

## RESEARCH ARTICLE

# A Registry Program for Familial Gastric Cancer Patients Referred to Cancer Institute of Iran

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### Abstract

**Background:** Gastric cancer is the second most common cause of cancer death. It has a poor prognosis with only 5-10% of hereditary etiology. If it is diagnosed, it could be helpful for screening the other susceptible members of a family for preventive procedures. Usually it is identified by symptoms such as presence of cancer in different members of family, some special type of pathology such as diffused adenocarcinoma, having younger age and multiple cancer syndromes. Hence, designing a registry program can be a more practical way to screen high risk families for a preventive program. **Materials and Methods:** Based on the inclusion criteria, a questionnaire was prepared. After pilot on a small number of patients, the actual data was collected from 197 patients and processed in SPSS 16.0. **Results:** Totally, 11.8% of the patients were younger than 45 years old. Blood type 'A' was dominant and males had a higher risk behavior with higher consumption of unhealthy food. Adenocarcinoma was reported in majority of cases. 21.8% of the patients had the including criteria for familial gastric cancer (FGC). **Conclusions:** The high percentage of FGC population compared to the other studies have revealed a need to design an infrastructural diagnostic protocol and screening program for patients with FGC, plus preventive program for family members at risk which could be done by a precise survey related to frequency and founder mutations of FGC in a national registry program.

**Keywords:** Familial cancer - gastric cancer - including criteria - cancer registry - cancer institute

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### Introduction

Gastric cancer is the second most common cause of cancer death in the world, after lung cancer (Caldas et al., 1999). Based on the data from Iran National Cancer Registry in 2005, gastric cancer is the second prevalent cancer in men and fourth cancer in women (The Ministry of Health Treatment and Education, 2005). Family history of gastric cancer in first degree relatives, low socioeconomic status (because of more exposure to food contaminated with bacteria), infection with *Helicobacter pylori*, smoking, salt-rich food, decreased acidity of stomach, history of gastric surgery, pernicious anemia, atrophic gastritis and long-term use of H2 antagonists have been considered as the possible risk factors (The Ministry of Health Treatment and Education, 2005).

Gastric cancer has poor prognosis because of its nature of ambiguous symptoms and delay in diagnosis. The overall 5-year survival of gastric cancer from 18 SEER geographical areas during 2002-2008 was 26.9% (Howlander et al., 1975-2009 (Vintage 2009 Populations)). Many factors such as anatomic appearance of the cancer (lower stomach better cured compared to higher stomach

means gastric cardia), lymph node involvement and distant metastasis can affect the prognosis (Rustgi, 2012).

Seeking different methods, such as the finding risk factors or the susceptible person, is very critical for finding a way to prevent cancer incidence (Giordano and Cito, 2012; Kato and Asaka, 2012). Screening cases of hereditary cancers by interview and genetic consulting is one of such methods to discover the members of families at risk (Scheuner et al., 2010).

Familial cancer is defined as the presence of the same or related (such as breast and ovary) cancer in a family, sometimes with unusual presentations (such as younger age of incidence or uncommon types of cancer like breast cancer in males), pair organ primary cancer (bilateral breast cancer) or multiple primary cancers. It is usually inherited as an autosomal dominant pattern with different types of gene penetration (Brose et al., 2003; Petrucelli et al., 2011).

Familial cancer comprises of approximately 10% of all gastric cancers in the world (Richards et al., 1999). Mutations of somatic cells in CDH1 gene, which is encoding epithelial adherence junction molecule E-cadherin, have been involved in the carcinogenesis of

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a considerable quantity of diffused types of gastric and invasive lobular breast carcinomas (Keller et al., 1999; Jiang et al., 2004). It is well established that prophylactic procedures such as prophylactic gastrectomy in patients at risk who have somatic mutations especially in CDH1 gene will increase the risk of cancer among members of a family with a hereditary cancer syndrome.

In this study a cancer registry system was devised to find out the prevalence of familial gastric cancer (FGC) among patients referred to the Cancer Institute of Iran and also a practical method to find out the population at risk in order to prevent gastric cancer.

### Materials and Methods

A criteria list was prepared according to standardized criteria of different countries. 30 patients who had referred to our cancer institute were interviewed as the pilot study. The aim of this pilot study was to evaluate the practical usage of the questionnaire and to estimate FGC prevalence.

After necessary modifications in the questionnaire, the final study was performed on 197 patients who had referred to our cancer institute from January 2010 to June 2012. All demographic information, clinical and pathology data, and family history were recorded. The patients were informed about the aim of the study prior to their enrollment and written consent was taken from them. Data elicitation was recorded in MS Excel 2010. After the primary analysis, the rest of the work was conducted with SPSS 16.0 (SPSS Inc).

### Results

Data was collected from 197 patients with gastric cancer. 23 patients (11.8%) were younger than 45 years old and 172 (88.2%) older than 45 years old. In case of marital status, 187 cases (91.2 percent) were married. Number of 129 cases (65.5%) were male and 68 cases (34.5%) were female (Table 1). Majority of the patients were living in Tehran province (48 cases, 24.4%), and the rest in the provinces of West Azarbayjan (25 cases, 12.7%) and Lorestan (18 cases, 9.1%). Concerning occupation, 77 cases (39.1%) had jobs with low income and high physical activity while 91 cases (46.2%) were working in jobs without physical activity. 10 cases (5.1%) were working with chemical agents (such as paint, petroleum).

**Table 1. Distribution of the Cases Based on Demographic**

Demographics		No.	%
Age	<45	23	11.8
	>45	172	88.2
Marital status	Married	187	91.2
	Single	5	2.4
	Other cases	5	2.4
Gender	Male	129	65.5
	Female	68	34.5
Occupation	Physical	77	39.1
	Non Physical	91	46.2
	Chemical	10	5.1
	Jobless	1	0.5
	N/A	18	9.1

**Table 2. Distribution of Cases Based on Blood Type Alcohol Consumption Smoking and Food Consumption**

Risk factor		Female		Male		Total	
		No.	%	No.	%	No.	%
Group	A+	12	32.4	25	67.6	37	18.8
	A-	0	0	2	100	2	1
	B+	7	38.9	11	61.1	18	9.1
	O+	4	15.4	22	84.6	26	13.2
	O-	1	33.3	2	66.7	3	1.5
	AB+	3	60	2	66.7	5	2.5
Alcohol consumption	N/A	41	38.7	65	61.3	106	53.8
	Yes	3	15	17	85	20	10.2
	No	52	36.9	89	63.1	141	71.6
Smoking	N/A	13	36.1	23	63.9	36	18.3
	Heavy smoker	14	29.8	33	70.2	47	23.9
	Smoker	3	8.6	32	91.4	35	17.8
Smoked food	Social Smoker	3	15.8	16	84.2	19	9.6
	No Smoking	48	50.5	47	49.5	96	48.2
	N/A	0	0	1	100	1	0.5
Salty food	Low	19	31.7	41	68.3	60	30.5
	Moderate	11	39.3	17	60.7	28	14.2
	High	1	14.3	6	85.7	7	3.6
	N/A	37	36.3	65	63.7	102	51.8
Nitrite	Low	22	36.7	38	63.3	60	30.5
	Moderate	11	30.6	25	69.4	36	18.3
	High	3	1.5	19	86.4	22	11.2
	N/A	32	40.5	47	59.5	79	40.1
HP infection	Low	29	39.7	44	60.3	73	37.1
	Moderate	12	21.1	45	78.9	57	28.9
	High	1	16.7	5	83.3	6	3
	N/A	26	42.6	35	57.4	61	31
HP infection	Yes	15	42.9	20	57.1	35	17.8
	No	49	32.9	100	67.1	149	75.6
	N/A	4	30.8	9	69.2	13	6.6

**Table 3. Distribution of Cases According to Pathology Report**

Pathology	No.	%
Adenocarcinoma		
Signet Ring Adenocarcinoma	22	11.2
Adenocarcinoma	99	50.3
Infiltrative Adenocarcinoma	1	0.5
Invasive Adenocarcinoma	11	5.6
diffuse type adenocarcinoma	11	5.6
intestinal type Adenocarcinoma	7	3.6
Undifferentiated Adenocarcinoma	1	0.5
poorly differentiated carcinoma	20	10.2
Others	172	87.3
Other than adenocarcinoma	2	1
SCC	1	0.5
	3	1.5
N/A	22	11.2

**Table 4. Distribution of Cases According to Family Cancer History**

History	First-degree relative		Seconds-degree relative		Third-degree relative	
	No.	%	No.	%	No.	%
No history	150	76.1	175	88.8	188	95.4
1 relative	33	16.8	18	9.1	7	3.6
2 relatives	14	7.1	4	2	2	1
3 relatives	0	0	0	0	0	0
More than 3	0	0	0	0	0	0

However, 18 cases (9.1%) did not state their job condition (Table 1).

Among 91 cases who had information about their blood type, the majority (37 cases, 18.8%) were A+ and next was O+ (26 cases, 13.2%) (Table 2). Concerning high risk behavior, this was more obvious among males in 20

**Table 5. Inclusion Criteria for Familial Gastric Cancer**

{	Two or more gastric cancer in family, at least one of them diffused type, diagnosed before 50 y/o.
{	Three or more gastric cancer in any age, at least one of them diffused type.
{	Person younger than 45 y/o affected by diffused gastric cancer.
{	Person affected by diffused gastric cancer and lobular breast cancer.
{	Two persons in a family which one is affected by diffused gastric cancer and other by lobular breast cancer.
{	Two persons in a family which one is affected by diffused gastric cancer and the other by signet ring colon cancer.

cases with a history of alcohol consumption (17 cases, 85%) versus 3 cases (15%) in females. Also, the majority of smokers in any blood type (from heavy smokers to social smokers) were male. Consumption of unhealthy foods, i.e. smoked, salty, and nitrite added, also had a male predominance with 6 (85.7%), 19 (86.4%), and 5 cases (83.3%) respectively. Infection with *Helicobacter Pylori* (*H. Pylori*) was another risk factor. In this sense, 35 cases had a previous history of *H. pylori* (20 cases in males, 57.1% and 15 cases, 42.9% in females) (Table 2).

Adenocarcinoma was the dominant pathologic feature (172 cases, 87.3%) (Table 3). 33 cases (16.8%) had one first degree relative with a history of cancer and 14 cases (7.1%) had a history of two first degree relatives. Concerning second degree relatives with a history of cancer, 18 cases (9.1%) had one relative and 4 cases (2%) had two relatives. In addition, 7 cases had a third degree relatives (3.6%) and 2 cases (1 percent) had 2 third degree relatives (Table 4).

## Discussion

Cancer is the third cause of death in Iran (Mousavi et al., 2009; Kolahdoozan et al., 2010). Among cancers, gastric cancer has a high mortality rate and is second in cancer death all over the world (Everatt et al., 2012). According to the national cancer report of Iran, gastric cancer prevalence was second in females and fourth in men in 2005 (The Ministry of Health Treatment and Education, 2005). The highest incidence in females was in the provinces of Ardabil, Gilan, Mazandaran, Kordestan, and West Azarbaijan respectively, while in males, it was in Ardabil, Gilan, Mazandaran, West Azarbaijan and Kordestan. Although geographic distribution in patients of this center does not represent an exact disease prevalence of each area, it follows approximately the same dispersal pattern, as northern and west-northern provinces of Iran have the most number patients after Tehran province (The Ministry of Health Treatment and Education, 2005).

Mean of age in comparison to other reports was lower. For example, in a study in china during 2004-2008, the mean age was around 65 years old (ranging from 47 to 90) (Zhang et al., 2012). In China, incidence of gastric cancer is between 50-70 years of age and with 2/1 male to female predominance (Goldman and Schafer, 2012). Still in our study, the age distribution was compatible with other studies.

Gastric cancer usually affects those older than 45 years old. In this study, the population of younger patients was higher than most other studies to our knowledge (11.8%). In this sense, in a study on 33,236 patients with gastric adenocarcinoma in the United States, 8.3% were younger than 45 years old (Al-Refaie et al., 2011).

Studies have shown that blood type A has a higher risk of association with gastric cancer (Edgren et al., 2010). However, in our study many of the cases had no information about their blood type, yet 'A' was the dominant blood type among them.

Modifications in high risk behavior is essential in primary prevention of gastric cancer (Kang et al., 2011). Many studies have demonstrated an association between unhealthy food (i.e. smoked, salty, and nitrite added) and incidence of gastric cancer (Brenner et al., 2009; Strnad, 2010; Wang et al., 2009). In this study, however, this was not a significant risk for gastric cancer incidence, although this kind of high risk behavior was more prominent among males (Jacobs et al., 2007).

About 90% of gastric cancers are adenocarcinoma which are categorized into two categories of intestinal and diffused types based on Lauren's classification (Kumar, 2010). Rest of the pathologies include: lymphoma, GIST, and leiomyosarcoma (Kumar, 2010). In the diffused type of adenocarcinoma, the lesion does not make a glandular form to surround the gastric wall (leather wall) (Kumar, 2010). In our study, adenocarcinoma was the dominant feature of pathologic appearance.

About 43 cases of this study (21.8%) had the inclusion criteria (Table 5) for FGC which is a higher percentage compared to other reports. The usual population for FGC is 5-10% of the total gastric cancer population which in our study a higher incidence of familial type was seen (Barber et al., 2006). This could suggest a presumption of higher incidence of gastric cancer among Iranian population or just reveal the referral characteristics of our cancer institute which its younger patients have a family history of cancer referring to specialized centers. On the other hand, it might be a warning for increased number of familial cases in Iran which requires a national survey for approval. In many cases of FGC, E-cadherin (CDH1) gene mutation is responsible for hereditary enhancement of cancer susceptibility. Families with this mutation have 80% lifetime risk of developing gastric cancer (Kaurah & Huntsman, 2011).

Screening for FGC is a critical procedure and since it has a higher risk of incidence, prophylactic gastrectomy is recommended to the members who have inherited the mutant gene (Chen et al., 2011). The importance of screening for prevention is that it will decrease cancer incidence and mortality by lowering the annual burden of society for cancer treatment and control (Winawer, 2005). Finding the familial syndromes, susceptible members and genotypes requires precise interview with pedigree.

In conclusion, what we have shown in this study is a higher percentage of familial gastric cancer which may suggest a necessity to perform a national survey for incidence of FGC. Screening the families at risk is another ongoing program by our team to seek out members of such

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