageal cancers during 1991 – 2001. The risk ratios show the average of annual variations. Risk ratios greater than one imply a rising pattern.

Site	Type	Linear effect of year	P value
		Risk ratio(95% CI)	
Stomach	Adenocarcinoma	0.99 (0.97 – 1.01)	0.66
	Lymphoma	1.07(0.97 – 1.19)	0.18
	Sarcoma	0.99(0.84 – 1.16)	0.91
	others	1.036(0.9 – 2.01)	0.14
	All	1(0.98 – 1.02)	0.94
Esophageal	Adenocarcinoma	1.11(1.03 – 1.2)	0.005
	SCC	1.03(0.99 – 1.08)	0.14
	All	1.05(1.01 – 1.09)	0.008

Table 4. The effects of sex and age on the risks of gastric and esophageal cancers, classified by pathologic type.

Site	Type		Risk ratio (95% CI)	P value	
Gastric	Adenocarcinoma	Sex			
		Male	1		
		Female	0.62 (0.23 – 1.63)	0.33	
		Age			
		<40	1		
		40–59	15.75 (4.21 – 54.6)	<0.001	
	>60	62.27 (20.50 – 189.31)	<0.001		
	Lymphoma	Sex			
		Male	1		
		Female	0.61 (0.24 – 1.55)	0.3	
		Age			
		<40	1		
		40–59	26.24 (7.82 – 88.03)	<0.001	
	>60	38.57 (11.36 – 130.91)	<0.001		
	Sarcoma	Sex			
		Male	1		
		Female	1.18 (0.27 – 5.20)	0.83	
		Age			
<40		1			
40–59		1.02 (0.09 – 11.32)	0.98		
>60	9.3 (1.91 – 45.52)	0.006			
All types	Sex				
	Male	1			
	Female	0.6 (0.23 – 1.60)	0.31		
	Age				
	<40	1			
	40–59	15.01 (4.29 – 52.50)	<0.001		
>60	57.35 (18.78 – 175.10)	<0.001			
Esophageal	SCC	Sex			
		Male	1		
		Female	0.95 (0.39 – 2.27)	0.9	
		Age			
		<40	1		
		40–59	19.56 (6.35 – 60.26)	<0.001	
	>60	61.6 (22.01 – 172.60)	<0.001		
	Adenocarcinoma	Sex			
		Male	1		
		Female	0.29 (0.14 – 0.62)	0.001	
		Age			
		<40	1		
40–59		78.8 (16.70 – 37.84)	<0.001		
>60	344.4 (84.20 – 1665.00)	<0.001			
All types	Sex				
	Male	1			
	Female	0.73 (0.28 – 1.86)	0.5		
	Age				
	<40	1			
	40–59	22.53 (6.8 – 74.72)	<0.001		
>60	78.73 (26.5 – 233.90)	<0.001			

Using negative binomial regression, the risk ratios and their confidence intervals were estimated.

respectively. For esophageal cancer, it was three and 1.8 in males and females, respectively.¹² These data are almost one fifth compared with the upper GI cancer rates in northwestern province of

Ardabil.⁹ The cancer rates obtained by our pathology-based survey were lower than the rates obtained in population-based cancer registry in Kerman. This is expectable and is because of

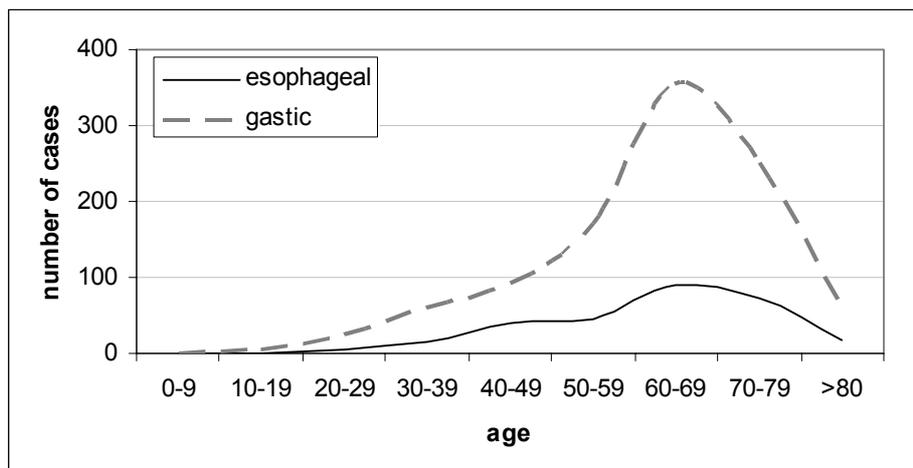


Figure 2. Age distribution of esophageal and gastric cancers.

difference in survey methods. The aim of our study was specifically to look for trends in the incidence of ESCC, ACE, and gastric cancer during a period of 12 years in Kerman, which is a relatively low-prevalence area for upper GI cancer in Iran.

This study showed that during 1991 – 2002, the risk of gastric cancer was constant; while the risk of esophageal cancer, particularly ACE, raised considerably (3% and 11% rise per year in the risks of ESCC and ACE, respectively). Previous studies in northern¹⁰ and southern¹⁸ Iran have confirmed the declining incidence of ESCC. The reason for this declining incidence of ESCC is thought to be due to improving socioeconomic status with better nutrition during the last 30 years.^{10,19}

Up to the knowledge of the author, this study for the first time showed that the incidence of ACE was increasing in low-incidence area of ESCC in

Iran, which is similar to the western countries. The main risk factors for ACE are obesity, GERD, and smoking.¹⁶ The prevalence of obesity and GERD are increasing in Iran similar to the western countries;^{14,15} therefore we should expect this increasing trend of ACE to be continued in the future similar to the western countries during the last 30 years.

The shortcomings in our study are the retrospective nature of the study in a setting of poor-quality keeping of medical records in medical centers (especially in private ones). In addition, some of the medical centers did not use the International Classification of Disease (ICD) coding system at the time of diagnostic procedures, making it impossible to classify all patients with cancer perfectly. The fact that we were not able to classify the gastric cancers according to their locations of NCGC and GCC may have resulted in

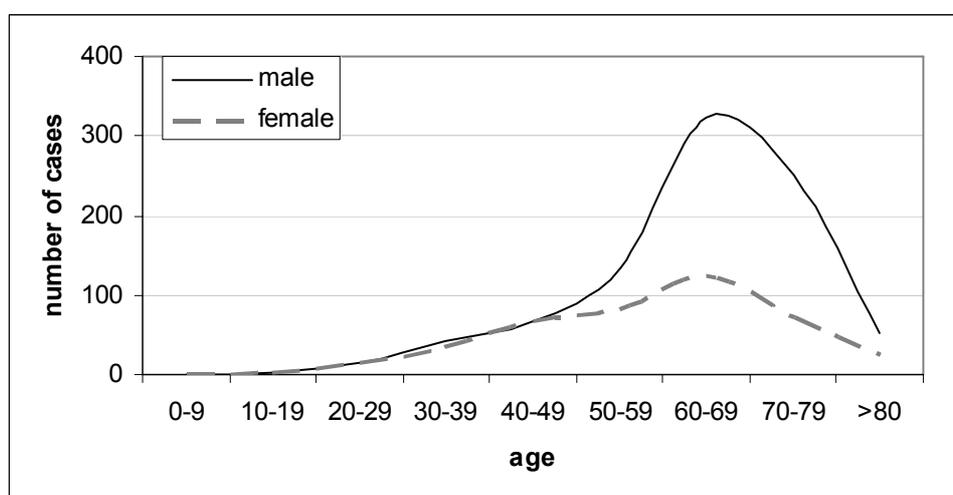


Figure 3. Age distribution of upper gastrointestinal cancers, classified by sex.

some of GCCs misclassified as ACEs. A major problem during the study of gastroesophageal junction cancer is the lack of universally accepted and clearly reproducible anatomic landmarks separating cardia from distal esophagus. Even when landmarks are defined, cancer frequently destroys the anatomy and makes landmarks unrecognizable. Therefore, misclassification of gastric cancer occurs frequently.

In conclusion, we showed that the risk of upper GI cancers in Kerman Province was much lower than that in the country. In addition, we found that the incidence of ACE was increasing in Kerman in recent years.

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