

## MINI-REVIEW

# Gastric Cancer in Ardabil, Iran - a Review and Update on Cancer Registry Data

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### Abstract

The incidence rate of gastric cancer in western countries has shown a remarkable decline in recent years while it is still the most common cancer among men in Iran. Ardabil, a North Western province, was found to have the highest rate of GC in Iran and one of the highest gastric cardia cancer rates in the world. We used the most recent data from Ardabil cancer registry to update on the incidence and mortality of GC and performed an extensive search of the English and Persian literature in Pub Med, Embase and all 5 Persian web-based databases, respectively, to summarize all possible risk factors for GC in Ardabil. The age-standardized incidence rate of gastric cancer was 51.8 (95% CI: 47.8-55.8) in men and 24.9 (95% CI: 21.5-27.2) in women per 100,000. Age-standardized mortality rates for gastric cancer in this population were 32.2 (95% CI: 29.1-35.3) and 16.3 (95% CI: 13.9-18.6). The gastric cardia sub-site was the most common location (32.7%) in Ardabil. According to our review *H.pylori* infection, gastroesophageal reflux symptoms, tobacco smoking, and high intakes of salt, red meat and dairy products increase the risk of GC while diets with a high content of allium vegetables and fruits, especially citrus fruits, and consumption of fresh fish, were significantly protective against GC. We conclude that Ardabil has the highest rate of GC in Iran and one of the highest rates of gastric cardia cancer in the world, with no evidence of decline in incidence since 2000. In addition to *H.pylori* infection, the epidemic of gastroesophageal reflux disease and several dietary factors may be responsible for the very high incidence of gastric cardia cancer in Ardabil.

**Keywords:** Gastric cancer - cardia site - time trends - risk factors - Ardabil, Iran

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### Introduction

Gastric cancer is the fourth most common cancer and the second leading cause of worldwide cancer-related deaths (Parkin et al., 2005), with a wide variation in incidence rates across different geographical areas (Parkin, 2004). In Iran gastric cancer is the most common cancer in male and it is reported to be the third cancer after Breast and Colorectal cancers in female (Mousavi et al 2008; Malekzadeh et al., 2009).

The highest ASR of GC in the world has been reported from Japan (Hiroshima and Yamagata Prefecture) that was more than 79/100,000 for males and more than 30/100,000 for females whereas the lowest rates has been reported from Mozambique that was 0.9/100,000 for males and 1.3/100,000 for females (Cancer Incidence in Five Continents, 2007). A variety of an etiological factors have been put forward to account for these differences, including *Helicobacter pylori* prevalence (The Euro gast Study Group, 2007) as well as dietary (Tsugane, 2005;

Tsugane and Sasazuki, 2007) and genetic variations between different populations (Brenner et al., 2000). There is a geographic distribution for high incidence areas for GC in Asia that extends from Japan, Korea and some parts of China to north of Iran in Caspian Sea littoral (Kelley and Duggan, 2003; Sadjadi et al., 2003). Ardabil, a north western province of Iran that is located in Caspian Sea littoral, was reported to have the highest incidence rate of gastric adenocarcinoma in the whole country (Sadjadi et al., 2003). According to an active cancer surveillance program in Ardabil Province, covering a period of four years (1996-1999), GC constitutes 31% of all malignancies seen in this region (Sadjadi et al., 2003), with an incidence rate (ASR) of 49.1 in males and 25.4 in females. The incidence for cardia sub site was 26.4 and 8.6 for male and females respectively and constitutes the major component of gastric cancer in Ardabil (Derakhshan et al., 2004). We aimed to update the incidence trend of GC and review all studies that focused on risk factors of GC in Ardabil.

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## Incidence Trend of GC in Ardabil

Data of all newly diagnosed gastric cancers among permanent residents of Ardabil province between 2004 and 2006 were obtained from the Ardabil population based cancer registry and compared with same rate in 1996 (Sadjadi A et al., 2003). The Ardabil cancer registry (ACR) actively collects information of cancer incidence and stage at diagnosis from hospitals, pathology laboratories, radiology and rural and urban health centers, chemotherapy facilities and drugs and alcohol investigation unit as well as private physicians' clinics.

Incidence rates were age-adjusted to the world's 2000 standard population in 18 age categories of 5 years each (0-4, 5-9... 85+), and expressed per 100,000. To minimize the misclassification of lower esophagus cancer and gastric cardia, we compare all the available endoscopy and surgical reports with our registered hard copies for gastric cancer. The third edition of the International Classification of Diseases for Oncology (ICD-O III) was used for coding the subtypes of stomach cancer (Zhou et al., 2008). During the period of 2004 to 2006 more than 1973 reports of GC cases were registered in Ardabil cancer registry and after elimination of duplicate cases 1038 new cases were recorded (notification per case=1.9). Of the total 1038 cases 740 (71.3%) cases were registered based on Pathology reports, 46 (4.4%) cases were based on clinical investigation or imaging, 67 (6.4%) cases were based on clinical reports such as endoscopy report and 185 (17.8%) cases were registered based on death certificate only (DCO=17.8%). The mean age of the patients was 66.5 ±11.7 years for both sexes; and men had slightly higher age at the time of cancer diagnosis, being 67.4 (±11.1) compared to women with mean age of 64.5 (±12.8). The most common age group was 70-74 years in both sexes. The youngest patient was 16 years old and the oldest one was 95 years old.

Crude incidence rate of GC was 27.8/100,000 for both gender together and was 38.3/100,000 and 17.0/100,000

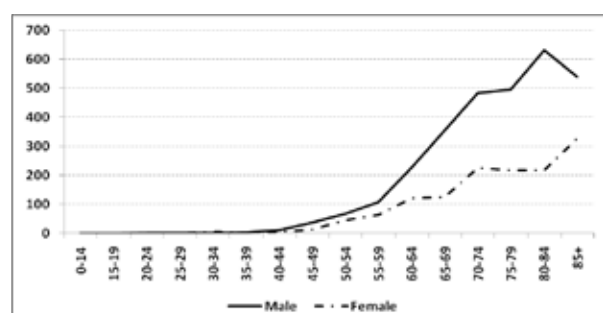


Figure 1. Age-specific Incidence Rate of Gastric Cancer in Ardabil by Gender (2004-6)

Table 1. Incidence and Mortality Rates of Gastric Cancer in Ardabil (2004-6)

Gender	Incidence					Mortality				
	Total n	Crude Rate	ASR /10 <sup>5</sup>	95% CI	ASR 95% CI	Total n	Crude Rate	ASMR /10 <sup>5</sup>	95% CI	ASMR 95% CI
Male	727	38.3	51.8	47.8-55.8	55.8	465	24.5	32.2	29.1-35.3	35.3
Female	311	17.0	24.9	22.0-27.8	27.8	206	11.3	16.3	13.9-18.6	18.6
Both Sexes	1038	27.8	39.1	35.6-42.5	42.5	671	18.0	24.7	21.9-27.4	27.4

ASR=Age standard rate; ASMR=Age standard mortality rate

for male and female respectively. The age standard incidence rate (ASR) of GC was 51.8 (95% CI: 47.8-55.8) and 24.9/100,000 (95% CI: 21.5-27.2) for male and in female respectively (Table 1).

Using the standardized rate ratio (SRR) of gastric cancer in comparing the present rate with the previous report from Ardabil cancer registry there was no significant difference in incidence of GC between two periods of time (Male SRR=0.8 & Female SRR=0.9). By comparison of GC incidence in Ardabil with the national report of Iran in 2006 (Mousavi, 2008) we found that incidence of GC in Ardabil is more than 3-fold higher (male SIR=323.1, Female SIR=353) than national report of gastric cancer in male and female in Iran.

In 339 (32.7%) cases, tumor originated from gastric cardia. Gastric body (including greater and lesser curvatures), antrum and pylorus were the site of tumor in 175 (16.9%), 110 (10.6%) and 11 (1.1%) of patients, respectively. In 403 (38.8%) cases, details of tumor location were unknown (stomach, NOS).

Based on the Lauren pathologic classification 501(67.7%) cases were reported as intestinal type and 224 (30.3%) cases were diffuse type (Table 3).

We examined the association of adenocarcinoma's subtype and their location in cardia versus non-cardia regions of stomach and found that diffuse type adenocarcinoma is more common in non-cardia region rather than cardia of stomach (p<0.05). A dramatic decrease was found for both sexes in the incidence of stomach cancer for Iranian immigrants to British Columbia Canada (Yavari et al., 2006).

## Mortality of GC in Ardabil

During 3 years (2004-2006) 671 cases of GC were deceased, 465 (69.3%) of them were male and 206(30.7%) were female (Male to female ratio was 2.3). The mean age for gastric cancer related death was 67.9±11.7 years for both sexes; (female 66.2±12.2 and male 68.8±11.4). The youngest person was 18 years old and the oldest one was 100 years old. The crud mortality rate of GC was 18 per 100,000 for both sex (24.48 in male and 11.3 in female). The age adjusted mortality rate (ASMR) of GC was 24.7/100,000 (95% CI: 21.9, 27.4) for both sex and for male and female was 32.2 (95%CI: 29.1, 35.3) and 16.3 (95%CI: 13.9, 18.6) respectively (Table 1).

## Cardia versus Non-cardia gastric Cancer

Despite the small size (<10%) of the cardia relative to the remaining parts of stomach, cancer of this site

**Table 2. Topography of Gastric Cancer in Ardabil without DCO (2004-6)**

Subtype of Stomach	Sex		Total N (%)
	Female (%)	Male (%)	
Cardia	102 (32.8)	237 (32.6)	339 (32.7)
Body	44 (14.1)	131 (18.0)	175 (16.9)
Antrum	24 (7.7)	86 (11.8)	110 (10.6)
Pylorus	6 (1.9)	5 (0.7)	11 (1.1)
Stomach, NOS	135 (43.4)	268 (36.9)	403 (38.8)
Grand Total	311 (100)	727 (100)	1038 (100)

**Table 3. Pathological Classification of Gastric Cancer in Ardabil for Pathology Reports Only (2004-6)**

Total N (%)	Sex		Morphology
	Female	Male	
501 (67.7)	135	366	Adenocarcinoma, intestinal type
224 (30.3)	74	150	Carcinoma, diffuse type
1 (0.1)	0	1	Pseudosarcomatous carcinoma
1 (0.1)	1	0	Carcinoid tumor, NOS
2 (0.3)	0	2	Small Cell carcinoma
11 (1.5)	5	6	Malignant Neoplasm
740 (100)	214	525	Total

has a distinct aetio-pathological features. Based on the recent data from IARC (WHO World cancer report 2008) cardia cancer accounts for more than 54% of male gastric cancer cases in Montana, USA and In Europe, Denmark (43%), Switzerland and UK (overall more than 30%) have largest recorded proportion of cardia cancer (Liu et al., 2004; Zhou et al., 2008). In contrast, Japan and Korea in East Asia, and South America countries which have been recorded as high risk areas for gastric cancer (Brown et al., 2002), the proportion of cardia cancer is almost always less than 10%. The incidence of cardia cancer in the Ardabil region is substantially higher than available reports from European countries, U. S. A. Japan and Korea (Derakhshan et al., 2004) While progression of *H. pylori*-induced superficial gastritis to chronic atrophic gastritis to intestinal metaplasia and dysplasia is the main pathologic event in majority of non-cardia cancers, cardia cancer show less prominent and even reverses relationship with *H. pylori* infection and subsequent atrophic gastritis. Based on recent study in Ardabil and similar observation from Finland gastric cardia cancer seems to be a heterogeneous group of two types of tumours, one group being aetiologically similar to non-cardia gastric cancers and another group being similar adenocarcinoma of distal oesophageal with more intestinal to diffuse subtype ratio and reverse relationship with *H. pylori* infection and atrophic gastritis (Derakhshan et al., 2008).

## Risk Factors of Gastric Cancer in Ardabil

### *H. Pylori* infection

We have already shown that in Ardabil close to 90% of normal population have *H. pylori* gastritis and up to 35% have concomitant corpus atrophic gastritis (Malekzadeh et al., 2004). Although it has been reported that *H. pylori*

seropositivity, particularly cag-A+ strains are inversely associated with the risk of gastric cardia adenocarcinomas (Hansen et al., 1999, Kamangar et al., 2006), the results of an investigation in Ardabil clearly showed that the extent of inflammation of the cardia in individuals with *H. pylori* infection is comparable with the changes occurring in the antral region (Sotoudeh et al., 2008) and in other survey that were conducted in Ardabil, it had been found that more than 98% of people 40 years old and above have been infected with *H. pylori* and almost all of them had *H. pylori* associated chronic gastritis involving the antrum, corpus, and cardia (Malekzadeh et al., 2004). Recent findings about *H. pylori* associated inflammation in cardia, supported that *H. pylori* infection could be a risk factor for cardia cancer (Chow et al., 1998).

### Family history of GC

There is also increasing evidence that genetic predisposition, plays an important role (Yaghoobi et al., 2004) in pathogenesis of gastric cancer. It seems that the development of GC before the age of 50 is likely to be accompanied by familial susceptibility (Palli et al., 1994). Relatives of patients with intestinal type of GC have a 1.4-fold increase in the risk, compared to the 7.0-fold risk increase in relatives of patients with diffuse type (Lagergren et al., 2000) and family history of GC was associated to risk of cardia cancer (Chen et al., 2004). It has been shown that combination of infection with a CagA positive *H. Pylori* strain and a positive familial history for GC, had a more than 8-fold total risk of gastric cardia carcinoma and a 16-fold risk of non-cardia gastric carcinoma (Chen et al., 2004). In a case-control study that was conducted in Ardabil, family history of GC for first degree relatives, significantly increased the risk of gastric cancer (Pourfarzi et al., 2009)

### Diet and GC

Among the main external environmental factors that are: low socioeconomic status, crowding, poor hygienic conditions, and diet; diet has been linked to the etiology of gastric cancer in numerous international studies (Kono and Hirohata, 1996; Key et al., 2004; Tsugane, 2005; Tsugane and Sasazuki et al., 2007). A recent report of a joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) expert consultation conducted that salt-preserved food and salt "probably" increase the risk of GC, whereas fruit and vegetables "probably" decrease the risk (World Health Organization, 2003). Based on data extracted from a culturally appropriate FFQ in Ardabil it has been shown that the risk of GC increased with food items high in fat and sugar, salted and roasted seeds and nuts, and frying as the main method of cooking. The results also show a protective effect of GC for fruits and vegetables, vitamin C, and zinc, and using refrigerator for food preservation (Pakseresht et al., 2008). Lower education and income levels and illiteracy also seems to be risk factors for GC although the low socioeconomic status may be related to some specific living conditions which increase the possibility of exposure to GC risk factors (Pakseresht et al., 2008) Substantial evidence, mainly from case-control studies in Ardabil, suggests that risk is

increased by high intakes of some traditionally preserved salted foods, especially meats and pickles, high salt intake, daily consumption of red meat and dairy products and with hot and strong tea and that risk is decreased by of high intake of alliums vegetables, fruits and fresh fish (Pourfarzi et al., 2009).

**Smoking**

An extensive review by International Agency for Research on Cancer indicates that smoking is a moderate risk factor for gastric cancer (IARC, 2004), it has been confirmed that smoking had a significant association with both gastric cardia and non-cardia cancer in at least two separate studies in Ardabil (Derakhshan et al., 2008; Pourfarzi et al., 2009).

**Gastroesophageal reflux disease and cardia gastric Cancer**

Gastroesophageal reflux disease is very common in Ardabil and up to 25% of normal population more than 40 year of age have some evidence of reflux esophagitis in endoscopy (Malekzadeh et al., 2004). Barrett’s esophagus that has been reported to be very rare in China (Kikuchi et al., 1995; Limburg et al., 2001) was found to be a common endoscopic finding in Ardabil (Malekzadeh et al., 2004). Demographic differences and diverging trend in incidence of GCC and NCGC in Western countries point to the fact that the two tumors may be epidemiologically distinct and therefore the anatomic sub site of gastric tumor should be taken into account in studies of etiology and carcinogenesis of this fatal cancer. Evidences are now accumulating for different types of exposure to environmental carcinogen for CGC among others; nitric oxide (Iijima et al., 2002) overeating, obesity (Calle et al., 2002) and resulted hyperacidity in cardia region (Moriya et al., 2002) which are the consequences of life-style changes and other infection like Epstein-Barr virus (Corvalan et al., 2001).

**Other environmental risk factors (Table 4)**

It has been shown that higher concentration of selenium and zinc in drinking water may protect against gastric carcinogenesis (Nakaji et al., 2001). In searching for the

**Table 4. Major Risk Factors for Gastric cancer in Ardabil**

Risk factors	Non Cardia	Cardia
<i>H.pylori</i>	•	•
Tobacco smoking	•	•
Positive family History	•	•
Male gender predominance	•	•
Gastroesophageal Reflux	---	•
Obesity	---	•
Low Socioeconomic status	•	----
Low consumption of Vitamin C	•	-----
Daily consumption of red meat	•	-----
Highly-salted and/or high-temperature-roasted seeds	•	----
Low consumption Allium vegetables	•	---
Low consumption of fresh fruit and vegetables	•	----

possible etiologies of increased upper GI (gastrointestinal) cancer incidence in Ardabil, Nouraie et al showed a lower level of selenium in the serum of normal Ardabil residents comparing to other provinces in Iran (Nouraie et al., 2004).

It has been reported that extraordinary high exposure to radon, radium or natural uranium in drinking water was associated with increasing the risk of GC in Finland (Auvien et al., 2005). In a national survey of radioactivity in drinking water supplies in Iran, during 1994-95, the Uranium concentration in all mineral and drinking waters of Ardabil province were found less than maximum containment level (MCL) of uranium in water resources and were considered to be acceptable for public health (Alighadri et al., 2004). The other environmental carcinogen that may be responsible for occurrence of GC in Ardabil is the high concentration of nitrate in food especially in agricultural products that need more investigation (Derakhshan et al., 2008).

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