

# The Features of Esophageal Cancer in Ardabil Province: Report of a Population-based Cancer Registry in Northwest Iran

Pourfarzi F<sup>1</sup>, Barak M<sup>1</sup>, Babaei M<sup>1</sup>, Rahimi G<sup>1</sup>, Malekzadeh R<sup>2</sup>, Yazdanbod A<sup>1</sup>

<sup>1</sup>Gastrointestinal Cancers Research Center (GICRC), Ardabil University of Medical Sciences, Ardabil, Iran

<sup>2</sup> Digestive Disease Research Center (DDRC), Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

## ABSTRACT

**Background:** Evidence shows that the mortality rate of esophageal cancer (EC) in Ardabil Province is among the highest worldwide. Studies on the epidemiological profile of EC in Ardabil are scarce. We aim to study the characteristics of EC in Ardabil using data from the recently established Ardabil Cancer Registry (ACR).

**Materials and Methods:** This study has been accomplished based on data collected in ACR between 2004 and 2006. Cases reported to ACR were coded based on the third edition of the International Classification of Diseases for Oncology (ICD-O III). The age-standardized incidence rates (ASR) and the standard rate ratio (SRR) have been calculated for each district in Ardabil Province.

**Results :** A total of 549 new cases of EC were registered within ACR during the study period. The ASR was 19.5 for men and 19.7 for women per 100,000 person-years. The majority of cases (79.1%) were diagnosed based on pathology. The most common morphology of EC was squamous cell carcinoma (SCC, 73%) followed by adenocarcinoma (17.8%). The ASR was significantly higher in northern districts of the province ( $p < 0.001$ ); highest in Meshkinshahr (27.2/100,000) and lowest in Nir (7.6/100,000). The male:female ratio approximated one in the northern and above 2.5 in the southern districts.

**Conclusion :** Our results demonstrate that the increased incidence of EC in Ardabil is mainly due to an increase in the incidence of esophageal adenocarcinoma (ACE) during recent years. The almost equal incidence of EC among men and women, and its geographical pattern across the province indicate the possible role of environmental risk factors, which need further investigations.

**Keywords:** Esophageal cancer; Incidence; Mortality; Ardabil, Iran

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## INTRODUCTION

Esophageal cancer (EC) is the eighth most common cancer and the sixth most common cause of cancer death worldwide (1). In Iran an estimated total of 6500 EC cases occur each year, of which 5800 pa-

tients die from EC within the same year (2,3). Survival analysis of EC in Ardabil has revealed that the mean survival rate for patients with EC is only 12.1 months; therefore, Ardabil Province has one of the highest mortality rates for EC in the world (4).

There is a distinct geographical distribution of EC in Asia which is known as a "Central Asian Esophageal Cancer Belt" that extends from north central China to Kazakhstan and northern parts of Iran in the Caspian Sea littoral (5). The earliest reports of high incidence areas of EC in northern parts of Iran have arisen from the first population-based cancer registry established in the mid-1960s and early 1970s as a joint collaboration between Tehran University of Iran and the International Agency of Cancer Research (IARC) (6,7).

### Corresponding author:

Gastrointestinal Cancers Research Center (GICRC) ,  
Ardabil University of Medical Sciences , Ardabil, Iran  
Telefax : + 98 451 2246666

E-mail: yazdan40@yahoo.com

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Initial results from this cancer registry have emphasized the very high incidence of EC in the southeastern areas of the Caspian Sea littoral, which decreased by moving toward southwestern regions located a few hundred kilometers away (6,7).

Ardabil Province is one of the Azeri inhabited provinces located in northwestern Iran, an area 70 km inland from the western Caspian coastline (Fig. 1), with an area of about 17953 km<sup>2</sup> or 1.09% of the total area of Iran. This province consists of 9 urban districts: Meshkinshahr, Parsabad, Germe and Bilesavar in the northern part; Ardabil, Nir and Namin in the central part; and Kousar and Khalkhal in the southern region of the province. There is a common border of 285.5 km with the Republic of Azerbaijan. The capital city of Ardabil is located in the center of the province, where the majority of diagnostic and treatment facilities are located. Sabalan Mountain, a silent volcano located in Meshkinshahr district, is the third highest mountain in Iran with an altitude of 4821 m. According to the 2006 census, the population of Ardabil Province is 1,228,155 (1.9% of the total population of Iran). The population of Ardabil is relatively young, with 76% below the age of 40 years.

A population-based cancer survey conducted between 1996 and 2000 in Ardabil Province showed that EC was the second most frequent cancer in both genders (8). According to Babaei et al., a recently published report from the Ardabil Cancer Registry (ACR) noted a slightly increased incidence of EC over a 4 year time period in Ardabil Province (9).

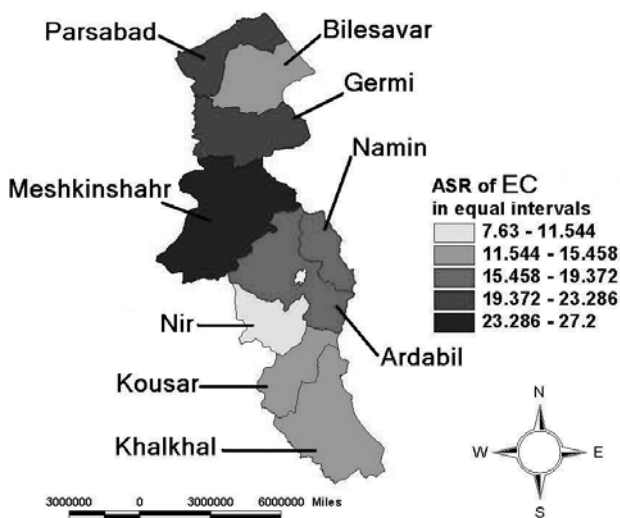


Fig. 1: Districts of Ardabil Province.

This study aims to provide an updated report of ACR. It is the first ongoing population-based cancer registry in Iran that was established in 2003 with collaboration of the International Agency for Research on Cancer (IARC), Digestive Diseases Research Center (DDRC) of Tehran University, and Ardabil University of Medical Sciences (ARUMS). ACR provides data on cancer incidence and stage at time of diagnosis from hospitals, pathology laboratories, radiology centers, ambulatory surgical centers, chemotherapy facilities, the Drug and Alcohol Investigation Unit and physicians' offices.

## MATERIALS AND METHODS

Data from all newly diagnosed EC cases between 2004 and 2006 were actively collected by ACR. Cases reported to ACR were initially checked for duplication, were then defined by codes according to the third edition of the International Classification of Diseases for Oncology (ICD-O III), and were finally entered into a database (10). The collected data included: age, gender and place of residence, method of diagnosis, morphology, and origin of the cancer.

Crude incidence rates and age-standardized incidence rates (ASR) were calculated for both men and women, and for each of the 9 districts of Ardabil Province. The standard rate ratio (SRR) was separately calculated for each district and compared between districts. To avoid the effect of comparing heavily populated districts (e.g., Ardabil district with 40% of the province's total population), with the province rate, the rate for each district was compared with the rate in the remainder of Ardabil Province (e.g., Meshkinshahr with total province minus Meshkinshahr). We have corrected the results for cases with unknown age by multiplying the standardized rate (based on cases with known age) by T/K, where T is the total number of cases of cancer with the same type in cases of the same sex and K is the number occurring in cases with known age (11).

## RESULTS

During the study period, 549 new cases of EC were registered. Diagnosis was based on death certificate only (DCO=12.9%) in 71 cases, clinical examination only (4.3%), clinical/paraclinical investigation (3.3%), and confirmed pathology (79.1%). ASR of EC was 19.5 in men and 19.7 in women per 100,000 person-years (Table 1). The most common morphology

in our cases was squamous cell carcinoma (SCC, 73%). Esophageal adenocarcinoma (ACE) accounted for 17.8% of all cases. In 35.5% of cases the tumor originated in the middle third of the esophagus (Table 2), whereas the lower third constituted 32.4% of cases and was significantly more common in men. The risk of cancer originating in the middle third of the esophagus was higher among women compared to men. The incidence of EC was significantly higher in northern parts of the province. The highest incidence

rate (27.2/100,000) was detected in Meshkinshahr, a district close to the silent volcano of Sabalan. The incidence of EC in southern Ardabil Province, such as Khalkhal and Kosar, was significantly lower than the rest of the province. The lowest incidence rate was observed in Nir district (7.6/100,000). The male to female ratio was around one in northern and above 2.5 in southern districts (Table 3, Fig. 1). Figure 2 shows the age-specific crude rate of EC by sex rising with age with a little notching in the 80-84 age groups in

**Table 1:** Age-standardized incidence rate (ASR) of esophagus cancer in males and females (Ardabil, 2004-6).

Cancer	Total	Crude Rate	ASR (W)	95% CI		Cumulative Risk	
				Lower	Upper	0-64	0-74
Male	290	14.2	19.5	17.0	22.0	0.9	2.3
Female	259	13.6	19.7	17.2	22.2	1.0	2.1
Both sexes	549	13.9	19.7	17.92	21.48	0.99	2.24

**Table 2:** Subtypes of esophageal cancer (Ardabil, 2004-6).

	Female	Male	Total (%)
Upper third of esophagus	16	8	24 (5.0)
Middle third of esophagus	91	79	170 (35.5)
Lower third of esophagus	53	102	155 (32.4)
Overl. lesion of esophagus	4	0	4 (0.8)
Esophagus, NOS	60	65	125 (26.1)
Total	224	254	478 (100)

Overl.=Overlapping  
NOS=Not otherwise specified

**Table 3:** Ranking of Ardabil districts for esophageal cancer, both sexes (Ardabil, 2004-6).

Ranking	District	ASR	SE	SRR	Male/female ratio
1	MeshkinShahr	27.2 <sup>++</sup>	3.9	1.47	1.1
2	Parsabad	22.3 <sup>++</sup>	4.7	1.14	1.19
3	Germi	21.2 <sup>+</sup>	4.5	1.09	0.80
4	Namin	18.1 <sup>NS</sup>	4.9	0.92	1.36
5	Ardabil	16.3 <sup>NS</sup>	1.8	0.82	0.94
6	Kousar	14.6 <sup>-</sup>	7.4	0.74	6.0
7	BileSavar	14.1 <sup>-</sup>	4.9	0.71	0.64
8	Khalkhal	15.2 <sup>-</sup>	3.6	0.69	2.44
9	Nir	7.6 <sup>--</sup>	4.6	0.38	4.0

ASR= Age-standardized rate (direct method)

SE= Standard error

SRR= Standard rate ratio (indirect method)

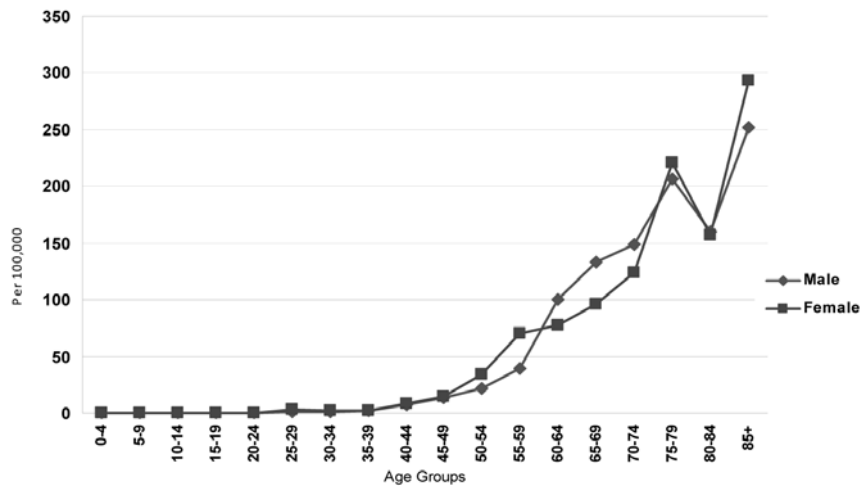
/++= Significantly higher than remainder of Ardabil Province, p<0.01.

/+= Significantly higher than remainder of Ardabil province, p<0.05.

/- = Significantly lower than remainder of Ardabil province, p<0.05.

/-- = Significantly lower than remainder of Ardabil province, p<0.01.

/NS = No significant difference with the remainder of Ardabil Province.



\*\*In this figure, change the following: "Age Groups" to "Age groups".

**Fig. 2:** Age specific crude rate of esophageal cancer in males and females, (Ardabil-2004-6).

both sexes. The explanation for such a notch can be inaccurate recording of age in elderly cases, underascertainment in this age group, or just a random variation.

## DISCUSSION

Despite a declining trend in the incidence of esophageal SCC in most parts of the world, the rate of ACE is rapidly increasing, particularly in Western countries (12-14). As recently as 1975, about 75% of EC cases diagnosed in the United States were SCC and the remaining 25% were adenocarcinomas. During the past 20 years, the incidence of SCC has decreased in the US population, while the rate of adenocarcinoma has increased among white men by 450% and among black men by 50% (15,16). Up to 2005, SCC had been reported as the most prevalent type of EC in developing countries including Iran and China, and accounted for over 90% of cases (16). Recent reports from the Gonbad area in northeast Iran also indicate a high prevalence for esophageal SCC (17). Our study clearly has shown an increasing incidence of ACE in Ardabil. The proportion of ACE has increased from less than 15% ten years ago to more than 27% in this study (16). This is in agreement with recent epidemiologic evidence from Iran showing an increase in adenocarcinoma prevalence (17,18) and is at least partly due to the epidemic of obesity and gastro-esophageal reflux disease in Iran, specifically in Ardabil during the past 30 years (19-22). This increase in ACE rate parallels a high rate of esophageal SCC and contrib-

utes to the increasing rate of EC in Ardabil.

The ASR of EC is 19.5 in men and 19.7 in women per 100,000. This rate is higher than that reported in the first cancer surveillance in Ardabil Province during a period of four years (1996-1999). According to this report, EC ranked second among the five most common cancers in Ardabil with an ASR of 15.4 per 100,000 for men and 14.4 per 100,000 for women (8). The explanation for this increase in the incidence of EC is probably two fold; an increase in the incidence of ACE and misclassification of gastric cardia cancer as EC. A concurrent increase in the rate of ACE and gastric cardia cancer, which has already been reported from Ardabil is in line with this observation (19,23,24). The etiology and risk factors for SCC in northeastern Iran have been extensively studied during the past 10 years (2,6,16). According to the results of these studies the main risk factors are: consumption of hot tea (OR=10), non-hygienic water (OR=8), fried and grilled meat (OR=7.5), family history of EC (OR=2.3), opium consumption (OR=2.2), smoking tobacco (OR= 1.8) (25-27). The main suspected mutagens are N-nitroso compounds and polycyclic aromatic hydrocarbons (28,29).

EC occurs more frequently in men than women with a male to female ratio of 3 throughout different countries. However, the incidence is approximately equal for both genders in high incidence areas with the male to female ratio close to 1 (8). In the current report, in the male to female ratio of EC is almost one Ardabil Province (1.01), which is in agreement with similar reports from

other high incidence areas such as northeast Iran and Linxian China., This finding can provide plausible evidence for the role of different types of environmental risk factors in EC incidence. In addition, the incidence of EC was significantly higher in northern parts of the province. The highest incidence rates were observed in Meshkinshahr, Parsabad and Germe. In these districts the male/female ratio was almost one and similar to those of a high incidence area, while the incidence in the southern parts of the province (Khalkhal and Kossar) was significantly lower, with the male to female ratios greater than 2.5. The ASRs as well as sex distribution were similar to Western countries.

## REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide Version 2.0. Lyon: IARC Press; 2004.
2. Malekzadeh R, Semnani SH, Sajadi AR. Esophageal cancer in Iran. *Govareh* 2008; 13:25-34.
3. Sadjadi A, Nouraie M, Mohagheghi MA, Mousavi-Jarrahi A, Malekzadeh R, Parkin DM. Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev* 2005;6:359-63.
4. Samadi F, Babaei M, Yazdanbod A, Fallah M, Nouraie M, Nasrollahzadeh D, et al. Survival rate of gastric and esophageal cancers in Ardabil province, North-West of Iran. *Arch Iran Med* 2007;10:32-7.
5. Boyle P, Levin B. World cancer report 2008. Lyon: International Agency for Research on Cancer (IARC) press 2008.
6. Kamangar F, Malekzadeh R, Dawsey SM, Saidi F. Esophageal cancer in Northeastern Iran: a review. *Arch Iran Med* 2007;10:70-82.
7. Marjani HA, Biramijamal F, Hossein-Nezhad A, Islami F, Pourshmas A, Semnani S. Prevalence of esophageal cancer risk factors among Turkmen and non-Turkmen ethnic groups in a high incidence area in Iran. *Arch Iran Med* 2010;13:111-5.
8. Sadjadi A, Malekzadeh R, Derakhshan MH, Sepehr A, Nouraie M, Sotoudeh M, et al. Cancer occurrence in Ardabil: results of a population-based cancer registry from Iran. *Int J Cancer* 2003;107:113-8.
9. Babaei M, Jaafarzadeh H, Sadjadi AR, Samadi F, Yazdanbod A, Fallah, et al. Cancer Incidence and Mortality in Ardabil: Report of an Ongoing Population-Based Cancer Registry in Iran, 2004-2006. *Iran J Public Health* 2009;38:35-45.
10. Fritz AG. International classification of diseases for oncology = ICD-O. 3rd ed. Geneva: World Health Organization; 2000.
11. Doll R, Smith PG. Comparison between registries: Age-standardized rates. In: Waterhouse J, Muir C, Shanmugaratnam K, Powell J, editors. Cancer incidence in five continents. Lyon: International Agency for Research on Cancer; 1982. p. 671-4.
12. Semnani S, Sadjadi A, Fahimi S, Nouraie M, Naeimi M, Kabir J, et al. Declining incidence of esophageal cancer in the Turkmen Plain, eastern part of the Caspian Littoral of Iran: a retrospective cancer surveillance. *Cancer Detect Prev* 2006;30:14-9.
13. Thomas RJ, Lade S, Giles GG, Thursfield V. Incidence trends in oesophageal and proximal gastric carcinoma in Victoria. *Aust N Z J Surg* 1996;66:271-5.
14. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049-53.
15. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. *Semin Oncol* 1999;26:2-8.
16. Islami F, Kamangar F, Nasrollahzadeh D, Møller H, Boffetta P, Malekzadeh R. Esophageal cancer in Golestan Province, a high-incidence area in northern Iran - a review. *Eur J Cancer* 2009;45:3156-65.
17. Islami F, Kamangar F, Aghcheli K, Fahimi S, Semnani S, Taghavi N, et al. Epidemiologic features of upper gastrointestinal tract cancers in Northeastern Iran. *Br J Cancer* 2004;90:1402-6.
18. Derakhshan MH, Yazdanbod A, Sadjadi AR, Shokoohi B, McColl KE, Malekzadeh R. High incidence of adenocarcinoma arising from the right side of the gastric cardia in NW Iran. *Gut* 2004;53:1262-6.
19. Derakhshan MH, Malekzadeh R, Watabe H, Yazdanbod A, Fyfe V, Kazemi A, et al. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut* 2008;57:298-305.
20. Malekzadeh R, Mohammadnejad M, Merat S, Pourshams A, Etemadi A. Obesity pandemic: An Iranian perspective. *Arch Iran Med* 2005;8:1-7.
21. Malekzadeh R, Nasseri-Moghaddam S, Sotoudeh M. Gastroesophageal reflux disease: The new epidemic. *Arch Iran*

## CONCLUSION

Our data show that EC is the second most common cancer in Ardabil, with a trend toward an increase in the rate of ACE. Further studies are necessary to determine risk factors of EC in the northwest areas of Ardabil Province, in comparison with northeastern Iran.

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- Med* 2003;6:127-40.
22. Malekzadeh R, Sotoudeh M, Derakhshan MH, Mikaeli J, Yazdanbod A, Merat S, et al. Prevalence of gastric precancerous lesions in Ardabil, a high incidence province for gastric adenocarcinoma in the northwest of Iran. *J Clin Pathol* 2004; 57:37-42.
  23. Yazdanbod A, Arshi S, Derakhshan MH, Sadjadi A, Malekzadeh R. Gastric Cardia Cancer; The Most Common Type of Upper Gastrointestinal Cancer in Ardabil, Iran: An Endoscopy Clinic Experience. *Arch Iran Med* 2001;4:76-9.
  24. Haghdoost AA, Hosseini H, Chamani G, Zarei MR, Rad M, Hashemipour M, et al. Rising incidence of adenocarcinoma of the esophagus in Kerman, Iran. *Arch Iran Med* 2008;11:364-70.
  25. Islami F, Nasrollahzadeh D, Kamangar F. Tea drinking habits and risk of esophageal cancer in northern Iran 2008. *BMJ* 2009;338:b929.
  26. Akbari MR, Malekzadeh R, Nasrollahzadeh D, Amanian D, Sun P, Islami F, et al. Familial risks of esophageal cancer among the Turkmen population of the Caspian Littoral of Iran. *Int J Cancer* 2006;119:1047-51.
  27. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet C, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer* 2008;98:1857-63.
  28. Abedi-Ardekani B, Kamangar F, Hewitt SM, Hainaut P, Sotoudeh M, Abnet CC, et al. Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran. *Gut* 2010;59:1178-83.
  29. Ponder B. Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran. *Arch Iran Med* 2010,13,457-8.