Original Article

Six-fold Difference in the Stomach Cancer Mortality Rate between Northern and Southern Iran

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Abstract

Background: Stomach cancer is the most common cancer in Iran. A multi-ethnic population and wide variation in the environmental risk factors may lead to variations in cancer risk within this country. We have designed an ecological study and evaluated geographical variation regarding mortality from stomach cancer and its established risk factors in Iran.

Methods: We used the Iranian National Causes of Death Registry and estimated the age-standardized mortality rates (ASMR) of stomach cancer in 29 Iranian provinces, stratified by sex and area of residence (rural/urban).

Results: The average ASMR of stomach cancer among Iranian males was 15 per 100,000 and for females it was 8.1 per 100,000. The highest and lowest mortality rates were observed in Kurdistan with an ASMR of 29.1 per 100,000 in northwestern Iran and Hormozgan that had an ASMR of 5.0 per 100,000 in southern Iran. Males had approximately a two-fold higher ASMR compared to females, as did rural residents when compared with urban residents. The prevalence of *H. pylori* infection was about 90% in the province of Ardabil (a high-risk area) and 27% in the province of Sistan-Baluchistan (a low-risk area).

Conclusions: The wide geographical variation and high mortality rate of stomach cancer in Iran is likely due to differences in the exposure to the environmental risk factors among people living in the high- and low-risk areas, particularly *H. pylori* infection, a well-established risk factor of stomach cancer.

Keywords: Cancer, epidemiology, Iran, mortality, stomach

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Introduction

Stomach cancer is the second highest cause of cancer mortality worldwide.[1] Although the incidence rate of stomach cancer has decreased in the Western world, its incidence and mortality have increased or remained stable in middle and low income countries.[2] Stomach cancer is usually diagnosed in very advanced stages and its prognosis is poor. Efforts to improve the treatment outcome of stomach cancer have been discouraging. Therefore, stomach cancer prevention is prioritized, particularly in high-risk areas.[3]

According to Globocan 2008, stomach cancer is the most common cancer in Iran.[1,4] While high incidence rates of stomach cancer have been reported from different geographic areas in Iran,[5,6] Ardabil Province in northwestern Iran has the highest rates of stomach cancer for both males [age-standardized incidence rate (ASR) = 50 per 100,000] and females (ASR = 24 per 100,000).[7] On the other hand ASRs for stomach cancer are considerably low in Kerman Province, which is located in the central part of the country.[8]

Iran has a multi-ethnic population of over 70,000,000 with a wide variation in climate and environmental factors, such as cold, mountainous weather in the northwest and west, high humidity in the Caspian Littoral area in the north, and dry, hot weather in the deserts located in the central and southern regions of the country.[9] Such a large variation in ethnicity and environmental factors indicate potential differences in the risk profile of the Iranian population with regards to different cancers, including stomach cancer.

Screening and treatment of *H. pylori*, the most important risk factor for stomach cancer, is recommended as the most reasonable risk reduction strategy for its prevention in high-risk populations according to the Asia-Pacific Consensus Guideline in 2008.[3] However, implementation of this recommendation is challenging due to economical and practical reasons. Most people are infected with *H. pylori* in high-risk areas. In Ardabil Province, *H. pylori* infection has been estimated to be approximately 90%.[10] Therefore, epidemiological studies are warranted to define high-risk groups and explore new options for stomach cancer prevention.

Ecological studies and evaluation of the geographic patterns and epidemiology of stomach cancer may help measure the exact burden of stomach cancer in Iran and identify high-risk regions that need efficient interventions. Results from this type of study will lead to appropriate priority setting for research and cancer control programs. In addition, this study aims to evaluate the potential link between patterns of stomach cancer mortality in Iran and geographical distribution of *H. pylori* infection.

Materials and Methods

Due to a lack of validity and completeness of the nationwide cancer registry,[11] we used the nationwide mortality registry to study the geographical pattern of stomach cancer in Iran. We further studied the association of observed variations with the established risk factors.

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National Mortality Registry

After administrative planning, mortality data from different provinces was compiled and analyzed centrally by the Iranian Ministry of Health and Medical Education. The first report on cause-specific mortality rate published in 1998 was based on mortality data from four provinces. Later, the registration activity was extended to other provinces and subsequent reports covered more areas. From 2000–2003 the registry covered 10, 18, 19, and 23 provinces, respectively. In 2004 and 2005 the mortality registry covered almost the entire country and reported the cause-specific crude mortality rates for 29 provinces. To date, Tehran Province (the capital), with a population of 10,000,000 (about 14% of the country), has not been covered in the mortality registry.[12] In order to estimate the total number of deaths nationwide we added 10% of the reports to stratify the rate for both males and females, and for residential areas (rural/urban). The classification of rural and urban areas was based on the official classification and definitions provided by the Ministry of Health. In this study, we used cancer mortality data from the latter period (2004–2005).

Systematic review of the prevalence of *H. pylori* infection

We found no nationwide data that evaluated the pattern of *H. pylori* infection prevalence in Iran. Thus we systematically searched English (PubMed, ISI) and Farsi (SID, Magiran) databases and retrieved all published data regarding the prevalence of *H. pylori* infection in different parts of Iran. We only included papers that reported the prevalence of *H. pylori* infection among healthy individuals over the age of 40 years. Excluded from the analyses were studies that evaluated the prevalence among the younger age groups and children. In addition, studies that evaluated *H. pylori* infection among any disease population were excluded. If a study evaluated *H. pylori* infection among different age groups, we estimated the prevalence among the older age group based on data presented in the papers. Since we located only a few papers that met our inclusion criteria, we could only qualitatively evaluate the potential role of *H. pylori* infection in the pattern of stomach cancer with regards to age-standardized mortality rates (ASMRs).

Statistical analyses

We divided the number of stomach cancer mortalities by the total population of each province and estimated the crude mortality rates for stomach cancer. We estimated ASMRs for stomach cancer in 29 Iranian provinces using the age distribution of the standard world population.[13] We performed stratified analyses by sex and residence to determine the mortality rates for males and females and rural/urban residents. In addition we studied the frequency of stomach cancer mortality relative to the total cancer mortality in each region. The ASMRs were categorized into four strata (< 10, 10–14, 15–20, 20–24, and > 25 per 100,000) and the estimates were placed on a map of Iran using ArcGIS software (version 9.2) in order to provide a graphical representation of the mortality rate. We used STATA statistical software for analyses.

Results

In overall 12,804 stomach cancer death occurred in two years (2004–2005) in Iran, 8579 were males and 4225 were females (Table 1). This data indicate that annually about 4000 and 2000 death due to stomach cancer occur among Iranian males and females, respectively. Figure 1 presents the pattern of ASMRs for stomach cancer among males in 29 Iranian provinces. The northern part of the country, particularly the northwestern region, showed a considerably higher mortality rate for stomach cancer than provinces located in the southern and central regions of Iran.

Among males, the ASMR for stomach cancer was 15 per 100,000. Stomach cancer comprised 23.6% of the total cancer deaths (Table 1). The highest ASMR was observed in Kurdistan (29.1), followed by East (27.6) and West Azerbaijan (26.1) Provinces. In contrast, ASMRs for stomach cancer were considerably low in the southern parts of the country, including Hormozgan (5.0), Sistan-Baluchistan (5.3), and Bushehr (5.5) Provinces. The mortality rate was also relatively low in the central part of the country, including Yazd (7.1), Kerman (7.1), Khuzestan (8.2), Isfahan (8.4), and Fars (8.8) Provinces.

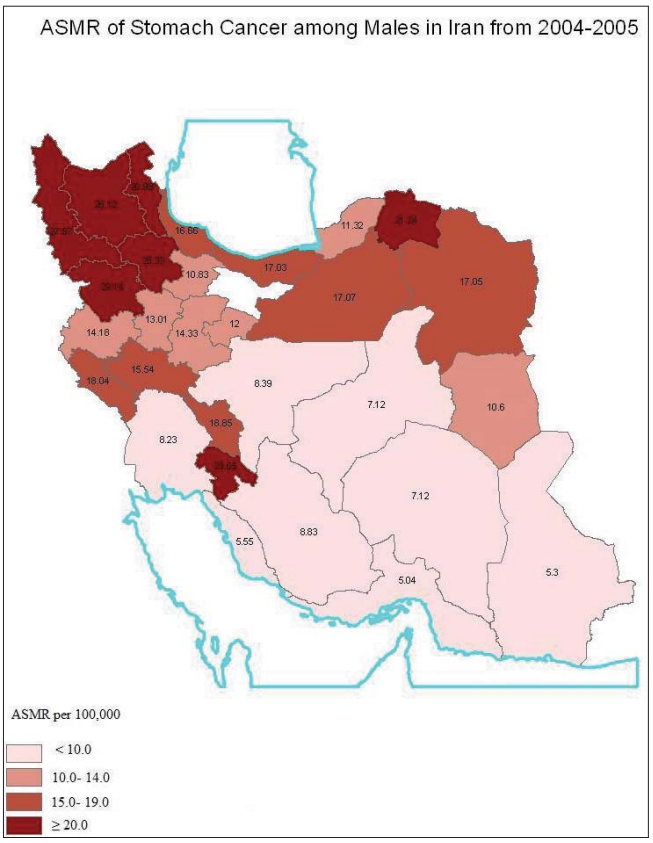

Figure 1. Geographical pattern of age-standardized mortality rate (ASMR) per 100,000 for stomach cancer among Iranian males. Note: There were no mortality data in the national mortality registry for the capital province (Tehran), located in the central part of the country.

A decreasing gradient from the north to the south was also observed among females. The highest ASMRs were recorded in Kurdistan (18.0), Ilam (15.9), West Azerbaijan (14.6), and East Azerbaijan (13.6), whereas provinces located in the southern and central part of the country such as Hormozgan, Sistan-Baluchistan, Southern Khorasan, Isfahan, Bushehr, Kerman, and Yazd had lower ASMRs for stomach cancer among females (Table 1). The ASMR for stomach cancer among females (8.1 per 100,000) was about half of the rate noted for males (15.0 per 100,000; Figure 2).

Stratified analysis according to residence showed that the ASMR in rural areas (21.5) was two-fold the rate in urban areas (10.6; Figure 3). The mortality rate among males who resided in rural

Table 1. Age-standardized mortality rate (ASMR) of stomach cancer among males in urban and rural areas of 29 provinces in Iran from.

Province	Males			Females		
	No. of cases* (2004–2005)	Percentage of all cancer deaths	ASMR	No. of cases* (2004–2005)	Percentage of all cancer deaths	ASMR
Kurdistan	366	33.8	29.1	194	31.5	18.0
West Azarbaijan	611	28.8	27.6	320	26.9	14.6
East Azarbaijan	915	26.2	26.1	447	20.3	13.6
Zanjan	214	30.8	25.3	94	25.0	10.8
Kohgilouyeh B	96	45.3	23.7	32	37.7	8.5
North Khorasan	139	27.4	21.2	73	24.4	12.1
Ardabil	225	33.3	21.0	114	32.6	11.7
Charmahal	132	31.7	18.9	67	30.9	10.8
Ilam	79	24.0	18.0	55	29.6	15.8
Semnan	100	21.8	17.1	42	15.6	7.3
Khorasan Razavi	792	27.6	17.1	378	21.2	8.8
Mazandaran	483	27.3	17.0	214	21.2	7.9
Gilan	443	26.6	16.7	191	21.2	7.3
Lorestan	229	27.1	15.5	136	26.8	11.4
Markazi	207	22.1	14.3	108	18.8	7.5
Kermanshah	242	20.0	14.2	119	17.7	7.8
Hamadan	225	27.0	13.0	109	22.0	7.1
Ghom	96	17.7	12.0	53	14.7	7.1
Golestan	130	19.9	11.3	58	14.3	5.5
Qazvin	104	18.9	10.8	77	20.3	8.6
South Khorasan	61	22.3	10.6	23	12.9	3.6
Fars	329	19.0	8.8	185	17.0	5.4
Isfahan	380	15.9	8.4	191	11.8	4.3
Khuzestan	234	16.0	8.2	130	14.2	5.0
Kerman	149	14.4	7.1	97	14.5	4.7
Yazd	67	11.5	7.1	38	8.8	4.7
Boushehr	38	10.7	5.6	27	9.1	4.6
Sistan	74	23.6	5.3	38	19.4	3.3
Hormozgan	47	19.1	5.0	24	14.5	2.3
Overall**	7207	23.6	15.0	3634	22.1	8.1
Tehran (estimated)	1372	—	15.0	591	—	8.1
Overall (Iran)	8579	23.6	15.0	4225	22.1	8.1

ASMR =Age Standardized Mortality Rate; *Number of cases for two years, 2004 and 2005; **No. of stomach cancer deaths for Tehran Province was estimated as an average of the mortality rate based on the other 29 provinces in the 14% of the population living in Tehran.

areas of Kurdistan was 45 per 100,000, while the overall ASMR among urban residents was 20.4 per 100,000. However, ASMRs among rural and urban residents in Sistan and Baluchistan, Kerman, Yazd, Khuzestan, and Ghom Provinces were almost equal.

H. pylori infection

We found only eight published reports on the prevalence of *H. pylori* infection among healthy Iranians over 40 years of age (Table 2). The highest prevalence was observed in the high-risk Ardabil Province located in the northwestern region (89.2%)[10] and the lowest prevalence was observed in the low-risk Sistan-Baluchistan Province in southeastern Iran (27%).[14] However, the prevalence was high in both Qazvin (87.5%) and Kerman (62%–85%) Provinces, which have been determined to be medium (ASMR: 10.8/100,000; Qazvin) and low-risk (ASMR: 7/100,000; Kerman) regions for stomach cancer.[15,16]

Discussion

We found extremely high mortality rates for stomach cancer in Iran, particularly among males who resided in the northwestern part of the country. There was a clear north to south gradient in the mortality rate of stomach cancer that ranged from 29.1/100,000 in Kurdistan Province in northwestern Iran to 5/100,000 in Hormozgan Province in the southern part of Iran. A similar pattern was observed for females.

Despite several strengths of our findings, this study was hampered by a few limitations. First, the mortality registry is still new in Iran and the validity and completeness of the data for cancer diagnosis has not yet been evaluated. Stomach cancer in its advanced stages with distant metastases to other organs (including the liver, lymph nodes, lungs, and bones) might be misdiagnosed and the type of cancer may be recorded as "unknown" on the

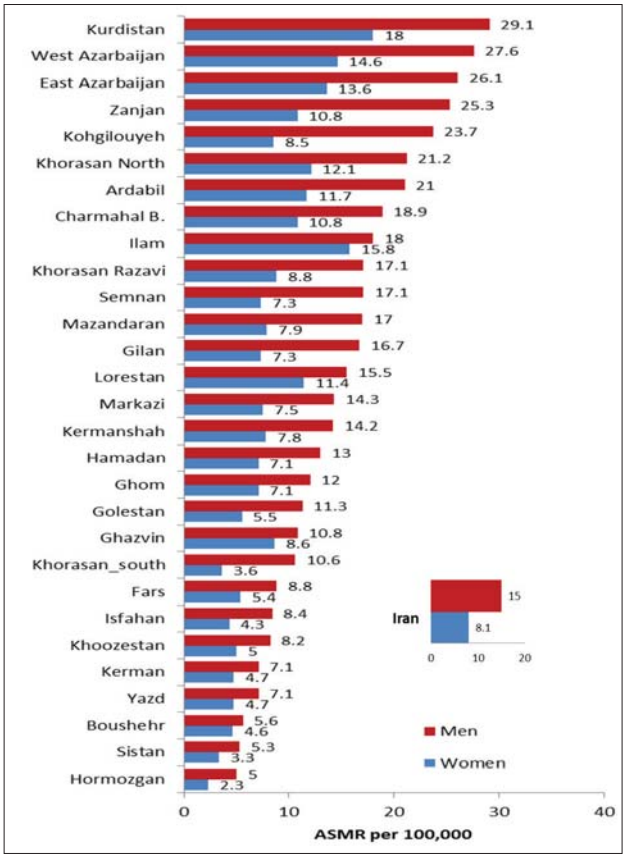

Figure 2. Age-standardized mortality rates (ASMR) of stomach cancer in 29 provinces among Iranian males and females.

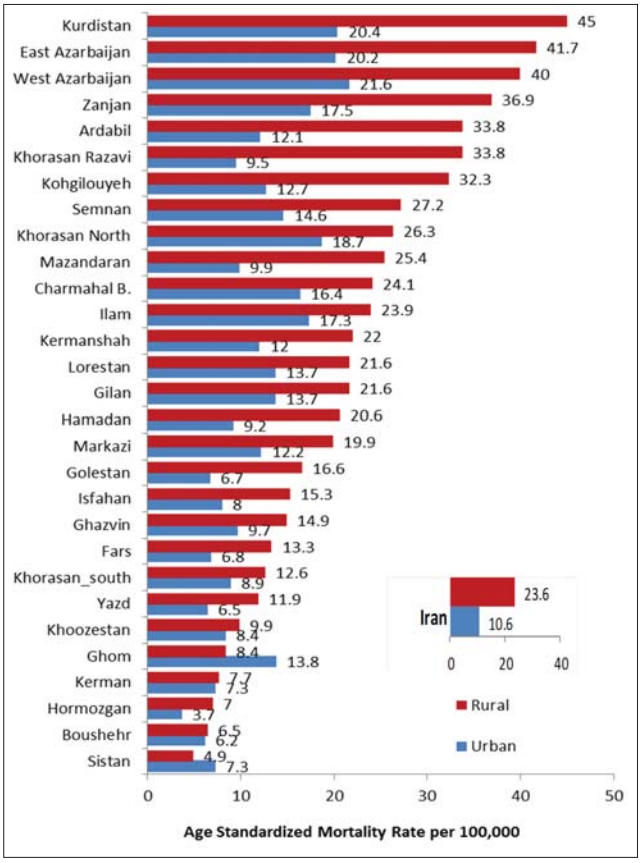

Figure 3. Age-standardized mortality rates (ASMR) of stomach cancer in 29 provinces among Iranian males stratified by residential place (rural/urban areas).

Table 2. Prevalence of *H. pylori* infection among Iranian general population over the age of 40 years who reside in various provinces of Iran.

Author, year	Area	Province	Risk of stomach cancer	Age (years)	Sample size	Prevalence (%)
Malekzadeh R, 2004[10]	Northwestern	Ardabil	High	> 40	1101	89
Sheikholeslami H., 2004*[25]	Northwestern	Ghazvin	High	> 40	120	88
Babamahmoudi F, 2001*[26]	North	Mazandaran	High	> 40	N/A	75
Ghadimia R, 2004[27]	North	Babol	High	Mean≈50	130	80
Alizadeh A, 2009[28]	West	Hamadan	High	> 40	570	82
Jafarzadeh A, 2006*[16]	Central	Kerman	Low	41–60	60	85
Zahedi MJ, 2002*[15]	Central	Kerman	Low	> 35	113	62
Metanat M, 2010[14]	Southeast	Sistan-Baluchistan	Low	> 30	85	27

*These papers were in Farsi and published in local journals.

death certificate, leading to an underestimation of the mortality rate. On the other hand, clinically diagnosed cancers arising from other intra-abdominal organs such as colorectal, hepatic, small intestine, and the pancreas might be registered as stomach cancer on the death certificates, which would inflate the mortality rate. Although misclassification of cancer types may exist, the mortality registry has been established based on a systematic approach and gradually extended from 5 to 29 provinces.[12] We have used the latest mortality registry data from 2004 and 2005 when the registry covered most of the provinces in Iran and reached relatively optimal accuracy and completeness. In addition, cancer is a chronic disease and misclassification in the death registry is less likely compared to other causes of death.[17] Finally, because of the central administration of the mortality registry, over- or underestimations of cancer mortality in different geographical regions should be non-differential. Although nationwide population-based cancer registration does not exist in Iran, available reports from population-based cancer registries have supported our findings.

The ASR of stomach cancer was elevated in Ardabil Province (ASR: 51.8/100,000),[7,18] however, it was relatively low in Kerman Province (ASR: 10.2/100,000).[8] Therefore, notwithstanding some reservations, we have concluded that the observed pattern and variations in the mortality rates of stomach cancer are reliable for policy making and priority setting.

A nearly six-fold excess mortality rate of stomach cancer in the northern part of Iran warrants a causal explanation. *H. pylori* infection is the strongest established risk factor for stomach cancer.[19,20] A pooled analysis of data from 12 nested case-control studies has shown a six-fold excess risk of stomach cancer due to *H. pylori* infection after ten years of follow-up.[19] We may link

the geographical variation in the risk of stomach cancer in Iran to the variation in the prevalence of *H. pylori* infection. Although few studies have evaluated the prevalence of *H. pylori* infection in the healthy Iranian adult population, available data support our expectations. A population-based survey in Ardabil Province has shown that 90% of the people who reside in this high-risk region are infected with *H. pylori*. The same study has shown that in this area 40% of the inhabitants live with atrophic gastritis, a strong predictive intermediate risk factor for stomach cancer which is associated with *H. pylori* infection.[10] We have also found a significantly lower prevalence of *H. pylori* infection in Sistan-Baluchistan Province (27%), which is a very low-risk area for stomach cancer in southeastern Iran.[14] However, in the low-risk Kerman Province the prevalence of *H. pylori* infection is relatively high at 60%–80%.[15,16] Further epidemiological data on the prevalence of *H. pylori* from different parts of Iran may uncover the role of this infection in the observed geographical patterns of stomach cancer in Iran. *H. pylori* strains that contain the Cag-A gene are known to cause more extensive inflammation in stomach mucosa and antibodies against Cag-A persist long after eradication.[20,21] Due to a variation in the ethnic groups that reside in high- and low-risk areas, studies on the association of host genetic factors and susceptibility genes to high-risk infection may be of assistance.

A north to south decreasing gradient in the incidence rate of stomach cancer has been previously reported in Europe and Asia.[22] The difference in Europe is 1.5-fold, where Europe is a known low-risk area for stomach cancer. However, in Japan and China, which are both high-risk countries for stomach cancer, a different geographical pattern has been reported. While a modest geographical variation in the incidence rate of stomach cancer was reported in Japan, an up to seven-fold difference in the incidence rate of stomach cancer was reported in China, which ranged from 145 per 100,000 in Changel Province to about 20 per 100,000 in Beijing.[21] Most of the high incidence areas were located in the mid-western parts of China, which included Gansu, Henan, Hebei, Shanxi, and Shaanxi Provinces. Although factors associated with socioeconomic status might account for a part of this geographical pattern, the reasons behind such a large regional variation within a country have not been explained. In Iran, socioeconomic status in the high and low incidence areas is similar. However, the high-risk areas in the northern part are mountainous with a cold and humid climate, while the low-risk areas in the central and southern part of the country have a dry and warm climate which results in a large variation in life style, nutrition habits, and food preservation methods, among others. In addition, people from different ethnicities in the high- and low-risk areas have differing genetic factors which may also play an important role in the epidemiology of stomach cancer in Iran.

Other established risk factors for gastric cancer include tobacco smoking, low consumption of fruits and vegetables, lack of a refrigerator at home, low socioeconomic status, male sex, high salt consumption, nutritional exposures, a positive family history of cancer, ethnicity, and genetic factors.[22] Tobacco smoking has been shown to increase the risk for stomach cancer. In a meta-analysis, this risk of stomach cancer among smokers compared to non-smokers increased by 1.5 to 2.5-fold, with a somewhat higher estimate in males than females.[23] Few case-control studies have shown a weak association between smoking and stomach cancer in Iran.[24] In addition to cigarette smoking, hookah smoking is practiced among Iranian men and women. Further epidemiological studies are required to see if the observed pattern could be associated with tobacco use in Iran.

Recent Asia-Pacific consensus guidelines recommend that screening and eradication of *H. pylori* infection (screen and treat strategy) is the most reasonable risk reduction strategy for gastric cancer prevention in high-risk populations.[3] In a cross-sectional endoscopic survey, an evaluation of *H. pylori* by histology and rapid urease test has shown that about 90% of people who resided in Ardabil Province were *H. pylori* infected.[10] Based on the Asia-Pacific guideline, most Iranian males who reside in high-risk provinces should undergo eradication of *H. pylori* infection. Although the cost effectiveness and feasibility of the recommended strategy should be studied in Iran, it would be more reasonable to target more high-risk groups and select a limited population for screening in these areas. There are proposals to measure levels of serum pepsinogen I (PGI) and pepsinogen II (PGII) and use the low serum PGI and PGI/PGII ratio as a marker to detect high-risk groups of people with atrophic gastritis for further investigation and active surveillance.[24] Population-based case-control and cohort studies in high-risk areas may also uncover etiologic factors for stomach cancer in Iran and assist with designing an appropriate prevention program.

In conclusion, the large geographical variation and high mortality rate of stomach cancer in Iran could be linked to *H. pylori* infection, smoking, living in a rural area, and a history of lack of refrigerator use. However, well-designed, large scale case-control and cohort studies, particularly in high-risk areas, are warranted to make a firm inference about the role of these factors on the etiology of stomach cancer. Until achieving an appropriate and cost-effective prevention program, we suggest primary prevention programs in the high incidence areas, including public awareness about stomach cancer risk factors. Decreasing salt intake, using fridge to keep the food, decreasing tobacco consumption, increasing consumption of fresh fruits and vegetables and etc. may decrease risk of stomach cancer. In addition, people and health care system should follow-up the gastric sign and symptoms suggesting *H. pylori* infection, peptic ulcer, and cancer. We further suggest conducting etiologic research in such a setting. The large geographical variation in the incidence of stomach cancer in I.R. of Iran and the differences in the life style and ethnicity of people who live in the high- and low-risk areas creates a unique opportunity for epidemiological and clinical research. Results of these types of research may shed additional light on etiology and prevention strategies for stomach cancer in the I.R. of Iran.

All authors declare no conflict of interest.

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