

## Review Article

UPPER GASTROINTESTINAL CANCER IN ARDABIL,  
NORTH-WEST OF IRAN: A REVIEW

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## Introduction

Cancer is a serious health problem worldwide, imposing a large economical and psychological burden as well as loss of life and productivity.<sup>1</sup> Lots of effort and money have been put in the fields of clinical, epidemiological, pharmacological, and biological research on cancer in the recent decades. Although we have witnessed dramatic progress in the field, but still there is a long way to go. Cancer is the third most common cause of death in Iran, accounting for 14% of the total death toll.<sup>2</sup> It stands just after cardiovascular events and accidents (46% and 17% of the total death toll respectively, Table 1) according to the latest census of the Iranian Ministry of Health and Medical Education (IMHME). Overall, gastrointestinal (GI) cancers cause about half of all cancer deaths in Iran. Of the 17,450 GI cancers recorded in the IMHME report, 7,560 (43.3%) were gastric cancers.<sup>2</sup> In other words, of every 100 people dying of cancer in Iran, 22 die of gastric cancer, and six from esophageal cancer. Unfortunately, both of these cancers come to medical attention when they are rather advanced and limited or no effective therapies are available for them. Theoretically, these cancers may be treatable in their early stage; therefore, finding them at the earliest possible stage may subject them to effective therapy. Other nations, such as the Japanese, have managed to decrease the toll of gastric cancer by effective screening programs and timely intervention.<sup>3</sup> Therefore, if we are to plan

meaningfully to combat this still deadly disease we should have accurate information about the epidemiology and clinical characteristics of various cancers, especially the upper GI cancers in Iran.

Earlier reports indicated that Ardabil, in North-West of Iran, had a rather high incidence of upper GI cancers.<sup>4-8</sup> In their 1973 report, Mahboubi et al reported that about 64% of all cancer deaths in Ardabil are due to esophageal and gastric cancers (56% esophagus and 8% stomach).<sup>4</sup> This background and the availability of facilities of a collaborating local medical university and easy means of air travel to the area made Ardabil an appropriate place for epidemiological and clinical cancer studies in the past few years. This review focuses on the background and recent studies done in the region as a model of cancer research in Iran.

## Background

The Public Health Research Institute (PHRI) of Tehran University and the International Agency for Research on Cancer (IARC) jointly established a cancer registry in the city of Babol in Mazandaran Province in the Caspian littoral in 1969.<sup>8</sup> The registry mainly covered the two provinces of Gilan and Mazandaran, and the nearby city of Ardabil. Information gathered by this cancer registry soon showed an unusually high incidence of esophageal cancer in the Caspian Littoral. Interestingly the distribution was rather uneven. The western parts of the Littoral (Ardabil) had a high incidence (age

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**Table 1.** The most common causes of death in Iran (2000).

Etiology	Percentage
CVD	46%
Accident	17%
Cancer	14%
Respiratory	6%
Others	17%

standardized ratio (ASR): 20.1 and 6.2 per 100,000 population for men and women, respectively), while the central parts had a lower incidence (ASR: 13.0 and 2.3 per 100,000 for males and females, respectively), and the eastern parts had an unusually high incidence (ASR: 165.5 and 195.3 per 100,000 for men and women, respectively).<sup>4-8</sup> This was especially evident in the Turkman plain in the East of the littoral having the above-mentioned ASR which was among the highest ever recorded in the world. Another point of interest was that esophageal cancer was more common among Turkman females. This cancer registry relied on clinical and simple radiological means for recording the final diagnoses, as endoscopy was not available, and surgery and histological diagnosis were not easily accessible locally. However, despite this shortcoming, it managed to draw the attention of interested national and international investigators who launched studies to unravel the possible risk factors for this high incidence of esophageal cancer in the region. These efforts came to a temporary halt during the revolution in 1979, but after a decade, a new generation of scientists restarted working in this field.

### **Geographical and demographic situation of the Ardabil Province**

The Ardabil Province, a mountainous land, with an area of 1,795 square kilometers (1.09% of the country's surface area), is located in the North-West of Iran, 50 km inland to the West of the Caspian Sea. The city of Ardabil, the capital of the province is located at 38° 14' 32" latitude N and 48° 17' 53" longitude E. Mount Sabalan, a dormant volcano, is located just beside the city of Ardabil. The climate is moderate with cold winters and cool summers. According to the 1999 census, the total population of the province is 1,128,864 (1.94% of the country's population), 46% of whom live in nine cities and the rest (54%) reside in rural areas. The majority of the population (more than 95%) is of Azari ethnicity, a branch of the Aryan Caucasoids. Therefore, the Azari language is the dominant language and all the residents are Muslims. Mean age of the population is 23 years and 63% of the population are below 25 years of age. Life expectancy at birth is 60 years for men and 61 years for women. Two-thirds of the males are farmers and 90% of females are housewives. The remainders are local industrial workers, white

collars, or executives. At the present time there are 21 outpatient clinics, 340 private offices, 49 medical laboratories, 7 histopathology laboratories, and 18 radiology centers actively working in the region, providing health services.

### **The new era**

Having this background and a very low migration rate as well as easy access to the region and presence of an enthusiastically collaborating local medical university, made Ardabil an appropriate place to continue what was started almost three decades before. Therefore, the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences (TUMS) launched a series of large-scale studies in the region with collaboration of Ardabil University of Medical Sciences and the National Cancer Institute (NCI, National Institute of Health, USA) and International Agency for Research on Cancers (IARC) (Lyon, France). These studies, which started in the autumn of 1999, were aimed to answer the following questions:

- What are the current incidence, prevalence, and mortality rates of esophageal and gastric cancer in the Ardabil Province?
- What is the prevalence of precancerous lesions (e.g. dysplasia, intestinal metaplasia...) in the population?
- What are the probable risk factors for developing upper GI cancers in this area?
- What preventive and therapeutic strategies may be the best to decrease the burden of disease in the region?

To answer these questions, to generate new hypotheses, and to find new appropriate questions, several projects were started in parallel.

An active cancer surveillance program<sup>9</sup> covering the years of 1996 to 1999, including about 14% of the total Iranian population, was launched in 5 provinces, one of which was Ardabil. The findings were rather interesting. This active surveillance showed that upper GI cancers (Table 2) are the most common cancers in the Ardabil among both females and males (skin cancers excluded). The registry showed that the annual ASR for all types of cancer was 132.0 per 100,000 population among males and 96.3 per 100,000 population among females. The most common cancers in men were stomach (ASR: 49.1/100,000), esophagus (ASR: 15.4/100,000), lung (ASR: 7.9/100,000), colorectal (ASR: 7.9/100,000), and urinary bladder (ASR:

7.6/100,000). Similar figures for females were as follows: stomach (ASR: 25.4/100,000), esophagus (ASR: 14.4/100,000), breast (ASR: 7.6/100,000), colon and rectum (ASR: 5.9/100,000), and lung (ASR: 3.6/100,000). Comparison of these data with those of Babol Cancer Registry reveals that the incidence of upper GI cancers in Ardabil has increased by 48% and 39% among males and females, respectively. Interestingly the incidence of esophageal cancer has actually declined while the incidence of gastric cancer has risen sharply, accounting for most of the increase in overall incidence. Currently gastric cancer accounts for 37% of all cancers in men and 25% of all cancers in women in Ardabil (as compared to 11% and 14%, respectively in the early 70s).<sup>4, 8</sup> The new cancer registry tried to have as accurate data as possible; therefore every effort was made to include all cases of cancer in the area, even those seeking medical advice in Tehran and Tabriz (the two major cities where patients may seek medical advice out of Ardabil). Overall, 3,455 cases of cancer were diagnosed in the study period. In this new cancer registry, 89.8% of cases had histological confirmation of their diagnoses, 9.1% had clinical diagnoses merely, and only 1.1% of records relied on death certificates. This is in contrast to the Babol Cancer Registry where only 27% of cases had a confirmed histological diagnosis. This reason as well as better and more widespread availability of medical care facilities in the region resulting in earlier and more accurate diagnoses, may account for a part of the difference between the results of the two cancer registries, but certainly not the whole change. Considering all confounders, a major part of this change can only be explained by a true change in the incidence of various upper GI cancers. These new data show that the ASR for gastric cancer in Ardabil is the fourth highest ever recorded worldwide (after Japan, Korea, and Costa Rica). Therefore, further studies to look for the etiology and possible risk factors, and precancerous lesions seemed logical. To support this was the findings of a serologic study done earlier showing that *Helicobacter pylori* (HP), a well-known class-one carcinogen for gastric cancer, was significantly more prevalent in Ardabil than in other parts of the country which have a lower incidence of gastric cancer (like Yazd in central Iran).<sup>10</sup> Of over 350 individuals younger than 20 years tested for HP antibodies in their sera in each region, 47.5% and 30.6% were positive in Ardabil and Yazd, respectively ( $p < 0.0001$ ). But

**Table 2.** Top 10 cancers in Ardabil compared to estimated cancer incidence for Iran by GLOBOCAN 2000 Ardabil Cancer Registry, GLOBOCAN 2000.

Site	Ardabil Cancer Registry										
	Male					Female					
	Crude	ASR	Site	Crude	ASR	Crude	ASR	Site	Crude	ASR	
Stomach	31.40	49.13	Stomach	14.23	25.42	Lung	29.6	34.9	Breast	34.9	35.7
Esophagus	9.66	15.42	Esophagus	7.96	14.36	Stomach	18.3	21.5	Cervix	15.7	16.1
Lung	5.08	7.95	Breast	4.71	7.60	Prostate	17.8	21.2	Colorectal	14.8	14.4
Colorectal	5.04	7.86	Colorectal	3.33	5.89	Colorectal	16.4	19.1	Lung and bronchus	11.2	11.1
Bladder	4.79	7.59	Lung	1.99	3.59	Liver	13.1	15.0	Stomach	10.6	10.4
Nervous system	3.14	4.44	Nervous system	2.25	3.13	Esophagus	9.1	10.8	Ovary, etc.	6.4	6.5
Oral cavity	2.50	3.75	Liver	1.30	2.28	Bladder	8.5	10.0	Corpus uteri	6.3	6.4
Prostate	2.25	3.45	Bladder	0.99	1.78	Oral	5.6	6.4	Liver	5.5	5.5
Non-Hodgkin's lymphoma	1.57	2.60	Oral cavity	0.99	1.71	Non-Hodgkin's lymphoma	5.5	6.1	Esophagus	4.4	4.5
Bone	1.44	1.69	Lymph leukemia	0.91	1.43	Larynx	4.7	5.5	Non-Hodgkin's lymphoma	4.0	4.0

similar studies from Fars and Tehran Provinces (with lower incidence of gastric cancer than Ardabil) did not show any difference in serologic prevalence of HP with Ardabil. Therefore, looking for other causes possibly related to gastric cancer in the region and their interactions with each other and HP is justified.

Another series of studies done in the region were two successive endoscopic surveillance studies performed in Ardabil and Meshkinshahr.<sup>10-11</sup> The aim of these studies was to look for precancerous lesions and possible risk factors. In these studies healthy people from the two regions were invited to undergo a medical examination and fill in a detailed questionnaire (covering demographics, dietary habits, lifestyle, occupation, major upper GI and non-GI symptoms, and family history of benign and malignant diseases). In addition, they were offered to undergo an upper GI endoscopy with Lugol's staining of the esophagus and systematic biopsies of the esophagus and stomach to look for precancerous lesions. Overall, 1,105 urban and rural households were selected by random cluster sampling and one person aged 40 years or older from each household was asked to participate. A total of 1,011 people were enrolled (among a population of 599,494). Of the 504 people studied in Ardabil, 36% had endoscopic esophagitis (mostly grades A and B according to the Los Angeles classification). None of them had dysplasia or squamous cell carcinoma in the esophagus and Lugol's staining did not pick up any precancerous lesion not seen on routine endoscopy. Ninety-five percent of the 1,011 subjects undergoing endoscopy in the two regions had active or inactive gastritis on histological examination. This is very important, as most of these were associated with HP (89%). Other findings in the stomach of these subjects were atrophy (38%), intestinal metaplasia (9%), glandular dysplasia (0.2%), and adenocarcinoma (0.3%). It should be reemphasized that none of these people had sought medical advice for any GI problem. In other words all of them were either asymptomatic or had only trivial GI symptoms not taking them to a doctor. Absence of precancerous esophageal lesions and a wide-spectrum of different types of pathologies found in the stomach support the findings of the mentioned cancer registry, which shows a decline in the incidence of esophageal cancer and a rise in that of gastric cancer in the region.

The latest study of these series has been done in the Aras Clinic.<sup>12-14</sup> The DDRC established this clinic as a base for its activities in the region. The clinic provides clinical and educational service on GI diseases to the local population. In this latter study, Aras investigators looked at the anatomical site distribution of the upper GI cancers diagnosed over a twenty-one-month period in Ardabil. The only gastroenterologist working in the region diagnosed four-hundred and ninety-nine upper GI cancers in 3,119 endoscopies done for various upper GI complaints. Of these 282 were gastric cancers. Most of these were located in the cardia (44%) followed by the antrum (29%), and the corpus (26%). This is in accord with the western trend of proximal migration of gastric cancers over the past half century, but interestingly the incidence of cardia cancer in Ardabil seems to be several orders higher than that reported from some western countries such as Scotland. The same group also looked at the axial view of the location of the cardia cancers. They observed that of the 125 cardia cancers identified, 53 were located on the right side (along the lesser curve of the stomach), seven on the left side (along the fundus), and the rest were circumferential. Therefore, of the 60 noncircumferential cardia cancers, 88% were located on the right side i.e. along the lesser curvature. This may be explained by the old theory of "canalis gastricus" or "magenstrasse" which implies that most of the liquid ingested by humans travel to the stomach along the lesser curvature side of the esophagus. Therefore if a luminal carcinogen is responsible for development of gastric cancer, it has a higher chance of being in contact with the lesser curve side of the stomach and cardia rather the right side. Although, this finding is of doubtful clinical significance at the time being, but it may have pathophysiological importance. These investigators' figures show a male to female ratio of 1.1 and 1.3 for cardia and noncardia gastric cancers, respectively. Similar data reported from Europe show a reverse ratio (0.45 and 0.35, respectively).

In searching for the possible etiologies of increased upper GI cancer incidence in Ardabil, Nourai et al looked at the level of selenium, a supposedly important trace element in carcinogenesis in the upper GI tract.<sup>15</sup> They showed that only 29% of the Ardabil population had a serum selenium concentration of more than 90 µg/L. Therefore, selenium deficiency may be responsible for a part of the upper GI cancers

found in the region. This is a preliminary study and needs confirmation in further well-designed studies.

Another interesting carcinogenesis theory is the nitrate and nitrosamine story. Nitrates have increased in our food by various means over the past few decades. We are using efficient methods, including nitrate containing fertilizers, to meet the growing need of the community for crops and agricultural products. Can this be somehow linked to the biological changes happening in our stomachs? Ardabil is an agricultural area, therefore considering such an explanation, one should look carefully at the local environmental changes.

### Conclusion

Upper GI cancers are the leading cause of cancer deaths in our country. According to the current information, parts of our country harbor a rather high incidence for these cancers, comparable to the highest incidences ever reported in the world. Considering the changing trends in this process, it may be a unique opportunity for investigators to record the pattern of change and look for possible underlying causes and risk factors. Is the more westernized way of living causing this change? Is there anything special to the habits and lifestyle of the people, which is responsible? Does it have anything to do with genetics and molecular aspects of life in the region? Can there be any link between environmental factors and the risk of cancer found in the region? Should all people in this high-risk areas be looked for HP and be treated as a means of prevention of cancer? These and many more unanswered questions are the focus of ongoing large-scale studies being performed in Ardabil and other parts of northern Iran. For the present time it can only be said that upper GI cancers are the leading cause of cancer deaths in our country and especially in regions like Ardabil, and that proximal gastric cancers (e.g. cardia cancers) and esophageal adenocarcinomas are rising. Thoughtfully designed epidemiological and clinical studies are pivotal to unravel the details of why and how these are happening and help to plan

what should be done to combat effectively with these still deadly diseases.

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