RESEARCH COMMUNICATION

Endoscopic Findings in a Mass Screening Program for Gastric Cancer in a High Risk Region - Guilan Province of Iran

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Abstract

Background & Objectives: Gastric cancer is a leading cause of cancer-related deaths in both sexes in Iran. This study was designed to assess upper GI endoscopic findings among people > 50 years targeted in a mass screening program in a hot-point region. Methods: Based on the pilot results in Guilan Cancer Registry study (GCRS), one of the high point regions for GC –Lashtenesha- was selected. The target population was called mainly using two methods: in rural regions, by house-house direct referral and in urban areas using public media. Upper GI endoscopy was performed by trained endoscopists. All participants underwent biopsies for rapid urea test (RUT) from the antrum and also further biopsies from five defined points of stomach for detection of precancerous lesions. In cases of visible gross lesions, more diagnostic biopsies were taken and submitted for histopathologic evaluation. Results: Of 1,394 initial participants, finally 1,382 persons (702 women, 680 men) with a mean age of 61.7±9.0 years (range: 50-87 years) underwent upper GI endoscopy. *H. pylori* infection based on the RUT was positive in 66.6%. Gastric adenocarcinoma and squamous cell carcinoma of esophagus were detected in seven (0.5%) and one (0.07%) persons, respectively. A remarkable proportion of studied participants were found to have esophageal hiatal hernia (38.4%). Asymptomatic gastric masses found in 1.1% (15) of cases which were mostly located in antrum (33.3%), cardia (20.0%) and prepyloric area (20.0%). Gastric and duodenal ulcers were found in 5.9% (82) and 6.9% (96) of the screened population. Conclusion: Upper endoscopy screening is an effective technique for early detection of GC especially in high risk populations. Further studies are required to evaluate cost effectiveness, cost benefit and mortality and morbidity of this method among high and moderate risk population before recommending this method for the GC surveillance program at the national level.

Keywords: Endoscopy - screening - gastric cancer - Guilan - Iran

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Introduction

Despite the remarkable decline in the worldwide incidence of gastric cancer (GC) and associated mortality rate, GC is still accounted as the fourth common cancer and the second leading cause of cancer-related death with 700,000 deaths annually (Parkin et al., 2005). In Iran, GC is the most common cancer among males and the third one among females (Mousavi et al., 2008a; Kolahdoozan et al., 2010). It accounts as the leading cause of cancer-related deaths in both sexes with an estimated burden than 80,000 disability adjusted life years (Naghavi et al., 2006; 2007)

Geographic distribution of GC shows a wide variability in incidence rate from north to south of Iran. Its incidence rate in north regions is relatively five-fold more than south regions (Malekzadeh et al., 2004). GC is more prevalent in North and Northwest of the country and its incidence rate in the northwest is more similar to eastern Asia which considered as hot point regions of GC (Sadjadi et al., 2003; Ferlay et al., 2004).

The majority cases of GC are being diagnosed in advanced stages, since it is usually asymptomatic in early stages and when symptoms appear it is in late stages leading to poor prognosis (Khedmat et al., 2011). The five year survival of early GC which is limited to mucosa and sub-mucosa is estimated 85-90%, while it decreases as less as 14% in advanced stages (Nakamura et al., 1992; Khedmat et al., 2011). The beneficial effectiveness of screening programs has been confirmed in its endemic regions. A significant reduction in mortality rate of GC has been reported in Japan with photofluorography screening (Miyamoto et al., 2007; Lee et al., 2006). Endoscopy has replaced photofluorography as the initial mass screening technique due to its high detection rate (Tusbono et al., 2000). Detection rates with endoscopy is 2.7 to 4.6 times higher than direct or indirect X-ray (Choi et al., 2009).

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Prevention unpublished works regarding cancer-related death in Guilan during 1999-2002 in the Gastrointestinal and Liver Diseases Research Center (GLDRC) confirmed gastrointestinal (GI) cancers as the leading cause of cancer-related death which led to 31.4% of all cancer deaths over the province; GC was alone responsible for 22.9% of these cancer-related deaths in Guilan province. These emerged the necessary of surveillance programs for GC especially among high risk population. This study is a part of a large-scaled study in hot point regions for GC designed to assess epidemiological aspect, prevalence of precancerous lesions and early gastric cancer among people > 50 years, prognostic value of screening biomarkers like pepsinogen I and II and the predictive factors for their serum levels. Here, we focused on upper GI endoscopic findings in the target population performed as a mass screening program. The histopathologic findings of this screening program for precancerous lesions are still under evaluation and will be reported in the future.

Materials and Methods

The pilot outcomes of Guilan Cancer Registry Study (GCRS) by management of GLDRC in Guilan University of Medical Sciences (GUMS) confirmed gastrointestinal cancers as the most common neoplasm in Guilan province (37%) and defined hot point regions for this cancer. The GCRS is a population-based cancer registry study which covers a population about 2.5 million and with a sample-size about 20,000 cases of various types of cancers. This study assesses the epidemiological aspects of all types of cancers with a specific focus on gastrointestinal tracts over a period of about 10 years in Guilan province -north of Iran. This study is designed and conducted as a mass screening program for GC between may 2010 to march 2011 in GLDRC to assess epidemiological aspect, prevalence of precancerous lesions and early gastric cancer among people ≥ 50 years in a hot point regions for GC Lashtenesha. The study protocol was first approved by ethics committee of GLDRC.

One of the defined hot point regions for GC was Lashtenesha district which is located in the northeast of Rasht, the capital of Guilan Province. Information regarding population distribution of this region, and target population (> 50 years) was collected through health-treatment centers. Lashtenesha has a population over 45000 persons (49.6% males, 50.4% females), among them 10500 persons have > 50 years old. Most of the people settled in rural regions (70.0%).

Two months prior the screening program, the target population was called mainly through two methods based on their locations. In rural regions, all people ≥ 50 years were defined with house-house direct refer by environmental health experts and Behvarzes (Auxiliary health personnel in health house network locally called the Behvarz) and with a close cooperation of health centers, sheriffdom and local governors. The study goals and its methods were explained in detail for each target individual and a specific code was given to him/her to refer in a defined day to a specific health center for further evaluation. In urban area, public media like local radio and TV and also placards were applied for announcement. In defined days, totally 1394 people referred for further evaluation. A detailed questionnaire was filled by three trained general practitioner including demographic characteristics, history of smoking, drug history and family history of GI cancers in the first-degree relatives. All participants underwent history taking and physical examination. The study goals and endoscopy procedure were again explained for each individual, a specific code was given to each participant and a time was set for endoscopy. An informed consent was obtained from each participant prior their enrollment.

Patients with gastric cancer or those with previous gastric surgery were taken apart. Participants who were consuming proton pomp inhibitors (PPIs) were ask to discontinue their drugs two weeks prior endoscopy. Patients who were under any antibiotics therapy were advised to complete their treatment and two weeks after finishing refer for endoscopy procedure. Those who were not able to discontinue their medications were excluded. All above works were performed as a prompt task. It took about 7 months to find target population, to apply inclusion and exclusion criteria, initial physical examination and setting appointment for endoscopy. All endoscopic procedures were scheduled to be performed in a one-month period in March 2011. Required equipments for upper GI endoscopy were established in the most accessible health center for participants. First, participants' history and physical examination were rechecked by a gastroenterologist to ensure fitting inclusion and exclusion criteria. Blood sampling was drawn to define hemoglobin (Hb), hematocrit (HCT), blood group (BG) and also for pepsinogen I and II and gastrin 17 levels.

Subsequent two local anesthesia using Lidocain 10% (with 10 min interval) upper GI endoscopy (videoendoscope, GIF-Q240Z; Olympus Co., Tokyo, Japan) was performed by six experienced endoscopists and cooperation of a trained staff. The endoscopy results were recorded in a prepared form for esophagus, stomach and duodenum. All participants underwent 6 biopsies: one specimens regarding rapid urease test (RUT) were taken from antrum and its result defined 30 minutes later, and also 5 further biopsies were performed from five defined points: a) Antrum, lesser curve, b) Antrum, greater curve, c) Angularis, d) Cardia and e) Body, greater curve for histologic evaluation and detection of precancerous lesion.

Table 1. Participants` Demographic and Clinical Data (n=1382)

Variable		Frequency
Male gender		49.2
Mean age (year)		61.7±9.0
Age group:	50-59	748 (54.1)
	60-69	333 (24.1)
	70-79	245 (17.7)
	≥ 80	56 (4.1)
Married		1361 (98.5)
Smoking		154 (11.1)
Family history of cancer		170 (12.3)
Drug history:	Aspirin	168 (12.2)
	Warfarin	6 (0.43)

Table 2. The Histopathologic Results of Suspicious Lesions in Endoscopic Survey

Endoscopy findings	Histopathology	Frequency (%)
Gastric mass (n=15)		
	Adenocarcinoma	2 (5. 6)
	Gastritis with severe dysplasia	1 (2. 8)
	Gastric + mild to mod dysplasia	1 (2. 8)
	Gastritis with metaplasia	5 (13.8)
	Hyper plastic polyp	3 (8.3)
	fundic polyp	1 (2. 8)
	Eosinophilic gastropathy	1 (2. 8)
	Hamartomatous polyp	1 (2. 8)
Gastric ulcers (n=16)		
	Adenocarcinoma	5 (13.8)
	Gastritis with sever dysplasia	1 (2. 8)
	Gastritis with mild dysplasia	1 (2. 8)
	Gastritis with metaplasia	2 (5. 6)
	Chromic gastritis	7 (19. 4)
Esophageal nodule (n=5)		
	S.C.C	1 (2. 8)
	Chronic esophagitis	4 (11. 1)
	Total	36 (100)

* 'SCC = squamous cell carcinoma

In cases of visible gross lesions, diagnostic biopsies were taken for histopathologic evaluations. All specimens were fixed in formalin 10%, labeled by participant's code and submitted for histopathologic studies.

Statistical analysis

Results were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the Student's t- test for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables. Statistical significance was based on two-sided design-based tests evaluated at the 0.05 level. All of the statistical analyses were performed using SPSS version 16 (SPSS Inc, Chicago, IL, USA) for Windows.

Results

Of 1394 initial participants, 12 persons were excluded due to not willing to endoscopy or respiratory problems; finally 1382 persons (702 women, 680 men) with the mean age of 61.7±9.0 years (range: 50-87 years) underwent upper GI endoscopy (Table 1).

RUT and histopathologic results of suspicious lesions

H. pylori infection based on the RUT was positive in 66.6% (920) of participants (68.2% in men, 65% in women). Endoscopic study revealed suspicious lesions in 36 patients (15 gastric masses, 5 esophageal nodule and 16 suspicious gastric ulcers). These patients underwent further bioscopy of involved site besides five mentioned sites to define the nature of lesions.

Gastric adenocarcinoma and squamous cell carcinoma of esophagus were detected in seven (0.5%) and one (0.07%) persons, respectively. All the above eight patients underwent surgery and subsequent follow up. The histopathologic results of all suspicious lesions are shown in Table 2.

Table 3. Abnormal Endoscopic Findings in Esophagus Detected in 1382 Participants

Variables		Frequency
Esophageal hiatal hernia		531 (38.4)
Size:	Small	438 (82.5)
	Moderate	69 (13.0)
	Large	24 (4.5)
Esophageal mucosal break		254 (18.4)
Grade:	A	163 (64.2)
	B	91 (35.8)
Esophageal CLE:		83 (6.0)
Short seg.		68 (81.9)
Long seg.		15 (18.1)
Esophageal ulcer		17 (1.2)
Size	<5↔5mm	8 (47.1)
	>5↔5mm-10↔10	7 (41.1)
	>10↔10mm-20↔20	1 (5.9)
	>20↔20	1 (5.9)
Count	1	14 (82.3)
	2	1 (5.9)
	3	2 (11.8)
Location:	Middle	1 (5.9)
	Lower	16 (94.1)
Esophageal varices		1 (0.07)
Esophageal nodule		5 (0.36)
Middle		1 (20)
Lower		4 (80)

* 'CLE= Columnar lined epithelium

Table 4. Endoscopic Features of Gastric Abnormalities Detected in the Mass Screening Program in a High Endemic Region for Gastric Cancer

Variables		Frequency
Mass		15 (1.1)
Location:	Cardia	3 (20.0)
	Fundus	2 (13.4)
	Body	1 (6.7)
	Angularis	1 (6.7)
	Antrum	5 (33.2)
	prepyloric	3 (20.0)
Size (mm)	≤ 0.5×0.5	3 (20.0)
	0.5×0.5-10×10	3 (20.0)
	10×10-20×20	8 (53.3)
	>20×20	1 (6.7)
Ulcer		82 (5.9)
Location:	Cardia	3 (3.7)
	Cardia-Antrum	1 (1.2)
	Fundus	2 (2.4)
	Fundus-Body	1 (1.2)
	Body-Antrum	4 (4.9)
	Angularis	1 (1.2)
	Greater curve	1 (1.2)
	Antrum	18 (23.0)
	prepyloric	51 (62.2)
Size (mm):	≤ 0.5×0.5	35 (42.7)
	0.5×0.5-10×10	33 (40.2)
	10×10-30×30	14 (17.1)
Hyperemia		1184 (85.7)
Erosion		726 (52.5)
Nodularity		910 (65.8)
Pylorus Deformity		4 (0.28)

Endoscopic findings in esophagus, stomach and duodenum

Endoscopic findings were registered in three parts: esophagus, stomach and duodenum, see Tables 3 to 5. A

Table 5. Endoscopic Features of Duodenal Abnormalities Detected in a High Endemic Region for Gastric Cancer

Variables		Frequency
Ulcer		96 (6.9)
Location:	Bulb	83 (86.5)
	D2	13 (13.5)
Size (mm):	≤ 0.5×0.5	18 (18.8)
	0.5×0.5-10×10	59 (61.5)
	10×10-20×20	12 (12.5)
	> 20×20	7 (7.3)
Count:	1	74 (77.1)
	2	16 (16.7)
	≥ 3	6 (6.2)
Hyperemia		326 (23.6)
Erosion		215 (15.6)
Nodularity		193 (14.0)
Bulbar deformity		22 (1.6)

remarkable proportion of studied participants were found to have esophageal hiatal hernia (38.4%). Esophageal ulcers were detected in 17 (1.2%) of patients which were mostly located in lower third portion of esophagus. Gastric ulcers were found in 5.9% (82) of screened population, mostly located in prepyloric area (62.2%), followed by antrum (24.4%). Gastric masses (15 cases) were mostly detected in antrum 33.3%), cardia (20.0%) and prepyloric area (20.0%). In more than 95% of cases with gastric mocusal hyperemia (1184 cases), erosion (726 cases) and nodularity (910 cases) antrum (Distal stomach) was involved either alone or accompanied with other parts. Duodenal ulcers were found in 6.9% (96) of studied population which were mostly located in bulb of duodenum (86.5%).

Discussion

More than two thirds of GCs in Iran refer in stage IV. The overall average GC incidence rate were reported to be 15.2 (8.1-49.1) and 6.7 (4.9-25.4) per 10^5 in males and females. Crude mortality rates are estimated at 15.5 and 8.4 per 10^5 in males and females (Mousavi et al., 2009). However Iran accounts as a medium-risk region for GC, but some north and northwest regions (like Guilan and Ardabil Provinces) constitute hot points for GC, even in some northern regions (Babol) the GC mortality rate for women ($26.9/10^5$) is higher than Japanese women ($20.9/10^5$) which is the most endemic country for GC (Ghadimi et al., 2007). Approximately all of recent reviews regarding GC in Iran have had consensus that surveillance programs for early detection of GC in highly selected groups may improve the overall prognosis of patients (Mousavi et al., 2009; Malekzadeh et al., 2009). Our pilot results of 10-year cancer study in GCRS revealed Lashtenesha as a hot point region for GC. Thus, GLDRC established this screening program conducting on individuals ≥ 50 years who settled in Lashtenesha which is a region with high incidence rate of GC.

Some epidemiological studies in high risk regions recommend 40 years old as an optimal age threshold for screening endoscopy (Liou et al., 2005) while 50 years old was selected as the cut point in our study. The participants had mean age of 61.7±9.0 years (range: 50-87 years). Smoking and family history of GI cancers were found in 11.1% and 12.3% of our population. It is reported that 18% of GC risk is attributed to smoking (The EUROGAST Study Group, 1993; González et al., 2003). A positive family history of GC is also an important risk factor (Fock et al., 2008). Other risk factors are high prevalence of *H. Pylori* infection, high dietary intake of salt, gastroesophageal reflux disease (GERD) and red meat and dairy products (Malekzadeh et al., 2009; Babaei et al., 2010; Pakseresht et al., 2011). *H. Pylori* infection confirmed in 66.6% of our studied population (68.2% in men, 65% in women). This rate is relatively lower than what had been reported from Ardabil (Northwest) and Babol (North) cities. More than 89% of adults > 40 years in Ardabil were reported to be positive for *H. Pylori* infection (Malekzadeh et al., 2004; Sotoudeh et al., 2008). In Babol, positive rates of *H. Pylori* infection based on URT were 78% and 82% for men and women, respectively (Ghadimi et al., 2007).

In our endoscopic screening survey, all participants underwent biopsies for RUT and also five defined biopsies which are currently under histopathologic evaluations and will be reported in the recent future. Only in cases with suspicious lesions in endoscopy (36 patients) the histopathologic evaluations were emergently performed to decide regarding treatment modalities. Asymptomatic gastric masses, esophageal nodules and suspicious gastric ulcers were detected in 1.1%, 0.4% and 1.2% of screened population. Emergent histopathologic evaluations of suspicious lesions revealed early gastric cancer and esophageal SCC in 7 (0.5%) and 1 (0.07%) of persons, respectively. All these eight patients underwent surgery and benefit early cancer detection. Previous reports of a screening program in Ardabil and Meshkinshahr from 2000 to 2001 illustrated a detection rate of 0.3% of gastric cancer among people over 40 years old (Malekzadeh et al., 2004). They assessed people > 40 years while we conducted our screening on people ≥ 50 years. Besides geographic and ethnical differences, GC is less prevalent in lower ages; these might explain observed difference between results of two studies to some extent. It is of important value to mention that our results are just based on the endoscopic evaluation of our participants.

A remarkable proportion of studied participants were found to have esophageal hiatal hernia (38.4%). Esophageal ulcer were detected in 17 (1.2%) of participants which were mostly located in lower third portion of esophagus. It was interesting that abnormal endoscopic findings including erosion, hyperemia and nodularity in gastric mucosa were detected in 52.5% (726), 85.7% (1184) and 65.8% (910) of participants, respectively. In more than 95% of these cases antrum (Distal stomach) was involved either alone or accompanied with other parts.

Asymptomatic gastric ulcers were found in 5.9% (82) of screened population, and their sizes were mostly less than 1×1 cm (82.9%). Duodenal ulcers were found in 6.9% (96) of studied population which were mostly located in bulb of duodenum (86.5%), were 1 (86.5%) or 2 (16.7%) numbers and their sizes were mostly (80.2%) less than 1×1

cm. In a survey on the 572 asymptomatic Taiwaneses who underwent upper gastrointestinal endoscopy simultaneous to a routine health check-up, 54 (9.4%) were diagnosed as having peptic ulcer disease (PUD). The prevalence of gastric ulcer, duodenal ulcer and both gastric and duodenal ulcers were 4.7%, 3.9%, and 0.9%, respectively (Wang et al., 2011). In our screening program prevalence of gastric ulcer (5.9%) and duodenal ulcer (6.9%) is relatively more than what found in asymptomatic Taiwaneses.

Generally, screening programs are conducted when the related disease is common, the surveillance program covers most of the high risk population, is cost-effective, has high specificity and sensitivity and there are required time and equipment for subsequent treatment. In Japan with a high incidence rate of GC, screening program has been begun since 1960 and using photofluorography which has led to a two-fold decrease in GC-related deaths among screened population (Miyamoto et al., 2007; Lee et al., 2006; Murakami et al., 1990). However, screening programs have not been such successful in low risk regions like United States (Green et al., 1991; Stael et al., 1991). Our studied region had high incidence rate of GC in pilot evaluation which justify surveillance program. Upper GI endoscopy was selected as choice technique in our program. However the beneficial effects of photofluorography have been proven in Japan, its low detection rate, high cost and risk of X-ray contact are some of its disadvantages. Experiences of countries with high incidence rate of GC like Korea and Japan can be so helpful. Besides high detection rate and high specificity and sensitivity, patients` intention has great effect on future compliance. In a study on 1625 Koreans over 40 years of age, 67% vs. 33% chose endoscopy vs. upper GI series for their proffered future screening program (Choi et al., 2009). Upper endoscopy is assistant dependent and slightly more costly to perform compared GI X-ray or GI series, but the cost to detect one case of GC is lower (Lee et al., 2010).

In our country considering the wide variation in incidence rate across geographic areas which varies even up to 5-fold, it does not seem much wise to recommend national screening program (Leung et al., 2007). The pattern in north and northwest regions especially Ardabil and Guilan provinces is more similar to eastern Asia with high incidence rate while in southern regions it is the same as south central Asia or north of Africa (Sadjadi et al., 2003; Sadjadi et al., 2007). This implies the priority of implementation of the Comprehensive National Cancer Control Program (CNCCP) to integrate research works, prevention programs and early detection surveillances (Mousavi et al., 2008b; Mousavi et al., 2007). It is important to take into consideration that these screening programs although reduce cancer-related mortality and morbidity through early detection, may not reduce incidence rate of GC. Primary prevention including reduction of *H.Pylori* infection especially in high risk population (Fock et al., 2008; Mohagheghi et al., 2009; Hussein et al., 2010), improved food production and preservation methods, attention to salt intake, cessation of smoking and adapting healthy life style may play important roles and are much cost-effective (The EUROGAST Study Group.,1993; Babaei etal.,2010).

In conclusion, our findings confirmed effectiveness of endoscopic screening for early detection of GC among > 50 years old people living in a high risk region. Further studies are required to evaluate cost-effectiveness, cost benefit and mortality and morbidity of this method among high and moderate risk population before recommending this method as GC surveillance program at national level. It is also necessary to establish studies with regard to effectiveness and prognostic value of recently introduced screening markers like pepsinogen I and II (Mukoubayashi et al., 2007; Yoshihara et al., 2007). These serologic markers have been measured in our survey to evaluate their prognostic values for detection of precancerous lesions which required completing histopathologic examination and will be reported in early future.

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References

Babaei M, Pourfarzi F, Yazdanbod A, et al (2010). Gastric cancer in Ardabil, Iran--a review and update on cancer registry data. *Asian Pac J Cancer Prev*, **11**, 595-9.

Choi KS, Kwak MS, Lee HY, et al (2009). Screening for gastric cancer in Korea: population-based preferences for endoscopy versus upper gastrointestinal series. *Cancer Epidemiol Biomarkers Prev*, **18**,1390-8.

Ferlay J, Bray F, Pisani P, et al (2004). GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide, Version 2.0.IARC Cancer Base no 5. Lyon: IARC Press, (http://www-depdb.iarc.fr/globocan2002.htm).

Fock KM, Talley N, Moayyedi P, et al (2008). Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol*, **23**, 351-65.

Ghadimi R, Taheri H, Suzuki S, et al (2007). Host and environmental factors for gastric cancer in Babol, the Caspian Sea Coast, Iran. *Eur J Cancer Prev*, **16**, 192-5.

González CA, Pera G, Agudo A, et al (2003). Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer*, **107**, 629-34.

Green PH, O'Toole KM, Slonim D, Wang T, Weg A (1988). Increasing incidence and excellent survival of patients with early gastric cancer: experience in a United States medical center. *Am J Med*, **85**, 658-61.

Hussein NR(2010). Helicobacter pylori and gastric cancer in the Middle East: a new enigma? *World J Gastroenterol*, **16**, 3226-34.

Kang JM, Kim N, Yoo JY, et al (2008). The role of serum pepsinogen and gastrin test for the detection of gastric cancer in Korea. *Helicobacter*, **13**, 146-56.

Khedmat H, Panahian M, Mashahdian M, et al (2011). Prognostic factors and survival in stomach cancer - analysis

of 15 years of data from a referral hospital in Iran and evaluation of international variation. *Onkologie*, **34**, 178-82.
Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H (2010). Five common cancers in Iran. *Arch Iran Med*, **13**,143-6.
Lee HY, Park EC, Jun JK, Choi KS, Hahm MI (2010). Comparing upper gastrointestinal X-ray and endoscopy for gastric cancer diagnosis in Korea. *World J Gastroenterol*, **16**, 245-50.
Lee KJ, Inoue M, Otani T, et al (2006). Gastric cancer screening and subsequent risk of gastric cancer: a large-scale population-based cohort study, with a 13-year follow-up in Japan. *Int J Cancer*, **118**, 2315-21.
Leung WK, Wu MS, Kakugawa Y, et al (2008). Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol*, 9, 279-87.
Liou JM, Lin JT, Wang HP, et al (2005). The optimal age threshold for screening upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. *Gastrointest Endosc*, **61**, 819-25.
Malekzadeh R, Derakhshan MH, Malekzadeh Z (2009). Gastric cancer in Iran: epidemiology and risk factors. *Arch Iran Med*, **12**, 576-83.
Malekzadeh R, Sotoudeh M, Derakhshan MH, et al (2004). Prevalence of gastric precancerous lesions in Ardabil, a high incidence province for gastric adenocarcinoma in the northwest of Iran. *J Clin Pathol*, **57**, 37-42.
Miyamoto A, Kuriyama S, Nishino Y, et al (2007). Lower risk of death from gastric cancer among participants of gastric cancer screening in Japan: a population-based study. *Prev Med*, **44**, 12-9.
Mohagheghi MA, Mosavi-Jarrahi A, Malekzadeh R, Parkin M (2009). Cancer incidence in Tehran metropolis: the first report from the Tehran Population-based Cancer Registry, 1998-2001. *Arch Iran Med*, **12**, 15-23.
Mousavi SM, Somi MH (2009). Gastric cancer in Iran 1966-2006. *Asian Pac J Cancer Prev*, **10**,407-12.
Mousavi SM, Ramazani R, Davanloo M, et al (2008a). National Cancer Registry Report 2005-2006. Ministry of Health, Deputy to Health Directory, Tehran, Iran; CDC_ Cancer Office.
Mousavi SM, Alamolhoda AA, Gouya MM, Lickiss NJ (2008b). Implementation of comprehensive national cancer control program in Iran: an experience in a developing country. *Ann Oncol*, **19**, 398-400.
Mousavi SM (2007). Comprehensive National Cancer Control Program in Iran. Ministry of Health, Deputy to Health Directory, Tehran, Iran; CDC_ Cancer Office.
Mukoubayashi C, Yanaoka K, Ohata H, et al (2007). Serum pepsinogen and gastric cancer screening. *Intern Med*, **46**, 261-6.
Murakami R, Tsukuma H, Ubukata T, et al (1990). Estimation of validity of mass screening program for gastric cancer in Osaka, Japan. *Cancer*, **65**, 1255-60.
Naghavi M, Jafari N (2007). Mortality views in 29 Provinces of Iran in 2004- Ministry of Health, Deputy for Health Directory, Research and Development Office, Tehran, Iran, (in Persian).
Naghavi M (2006). Mortality views in 29 Provinces of Iran in 2004- Ministry of Health, Deputy for Health Directory, Res & Development Office, 111-91.
Nakamura K, Ueyama T, Yao T, et al (1992). Pathology and prognosis of gastric carcinoma: findings in 10,000 patients who underwent primary gastrectomy. *Cancer*, **70**, 1030-7.
Pakseresht M, Forman D, Malekzadeh R, et al (2011). Dietary habits and gastric cancer risk in north-west Iran. *Cancer Causes Control*, **22**, 725-36.
Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.
Sadjadi A, Malekzadeh R, Derakhshan MH, et al(2003). Cancer occurrence in Ardabil: Results of a population-based cancer registry from Iran. *Int J Cancer*, **107**, 113-8.
Sadjadi A, Zahedi MJ, Darvish Moghadam S, et al (2007). The First population-based cancer survey in Kerman Province of Iran. *Iranian J Publ Health*, **36**, 26-34.
Sotoudeh M, Derakhshan MH, Abedi-Ardakani B, et al (2008). Critical role of Helicobacter pylori in the pattern of gastritis and carditis in residents of an area with high prevalence of gastric cardia cancer. *Dig Dis Sci*, **53**, 27-33.
Staël VHC, Eriksson S, Huldt B, Hammar E (1991). Endoscopic screening during 17 years for gastric stump carcinoma: a prospective clinical trial. *Scand J Gastroenterol*, **26**, 1020-6.
The EUROGAST Study Group et al (1993). An international association between Helicobacter pylori infection and gastric cancer. *Lancet*, **341**, 1359-62.
Tusbono Y, Hisamichi S (2000). Screening for gastric cancer in Japan. *Gastric Cancer*, **3**, 9-18.
Wang FW, Tu MS, Mar GY, et al (2011). Prevalence and risk factors of asymptomatic peptic ulcer disease in Taiwan. *World J Gastroenterol*, **17**, 1199-203.
Yoshihara M, Hiyama T, Yoshida S, et al (2007). Reduction in gastric cancer mortality by screening based on serum pepsinogen concentration: a case-control study. *Scand J Gastroenterol*, **42**, 760-4.