

RESEARCH COMMUNICATION

Gastric Cancer in Iran 1966-2006

Seyed Mohsen Mousavi^{1,2,3,4*}, Mohammad Hossein Somi³

Abstract

This review was carried out to provide an up-to-date perspective on gastric cancer clinicoepidemiological characteristics, to explain geographical differences, and to define public health priorities for prevention and early detection programs in Iran. A comprehensive search was conducted using different search engines and over 147 Persian medical journals from 1966 to December 2008. Inclusion criteria were published studies on gastric cancer clinical and epidemiological data. Abstracts only were excluded. Twenty five studies and two national cancer registry reports were also included. The average gastric cancer incidence rates were reported to be 15.2 (8.1 to 49.1) and 6.7(4.9-25.4) per 100,000 in males and females, respectively, with a ratio of 2.3:1 (1.5 to 2.7). More than two thirds of them were diagnosed in stage IV. Crude mortality rates were estimated at 15.5 and 8.4 per 100,000 in males and females. The trend for gastric cancer cases was increase from 1969 to 2004; antral adenocarcinoma was shifted to cardia adenocarcinoma in this period. The gastric cancer epidemiological aspects have changed during 4 decades; a Western pattern has been started in Iran where the incidence rate of adenocarcinoma of the most proximal cardia region and adjacent gastro-oesophageal junction has increased. Developing a gastric cancer early detection program, investigating gastric cancer risk factors, preventing patient and system delays, and providing national guidelines for treatment and palliation are all recommended.

Key Words: Gastric cancer - epidemiology - incidence - mortality - early detection - Iran

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Introduction

Despite gastric cancer decreasing trend in the world, it remains an important public health problem in Iran. Gastric cancer is the most common cancer among males and the third most common cancer among females (Mousavi et al., 2008). It constitutes the leading cause of death due to cancer in both sexes (Naghavi and Gafari, 2007), and its burden was estimated more than 80,000 disability adjusted life years (Naghavi, 2008).

According to the gastric cancer incidence rate in the world (Ferlay et al., 2004), its incidence rate in the north west of Iran (Sadjadi et al., 2003) is similar to eastern Asia, and in the south of Iran (Sadjadi et al., 2007) is the same as south central Asia or north of Africa. The gastric cancer incidence rate in the north was reported five times more than in the South of Iran; geographical difference was related to the difference of prevalence of *Helicobacter pylori* infection in those regions (Malekzadeh et al., 2004).

This review was carried out to provide an up to date perspective of gastric cancer clinicoepidemiological characteristics, to explain the geographical differences, and to define its public health priorities for preventing and early detection program in Iran.

Literature Survey

A comprehensive search was conducted to review published articles from 1966 to December 2008. Since the first report of gastric cancer was published in 1966 (Ratzer, 1966); this year was selected as starting point. Different search engines were used including: PubMed (<http://www.ncbi.nlm.nih.gov/sites/entrez> last accessed: Oct.2008), SID (<http://www.sid.ir/fa/index.asp> last accessed: Oct.2008) and IranMedex (<http://www.iranmedex.ir> last accessed: Oct.2008).

The following terms were used in the PubMed Database search: "Gastric cancer", Gastrointestinal cancer", "Stomach cancer" combined with the word "Iran" in their titles and abstracts. The search was repeated by replacing "cancer" with "malignancy" and "tumor". For SID and IranMedex Databases search, the Persian terms for gastric cancer were used. For the incidence rate data, the authors contacted each registry in Iran for a report.

The efforts to gather all published articles, particularly those published in Persian medical journals showed was the fact that they did not have a citation index, therefore many of them were searched by hand. Over 4000 issues of 147 Persian medical journals were assessed manually

¹Present Address: Department of Molecular Epidemiology, German Cancer Research Center, Heidelberg, Germany, ²Department of Community Medicine, Faculty of Medicine, ³Liver and Gastro Intestinal Diseases Research Center, (LGDR), Tabriz University of Medical Sciences, Tabriz, ⁴Cancer Institute, Cancer Research Center, Tehran University of Medical Sciences, Tehran, Iran For Correspondence: smmousavi@yahoo.com

from Iranian libraries Medical College Library of Tehran University, Iran University Reference Medical Library and Central Library of Tabriz University of Medical Sciences. Several authors were asked to provide us copies of their published manuscripts. In addition, references cited in the identified articles were searched manually. Abstracts were not included in this review. Inclusion criteria were published studies on gastric cancer clinical and epidemiological data.

Using these approaches, reports on gastric cancer clinicoepidemiological aspects were found in 39 full-text articles and one unpublished national database was added to this review (National Cancer Registry, 2008). Four studies were excluded because duplicated publication in Persian (Sharifi et al., 1999; Yazdanbod et al., 2000; Zahedi et al., 2005; Babaei et al., 2006), and 6 studies were excluded because the gastric cancer results were also reported in other publications (Mehrabi et al., 2004; Yazdanbod et al., 2001; 2004; Sadjadi et al., 2005; Esmaeilnasab et al., 2006; Marjani et al., 2007). Two studies were excluded because they were underreporting or lacking basic data (Azarm et al., 1997; Ganji et al., 2006). Finally, three studies were excluded because their full text was not available (Habibi, 1970; Haghghi, 1971; Dutz et al., 1979). Therefore, a total of 25 studies, and two national cancer registry reports (Mousavi et al., 2008; National Cancer Registry, 2008) were used for calculating summary statistics. There was no hypothesis for statistical testing. Range of data and standard sex ratio were used for presenting the findings.

Results

Gastric cancer incidence rates of the 6 studies (Sadjadi

et al., 2003; 2007; Babaei et al., 2005; Mohagheghi and Mosavi-Jarrahi, 2006; Mousavi et al., 2008; Semnani et al., 2008) and one national report (National Cancer Registry, 2008) are presented in Table 1. The gastric cancer incidence rate was reported 15.2 (8.1 to 49.1) and 6.7(4.9-25.4) per 100,000 in males and females respectively, male to female standard ratio was 2.3 (1.5 to 2.7). The gastric cancer constituted 12.7 (7.7-36.6) and 6.2 (5.1-24.5) percent of all cancers in male and female respectively. A study on 10,125 male, 9,105 female immigrants to British Columbia (Canada) reported, the gastric cancer incidence rate was 6.5 per 100,000 in females from 1988 to 2003; the data for male gastric cancer were not presented (Yavari et al., 2006).

Table 2 shows the gastric cancer demographic aspects based on 13 studies in Iran from 1988 to 2005. Fourteen percent of gastric cancer was reported in patients under 40 years old (Davood Abadi et al., 2003), and the minimum age group for stomach cancer was 5-9 years (Sadjadi et al., 2003; Babaei et al., 2005; Mohagheghi and Mosavi-Jarrahi, 2006).

Estimated mortality rate and burden of gastric cancer are shown in Table 3. Crude mortality rate of gastric cancer was estimated 15.5, and 8.4 per 100,000 in male and female respectively (Naghavi, 2006; 2008). More than two third of gastric cancer were diagnosed in the stage IV and less than 10% of cases were reported stage I or II (Hajiani et al., 2006; Sadighi et al., 2005).

Discussion

This report presents gastric cancer epidemiological data for the period 1966 to 2006. A major problem in this review was the fact that there is not a completed citation

Table 1. World population age standard incidence rate of gastric cancer in Iran

Geographical Setting	Pop x10 ⁶	DCA (%)	Sex	Incidence Rate per 100,000 population												Crude Rate	Percentage					
				15-9	20-4	25-9	30-4	35-9	40-4	45-9	50-4	55-9	60-4	65-9	70-4		75-9	80-4	>85	ASR	Total	M:F
National Cancer Registry Program (Mousavi, 2008 - National Cancer Registry, 2008)																						
Iran 03-7	68	NA	F	0.1	0.2	0.6	1.4	2.8	3.0	6.9	12.6	16.2	25.0	36.5	54.1	62.1	88.5	44.4	4.7	6.7	6.2	2.3
			M	0.1	0.2	0.8	1.3	3.6	7.2	12.2	35.5	38.8	56.8	61.1	148.2	142.1	272.1	102.2	11.9	15.2	12.7	
Ardebil 06	1.2	23.9	F	0.0	0.0	2.0	6.7	2.6	2.9	7.9	44.4	53.3	91.4	73.7	169.4	198.0	197.7	0.0	12.2	17.9	17.7	1.9
			M	0.0	1.6	0.0	2.2	5.1	12.0	20.6	17.5	88.7	139	186.0	465.8	437.2	454.9	203.5	28.1	35.1	28.7	
Golestan 06	1.6	12.8	F	0.0	0.0	1.6	0.0	0.0	6.8	9.2	24.1	31.1	25.9	71.6	90.6	224.0	230.7	42.9	8.5	12.1	9.1	2.0
			M	0.9	0.0	2.8	3.5	7.9	19.0	13.4	49.9	69.0	117.0	94.8	195.6	310.0	235.9	158.2	19.3	24.7	16.7	
Isfahan 06	4.0	1.9	F	0.3	0.0	1.7	4.5	1.5	3.3	4.5	13.9	9.5	16.6	42.0	45.2	123.1	239.4	78.6	5.5	7.7	5.6	1.8
			M	0.0	0.9	0.0	2.5	5.8	8.5	7.8	20.0	46.9	28.5	65.8	90.3	150.2	410.4	202.8	10.9	13.9	9.1	
Kerman 06	2.0	0.2	F	1.2	0.8	3.2	3.6	0	7.7	2.1	11.8	14.2	17.7	24.5	16.9	28.7	52.5	0.0	3.7	4.9	5.1	1.7
			M	0.0	0.9	0.0	2.4	1.4	9.5	5.5	21.7	26.9	14.8	27.3	64.3	61.5	161.1	108.1	6.1	8.1	7.7	
Lorestan 06	1.8	37.3	F	0.8	2.2	4.4	1.6	1.9	10.0	11.4	28.7	52.6	65.7	126	152.2	245.8	319.7	0.0	13.3	19.2	16.9	1.5
			M	0.0	0.0	0.0	0	3.7	6.4	27.2	71.2	27.3	87.8	115	294.6	314.2	844.5	292.4	22.2	28.6	21.7	
Provincial Cancer Registry Programs																						
Ardebil 96-9	1.1	3.6	F				1.0			1.7		12.4		41.4				144.1	14.2	25.4	24.5	1.9
(Sadjadi, 2003)			M				1.0			4.1		11.2		57.4				356.0	31.4	49.1	36.6	
Kerman 96-00	2.0	3.2	F				0.0			1.5		5.6		9.1				25.9	3.1	5.1	5.8	2.0
(Sadjadi, 2007)			M				1.0			1.1		4.1		15.1				69.4	6.6	10.2	10.3	
Semnani 97-01	0.3	NA	F				0.0			3.0		0.0		16.3				94.5	10.8	14.8	NA	2.7
(Babaei, 2005)			M				0.5			0.8		6.0		31.2				247.0	28.3	39.6	NA	
Tehran 98-01	7.4	24.0	F	0.1	0.2	0.8	1.6	3.0	5.3	7.8	17.3	21.8	38.5	51.8	85.3			114.8	7.2	10.0	6.6	2.0
(Mohagheghi, 2006)			M	0.2	0.3	0.7	2.1	3.6	7.9	13.7	24.8	35.2	70.2	127.0	168.9			267.7	14.0	19.7	11.5	
Golestan 06	1.6	NA	F				0.0			0.0		7.1	9.1	46.0				94.2	7.5	12.1	7.1	2.6
(Semnani, 2008)			M				0.0			0.5		0.7	6.1	36.3	120.3			249.0	19.7	32	16.4	
East Azerbaijan 3.6	NA		F	0.0	0.0	0.0	1.4	1.6	4.8	13	27.0	29.7	51.2	70.4	94.5	82.7	70.2	120.0	8.5	11.6	8.5	2.2
(Somi, 2008)			M	0.5	0.8	0.5	0.0	1.5	6.5	18.2	25.7	64.1	117.1	161.0	271.2	257.3	317.5	263.1	23.7	25.9	15.6	

Pop, Population; DCA, DeathCertificate only; M:F StandardMale to Female Ratio; NA: Not Available

Table 2. Gastric Cancer Demographic Characteristics in Iran

First author	Geographical location	Year of study	Number (M:F Ratio)	Mean Age (Range)	Most common localization	AC
Babaei Brojeni (1993)	Zanjan	1988-1992	46 (2.1)	57.9 (28-87)	Antrum (56%)	87%
Asadipouya (1997)	Fars	1989-1991	517 (3.1)	53.5 (18-90)	NA	97-98%
Davoodabadi (2003)	Kashan	1994-2001	141 (2.8)	NA (30-82)	Antrum (44%)	97%
Hajiani (2006)	Khuzestan	1996- 2002	127 (2.6)	60.6 (21-91)	Cardia 1999 to 2001 Distal third (88.4%)	94.5%
Molanaei (2000)	Kordestan	1999	54 (NA)	63.5 (23-88)	NA	98%
Hoda (2003)	Guilan	1999-2000	248 (2.7)	61.5 (24-84)	NA	93%
Noorinayer (2005)	Tehran*	1999-2001	943 (2.7)	NA	Distal (39.8%)	NA
Irvani (2006)	Tehran	1999-2005	400 (2.5)	63.5 (NA)	Antrum (43%)	97%
Somi (2006; 2008)	East Azerbaijan	1999-2004	588 (2.5)	65.7 (15-89)	NA	NA
Derakhshan (2004)	Ardebil	2000-2003	282 (NA)	NA (22-90)	Cardia (43%)	99%
Islami (2004)	Golestan	2001	117 (2.9)	NA	Cardia (49.5%)	99%
Mohebbi (2008)	Mazandaran	2001-2005	1663 (2.7)	65.2 (NA)	NA	NA
Hosseini (2007)	Zanjan	2004-2005	63 (3.2)	61.5 (41-81)	Cardia (49.2%)	NA

M:F, Male to Female; AC, Adenocarcinoma; *and 7 provinces

Table 3. Estimated Mortality Rate and Burden of Gastric Cancer in Iran in 2004

Age group	Estimated population of 29 provinces			Mortality Rate (per 1,000,000)			DALY		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0-1	470,162	443,387	913,549	0.28	0.28	0.28	54	51	105
1-4	1,839,396	1,760,835	3,600,231	0.07	0.15	0.11	50	113	163
5-14	6,516,174	6,169,038	12,685,212	0.19	0.14	0.16	565	401	966
15-49	15,598,266	15,072,619	30,670,885	2.31	1.85	2.08	10,930	9145	20,075
50-69	2,606,312	2,578,892	5,185,204	60.83	33.33	47.17	24,117	12,770	36,887
70+	936,651	82,525	1,019,176	253.61	134.58	197.97	16,208	6,453	22,661
Total	27,966,961	26,107,296	54,074,257	15.46	8.41	12.02	51,924	28,403	80,327

DALY, Disability Adjusted Life Years (DALY)

index for published articles in Persian medical journals. Therefore most of the data were unavailable in articles to allow for appropriate documentation; therefore some published articles might be missed for reviewing.

Although it was supposed that gastric cancer incidence rate was high in Iran, this high incidence rate was based on the reports from the regions in north east and north west of Iran (Sadjadi et al., 2003; Islami et al., 2004). According to the published data of Middle East Cancer Consortium (MECC) on cancer incidence in four member countries (Cyprus, Egypt, Israel, and Jordan) over the period 1996-2001; the age standard incidence rate (ASR) for gastric cancer was low among Egyptians (2.9); similar among Cypriots, Israeli Arabs, and Jordanians; and high among Israeli Jews (8.5) (MECC,2005). It was reported 10.4 and 4.8 per 100,000 in male and female respectively by US Surveillance, Epidemiology, and End Results (SEER) in 2005 (Ries et al., 2005; Jemal et al., 2008) and 14 and 5.6 per 100,000 in males and females, respectively by UK data in 2005 (<http://info.cancerresearchuk.org/cancerstats/types/stomach/incidence/> last accessed : Oct.2008). Gastric cancer incidence in Iran was a little higher than MECC and USA, and significant difference was not seen with UK report; but it is significantly lower than the incidence in Japan, Korea and Eastern Asian (40-60 in males and 20-27 in females) (Inoue and Tsugane, 2005).

The gastric cancer incidence rate was reported higher in Ardebil (North West) than the other provinces. It might be due to the differences in the method for cancer

registration, prevalence data from referral endoscopic clinic, facilities for diagnosis, and high probable risk factors. It should be suggested; after establishing the endoscopic clinic at Ardebil by Digestive Disease Research Center (Malekzadeh et al., 2004), more endoscopies were done (Derakhshan et al., 2004). During this intervention, more gastric cancers were diagnosed and all of them were registered by an established population based cancer registry (Sadjadi et al., 2003; Babaei et al., 2006). This data are more supposed to be the prevalence cases than the incidence cases. However, this pattern is more like to the report for esophageal cancer in the North of Iran: esophageal cancer incidence rate was reported 263 and 206 per 100,000 in females and males respectively in Caspian Littoral in 1975 (Horomozdiari et al., 1975), it was reported 19.9 and 22.8 in females and males respectively in 2006 (Semnani et al., 2008); these data show the esophageal cancer incidence rate has decreased more than 10 times during 3 decades without any organized intervention in that region which it seems impossible; the decrease in esophageal cancer cases by 18% to 48% in Shiraz and Tehran from 1972 to 1995 seems more reliable (Yazdizadeh et al., 2005). These documents show the esophageal cancer data for 1975 in the northern regions of Iran that might be prevalence cases. This interpretation might be used for Golestan (north east) data as another high incidence rate for gastric cancer (Islami et al., 2004; Semnani et al., 2008).

The only study about Iranian immigrants has not contained a reliable data for gastric cancer because poor

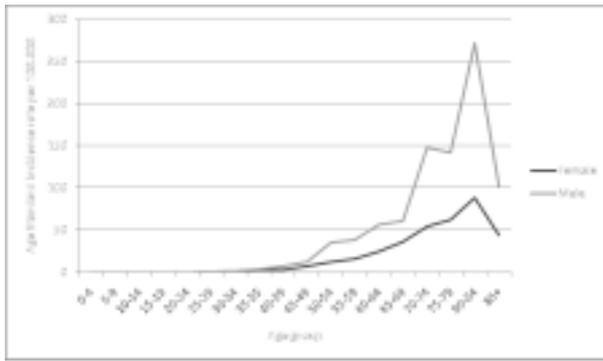


Figure 1. Age-specific Incidence Rate of Gastric Cancer per 100,000 Population in Iran in 2006

methodology (Yavari et al., 2006). More investigations should be carried out to study gastric cancer among Iranian immigrants in multi geographical settings (e.g. USA, Canada, Sweden, etc.) to find the environmental effects on gastric cancer incidence rate (Tsugane et al., 1990; Maruyama et al., 1998; Hemminki et al., 2002; 2003).

Figure 1 shows an overall increasing trend for age peaking at age 80-84 with a declining trend for older men and women in 2006. This pattern was defined for the other cancers in Iran (Mousavi et al., 2008). Case ascertainment methods, data collection and sources of information, and misdiagnosed cases in over 85 years old persons might be part of factors.

A study in Ardabil in 1973 reported 64% of all cancer deaths were due to esophageal and gastric cancers (56% esophagus and 8% stomach) (Mahboubi et al., 1973); this pattern had changed in 2004 where 45.5% of all cancer deaths were reported due to esophageal and gastric cancers (11.7% esophagus and 33.8% stomach) (Naghavi, 2006). According to available data (Yazdizadeh et al., 2005; Abdi-Rad et al., 2006), the trend of gastric cancer cases has increased from 1969 to 2004; it was explained the prevalence of cancers in the upper and middle third of the stomach have increased and that of the lower third has decreased. These changes were seen in both sexes and age groups and it was more significant in younger persons (Abdi-Rad et al., 2006), however in comparison with the report on 1971 (Haghighi, 1971), the percentage of gastric cancer to total cancer has not increased; based on this study, antral adenocarcinoma (distal part) was considered to be the predominant type of gastric cancer in Iran. As Table 2 shows, near to all studies supported this finding, but cardia adenocarcinoma (proximal part) was found to be more common gastric cancer localization by the studies in Kashan, Golestan, and Ardebil (Davood Abdi et al., 2003; Islami et al., 2004; Derakhshan et al., 2004). Zanzan study reported 56% antrum adenocarcinoma from 1988 to 1992 (Babaei, 1993), this was changed to cardia adenocarcinoma up to 49.2% in 2005 (Hosseini et al., 2007). These findings suggest, the western pattern has been started in Iran; where the incidence rate of adenocarcinoma of the most proximal cardia region and adjacent gastro-oesophageal junction has increased over the past 25 years (Powell et al., 1990; Blot et al., 1991; Botterweck et al., 2000); in contrast, adenocarcinoma of the more distal stomach (non-cardia cancer) has been

progressively falling in incidence at least for the last 50 years (Kelley et al., 2003).

Based on a report on Ardebil and Meshkinshahr from 2000 to 2001 which was more like a screening program, the gastric cancer detection rate was 0.3% among people over 40 years old. The stage of gastric cancer was not defined in this study, but the participation rate was very high (more than 90%) (Malekzadeh et al., 2004). However, mortality reduction, cost effectiveness and cost benefits of this method should be assessed by more pilot studies before recommending this method for gastric cancer control program at the national level.

The estimated mortality data for gastric cancer (Naghavi, 2006, Naghavi, 2008) were similar to its incidence data; this is compatible to the reports on gastric cancer survival studies (Sadjadi et al., 2005; Yazdanbod et al., 2005; Zeraati et al., 2005; Moghimi et al., 2007).

Gastric cancer's specific feature in Iran: the patients are diagnosed at advanced stages (III, IV) mostly. The probable causes can be classified into two categories. The first one might be due to Patients' Delay: all factors which caused delaying for caring by the patients. Patients' low socioeconomic level and low awareness to the diseases' symptom and prevention might be the most association factors. The second might be due to System's Delay: all factors which caused delaying for providing diagnostic and treatment facilities by the health system. Mismanagement and ineffective cares by general practitioners or specialists, lack of access to the health care systems, high costs of diagnostic and treatment interventions, and lack of supportive cares might be played as a part of this delay (Hajjani et al., 2006; Hosseini et al., 2007; Khorgami et al., 2007). It is recommended to select the evidence based strategies for preventing these delays for gastric cancer control program. Mass awareness, revising the medical education, providing the basic facilities for diagnosis and treatment might be the essential activities. The results of gastric cancer clinical trial are not interpreted by this review because of little studies (Ghavamzadeh et al., 1993; Sadjadi et al., 2006).

Regarding future activities and perspectives: it can be concluded that gastric cancer prevention should be a governmental priority in Iran. Implementing the Comprehensive National Cancer Control Program (CNCCP) is recommended (Mousavi et al., 2007; 2008) in this field. Research on gastric cancer risk factors and investigation of the causes of geographical differences in incidence rates are high priorities for research centers.

The gastric cancer control program should be integrated in the CNCCP by focusing on prevention, and early detection. Although on currently available evidences, population screening cannot be recommended; gastric cancer early detection should be piloted and its methods for case finding and referring the suspected cases should be clarified. The cost benefit and cost effectiveness of this method should be assessed and reported before implementing this method at the national level.

The local clinical trials should be supported to provide the evidences for the next 5-10 years in the area of gastric cancer treatment and palliative cares, and using experts' consensus for patient treatment at the present time for an

urgent strategy to provide its national guideline protocol. Palliative therapy and supportive cares are neglected issues for the gastric cancer cares in Iran, it is highly recommended to provide its national protocols and to integrate it in the primary health care settings. It is expected the gastric cancer incidence cases will increase at the starting point of the gastric cancer early detection program in Iran, and then it will decrease after these stages. This pattern might be used as an index for assessing and evaluating in future.

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