ORIGINAL ARTICLE

high incidence province for gastric adenocarcinoma in the northwest of Iran

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J Clin Pathol 2004;**57**:37–42

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Accepted for publication 13 July 2003

Background/Aims: Ardabil Province, in northwestern Iran, has the highest rate of gastric (predominantly cardia) adenocarcinoma in Iran. This study aimed to investigate the feasibility of endoscopic screening and to look for associated *Helicobacter pylori* infection and gastric precancerous lesions.
Methods: One thousand one hundred and five adult volunteers, residents of Ardabil and Meshkinshahr, districts, 40 years old and above were selected and invited by a simple random household canvass in rural and urban locations. Informed consents were obtained and upper gastrointestinal video endoscopy was performed to biopsy all visible lesions and standard sites in the antrum, corpus, and cardia
Results: One thousand and eleven of the invited individuals agreed to participate, including 494 men and 517 women, with a mean (SD) age of 53.32 (10.39) years. Endoscopy was well tolerated by all subjects; 96.7% of antral and 80.7% of cardia mucosal biopsies were satisfactory. The urease test or histology for *H pylori* was positive in at least 89.2% of subjects. Histological evidence of mucosal atrophy was seen in 39.3% of antral and 21.9% of cardia samples. Chronic gastritis with or without activity, reactive atypia of glandular epithelium, intestinal metaplasia, dysplasia, and cancer were found in 95.1%, 38.0%, 8.7%, 0.2%, and 0.3% of antral and 85.3%, 22.9%, 3.8%, 0.3%, and 0.1% of cardiac biopsies, respectively.
Conclusion: Endoscopic screening for upper gastrointestinal diseases was feasible and well tolerated in Ardabil, Iran. Most subjects showed *H pylori* infection. Atrophic gastritis, reactive atypia, and intestinal metaplasia were common in antrum, corpus, and cardia subsites.

Gastric adenocarcinoma is the second most common cause of cancer related mortality in the world.[1 2] This tumour is also the most common gastrointestinal (GI) malignancy in Iran.[3 4] Ardabil, a northwestern province of Iran, was reported to have the highest incidence of gastric adenocarcinoma in the whole country. According to an active cancer surveillance programme in Ardabil Province, covering a period of four years (1996–1999), this lesion constitutes 31% of all malignancies seen in that region, with an incidence rate of 49.1 and 25.4/100 000/year for men and women, respectively.[5] A prospective study of patients with upper GI malignancy diagnosed in a single referral centre in the city of Ardabil during a period of one year revealed that the proximal stomach (cardia) is the most common location for malignancy in the upper GI, constituting about 50% of the cases in that series.[6] *Helicobacter pylori* is known to be involved in the multistep process that finally leads to gastric adenocarcinoma, with estimates of attributable risk up to 75%.[7 8]

> ''Eradication of *Helicobacter pylori* infection is a promising option for the prevention of gastric cancer, at least in high risk regions of the world''

This organism has been classified as a member of the group 1 carcinogenic agents by the World Health Organisation.[9] A recent study using an animal model has clearly shown that long term *H pylori* infection of the gastric mucosa can progress to adenocarcinoma.[10] Uemura *et al* showed that both intestinal and diffuse type gastric adenocarcinoma were closely associated with *H pylori* infection.[11] This evidence, together with the very low five year survival rate of gastric cancer, favours the notion that eradication of *H pylori* infection is a promising option for the prevention of gastric cancer, at least in high risk regions of the world. There is also some evidence to support the protective effects of antioxidants, such as β carotene and ascorbic acid, against gastric cancer,[12] and the results of a recently published randomised controlled trail revealed that *H pylori* eradication, together with supplementing the diet with antioxidants as a preventive strategy has considerable public health potential.[13]

During a scientific collaboration between the Digestive Disease Research Centre (DDRC) of Tehran University of Medical Sciences and Ardabil University of Medical Sciences, aimed at devising a preventive strategy for gastric cancer in Ardabil, we sought to investigate the feasibility of endoscopic screening studies and to monitor the prevalence of *H pylori* infection and its related precancerous lesions in the residents of two major districts of the Ardabil Province.

MATERIALS AND METHODS

Study population

Our study was performed between June and September 2000 in Ardabil district, which has a total population of 435 487, and July and September 2001 in Meshkinshahr district, which has a population of 164 007. In total, 1105 households

Abbreviations: DDRC, Digestive Disease Research Centre; GI, gastrointestinal; IM, intestinal metaplasia

were canvassed in both districts. Part of each city was selected on a random basis, incorporating the adjoining rural area lying within a distance of 5–50 km from the city limits, an area that included 17 villages in Ardabil and 19 villages in Meshkinshahr. Expert local health professionals interviewed those members of the family who were aged 40 years or more, and thoroughly explained the purpose and procedure of the study to them. One individual from the target age group in each family was randomly selected to be invited to participate in our study. If such an individual was not available, or was excluded by any of the exclusion criteria, the immediate neighbour to the right hand side was referred to for the same process. Exclusion criteria used in our study were: unwillingness to participate at any stage of the study and for any reason, inability to tolerate upper GI endoscopy for any reason decided by the health professional during the interview or the gastroenterologist in charge at the time of endoscopy, history of known gastrointestinal disease in the past, or the presence of significant benign or malignant upper GI disease. All the individuals who were willing to participate were transferred to the site of study on the appointed day.

PROCEDURES

Upon arrival at the endoscopy clinic on the appointed day, the purpose of our study and the risks and benefits of the procedures were explained to the participants for the second time and the individuals signed a written informed consent to undergo the procedures necessary for our study. The study protocol and the informed consent used for this investigation were approved by the ethics committee of the DDRC, Tehran University of Medical Sciences before the study.

Before endoscopy, each participant was interviewed by a trained interviewer (general practitioner) to obtain the necessary information by filling in a questionnaire. The questionnaire was designed to collect demographic, nutritional, and important life style information. Specific sections included questions covering the staple diet and nutritional variety, food preservation facilities, and source of drinking water. Other sections included questions about life style and habits including smoking, alcohol, and drug abuse. Pertinent history for any important health problem with emphasis on important GI symptoms was obtained. The individuals were asked about any history of upper GI malignancy in first degree relatives.

After the interview, a limited physical examination was performed including the recording of height and weight. A few drops of blood taken from the tip of a finger punctured by a lancet under disinfected conditions were collected on to a Watman No. 1 filter paper to be used as a source of DNA for possible future molecular studies. Nails were clipped from the fingers and toes and about 0.5 g of the individual's hair was cut for future assessment of trace elements and toxicological studies deemed important in gastric carcinogenesis.

The participants then underwent standard upper GI video endoscopy under sedation with Midazolam (5–7.5 mg slow intravenous push) under monitoring and local anaesthesia of pharyngeal mucosa with 10% Lidocaine spray. A list of the endoscopic findings, using a special coding system for different lesions and a special endoscopy report form, were used to record the visual findings and generate an endoscopy report for future clinical decisions for the participant if necessary. The gastroenterologists in charge of the endoscopy procedure were assisted by trained personnel and general practitioners during the endoscopy and documentation of the endoscopic findings. Images of all the abnormal findings in the oesophagus, stomach, and duodenum were captured. Gastric biopsies were taken from the following sites:

- Incisura angularis for rapid urease test (first biopsy).
- Antrum, two biopsies, one between the incisura angularis and pyloric canal and the other on the opposite side over the greater curvature.
- Cardia, two biopsies 0.5 to 1.0 cm below the gastro–oesophageal junction on the anterior and posterior gastric wall.
- All the visible lesions (number of biopsies and sites decided according to the endoscopic features noted by the gastroenterologist).

In addition to the above biopsies, two more biopsies from the corpus at greater and lesser curvature were obtained in 508 individuals studied in Meshkinshahr.

All the biopsies were received by trained pathology assistants present in the endoscopy room, who flattened and oriented the samples by the muscularis mucosa side over small pieces of filter paper. These samples were immediately and completely submerged in neutral buffered formalin in clearly labelled containers. Records of the numbers and sites of the biopsies were kept using special forms and a coding system. At the end of the procedure, the data recorded on the endoscopy and pathology forms were rechecked to ensure that they were correct. The results of the rapid urease test were documented on both forms as soon as available. The pathologist in charge supervised the process of tissue orientation, fixation, labelling, and recording.

After the endoscopy, the participants were transferred to the recovery room to be kept under close observation, with control of vital signs, until they had completely recovered from sedation. The individuals were then discharged to be returned to their residential area or taken to the gastroenterologist so that further clinical measures or treatments could be decided upon if any abnormality was noted during the endoscopy. Appropriate medications were given free of charge if necessary.

All the tissue samples were transferred to the DDRC research pathology laboratory in Tehran, processed, and embedded in paraffin wax blocks, according to standard protocols. Histological sections were stained by the haematoxylin and eosin method.

The histological sections were reviewed by three pathologists with a special interest and experience in GI pathology; they were informed of the site of each biopsy, but had no knowledge of the endoscopic and clinical findings. Special forms were used to record the pathological findings. All the diagnostic criteria used for our survey were discussed and sample slides were reviewed by the pathologists before the study was undertaken to minimise interobserver variations as much as possible. For the sake of quality assurance, 1/10 of the samples were randomly checked by another pathologist in the team, and all the cases with crucial histological findings were reviewed and discussed in joint sessions.

HISTOLOGICAL CRITERIA AND DEFINITIONS

Gastritis

Gastritis is defined as the presence of increased numbers of inflammatory cells of any kind in the lamina propria. However, a few scattered lymphocytes and rare plasma cells can normally be seen and tolerated in the normal gastric antral and cardiac mucosa. Active chronic gastritis is defined as increased numbers of lymphocytes and plasma cells (chronic gastritis), accompanied by polymorphonuclear leucocytes. These polymorphonuclear leucocytes may show evidence of glandular invasion, similar to the crypt abscesses seen in inflammatory bowel diseases.[14]

Mucosal atrophy

Mucosal atrophy is defined as the separation of the mucosal glands and a decrease in the thickness of mucosa, greater in

severity than that seen in inflammation of the lamina propria, and usually associated with an increase in the stromal matrix.[14]

Intestinal metaplasia

Intestinal metaplasia (IM) is defined as metaplastic transformation of gastric glandular and surface epithelium towards intestinal mucosal elements including goblet cells, absorptive cells, and Paneth cells. The presence of definite goblet cells is the minimum requirement for the histological diagnosis of IM.[14]

Dysplasia

Dysplasia is defined as unequivocal histological evidence of neoplastic transformation of epithelial cells, including a constellation of enlargement, hyperchromasia, irregularity, and pleomorphism of nuclei, nuclear roundening and loss of polarity, increased mitotic activity with abnormal figures, decreased cellular mucin content, crowding, and stratification of the epithelial cells. These changes should be limited to the epithelium confined to the intact basement membrane, with no evidence of invasion to the lamina propria or surrounding tissue reaction (desmoplasia). The severity (grade) of dysplasia depends on the intensity and extent of the involvement of the glandular and surface epithelium of the gastric mucosa, and is usually classified as low or high grade.[14 15]

Reactive atypia

Reactive atypia is defined as cytological and histological changes similar to low grade dysplasia with coexistence of active inflammation and/or ulceration. This lesion is also called indefinite for dysplasia in some classifications.[16] To avoid misclassification we used the term reactive atypia instead of low grade dysplasia or indefinite for dysplasia.

Adenocarcinoma

Adenocarcinoma is diagnosed when the malignant cells invade the lamina propria in single cell, glandular, or solid nest arrangements, usually accompanied by fibrosis of the surrounding tissue (desmoplasia).[14 16]

Statistical analysis

The data were expressed as mean (SD), and 95% confidence intervals were calculated for all point prevalences of the histological findings. The presence of a variable (for example, active chronic gastritis) in at least one biopsy sample from the antral site was considered a positive finding. The absence of abnormal findings in all specimens from the same biopsy site was considered as normal. All data were analysed using SPSS10.0 for Windows.

RESULTS

One thousand and eleven individuals, or 91.5% of those found eligible, accepted the invitation to participate in our study: 494 (48.9%) men and 517 (51.1%) women. The youngest participant was 40 and the oldest 92 years old (mean age, 53.32; SD, 10.39). Five hundred and seven (50.1%) participants were residents of the Ardabil and Meshkinshahr cities and the remaining 505 (49.9%) were from rural areas. Except for one case of temporary respiratory depression following Midazolam, which was reversed promptly, all participants tolerated complete oesophago–gastro–duodenoscopy uneventfully. Table 1 summarises the life styles, dietary habits, and body weights of the individuals investigated.

Endoscopy was reported to be normal in 198 (19.6%) of the subjects. Table 2 summarises the important endoscopic findings. Nine hundred and eighty three (97.2%) antral and 816 (80.7%) cardia mucosal biopsies were considered satisfactory on histopathological examination. The number of satisfactory tissue samples from the corpus was 505 of 508 biopsies performed (99.4%). The main causes of deferral of samples for pathological diagnoses were inadequate specimens as a result of small biopsies and lack of proper orientation of the tissue (2.8% of antral, 0.6% of corpus, and 5.6% of cardia biopsy specimens). One hundred and twelve (13.7%) of the attempted cardia biopsies showed only squamous oesophageal mucosa. This is because it is technically difficult to biopsy this site, resulting in more sampling errors compared with the corpus and antrum.

The rapid urease test and/or histology were reported to be positive in 883 of 990 (89.2%) subjects in whom the tests were performed. Table 3 summarises the histopathological findings. At the cardiac mucosa, 306 of 816 subjects (37.5%) had atrophic gastritis, IM, reactive atypia, or glandular dysplasia. These findings were present in 262 of 505

Table 1 Dietary habits, life style, and nutritional status

Findings	N	%
Meat consumption (n = 1008)		
Less than once a week	229	22.7
1–4 times a week	598	59.3
5–7 times a week	174	17.7
Fresh fruit (n = 1007)		
Less than once a week	244	34.5
1–4 times a week	490	48.7
5–7 times a week	196	16.8
Fresh vegetables (n = 1006)		
Less than once a week	347	56.3
1–4 times a week	156	31.0
5–7 times a week	64	12.7
Staple diet (n = 1007)		
Wheat	847	84.1
Rice	149	14.8
Other	11	1.1
Habits (n = 1011)		
Tobacco smoking	302	29.9
Opium smoking	18	1.8
Alcohol consumption	35	3.5
Body mass index (BMI)		
Mean (SD), 27.1 (4.7)		
BMI $\leqslant$20	25	3.4
20< BMI $\leqslant$25	244	33.4
25< BMI $\leqslant$30	290	39.7
30< BMI $\leqslant$35	121	16.6
BMI >35	51	7.0
Digestive symptoms (>once/month)		
Pyrosis	535	52.9
Epigastric pain	443	43.8

Table 2 Endoscopic findings

	Total (n = 1011)	
Finding	N	%
Stomach		
Erythema	688	68.1
Erosion	107	10.6
Friability	3	0.3
Nodularity	48	4.7
Polyp	9	0.9
Ulcer gastric	30	3.0
Ulcer (duodenal)	19	1.9
Atrophic mucosa	2	0.2
Raised/thickened area	3	0.3
Normal	198	19.6
Oesophagus		
GERD A	280	27.7
GERD B, C, D	71	7.0

GERD, gastro-oesophageal reflux disease.

Table 3 Histopathological findings of gastric cardia, corpus, and antral biopsies

	Antrum (983)		Corpus (505)		Cardia (816)	
Histological findings	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Normal	30	3.1 (2.0 to 4.2)	37	7.3 (5.0 to 9.6)	111	13.6 (11.2 to 16.0)
Chronic gastritis	338	34.4 (31.4 to 37.4)	271	53.7 (49.3 to 58.1)	224	27.5 (24.4 to 30.6)
Active chronic gastritis	765	77.8 (75.2 to 80.4)	303	60.0 (55.7 to 64.3)	472	57.8 (54.4 to 61.2)
H pylori infection	818	83.2 (80.9 to 85.5)	328	65.0 (60.8 to 69.2)	492	60.3 (56.9 to 63.7)
Reactive atypia	431	43.8 (40.7 to 46.9)	109	21.6 (18.0 to 25.2)	187	22.9 (21.3 to 24.5)
Atrophic changes	444	45.2 (42.1 to 48.3)	232	46.9 (42.6 to 51.2)	179	21.9 (20.5 to 23.3)
Intestinal metaplasia	128	13.0 (10.9 to 15.1)	42	8.3 (5.9 to 10.7)	31	3.8 (2.5 to 5.1)
Glandular dysplasia	2	0.20 (−0.07 to 0.47)	1	0.2 (0.01 to 0.39)	2	0.25 (−0.09 to 0.58)
Adenocarcinoma	3	0.31 (−0.03 to 0.65)	0	0	1	0.12 (−0.11 to 0.35)

Antrum: positive finding in at least one of Bx1, Bx2, or Bx3; corpus: positive finding in at least one of Bx4 or Bx5.
CI, confidence interval.

(51.9%) of corporal biopsies and in 650 of 983 (66.1%) of the antral biopsies. Table 4 shows the distribution of atrophy at different biopsy sites of the gastric mucosa in 508 cases from Meshkinshahr.

Statistical analysis (table 5) revealed no significant correlation between demographic factors and precancerous lesions, but it did show a protective effect of meat (p for trend < 0.05) and fresh vegetable (p for trend < 0.01) consumption for antral IM only, but not for corpus or cardia IM.

DISCUSSION

Gastric carcinogenesis involves a slow but continuous stepwise evolution from superficial gastritis, glandular atrophy to metaplasia, dysplasia and, finally, to adenocarcinoma.[15 17] This slow process of carcinogenesis, which may well extend over decades, provides an excellent opportunity for early detection and intervention to prevent further progression or regression of the carcinogenic process. This is especially true because *H pylori* (which is readily treatable) is known to be the main aetiological agent and initiating carcinogen. Uemura *et al* have already shown that in Japan all patients who developed gastric cancer were infected with *H pylori*.[11] This finding may mean that other aetiological factors alone are not sufficient to induce gastric cancer and that *H pylori* plays a pivotal role in the process of gastric carcinogenesis.

In Ardabil, which has the highest mortality from gastric cancer in Iran, we carried out a cross sectional endoscopic screening study to look for precancerous gastric lesions, with the aim of designing an appropriate preventive and interventional strategy to decrease the mortality from this fatal cancer. We have identified a range of precancerous lesions, the most notable of which were chronic active *H pylori* associated gastritis in at least one of the biopsy sites in more than 90% of subjects. Atrophic gastritis, reactive atypia, IM, and dysplasia were seen in at least one biopsy site in 71.8% of subjects. The rate of IM and dysplasia was not as high as that reported from China[18 19] or Columbia.[20] The reasons for this discrepancy may be (1) the age standardised rate for gastric cancer in Ardabile is 50, which is lower than in Linqu in northeast China or the Narin∼o region of Colombia, where it is around 70 and (2) to prevent misclassification, we classified the less advanced lesions of low grade dysplasia and indefinite for dysplasia as reactive atypia, rather than dysplasia. We used only the urease test and histology (haematoxylin and eosin staining) to look for *H pylori* and in 89.2% of the subjects, at least one of the tests was positive.

Table 4 Distribution of atrophy in 508 subjects from Meshkinshahr with corpus biopsies

Site	N (%)	Subsite	N (%)
Cardia (n = 492)	142 (28.9%)	Cardia+antrum+corpus	112 (22.0%)
		Cardia+antrum	13 (2.6%)
		Cardia+corpus	10 (2.0%)
		Cardia only	7 (1.4%)
Corpus (n = 505)	223 (45.9%)	Corpus+antrum+cardia	112 (22.0%)
		Corpus+antrum	86 (17.2%)
		Corpus+cardia	10 (2.0%)
		Corpus only	15 (3.0%)
Antrum (n = 508)	270 (53.1%)	Antrum+corpus+cardia	112 (22.0%)
		Antrum+corpus	86 (17.2%)
		Antrum+cardia	13 (2.6%)
		Antrum only	59 (11.6%)

If we had also used serology or the breath test, or a more specific stain, such as Giemsa, the rate of *H pylori* positivity would probably have been higher, perhaps approaching 95–98%. It seems that in Ardabil almost all people 40 year old and above had *H pylori* associated chronic gastritis involving the antrum, corpus, and cardia, which was more severe in the antrum and corpus and became less prominent in the cardia. In contrast to the high risk populations of Japan, China, and Columbia, where more than 60% of gastric cancers are located in the antrum, in Ardabil more than 60% of gastric cancers are located in the proximal stomach, mainly in the cardia.[6 21]

Adenocarcinoma of the gastric cardia has a different biological behaviour, with a worse outcome and a shorter survival compared with its distal counterpart. Although *H pylori* infection is well established as the main risk factor for non-cardia gastric cancer, studies from the USA and Europe have provided some evidence that cagA+ strains may have an inverse relation with gastric cardia and oesophageal adenocarcinomas,[22–25] but reports from high risk regions[26 27] of Asia emphasise that these strains may also be a risk factor for proximal gastric cancer. It remains to be determined what proportion of proximal gastric cancer in these high risk regions of the world is the result of non-*H pylori* related factors.

> ''The adoption of a Western type life style and exposure to some additional, unknown environmental carcinogens may be the reason for the increasing rate of cardia cancer in Ardabil''

The diverging trend in the incidence of gastric cancer in these two subsites in Western countries points to a different aetiology. Exposure to environmental carcinogens (such as nitric oxide),[28] overeating, obesity,[29] and resultant hyperacidity in the cardia region,[30] which are the consequences of life style changes, seem to be more important in the pathogenesis of cardia gastric cancer.

During the past two decades, the Ardabili residents, who were all infected with *H pylori* during childhood,[31] have

Table 5 Important dietary factors in patients with and without intestinal metaplasia (IM) in different parts of the stomach

	Antrum			Corpus			Cardia		
	With IM	No IM	p Value	With IM	No IM	p Value	With IM	No IM	p Value
Meat consumption			<0.05			0.16			0.07
<1/week	48	181		17	124		13	172	
1–4/week	55	543		19	270		13	471	
5–7/week	25	131		6	69		5	142	
Fresh fruit			0.27			0.50			0.22
<1/week	52	290		17	157		14	267	
1–4/week	55	424		18	228		13	384	
5–7/week	21	143		7	78		4	134	
Raw vegetables			<0.01			0.17			0.13
<1/week	81	460		27	251		21	428	
1–4/week	38	284		12	154		8	259	
5–7/week	9	111		3	58		2	98	

gradually adopted a Western pattern of life style. More than 60% are overweight, with a body mass index of more than 25 (table 1), and most have access to adequate numbers of calories, mainly from bread, fat, and meat, whereas 35% and 24% still do not eat enough fresh vegetables and fruit, respectively (table 1). More than 50% have at least one episode of pyrosis each week and 35% of them were found to have evidence of at least mild erosive oesophagitis.

It seems plausible that although *H pylori* infection probably plays a pivotal role in the initiation of the carcinogenic process in the antrum, the adoption of a Western type life style and exposure to some additional, unknown environmental carcinogens may be the reason for the increasing rate of cardia cancer in Ardabil. Although we found that fresh vegetable and meat consumption had a protective effect against antral IM (table 5), our study failed to demonstrate a significant correlation with other dietary or demographic factors because of the small numbers of subjects with cancer and precancerous lesions. Further studies specifically designed to look for these correlations should be performed, such as case control studies using food frequency questionnaires.

The interaction between *H pylori* induced carcinogenesis and hyperacidity induced hyperproliferation of the proximal gastric mucosa is also an interesting area of investigation. It is probable that *H pylori* infection does not play a permissive role, as it most likely does in non-cardia gastric cancer, but it may be considered an additive risk, especially in high risk areas of the world, where both *H pylori* infection and gastric cancer are more common.

Previous studies have indicated that screening for the detection and treatment of *H pylori* infection to prevent gastric cancer is potentially cost effective if at least 30% of cancers attributable to *H pylori* can be prevented.[32] The results of reported interventional trails from Japan and Columbia are very encouraging, and favour the notion that the eradication of *H pylori* infection is a promising option for the prevention of gastric cancer, at least in high risk regions of the world; therefore, non-cardia gastric cancer may in the future be considered as a largely preventable disease.[11 13]

The role of dietary nitrate derived nitric oxide in the aetiology of gastro–oesophageal junction cancer in Scotland[22] has recently been related to the excess use of nitrogenous fertilisers and associated increased dietary nitrate exposure. In Ardabil, like other parts of Iran, there has been more than a 15 fold increase in the use of chemical nitrogenous fertilisers. Ardabil Province has also some geographical similarities with other high incidence areas of gastric cancer, the so called volcanic countries, such as Costa Rica, Chile, and Japan, by being located near a silent volcano named Sabalan. Therefore, a similar environmental factor, such as nitrous volcanic soils, may contribute to the higher incidence of upper GI cancer in this area.[33]

Further epidemiological studies need to be performed to evaluate the role of dietary nitrates and other carcinogens, which could be secreted in saliva and accumulate in the cardia, in the pathogenesis of gastric cardia cancer.

Epidemiological studies should also be performed in different ethnic subgroups of northern, central, and south Iran with different prevalence rate for tumours looking at all four major types of upper GI cancers, including cancers of the distal stomach and gastric cardia, in addition to adenocarcinoma and squamous cell carcinoma of the oesophagus.

Our study indicates that, in Ardabile, adequate planning and resources may make such studies feasible and economic. Our findings are relevant to populations with very high gastric cancer rates and a very high prevalence of *H pylori* infection. They may be less relevant to populations with a low gastric cancer risk, with a low prevalence of gastric cancer.

Take home messages

- Endoscopic screening for upper gastrointestinal diseases was feasible and well tolerated in Ardabil, Iran, a high risk region for gastric cancer
- Most subjects showed *Helicobacter pylori* infection
- Atrophic gastritis, reactive atypia, and intestinal metaplasia were common in the antrum, corpus, and cardia subsites

ACKNOWLEDGEMENT

This study was supported by a grant from the Academy of Medical Sciences of the Islamic Republic of Iran. Our appreciation is expressed to all medical students of Islamic Azad University of Ardabil, health personnel of Ardabil district, and all the kind people of Ardabil who were the subjects of this survey for their collaboration, and to Dr S M Dawsey of the Cancer Prevention Studies Branch, National Cancer Institute, Bethesda, Maryland, for valuable suggestions and comments.

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