

## RESEARCH ARTICLE

# A 10-year Study of Esophageal Cancer in Guilan Province, Iran: The Guilan Cancer Registry Study (GCRS)

Fariborz Mansour-Ghanaei<sup>1\*</sup>, Abtin Heidarzadeh<sup>2</sup>, Mohammad Reza Naghipour<sup>2</sup>, Farahnaz Joukar<sup>2</sup>, Ali Kord Valeshabad<sup>2</sup>, Mohammad-Sadegh Fallah<sup>2</sup>, Seyed Mahmoud Rezvani<sup>3</sup>, Massih Sedigh-Rahimabadi<sup>2</sup>, Hasan Rokhshad<sup>3</sup>, Arsalan Dadashi<sup>3</sup>

### Abstract

**Background:** Northern Iran counts as one of the highest prevalence regions for esophageal cancer (EC) worldwide. This study was designed to assess the epidemiologic aspects of EC in north central and northwest Iran over a 10 year period. **Materials and Methods:** The Guilan cancer registry study (GCRS) is a population-based cancer registry study featuring retrospective (1996-2003) and prospective (2004-2005) phases. A detailed questionnaire based on WHO standards for cancer registration was applied to gather the required information. Two trained physicians coded information using ICD-O-3 in close coordination with an expert pathologist. **Results:** A total of 19,936 cases of malignancy (mean age 55.4±18.0 years, range: 1-98 years) were registered, including 1,147 cases (670 males, 447 female; mean age: 64.0±11.5 years) of EC. In 1996 the male/female ratio among patients with EC was 1.25 which increased to 1.53 in 2005. The lower third of the esophagus still remained the most common site of tumors. The average age-standardized rate (ASR) was 6.9 and 4.1 per 10<sup>5</sup> men and women, respectively. In 1996, the ASRs were 7.2 and 5.2 per 10<sup>5</sup> men and women which decreased to 6.9 and 4.1 per 10<sup>5</sup> in 2004-2005. Squamous cell carcinoma (SCC) was the most prevalent histological subtype of EC accounting over 80% of cases. **Conclusions:** However the prevalence of adenocarcinoma (ADC) showed an increase to 18.4%. Guilan province may be considered a relatively low incidence region for EC.

**Keywords:** Esophageal cancer - cancer registry study (GCRS) - Guilan - Iran

*Asian Pacific J Cancer Prev*, 13 (12), 6277-6283

### Introduction

The increasing number of annually new cases of cancer, the high mortality rate and its heavy burden on society and people make the importance of deep and targeted cancer surveys inevitable. The overall incidence rate of various types of cancer is estimated to increase by 45% in developed countries by 2030. Cancers accounted as the second most common causes of non-accidental deaths in Iran with an estimated 51,000 new cases annually (Naghavi., 2000; Parkin et al., 2005; Kamangar et al., 2006). The gastrointestinal (GI) tract is the most common site of cancer (about 38%), in which esophagus accounted as one of the important cancer origin in Iran. About 5,800 of 35,000 annually cancer deaths in Iran are due to esophageal cancer (EC) (Sadjadi et al., 2005). With a five year survival of less than 10%, EC accounted as a highly lethal cancer. Squamous cell carcinoma (SCC) is

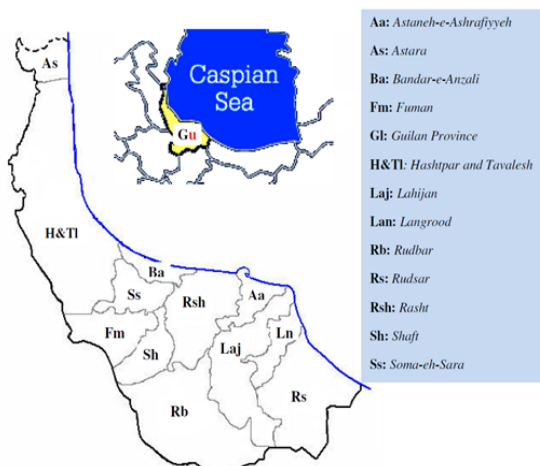
constitutes most of EC worldwide (Samadi et al., 2007), however in western countries adenocarcinoma (ADC) represents about 60% of EC (Brown and Devesa., 2002; Ke, 2002) and a slight increase has been detected in ADC of distal esophagus in developing countries (Haghdoust et al., 2008). The geographic distribution of EC shows a wide range of incidence rate all over the world (Parkin et al., 2005; Kamangar et al., 2006), ranging from 3/10<sup>5</sup> person-years in the Unites States white population (Brown and Devesa, 2002) to >100/10<sup>5</sup> person-years in some areas of china (Perry et al., 1983). Highly-risk geographic areas appear to extend from northeast Iran to China which consists area of Central and East Asia, including Turkmenistan (Saenko, 1975), Uzbekistan (Saenko, 1975), Karakal Pakistan (Zaridze et al., 1992), Kazakhstan (Kairakbaev, 1978), and central areas of China (Ke, 2002). This area now called as "Central Asian Esophagus Cancer Belt" which is relatively along with the

<sup>1</sup>Medicine Department, <sup>2</sup>Gastrointestinal and Liver Diseases Research Center (GLDRC), <sup>3</sup>Health Department, Guilan University of Medical Sciences, Rasht, Iran \*For correspondence: ghanaei@gums.ac.ir, ghanaie@yahoo.com

old path of Silk Road. In the mid 1960s, the first reports of high incidence rate of EC in Iran were published which approximately contained 3-4% of all registered cancer (Sadjadi et al., 2003; 2007; Babaei et al., 2005; Semnani et al., 2006). The first well designed cancer registry study was conducted in 1967 by Mahboubi et al. (1973) in the Caspian Littoral of Iran which presumed to have a high incidence rate of EC. They concluded that in northeast of Iran EC is more common than almost any tumor anywhere in the world with a similar male/female distribution which was in contrast to other sites of the world which show a male superiority in EC. This area is known as Golestan province. Golestan province in the northeast Iran is one of the very high-risk areas of the world (Samadi et al., 2007). However there have been a variety number of studies about epidemiologic pattern, incidence trends and etiology of EC in northeast Iran (Golestan province), since 1967 a few number of similar studies have been conducted in northern and northwest Iran (Guilan province). In this population-based cancer study in Guilan province it has been tried to assess the epidemiologic aspects of EC in northwest Iran in a period about 10 years from 1996-2005.

*Guilan province*

Guilan (Gilan) is one of the Northern provinces of Iran. It is about 235 kilometers long and between 25-10<sup>5</sup> kilometers wide. This province lies along the south and south-west borders of Caspian Sea and from the north it is surrounded by Alborz Mountain. It is between Mazandaran province in the east and Ardabil province in the west. It is more than 14,000 square kilometer and has a population about 2.5 millions (49.8% male, 50.2% female). The population of the province is young: in 2005, 21.26% had <15 years of age and only 7.3% were >65 years. However the population is aging compared to 1996. In 1996, 34.5% had <15 years of age, and only 5.7% were >65 years. In this province 53.9% live in urban areas and 85.06% had jobs. Most of the men (87.6%) and women (78.6%) are able to literate. Rasht is the capital city of the province which is located at the center of it. Other main cities of the province include; Astara, Astaneh-e-Ashrafiyyeh, Bandar-e-Anzali, Fuman, Lahijan, Langrood, Rudsar, Rudbar, Shaft, Soma-eh-Sara and Talesh. The location, geographical and statistical characteristics of Guilan cities are shown in Figure 1.



**Figure 1. Guilan Province, its Location and Main Cities**

**Materials and Methods**

*Guilan cancer registry study (GCRS)*

Since the first reports of high incidence of EC in the north regions of Iran in early 1970s (Mahboubi, 1971; Kmet and Mahboubi, 1972), an increasing numbers of studies have been focused to assess its incidence, risk factors and geographic distributions (Hewer et al., 1978; Malaveille et al., 1982; Ghadirian, 1985; 1987; Saidi et al., 2000; Sepehr et al., 2000; 2005; Kamangar et al., 2007; Moradi et al., 2007; Islami et al., 2009; Pourshams et al., 2010; Sadjadi et al., 2010). Despite the high incidence rate of EC in the nearby Golestan province, 300 km to the East of Guilan with estimated incidence rates of 109/10<sup>5</sup> among men and 174/10<sup>5</sup> among women, low incidence rates of EC in Guilan province (15/10<sup>5</sup> and 5.5/10<sup>5</sup> among men and women) have been raised lots of questions without definite answers. Our pilot studies in the Gastrointestinal and Liver Diseases Research Center (GLDRC) in Guilan University of Medical Sciences (GUMS) confirmed gastrointestinal cancers as the most common neoplasm in Guilan province (37%). These pilot findings emerged the importance of a population-based study on cancer registry and epidemiology. Simultaneously, similar studies were conducted in other provinces to reach one-legged information about the epidemiology of cancers in the country. Thus, GCRS was conducted with management of GLDRC and Guilan Health Center in May 1996.

*Primary and secondary goals*

The primary goals were (i) to register all cases of all types of cancer all over the Guilan Province with focus on GI neoplasm between 1996 and 2005, (ii) to define trend of cancer incidence and its associated factors, (iii) to find geographic distribution of various neoplasm over the province, iv) to establish cancer committees and training physicians, staffs based on the designed standards. Other further goals were: (i) Conducting primary prevention programs based on the information gained in primary study to define vulnerable population, (ii) Establishment of cost-effective secondary programs such as screening program and early diagnosis of common cancers in Guilan province, (iii) Providing acceptable care and follow up of treatments. Considering the primary goals and population distribution of Guilan province, the province divided in 4 distinct regions. Region 1: Astara, Talesh (with probable incidence rate of 220 cases/ years) Region 2: Astaneh-e-Ashrafiyyeh, Lahijan, Langrood, Rudsar, Amlash, Siahkal (with probable incidence rate of 660 cases / year) Region 3: Bandar-e-Anzali, Rezvanshahr, Shaft, Soma-eh-Sara, Fuman, Masal (with probable incidence rate of 540 cases/ years) Region 4: Rasht, Rudbar (with a probable incidence rate of 830 cases/ year. A brief look on patients' admission algorithm in the hospitals showed different sources to obtain registered cases of cancer including surgical and non-surgical wards, diagnostic intervention centers like endoscopy and hematology and medical record center. A team of trained physicians regularly visited all health centers, pathology clinics, hospitals and private clinics in all province main cities. After proposing the project they collect all cases of cancer that had been

diagnosed since May 1996. Then they gave the health workers (responsible doctors of each unit) a check list and some contact numbers, so they were able to inform GLDRC of new cases. The places to collect data were: 1) All centers for tissue sampling, private, general and educational hospitals, surgical Clinics, dental clinics, private offices of surgeons, oncologists, dermatologists, internists, orthopedics, urologists, head and neck surgeon, ophthalmologists, Gynecologists and ENT. 2) Private and non-private imaging centers including gamma scan and radiotherapies. 3) Diagnostic centers including hematologic and histopathologic laboratories.

#### Data registry

A detailed questionnaire appropriate to Can-Reg4 -a standard cancer registry software designed by International Agency for Research on Cancer (IARC)-and based on world health organization (WHO) standards for cancer registry was applied to gather required information. The information included demographic characteristics such as identifications, age, sex, place of residence now and past, place of treatment and biopsy, location of biopsy, and probable diagnosis. Collected data transfer to a primarily prepared software (Can-Reg) in Persian font and duplicate cases with similar demographic characteristics and diagnosis in various data base were omitted. All incomplete forms were returned to its center to complete retained information as it was possible. During registration quality of data gathering was assessed using lot quality assurance sampling (LQAS). Random samples were obtained in different levels and were compared to the primary registered data by a third trained staff. The less acceptable level for quality of data was defined 95% consistence of all demographic characteristics and definite or probable diagnosis. Required sample size for quality control was calculated using (a sample size calculator for LQAS surveys). Finally with close cooperation with other cancer registry centers in neighbor provinces including Ardabil and Cancer Institute of Tehran university of Medical Sciences (TUMS), all cancer cases of Guilan province which were recorded in their data bank were extracted and compared to our data bank to define those cases that settled in Guilan province but had traveled to those centers for treatment services and were not registered to our data bank. Finally, two trained general physicians coded information using ICD-O-3 using histopathologic study results and with close coordination of an expert pathologist. The code which both physicians chose was considered as the diagnosis. In cases of different diagnosis a third expert specialist received data and defined the diagnosis. The GCR program contains two retrospective and prospective phases. The retrospective phase investigates all cases of cancers in a period of 8 years (1996-2003), and the prospective study registered all new cases of cancer up to 2005. However, all cases of cancers in all parts of body have been registered with a sample size of about 20,000 cases. These data consisted of patients` demographic characteristics plus their cancer details. Unfortunately, after finishing the first phase, mainly because of financial shortage, this project was paused in 2006. Here we focused on esophageal cancer

and report the epidemiological aspects of this cancer in Guilan province in a population-based cancer registry study in a period of 10 years.

#### Statistical analysis

Results were reported as mean±standard deviation (SD) or median for quantitative variables and percentages for categorical variables. The groups were compared using the Student's t-test, and Pearson's correlation coefficient for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables. P values of 0.05 or less were considered statistically significant. In 2009 the data registry bank was revised again, duplications were corrected and necessary adjustments (during the time the province main cities had been changed) was performed. Crude cancer statistics and detailed population data of Guilan province (from censuses 1996 and 2006) were considered. Person-years of the population at risk were calculated using each year method. The crude (all-ages) and age-specific rates per 100,000 person-years were calculated separately. An average annual age-standardized incidence rates (ASR) per 100,000 person-years were computed by the direct method using the World Standard Population. All the statistical analyses were performed using SPSS version 16 (SPSS Inc, Chicago, IL, USA) for Windows and MS EXCEL version 2007.

## Results

#### All types of cancer

At initial a total number of 24,865 cases of malignancies were registered all over the Guilan province. The data was reviewed and rechecked with those were recorded in neighbor provinces and Cancer Institute of TUMS, and repeated cases with similar demographic characteristics and diagnosis were omitted. Finally, a total number of 19,936 cases of malignancy (mean age 55.4±18.0 years, range: 1-98 years) proved by imaging, tissue biopsy or both were registered during 10 years all over the province. Males were slightly more involved (53.5% male vs. 46.5% female) and their diseases were diagnosed in older ages (58.9±17.6 years in males vs. 57.5±17.5 in females, P<0.001). The most common cancer was stomach cancer, followed by breast cancer, bladder cancer, esophagus

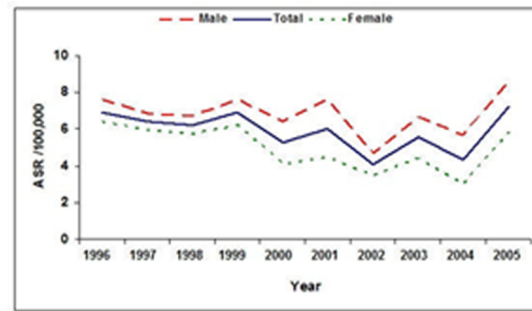
**Table 1. The Most Common Cancer in Men and Women in Guilan Province in a Period of 10 Years**

Cancer	Men		Women		Total	
	N	(%)	N	(%)	N	(%)
Stomach	1577	(14.8)	684	(7.4)	2221	(11.3)
Breast	52	(0.5)	1747	(18.8)	1799	(9.0)
Bladder	1031	(9.7)	232	(2.5)	1263	(6.3)
Esophagus	670	(6.3)	477	(5.2)	1147	(5.8)
Leukemia	588	(5.5)	367	(4.0)	955	(4.8)
Lung	512	(4.8)	153	(1.7)	666	(3.3)
Prostate	638	(6.0)	0	(0.0)	638	(3.2)
Colon	311	(2.9)	270	(2.9)	581	(2.9)
Uterus	0	(0.0)	565	(6.1)	565	(2.8)
Rectum	228	(2.1)	195	(2.1)	423	(2.1)
Others	5059	(47.4)	4580	(49.4)	9678	(48.5)
Total	10666		9270		19936	

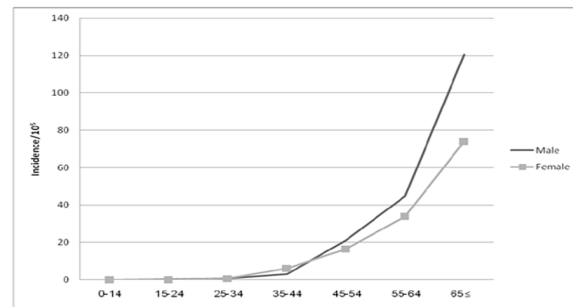
cancer, leukemia, lung, prostate, skin and colon cancers. Among men stomach cancer was the most prevalent neoplasm (14.8%), followed by bladder (9.7%) and prostate cancer (6.0%). In women breast cancer was the most prevalent (18.8%), stomach was the second (7.4%), followed by uterus cancer (6.1%). Table 1 shows the most common cancer in men and women in Guilan province in a period of 10 years.

**Esophageal cancer**

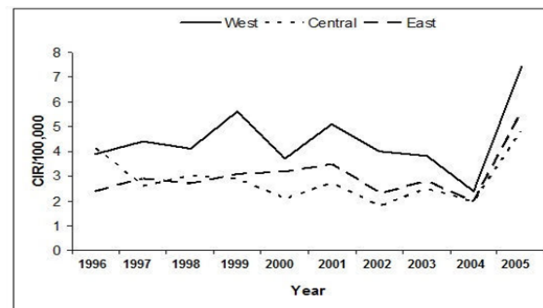
A total number of 1147 cases of EC (670 males, 447 female; mean age: 64.0±11.5 years, range: 19-97 years) were recorded during 10 years study. At initial and at the end of our study, the mean age of involved people relatively remains similar (1996: 64.6±10.7 vs. 2005: 64.9±12.4, P=0.786). In 1996 the male/female ratio among patients with EC was 1.25 which increased to 1.53 in 2005. Lower third portion of esophagus still remains as the most common site of tumor (1996:68.4%, 2005: 63.4%, P=0.727). However a slight increase has been detected in tumors located in the middle and upper third of esophagus. Over 40% of new cases of EC have been diagnosed in highest tumor grade. Table 2 shows changes in different variables at initial (1996) and at the end of the study (2005). In about 10 years study the average ASR was 6.9 and 4.1 per 10<sup>5</sup> men and women, respectively. In our study at initial in 1996, ASR was as low as 7.2 and 5.2 per 10<sup>5</sup> men and women which decreased to 6.9 and 4.1 per 10<sup>5</sup> in 2004-2005 while crude incidence rates of EC showed fluctuation with the time, but it slightly increased in this period. Table 3 summarizes changes of ASR and CIR of EC in Guilan province at initial and the end of the study. Figure 2 shows the changes of ASR in both



**Figure 2. Changes of ASR for Esophageal Cancer in Male and Female during the Time**



**Figure 3. Age-specific Rates of Esophageal Cancer by Sex**



**Figure 4. Changes of Crude Incidence Rate (CIR) in West, Center and East of Guilan Province during 10 Years Study**

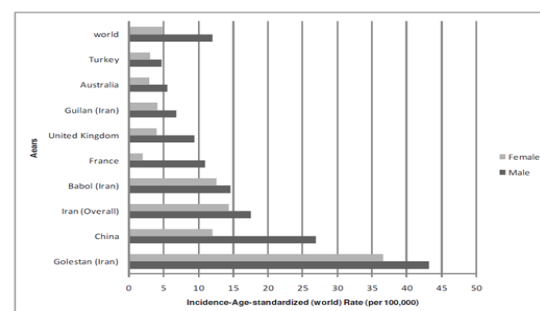
**Table 2. Changes in Different Variables at Initial (1996) and at the End of the Study (2005)**

Variables	At initial -1996	At the end -2005
Total number	108	152
Mean age (year)	64.6±10.7	64.9±12.4
Male gender	60 (55.6)	92 (66.5)
Site of esophagus	N=19	N=41
Upper	3 (15.8)	7 (17.1)
Middle	3 (15.8)	8 (19.5)
Lower	13 (68.4)	26 (63.4)
Grade of tumor	N=31	N=44
Well differentiated	5 (16.1)	9 (20.5)
Moderate differentiated	12 (38.7)	21 (47.7)
Poor differentiated	14 (45.2)	19 (43.2)
Histopathology		
SCC	73 (83.9)	73 (68.9)
ADC	13 (14.9)	33 (31.1)

**Table 3. Crude-sex Adjusted and Standardized Incidence Rates of Esophageal Cancer**

Period	Male		Female		Total	
	CR <sup>†</sup>	ASR <sup>‡</sup>	CR	ASR	CR	R
†: 1996-7	5.6	7.2	4	5.2	4.8	6.2
2005-6	6.8	6.9	4.1	4.1	5.5	5.5

\*SCC=Squamous cell carcinoma, ADC=Adenocarcinoma, GERD=Gastro-esophageal reflux, LES=lower esophagus sphincter; <sup>†</sup>CR=Crude Incidence; Rate/100000; <sup>‡</sup>ASR=Age-standardized Incidence Rate



**Figure 5. Comparison of Age Standardized Rates (ASR) Different Provinces of Iran and Other Countries**

genders during study period. The age-specific incidence rate of EC increases by age in both genders (Figure 3). Over 10 years SCC is still the most prevalent histological subtypes of EC accounting over 80% of cases. However the prevalence of ADC showed a considerable increase to 18.4% during this period. The ASR of EC found to be higher in west of Guilan province (4.1: 2.4-7.4) than East (2.9: 2.0-5.6) and center of the province (2.7: 1.8-4.8). The trend of CIR was relatively the same in West, Center and east of the province (Figure 4).



**Table 4. The Major Global Etiologies of Esophageal Cancer, Type of Cancer Probable Etiology**

SCC:	High risk area; (china, Iran)	Diet low in fresh fruits and vegetable, Drinking hot tea, Low socioeconomic status, Opium use and poor oral hygienic, polyaromatic hydrocarbons (PAH), Nitrosamine, Family history of cancer, Helicobacter pylori, smoking (tobacco)
	Low risk area; (USA, Europe)	Food habit, High alcohol consumption, Smoking (tobacco), Poverty, Helicobacter pylori
ADC		Obesity, GERD, Anatomic defects of cardia and LES, High economic status

## Discussion

Nearby 10 year investigation over Guilan province showed that stomach cancer is the most prevalent cancer (11.3%), followed by breast cancer (9.0%) and bladder (6.3%). Among men stomach cancer was the most prevalent neoplasm (14.8%), followed by bladder (9.7%) and prostate cancer (6.0%). In women breast cancer was the most prevalent (18.8%), stomach was the second (7.4%), followed by uterus cancer (6.1%). The prevalence of cancers in Guilan province was different from those Purshams et al found in Golestan province. They confirmed EC as the most prevalent cancer while esophagus was the fourth common cancer in Guilan.

Another interesting finding was the considerable prevalence of bladder cancer in Guilan province, especially among men while bladder cancer has not been mentioned even among 10 common cancers diagnosed in neighbor provinces (Pourshams et al., 2010). The main reason for this remarkable prevalence of bladder cancer in Guilan province have not been well assessed in previous works and targeted studies are required to answer these questions.

Our assessment confirmed the first reports of low incidence rate of EC in Guilan province (Mahboubi et al., 1973). The incidence rate is still low and has declined considerably in the past 30 years, even to about one-third of what had been reported by Mahboubi et al. (1973) (Table 3). This decreasing pattern may reflect the highly improved socioeconomic status in the province during past 30 years. However it should be taken into consideration that due to poor diagnostic technology in the past the probability of misclassification of gastric cancer cases as lower EC cases maybe an important cause. Consistent with this probability, simultaneous to improving diagnostic technology, the incidence rates of gastric cancer have been slightly increased while a reverse pattern detected for EC. At initial and at the end of our study, the mean age of involved people relatively remains similar (1996: 64.6±10.7 vs. 2005: 64.9±12.4, P=0.786). In 1996 the male/female ratio among patients with EC was 1.25 which increased to 1.53 in 2005.

Lower third portion of esophagus still remains as the most common site of tumor (1996:68.4%, 2004: 63.4%, P=0.727). However a slight increase has been detected in tumors located in the middle and upper third of esophagus. In spite of remarkable improvement in diagnostic techniques during these 10 years, over 40% of new cases of EC have been diagnosed in highest tumor grade. It emphasizes that only diagnostic techniques are not sufficient to diagnose new cases in early stages, targeted

educational programs and population-based screening studies are also required. Earliest studies about thirty-five years ago reported an ASR of 20 and 10 per 10<sup>5</sup> men and women (Mahboubi et al., 1973). In our study at initial in 1996, ASR was as low as 7.2 and 5.2 per 10<sup>5</sup> men and women which decreased to 6.9 and 4.1 per 10<sup>5</sup> in 2004–2005. The age-specific incidence rate of EC increases by age in both genders. It seems that crude incidence rates of EC have been increased a bit during this period but, ASRs have shown little decreases. These are probably because of aging of Guilan population and more similarity of them to the world standard population in 2005.

The ASRs as well as sex distribution and changes pattern during the time are more similar to western countries than what has been reported in Golestan province (Kollarova et al., 2007; Eser et al., 2010; Pourshams et al., 2010). Over 10 years SCC is still the most prevalent histological subtypes of EC accounting over 80% of cases. However the prevalence of ADC showed a considerable increase to 18.4% during this period. In developing countries including Iran SCC is still the most prevalent form of EC (Kamangar et al., 2007), however an increase has been reported in ADC prevalence (Semnani et al., 2006; Haghdoost et al., 2008). In contrast in western countries ADC is the major subtype which represents about 60% of EC (Brown and Devesa, 2000; Naghavi, 2000; Ke, 2002). Improvement of sanitary and public health condition, epidemic of obesity and gastro-esophageal reflux disease (GERD) (Malekzadeh et al., 2003; 2005) and decreased rates of H. Pylori infection may explain this seen increasing pattern in ADC to some extent (Derakhshan et al., 2008). SCC dominantly occurs in low-and middle-income countries and its main etiological factors are; smoking and alcohol. ADC is more related to the high-income countries, obesity and chronic gastro-esophageal reflux. Known risk factors of EC have been summarizes in Table 4 (Castellsague et al., 2000; Brown et al., 2001; Roth et al., 2001; Jansson et al., 2005; Yang et al., 2005; Gonzalez et al., 2006; Jakszyn and Gonzalez, 2006).

In contrast to what expected that incidence rate of EC is higher in northeast regions than northwest regions, the ASR of EC found to be higher in west of Guilan province (4.1: 2.4-7.4) than East (2.9: 2.0-5.6) and center of the province (2.7: 1.8-4.8). The pattern of crude incidence rate was relatively similar from West to East of the province over the time (Figure 4). This pattern was different to Golestan province in which the northeast region is the hottest epidemic region for SCC. These changing patterns among the narrow strip of northern regions of Iran mainly depend on genetic factors (in Gonbad and south-east parts of Caspian Sea the main ethnicity is Turkmen), particular consumption habits (eating very hot beverage, chewing Nas etc.) and some unknown factors (Pourshams et al., 2010).

In sum, the prevalence of EC varies considerably from south to north of the country (Table 5) as well as its different pattern all over the world (Mohebbi et al., 2006; Hossein et al., 2008). Even in a narrow region in northwest Iran the ASR varies in 3 neighbors provinces from 6.9 in Guilan to 10.5 in East Azarbaijan and 15.4 in Ardabil for

**Table 5. Comparison of Age Standardized Rates (ASR) for Different Provinces of Iran**

Province	Male/10 <sup>5</sup>	Female/10 <sup>5</sup>
Golestan (Northeast)	43.3	36.3
Ardabil (Northwest)	15.4	14.4
Babol (Northcenter)	14.6	12.7
Semnan (Middle)	11.7	8.8
East Azerbaijan (Northwest)	10.5	10.0
Guilan (Northwest)	6.9	4.1
Kerman (South)	3.0	2.1
Iran (overall)	17.6	14.4

male; and 4.1 in Guilan to 10.0 in East Azarbaijan and 14.4 in Ardabil for female (Mohebhi et al., 2006; Hossein et al., 2008). This implies the variable geographic distribution of EC which might due to many known and unknown environmental and ethnical reasons. As it is shown in Figure 5, ASRs of EC in males and females in Guilan province is more similar to western countries than other provinces of Iran and developing countries. It is lower than the overall values of the country and world, and even as compared with some developed countries like France and United Kingdom and more similar to Turkey and Australia (Kollarova et al., 2007).

The ASR for esophageal cancers in our study was something in between the low risk areas e.g. the US blacks (ASR=9), the US whites (ASR= 4) and Kerman province of Iran (ASR =3), on the one hand, and the medium risk areas including South Africa (Transkei; ASR= 33) and France (Calvados; ASR= 24), on the other hand. But it was far less than the high risk areas, for instance China (Linxian) and Gonbad city in Iran, each with an ASR for more than 100 per 100,000 (Baquet et al., 2005; Sadjadi et al., 2010).

However the ASR of EC in Iran has been much lower than what Mahboubi et al reported about 35 years ago, our country still accounted as a high endemic region for EC (Mahboubi et al., 1973). In this study we tried to cover all parts of the province and investigated all probable sources to find cancer cases. Finally, all double registered cases were omitted with a careful caution. Although all data were rechecked twice it is possible to make mistakes, however it is so rare. Endoscopic examination and histopathologic studies had not been performed for all the participants; we entered all existent data for analysis and comparison, however the sample size was low in some cases. Covering about 2.5 million people, the large sample size and about 10 years registry which cover about 20,000 cancer cases are some unique strengths of this survey.

In conclusions, Guilan province is a low incidence region for EC. The prevalence of EC has been declined over the time, the majority of cases are SCC, and however ADC has increased rapidly over the last decade. Targeted program are required to apply these findings in public health planning in the province.

## Acknowledgements

Authors would like to thanks all members of Guilan cancer registry center and GLDRC for their help preparation all data.

## References

- Babaei M, Mousavi S, Malek M, et al (2005). Cancer occurrence in Semnan Province, Iran: results of a population-based cancer registry. *Asian Pac J Cancer Prev*, **6**, 159-64.
- Baquet CR, Commiskey P, Mack K, et al (2005). Esophageal cancer epidemiology in blacks and whites: racial and gender disparities in incidence, mortality, survival rates and histology. *J Natl Med Assoc*, **97**, 1471-8.
- Brown LM, Devesa SS (2002). Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am*, **11**, 235-56.
- Brown LM, Hoover R, Silverman D, et al (2001). Excess incidence of squamous cell esophageal cancer among U.S. Black men: role of social class and other risk factors. *Am J Epidemiol*, **153**, 114-22.
- Castellsague X, Munoz N, De Stefani E, et al (2000). Influence of mate drinking, hot beverages, and diet on esophageal cancer risk in South America. *Int J Cancer*, **88**, 658-64.
- Derakhshan MH, Malekzadeh R, Watabe H, et al (2008). Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut*, **57**, 298-305.
- Eser S, Yakut C, Özdemir R, et al (2010). Cancer incidence rates in Turkey in 2006: a detailed registry based estimation. *Asian Pac J Cancer Prev*, **11**, 1731-9.
- Ghadirian P (1987). Thermal irritation and esophageal cancer in northern Iran. *Cancer*, **60**, 1909-14.
- Ghadirian P, Stein GF, Gorodetzky C, et al (1985). Oesophageal cancer studies in the Caspian littoral of Iran: some residual results, including opium use as a risk factor. *Int J Cancer*, **35**, 593-7.
- Gonzalez CA, Pera G, Agudo A, et al (2006). Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer*, **118**, 2559-66.
- Haghdoust AA, Hosseini H, Chamani G, et al (2008). Rising incidence of adenocarcinoma of the esophagus, in Kerman. *Arch Iran Med*, **11**, 364-70.
- Hewer T, Rose E, Ghadirian P, et al (1978). Ingested mutagens from opium and tobacco pyrolysis products and cancer of the oesophagus. *Lancet*, **2**, 494-6.
- Hossein SM, Mirinezhad K, Farhang S, et al (2006). Gastrointestinal cancer occurrence in East Azarbaijan: a five year study from North Western Iran. *Asian Pac J Cancer Prev*, **7**, 309-12.
- Islami F, Pourshams A, Nasrollahzadeh D, et al (2009). Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. *BMJ*, **338**, 929.
- Jakszyn P, Gonzalez CA (2006). Nitrosamine and related food intake and gastric and oesophageal cancer risk: a systematic review of the epidemiological evidence. *World J Gastroenterol*, **12**, 4296-303.
- Jansson C, Johansson AL, Nyren O, et al (2005). Socioeconomic factors and risk of esophageal adenocarcinoma: a nationwide Swedish case-control study. *Cancer Epidemiol Biomarkers Prev*, **14**, 1754-61.
- Kairakbaev MK (1978). Malignant neoplasms among ethnic groups in the Kazakh SSR. *Vopr Onkol*, **24**, 100-4.
- Kamangar F, Malekzadeh R, Dawsey SM, et al (2007). Esophageal cancer in northeastern Iran: A review. *Arch Iran Med*, **10**, 70-82.
- Kamangar F, Dores GM, Anderson WF (2006). Patterns of cancer incidence, mortality, and prevalence across five continents:

- Defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*, **24**, 2137-50.
- Ke L (2002). Mortality and incidence trends from esophagus cancer in selected geographic areas of China circa 1970-90. *Int J Cancer*, **102**, 271-4.
- Kmet J, Mahboubi E (1972). Esophageal cancer in the Caspian littoral of Iran: initial studies. *Science*, **175**, 846-53.
- Kollarova H, Machova L, Horakova D, et al (2007). Epidemiology of esophageal cancer--an overview article. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*, **151**, 17-20.
- Mahboubi E (1971). Epidemiologic study of esophageal carcinoma in Iran. *Int Surg*, **56**, 68-71.
- Mahboubi E, Kmet J, Cook PJ, et al (1973). Oesophageal cancer studies in the Caspian littoral of Iran: the Caspian cancer registry. *Br J Cancer*, **28**, 197-214.
- Malaveille C, Friesen M, Camus AM, et al (1982). Mutagens produced by the pyrolysis of opium and its alkaloids as possible risk factors in cancer of the bladder and oesophagus. *Carcinogenesis*, **3**, 577-85.
- Malekzadeh R, Mohamadnejad M, Merat S, et al (2005). Obesity pandemic: an Iranian perspective. *Arch Iran Med*, **8**, 1-7.
- Malekzadeh R, Nasseri-Moghaddam S, Sotoudeh M (2003). Gastroesophageal reflux disease: the new epidemic. *Arch Iran Med*, **6**, 127-40.
- Mohebbi M, Mahmoodi M, Wolfe R, et al (2008). Geographical spread of gastrointestinal tract cancer incidence in the Caspian Sea region of Iran: spatial analysis of cancer registry data. *BMC Cancer*, **8**, 137.
- Moradi A, Kalavi K, Qujeq D, et al (2007). Risk factors of esophageal cancer in Turkmen Sahra of Iran. *TJC*, **37**, 16-21.
- Naghavi M (2000). Death report from 10 provinces in Iran. Tehran, Ministry of Health.
- Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.
- Perry PE, Thomson EJ, Vijayalaxm I, et al (1983). Induction of SCE by opium pyrolysates in CHO cells and human peripheral blood lymphocytes. *Carcinogenesis*, **4**, 227-30.
- Pourshams A, Khademi H, Malekshah AF, et al (2010). Cohort profile: the golestan cohort study--a prospective study of oesophageal cancer in northern Iran. *Int J Epidemiol*, **39**, 52-9.
- Roth M, Qiao Y, Rothman N, et al (2001). High urine 1-hydroxypyrene glucuronide concentration in Linxian, China, an area of high risk for squamous oesophageal cancer. *Biomarkers*, **6**, 381-6.
- Sadjadi A, Marjani H, Semnani S, et al (2010). Esophageal Cancer in Iran: A Review. *Middle East J Cancer*, **1**, 5-14.
- Sadjadi A, Zahedi M, Moghadam S, et al (2007). The first population based cancer survey in Kerman Province of Iran. *Iran J Public Hlth*, **36**, 26-34.
- Sadjadi A, Nouraie M, Mohagheghi MA, et al (2005). Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev*, **6**, 359-63.
- Sadjadi A, Malekzadeh R, Derakhshan MH, et al (2003). Cancer occurrence in Ardabil: results of a population-based cancer registry from Iran. *Int J Cancer*, **107**, 113-8.
- Saenko AI (1975). The epidemiology of cancer in Central Asia. *Vopr Onkol*, **21**, 40-4.
- Saidi F, Sepehr A, Fahimi S, et al (2000). Oesophageal cancer among the Turkomans of North-East Iran. *Br J Cancer*, **83**, 1249-54.
- Samadi F, Babaei M, Yazdanbod A, et al (2007). Survival rate of gastric and esophageal cancers in Ardabil province, North-West of Iran. *Arch Iran Med*, **10**, 32-7.
- Semnani S, Sadjadi A, Fahimi S, et al (2006). Declining incidence of esophageal cancer in the Turkmen Plain, eastern part of the Caspian Littoral of Iran: a retrospective cancer surveillance. *Cancer Detect Prev*, **30**, 14-29.
- Sepehr A, Kamangar F, Fahimi S, et al (2005). Poor oral health as a risk factor for esophageal squamous dysplasia in northeastern Iran. *Anticancer Res*, **25**, 543-6.
- Sepehr A, Razavi P, Saidi F, et al (2000). Esophageal exfoliative cytology samplers. A comparison of three types. *Acta Cytol*, **44**, 797-804.
- Yang CX, Wang HY, Wang ZM, et al (2005). Risk factors for esophageal cancer: a case control study in southwestern China. *Asian Pac J Cancer Prev*, **6**, 48-53.
- Zaridze DG, Basieva T, Kabulov M, et al (1992). Oesophageal cancer in the Republic of Karakalpakstan. *Int J Epidemiol*, **21**, 643-8.