Middle East Special Report
Middle East Journal of Cancer; April 2017; 8(2): 103-108

Geographic, Sex and Age Distribution of Esophageal Cancer Incidence in Iran: A Population-based Study

Salman Khazaei*, Erfan Ayubi,***, Kamyar Mansori****,***** , Behzad Gholamaliee******, Somayeh Khazaei*******, Fatemeh Khosravi Shadmani******** , Mokhtar Soheylizad*********♦, Mohadeseh Sani**********, Shiva Mansouri Hanis*********

*Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
**Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
***Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
****Dezful University of Medical Sciences, Dezful, Iran
*****Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
******Department of Public Health, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
*******Department of Operating Room,School of Paramedicine, Hamadan University of Medical Sciences, Hamadan, Iran
********Modeling in Health Research Center, Institute for Future Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
*********Social Development and Health Promotion Research Center, Gonabad University of Medical Sciences, Gonabad, Iran
**********Department of public health, School of public health, Zabol University of Medical Sciences, Zabol, Iran
**********Social Determinants of Health Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

Abstract

Background: Esophageal cancer is the second most common malignancy in Iranian men and third most common in Iranian women.The aim of this study is to discover the geographic distribution for age-standardized incidence rate of esophageal cancer among both genders in Iran.

Methods: This ecological study used re-analysis medical records aggregated to provinces from the National Cancer Registry and Disease Control and Prevention Report of the Ministry of Health and Medical Education for esophageal cancer in 2008. For each province, we calculated the average annual age-standardized incidence rate.

Results: Squamous cell carcinoma was the most common histological type of esophageal cancer in males (65.4%) and females (75%). The age-standardized incidence rate for esophageal cancer in Western, Northwest, Northern and Northeast provinces of Iran were higher than other provinces. We observed the highest age-standardized incidence rate in both genders in the 80-84 year age group with 147.5 in males and 114.5 in females.

Conclusion: Given that the Western, Northwest, Northern, and Northeast provinces were hot zones for esophageal cancer in Iran, increased access to screening services and implementation of prevention programs should be considered.

Keywords: Esophagus cancer, Sex and age distribution, Incidence, Population-based study, Iran

♦**Corresponding Author:**
Mokhtar Soheylizad, PhD student
Gonabad University of Medical Sciences, Gonabad, Iran
Email: m.soheylizad@yahoo.com

Received: June 26, 2016; Accepted: November 21, 2016

Introduction

Esophageal cancer (EC) is one of the least studied and deadliest cancers worldwide because of its extremely aggressive nature and poor survival rate.[1] Esophageal cancer is the eighth most common cancer and the sixth leading cause of death from cancer worldwide.[2]

It affects more than 450,000 people worldwide and the incidence is rapidly increasing.[3] Etiological studies are required to explain the rapid increase of this lethal cancer.[1] Despite medical advances in recent decades, 5-year survival ranges from 15% to 25%.The best outcomes are associated with disease diagnosed in its early stages.[4] Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are two morphologies known for EC. Risk factors of alcohol, smoking, malnutrition, a history of head and neck cancer, and frequent consumption of beer are the main causes of SCC, while ADC is mostly associated with gastroesophageal reflux, Barrett's esophagus, obesity, age, and male gender. Exposure to X-rays also increases both types of cancer.[5,6] Geographically dispersed distribution is a significant feature of EC.[7] The highest incidence of EC in the world is reported in China, Northeastern Iran, Southeastern United States, and South Africa.[8]

The American Cancer Society (ACS) considered elimination of disparities in the burden of cancer as one of the overarching themes of the challenge goals.[9] Iran has several geographic, climatic, ethnic, racial, and cultural classifications that result in exposure to different risk factors in each part of the country. According to the multifactorial causes for EC, disparity for incidence of EC in different provinces should be reviewed.[10] Understanding the geographical and epidemiological characteristics of EC will be the key to elucidating the causes and risk factors for EC. This is the first essential step to achieve a clear, accurate picture of cancer in Iran and the cornerstone for development of any prevention strategies. Therefore, the present study attempts to discover the geographic distribution for the age-standardized incidence rate (ASR) of EC for both gender in Iran.

Materials and Methods

This ecological study used re-analysis of medical records aggregated to provinces from the National Cancer Registry (NCR) and Disease Control and Prevention Report by the Ministry of Health and Medical Education for EC in 2008. Data regarding EC has been gathered actively by the Iranian Cancer Registry on a pathology basis,

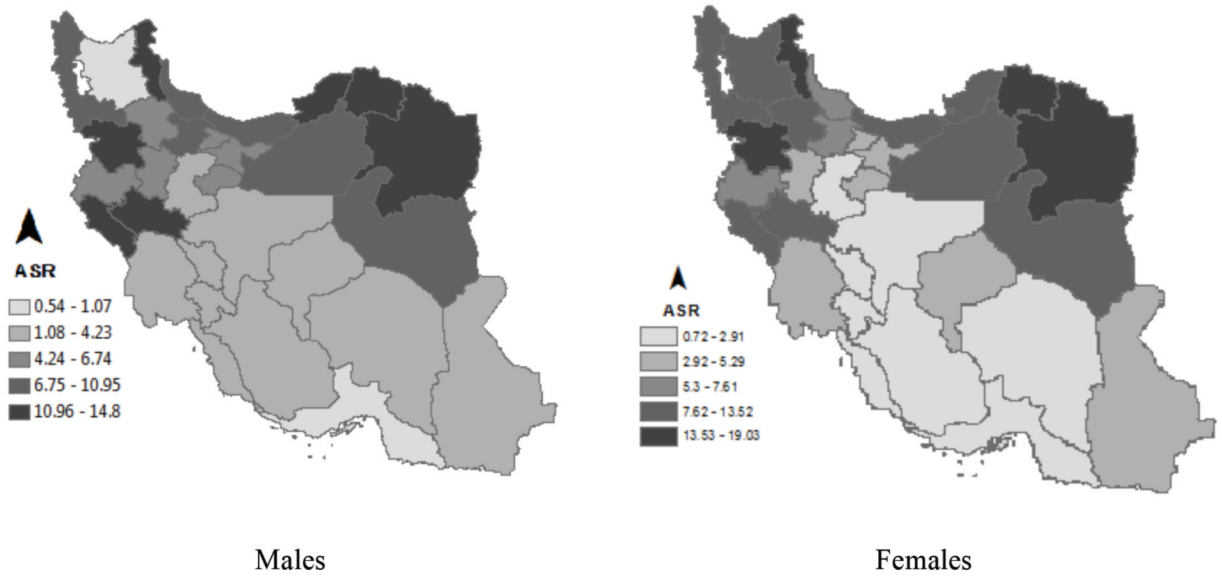

Figure 1. Geographic distribution of EC incidence rate in Iran by gender in 2008.

Table 1. Incidence of different morphologies of esophageal cancer (EC) in Iran according to gender in 2008.

Gender	ADC - NOS	Malignant neoplasm	SCC - NOS	Carcinoma NOS	SCC Keratinizing, NOS	SCC Microinvasive	Total	*P*-value
Male	370 (17.3%)	86 (4.0 %)	1400 (65.4%)	44 (2.05%)	39 (1.82%)	35 (1.6%)	1974	<0.001
Female	138 (7.7%)	75 (4.2%)	1336 (75.0%)	41 (2.3%)	34 (1.9%)	23 (1.3%)	1647	

ADC: Adenocarcinoma; SCC: Squamous cell carcinoma; NOS: not otherwise specified

which covers the entire country's pathology laboratories. However, hospital and death certificate records are not included in these datasheets. Data cleaning at the provincial level is carried out seasonally after deleting for repeated cases transmitted to the Iranian Ministry of Health.

Registered data are classified into three parts: 1) patient's identity characteristics of age, gender, race, and residence; 2) patient's clinical history; and 3) preclinical findings. Data on primary location of tumor, date of cancer diagnosis, morphology, histology, and diagnosis method are also registered.

Statistical analysis

For each province, we have calculated the average annual ASR per 100,000 person-years by the direct method using the World Standard Population. Age standardization is a technique used to allow comparisons between countries when the age profiles of the populations are quite different.

We used the chi-square test to compare EC morphology between males and females. The student's t-test was used to compare ASR between genders in each province. The data were presented using MS Excel 2010, Stata (version 11.2, Stata Corp, College Station, TX) and GIS, version 10.3.Significance level was $P<0.05$.

Results

Overall, 39222 EC cases were registered in 2008. Assessment of geographical distribution of the cases showed the most frequent cases of EC in the West, North, Northwest, and Northeast areas of Iran (Figure1).

According to Table 1, SCC is the most common form of EC in males (65.4%) and females (75.0%), followed by ADC with an incidence of 17.3% in males and 7.7% in females. A significant difference existed between morphology of EC among males and females ($P<0.001$).

Figure 2 shows the age-sex specific incidence of EC. The asymmetric shape of the pyramid indicates a more frequent occurrence of EC after 45-49 years of age, with the highest increase in incidence of 147.5 (men) and 114.5 (women) for the 80-84-year age group.

Table 2 lists the frequency, ASR, crude rate, percent of all cancers attributed to EC, and rank of EC among other cancers. Golestan (14.8) had the highest ASR for EC amongst Iranian men, whereas the lowest was reported in Markazi (2.19). This rate slightly differed in Iranian females. We noted the highest ASR in females from Ardebil (19.3), Kordestan (15.97), and Khorasan Razavi (14.32). The lowest ASR occurred in females from Bushehr (0.72), Chaharmahal and Bakhtiari (1.05), and Isfahan (1.88). In 6 provinces, EC

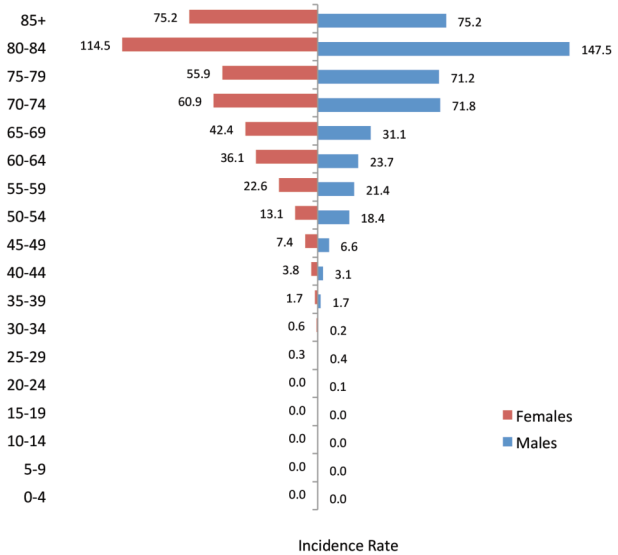

Figure 2. Age-sex pyramid for esophageal cancer (EC) incidence rates per 100,000 person-years in Iran for 2008.

Table 2. Statistics for esophageal cancer (EC) according to gender and province.

Province	Males					Females					
	Fre	CR	ASR	%	Rank	Fre	CR	ASR	%	Rank	*P*-value
East Azarbayejan	181	9.80	12.07	7.09	5	164	9.36	13.52	8.23	3	<0.001
Fars	54	2.46	3.58	2.25	›10	39	1.87	2.91	1.98	›10	<0.001
Khorasan Razavi	312	10.61	13.93	8.92	3	268	9.60	14.32	9.62	3	0.24
Isfahan	69	2.92	3.83	2.61	10	27	1.21	1.88	1.23	›10	<0.001
Gilan	87	7.13	9.31	6.21	5	44	3.80	5.99	4.25	6	<0.001
Kermanshah	48	5.00	6.53	4.69	7	45	4.94	7.61	5.50	5	<0.001
West Azarbaijan	92	6.29	8.20	7.61	4	109	7.86	12.22	14.47	3	<0.001
Semnan	26	8.62	10.53	5.42	7	23	8.03	12.10	6.10	4	<0.001
Kordestan	69	9.33	11.95	6.96	5	79	11.25	15.97	11.02	4	<0.001
Yazd	10	1.97	2.27	1.55	›10	14	2.91	4.83	2.43	›10	<0.001
Chaharmahal and Bakhtiari	15	3.42	4.23	3.81	7	3	0.72	1.05	1.09	›10	<0.001
Hamadan	37	4.25	5.63	3.46	8	22	2.66	4.06	3.29	8	<0.001
Ghazvin	36	6.20	8.06	6.75	6	20	3.63	5.63	4.65	6	<0.001
Zanjan	28	5.71	7.27	6.74	6	34	7.30	10.19	13.71	3	<0.001
Ilam	26	9.32	11.83	12.26	3	18	6.80	10.74	12.24	3	<0.001
Kohkiloyeh and Boyerahamad	6	1.85	2.50	2.33	10	4	1.30	1.92	2.25	9	0.003
Mazandaran	122	8.20	10.93	6.86	5	104	7.37	10.68	6.99	5	0.39
Tehran	283	4.14	5.16	2.70	10	230	3.54	5.29	2.66	›10	0.51
Lorestan	81	9.30	11.83	8.37	4	62	7.50	11.18	8.74	4	0.03
Khozestan	63	2.89	3.59	2.36	›10	51	2.47	3.53	2.12	›10	0.72
Markazi	11	1.58	2.19	1.92	›10	9	1.37	2.05	2.33	›10	0.29
Golestan	92	11.14	14.80	14.84	2	6	7.91	12.19	12.18	2	0.006
Qom	22	4.11	5.02	5.37	6	17	3.35	4.49	5.03	5	0.01
Ardebil	75	11.94	14.60	10.96	2	73	12.24	19.03	16.40	1	<0.001
Kerman	25	1.87	2.58	2.34	›10	22	1.73	2.38	2.59	›10	0.16
North Khorasan	35	8.44	11.42	11.71	3	37	9.40	14.42	14.86	3	<0.001
Bushehr	12	2.61	3.45	4.20	9	2	0.46	0.72	0.73	›10	<0.001
Hormozgan	5	0.72	0.99	1.66	›10	12	1.81	2.22	3.97	6	<0.001
Sistan and Balochestan	25	2.03	2.74	7.31	4	37	3.17	4.45	11.90	2	<0.001
South Khorasan	26	9.08	10.95	13.40	2	19	6.99	11.39	10.22	3	0.15
Total	2140	5.94	7.66	5.06	8	1782	5.22	7.77	5.26	5	0.6

Fr: Frequency, CR: Crude Rate, ASR: Age Standardized Rate

was not included the 10 most common cancers for men. In females, EC was not included among the 10 most common cancers in 9 provinces.

Discussion

Our study showed higher ASR for EC in the Western, Northwest, Northern and Northeast provinces of Iran compared to other Iranian provinces. In general, the high incidence of EC in these provinces could be justified with respect to a presumed belt for upper gastrointestinal tract cancers, including stomach and esophagus, which has originated in the Far East or East Asia (Japan, Korea, and China), and crosses the Central Asian countries (Uzbekistan and Turkmenistan) and the Near East (Iran, Caucasus and the Eastern Anatolia region of Turkey).[11] The difference in incidence rates among various geographical regions has been discussed in several studies.[2,10] Cancer is a heterogeneous mix of diseases. Different types of cancer are more common in some populations than others, sometimes substantially. Cancers have very different causes, some of which are well understood, whereas others are poorly understood. Differences in the regional and temporal distribution of risk factors determine the geographical and secular patterns for cancer.[12] Cigarettes, red meat, alcohol and hookah smoking, nass consumption (a chewing tobacco product), opium consumption, consumption of hot tea, poor oral health, low intake of fresh fruit and vegetables, and low socioeconomic status have been

associated with a higher risk of EC.[1] Iran's population consists of numerous ethnic groups and this diversity may affect the risk factors for EC. Food habits, in particular the consumption of certain foods, as well as behaviors and lifestyle associated with cancer risk factors vary among different cultures and ethnicities. This may affect the incidence of some cancer types, including EC in the geographic location of various ethnicities.

One of the strongest emerging risk factors, however, is obesity. Increases in the prevalence of obesity and incidence of esophageal ADC are parallel. Several epidemiologic studies have shown upwards of a threefold excess risk among overweight individuals.[1] Given the prevalence of obesity in different provinces of Iran as examined in many studies,[13] the geographical pattern for incidence of EC in this study was consistent with the prevalence of obesity. Golestan has the highest incidence of EC. This finding might be attributed to dietary habits such as consumption of hot tea in this province,[14] a particular lifestyle, or the presence of other risk factors in Golestan.

The results suggested that, overall, different forms of EC were higher in males compared to females. The incidence in men was slightly more than women. However, the statistical power of these tests are highly dependent on sample size. Accordingly, a slight difference in EC incidence rates across the compared groups could be statistically significant in a large sample, yet not practically or clinically important.

On the other hand, the incidence of EC increased with age in both sexes and reached a peak between the ages of 80 to 84. The higher incidence of EC among men in many studies has been shown in other parts of the world.[15] Studies reported increased tobacco and alcohol consumption as main risk factors for EC among men compared to women.[16,17] Job requirements for men compared to women might cause exposure to a number of agents associated with EC, such as carbon black, sulfuric acid, asbestos, polycyclic aromatic hydrocarbons, sulfur compounds, and lead.[18] Aging has been shown to increase the risk of cancer because cancers often occur in elderly people due to cumulative effect of exposure in the long term period.[19] With aging, the probability of DNA damage would increase. DNA damage has emerged as a major culprit in cancer and numerous diseases related to aging. The molecular basis of this phenomenon is unclear. However, in cancer, DNA alterations are a major culprit.[20]

Our study had limitations. The results might not be generalized to other countries and other regions of the world because we did not address specific risk factors for EC. Therefore, we recommend additional studies in other geographic regions of the world to determine possible risk factors for certain regions.

This study determined the hot zones of EC in Iran and could be considered a guideline for policy makers to allocate diagnostic and therapeutic interventions. The results have shown that the Western, Northwest, Northern, and Northeast provinces need additional attention. Increased access to screening for early detection is beneficial and cost-effective, particularity in high incidence regions.

Conflict of Interest

No conflict of interest is declared.

Acknowledgement

The Authors would like to thank the National Cancer Department staff in Ministry of Health and Medical Education for providing and administrating data for research in cancer epidemiology in Iran.

References:

1. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol.* 2013;19(34):5598-606.
2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet.* 2013;381(9864):400-12.
3. Hardikar S, Onstad L, Blount PL, Odze RD, Reid BJ, Vaughan TL.The role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: a prospective study of Barrett's esophagus. *PLoS One.* 2013;8(1):e52192.
4. Cheng ML, Zhang L, Borok M, Chokunonga E, Dzamamala C, Korir A, et al. The incidence of

oesophageal cancer in Eastern Africa: identification of a new geographic hot spot? *Cancer Epidemiol.* 2015;39(2):143-9.
5. Wang FR, Fang QQ, Tang WM, Xu XS, Mahapatra T, Mahapatra S, et al. Nested case-control study of occupational radiation exposure and breast and esophagus cancer risk among medical diagnostic w ray workers in Jiangsu of China. *Asian Pac J Cancer Prev.* 2015;16(11):4699-704.
6. Nun-Anan P, Vilaichone RK. Late stage and grave prognosis of esophageal cancer in Thailand. *Asian Pac J Cancer Prev.* 2015;16(5):1747-9.
7. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-86.
8. Chong VH, Telisinghe PU, Chong CF. Esophageal cancer in Brunei Darussalam over a three decade period: an epidemiologic study of trends and differences between genders and racial groups. *Asian Pac J Cancer Prev.* 2015;16(9):4123-6.
9. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin.* 2004;54(2):78-93.
10. Esmaeimzadeh N, Salahi-Moghaddam A, Khoshdel AR. Geographic distribution of important cancers in Iran. *Hormozgan Medical Journal.* 2015;19(2):73-84.
11. Rasool S, A Ganai B, Syed Sameer A, Masood A. Esophageal cancer: associated factors with special reference to the Kashmir Valley. *Tumori.* 2012;98(2):191-203.
12. Vineis P, Wild CP. Global cancer patterns: causes and prevention. *Lancet.* 2014;383(9916):549-57.
13. Kelishadi R, Haghdoost AA, Sadeghirad B, Khajehkazemi R. Trend in the prevalence of obesity and overweight among Iranian children and adolescents: a systematic review and meta-analysis. *Nutrition.* 2014;30(4):393-400.
14. Sadjadi A,Marjani H, Semnani S, Nasseri-Moghaddam S. Esophageal cancer in Iran: A review. *Middle East J Cancer.* 2010;1(1):5-14.
15. Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. *Chin J Cancer.* 2012;31(6):281-6.
16. Moosazadeh M, Ziaaddini H, Mirzazadeh A, Ashrafi-Asgarabad A, Haghdoost AA. Meta-analysis of smoking prevalence in Iran. *Addict Health.* 2013;5(3-4):140-53.
17. Baheiraei A, Hamzehgardeshi Z, Mohammadi MR, Nedjat S, Mohammadi E.Alcohol and drug use prevalence and factors associated with the experience of alcohol use in Iranian adolescents. *Iran Red Crescent Med J.* 2013;15(3):212-7.
18. Charbotel B, Fervers B, Droz JP. Occupational exposures in rare cancers: A critical review of the literature. *Crit Rev Oncol Hematol.* 2014;90(2):99-134.
19. Mallath MK, Taylor DG, Badwe RA, Rath GK, Shanta V, Pramesh CS, et al. The growing burden of cancer in India: epidemiology and social context. *Lancet Oncol.* 2014;15(6):e205-12.
20. Hashimoto S, Anai H, Hanada K. Mechanisms of interstrand DNA crosslink repair and human disorders. *Genes Environ.* 2016;38:9.