

## Review Article

## Gastric Cancer in Iran: Epidemiology and Risk Factors

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Although the global incidence of gastric cancer has been decreased dramatically in recent decades, it is the most common cancer in north and northwest Iran. The wide variation in incidence across different geographical areas and higher proportion of cardia cancer are two main characteristics of gastric cancer in Iran. Current investigations indicate that a high prevalence of *H.pylori* infection, high dietary intake of salt and smoking are the main environmental factors of gastric cancer in Iran. Gastroesophageal reflux disease is another contributing factor in populations with a higher incidence of gastric cardia cancer. While interventions on modifiable environmental risk factors should be considered as the main modality to reduce gastric cancer development, surveillance programs for early detection of cancer in highly selected groups may increase overall survival rates in potential patients in this country.

*Archives of Iranian Medicine, Volume 12, Number 6, 2009: 576 – 583.*

**Keywords:** Cardia • gastric cancer • *H.pylori* • Iran • non-cardia

## Introduction

Gastric cancer is the fourth most common cancer and second leading cause of cancer related death in the world. According to a global estimation, more than 930,000 new cases of gastric cancer are being diagnosed each year and a minimum of 700,000 patients die from the disease.<sup>1</sup> Until recently, gastric cancer was the most common cancer in the world, but its incidence has decreased dramatically in most of the western and Japanese populations.

The reason for the striking decrease in gastric cancer incidence is unclear; however simultaneous wide-spread usage of modern food preservation techniques and refrigeration may play a role. The general improvement in nutritional state and availability of sufficient fresh fruits and vegetables is another protective factor.<sup>2</sup>

There is a wide variation in the incidence of gastric cancer in different geographical regions.

The highest risk areas with an age standardized incidence rate (ASR) of more than 20 per 100,000 person-years in men are: Japan, Korea, China, Chile, Costa-Rica and Brazil. The intermediate risk areas are those populations with an ASR between 10 and 20 which include: Italy, the UK, Germany, the Netherlands and Turkey. Low risk populations for gastric cancer are those with an ASR of less than 10 and are: the USA, Canada, Sweden, Denmark, Egypt, India and Australia.<sup>3</sup>

In Iran, while the northern and northwestern regions are high risk areas for gastric cancer, there are several intermediate and low risk populations in other geographical areas. The marked variation of gastric cancer risk in different geographical areas in one side and striking differences in frequency of possible environmental risk factors on the other side, make the country an opportunity for research on gastric cancer etiology. In this review we will try to illustrate current epidemiological aspects of gastric cancer in Iran, including investigated risk factors and issues on primary and secondary prevention strategies.

## Incidence of gastric cancer in Iran

Most northern and northwestern regions of Iran are at a high risk for gastric cancer. A strong spatial clustering of gastric cancer in both men and women has been described in Mazandaran and

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Accepted for publication: 23 September 2009

Golestan, two provinces located on the Caspian Sea shore line.<sup>4</sup> Ardabil, a northwestern province, has the highest incidence of gastric cancer in Iran with an ASR of 49.1 and 25.4 in men and women.<sup>5</sup> The provinces of Semnan, Golestan, and East Azerbaijan as well as the Tehran metropolitan area also have high rates of gastric cancer in both men and women.<sup>6-9</sup> In contrast to the northern areas, Kerman, a province in the south, shows a lower incidence of gastric cancer with a rate of 10.2 and 5.1 in men and women<sup>10</sup> (Table 1). It is important to note that the higher incidence rate of gastric cancer in Ardabil is due to higher rates of gastric cardia rather than non-cardia cancer, being 26.4 and 8.6 in men and women, respectively.<sup>11</sup> This is in contrary to other high-risk area i.e. Japan, where non-cardia cancer remains as a major part of gastric cancer. The proportion of non-cardia to cardia cancer in low risk areas of Iran such as Khuzestan, southwest Iran, is 85% which is much higher than Ardabil in the northwest.<sup>12</sup> A recent study by Abdi-Rad et al. showed that the proportion of proximal gastric cancer to those located in mid and distal third of stomach in Tehran, Iran's capital is increasing.<sup>13</sup> High incidence of the gastric cardia cancer in northern Iran, where squamous cell carcinoma of oesophagus is prevalent, is a feature of this cancer which may imply some common risk factors for both cancers.<sup>15</sup> This hypothesis has been supported by studies from other high incidence areas in northern China.<sup>16</sup>

**Table 1.** Annual incidence of gastric cancer in Iran, reported from different cancer registries presented as age standardized rate (ASR) per 100,000 person-year

Province	Location	ASR Men	ASR Women	Ref.
Ardabil	Northwest	49.1	25.4	5
East Azerbaijan	Northwest	26.0	11.6	8
Golestan	Northeast	27.8	8.3	7
Kerman	Southeast	10.2	5.1	10
Semnan	Central	36.9	14.8	6
Tehran	Central	19.8	10.0	9
Iran (estimate)		26.1	11.1	14

ASR=age standardized incidence rate; Ref.=reference

### Risk factors of gastric cancer in Iran

Gastric cancer is a multi-factorial disease and develops as a result of continuous cell damage caused by life-long exposure to different carcinogens. The intestinal histological subtype of gastric adenocarcinoma, as the most common form of gastric cancer, develops in an inflammatory

background induced by *H.pylori* related chronic gastritis and progresses to atrophic gastritis, intestinal metaplasia, glandular dysplasia and eventually adenocarcinoma.<sup>17,18</sup> Many environmental factors including smoking, high salt intake, and a diet with an insufficient level of antioxidants are involved in the pathogenesis of gastric cancer (Table 2). Endogenous and host factors, including those related to male gender,<sup>19</sup> and several genetic backgrounds are known risk factors to a lesser extent.<sup>20,21</sup> In addition to the well-established risk factors of gastric cancer, which are mainly applicable to classic non-cardia cancer, gastroesophageal reflux disease (GERD) is one of the main risk factors of cardia cancer (Figure 1). The association of these tumors with both *H.pylori* related pathway and GERD indicates two distinct types of tumors arise from anatomic cardia region.<sup>22</sup>

### *Helicobacter pylori* infection

In 1994, a working group of the International Agency for Research on Cancer (IARC) introduced *H.pylori* as a first degree carcinogen for gastric cancer.<sup>23</sup> There is strong evidence of increased gastric cancer risk in populations with that have higher rates of *H.pylori* infection.<sup>24</sup>

The *H.pylori* infection rate is very high in the Iranian population (Table 3). More than 89% of adults aged 40 or older in Ardabil province were infected in a population based study performed on 2001 – 2 by our team.<sup>25,26</sup> In Babol, on the Caspian Sea shoreline, *H.pylori* infection, as determined by urease breath test, has been reported in 78% of men and 82% of women.<sup>27</sup> A population based study on pastoral nomads revealed that 86% had *H.pylori* infection, diagnosed serologically.<sup>28</sup> In a large cross-sectional study in Tehran the overall infection rate was 69% which correlated positively with age, i.e. the highest prevalence was 79% in the 46 – 55 age group.<sup>29</sup> Furthermore, the acquisition age of *H.pylori* infection in Iran seems to be very low. Based on a study from Shiraz, in southern Iran, 82% of children aged nine months and 98% of two year old children were *H.pylori* infected.<sup>30</sup> A higher prevalence of infection in children and adults and its correlation with age has also been reported from Rafsanjan, another southern region of Iran.<sup>31</sup>

Several virulence determinants of *H.pylori* have been recognized and linked to different outcomes of infection. The high molecular weight protein cagA encoded by cytotoxin associated gene A

**Table 2.** Prevalence of *H.pylori* infection in Iran in population based studies, detected by different diagnostic techniques

Population	Prevalence	Subjects	Age Mean ( $\pm$ SD)	Assessment Method	Ref.
Ardabil	All: 89%	M: 494 F: 517	53 ( $\pm$ 10)	Histology/Rapid urease test	25,26
Babol	M: 78% F: 82%	M: 50 F: 80	M: 51 ( $\pm$ 2) F: 50 ( $\pm$ 1)	Urease breath test	27
Tehran	All: 69%	M: 968 F: 1358	36 ( $\pm$ 14)	Serology	29
Shiraz	M: 81% F: 83%	M: 308 F: 284	8 months -15 years	Faecal antigen test	30
Rafsanjan	M: 72% F: 62%	M: 114 F: 86	48 ( $\pm$ 16)	Serology	31
Rafsanjan	M: 52% F: 42%	M: 187 F: 199	10 ( $\pm$ 4)	Serology	31
Nahavand	All: 71%	M: 653 F: 865	36 ( $\pm$ 20)	Serology	32

(cagA) is present in 60 – 70% of *H.pylori* strains and has been shown to be related to a greater risk of gastric cancer in some populations.<sup>33</sup> In Iran, the majority of *H.pylori* infected subjects are cagA positive strains. The prevalence lies between 66% and 91% in different ages and geographic regions.<sup>31,34–36</sup> Despite the high prevalence of cagA positive *H.pylori* in the Iranian population, its contribution to an excess cancer risk is unclear. In an attempt to clarify the role of cagA as a higher risk of gastric cancer in Iran in comparison to its neighbouring country Iraq, where risk of this cancer is low, investigators found similar proportions of cagA positive strains in both countries. Interestingly, cagA alleles encoding four or more tyrosine phosphorylation motifs were found in 12% of the Iranian strains but none of the Iraqi strains.<sup>37</sup> Another toxicity determinant of *H.pylori* is the vacA antigenic region. One natural polymorphic type of this antigen called vacA i-1 has been shown to be associated with increased gastric cancer risk in Iran.<sup>38</sup> Other antigenic determinants of *H.pylori* such dupA have been studied in the Iranian population and have not shown any clear relationship with gastric cancer risk.<sup>39,4</sup>

### Atrophic gastritis

Atrophic gastritis is another well-established risk factor of gastric cancer. As an intermediate step in the carcinogenesis cascade of most intestinal type tumors and some diffuse types of adenocarcinoma, its prevalence in the population

strongly correlates with the incidence of cancer. The prevalence of atrophic gastritis in high incidence areas of gastric cancer in Iran has been reported by few studies. In our population-based study on more than a thousand people in Ardabil, atrophic gastritis as detected by histology was found in 45%, 47%, and 22% of gastric antral, body and cardiac biopsies, respectively.<sup>25</sup> Later, in a case control study from the same region we showed a strong association between atrophic gastritis defined by low pepsinogen I/II, and non-cardia gastric cancer and also a partial relationship with a subgroup of gastric cardia cancer.<sup>22</sup> A higher prevalence of serologic atrophic gastritis has also been reported from Babol being 51% and 53% in studied men and women.<sup>27</sup>

### Smoking

The risk of gastric cancer in tobacco smokers is almost twice as high as non-smokers.<sup>41</sup> Based on the European Prospective Study (EPIC), an estimated 18% of gastric cancer risk is attributable to smoking.<sup>42,24</sup> Smoking in Iranian men is common and according to a national surveillance, at least 30% of men aged 25 and over are smokers.<sup>43</sup> Similar high rates have been shown in a few other studies.<sup>22,25,27</sup> The robust relationship between cigarette smoking and gastric cancer risk has been confirmed in our own study.<sup>22</sup>

### Salt and salted food

High intake of salt is a known risk factor of gastric cancer. Substantial evidence from

**Table 3.** Investigated risk factors of gastric cancer in Iran

Risk Factor	Association with cancer	
	Global	Iran
<i>H. pylori</i> infection	Strong	Strong
<i>H. pylori</i> virulence antigens (cagA, and dupA)	Inconclusive	Inconclusive
<i>H. pylori</i> virulence antigens vacA-i1	Inconclusive	Suggestive
Atrophic gastritis	Strong	Strong
Smoking	Intermediate	Intermediate
High salt intake	Strong	Strong
Low selenium	Suggestive	Suggestive
Red meat	Suggestive	Suggestive
Low fruit and vegetable intake	Intermediate	Suggestive

ecological, case control, and cohort studies strongly suggest that the risk of gastric cancer may increase with the high intake of some traditional salt-preserved foods and salt per se.<sup>44</sup> According to the results of one of the best ecological studies, INTERSALT, the median urine sodium level of subjects from 39 populations of 24 countries was strongly correlated with gastric cancer mortality rates.<sup>45</sup> In Iran, a study from Babol, northern Iran, showed very high salt intake reflected by urinary salt excretion in both men and women when compared to the recommended daily salt intake by World Health Organization.<sup>27</sup> Another study from Ardabil, northwest Iran, showed a significant increased risk of gastric cancer in those who had a preference for higher salt intake.<sup>46</sup> The underlying mechanism of carcinogenesis induced by salt has not been completely understood. A number of histological events including gastric epithelial hyperplasia, parietal cell loss, and intestinal metaplasia have been described in animal studies.<sup>47,48</sup> Induction of interleukin-1 $\beta$  expression in *H.pylori* infected epithelial cells by hyperosmotic stress of salt may also explain the mechanism of increased risk of gastric cancer in infected people with high intake of dietary salt.<sup>49</sup> A recent study suggests that a high salt diet acts synergistically with *H.pylori* infection to enhance inducible nitric oxide and cyclooxygenase-2 expression in gastric mucosa.<sup>50</sup>

### Other dietary factors

The protective effects of fresh fruits and vegetables and their antioxidant contents against gastric cancer have been shown by numerous epidemiological studies.<sup>51-53</sup> The beneficial effects of fresh fruit and most antioxidants including

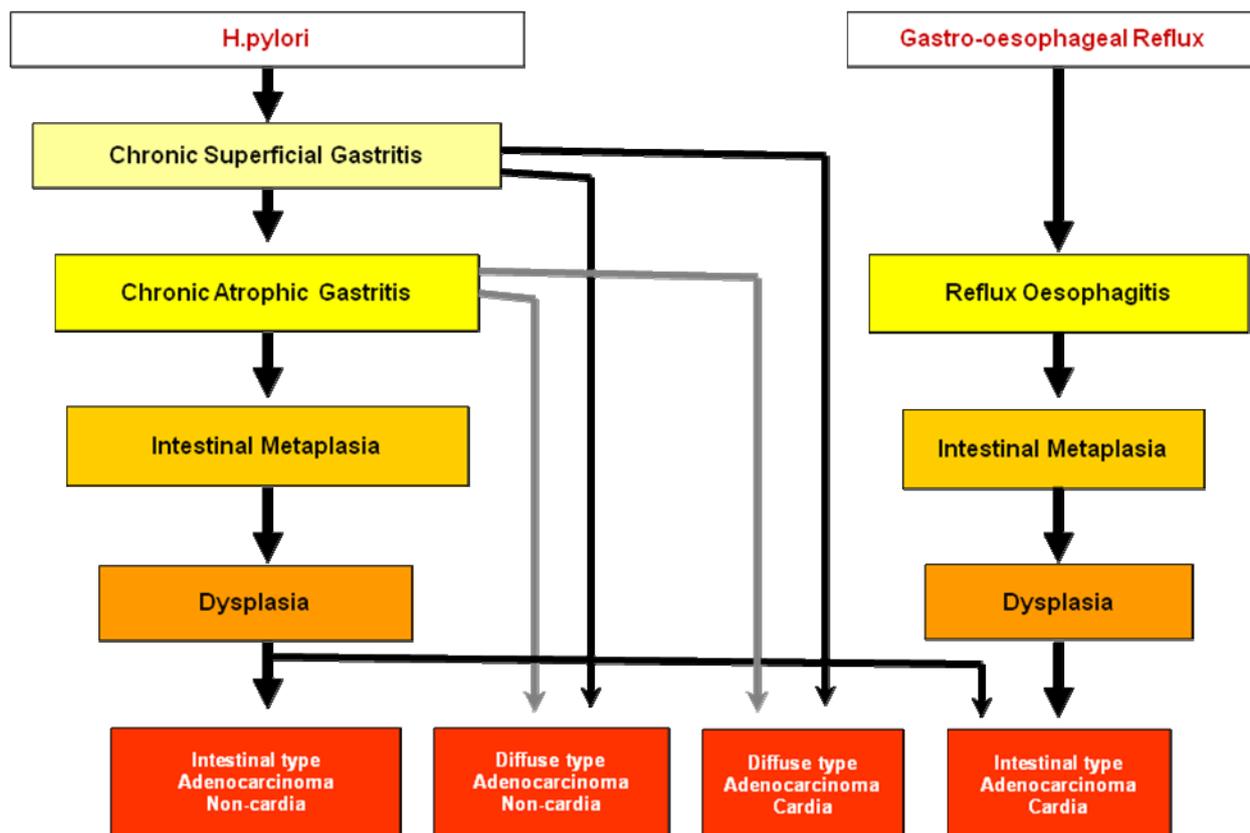
vitamin C, tocopherols, and lycopene seems to be specific to non-cardia cancer rather than those located in the cardia sub-site.<sup>54</sup> In Ardabil, high intake of fruits, allium vegetables and fresh fish is associated with a lower risk of gastric cancer.<sup>46</sup>

Frequent consumption of red meat is probably another risk factor for gastric cancer in Ardabil.<sup>46</sup> In our previous study from the same region, the frequent intake of red meat was associated with a higher rate of intestinal metaplasia of gastric mucosa.<sup>25</sup> The increased risk of gastric cancer by frequent consumption of red meat has been reported by a number of studies worldwide.<sup>55,56</sup> Although the exact mechanism of gastric cancer development by red meat is not clear, a few plausible mechanisms have been suggested to explain the causal association between red meat intake and gastric cancer. These mechanisms involve potential effects of high levels of hem in red meats, fat and protein, nitrite and nitrosamines, and of salt, as well as heterocyclic amines and polycyclic aromatic hydrocarbons.<sup>57</sup>

Selenium is another highly investigated dietary component with a potential protective effect against gastric cancer. Several epidemiological studies suggest a significant inverse association between selenium and gastric cancer risk, most likely on gastric cardia cancer.<sup>58-60</sup> The results of interventional studies using selenium supplementations in China are weakly supportive.<sup>61-63</sup> Based on our ecologic study, the serum selenium levels of healthy adults in Ardabil, where gastric cardia cancer is very common, are significantly lower than that of subjects from three other populations with a lower incidence of gastric cancer.<sup>64</sup> The possible protective effect of selenium against cancer may explained by reduction of oxidative stress and DNA damage, promotion of DNA repair and apoptosis through p53 tumor suppressor gene, and induction of phase II conjugating enzymes for detoxification of carcinogens.<sup>65</sup>

### Primary prevention of gastric cancer

As discussed earlier, a great majority of the patients with gastric cancer have a current or past history of *H.pylori* infection.<sup>66-68</sup> The high rate of *H.pylori* has been shown in our recent study on Iranian patients with gastric cancer, being 94% and 83% in the cases with non-cardia and cardia cancers, respectively.<sup>22</sup> Based on the current consensus, *H.pylori* is a necessary but not sufficient risk factor for non-cardia gastric



**Figure 1.** Histological cascade for carcinogenesis of gastric cancer in non-cardia versus cardia locations. Note two types of cardia cancer, one group related to GORD, is mainly intestinal subtype and other group is mixture of intestinal and diffuse subtypes and related to *H.pylori* induced gastritis

adenocarcinoma.<sup>69</sup> Other well-established risk factors including salt, smoking, and dietary factors may promote gastric cancer development in an inflammatory background developed by the *H.pylori* infection. Perhaps the dramatic decline in incidence of gastric cancer in North America and Western Europe is mainly due to a gradual disappearance of *H.pylori* infection in new generations. Therefore, any preventive strategies against *H.pylori* infection would be a most reasonable action to reduce gastric cancer incidence.<sup>70</sup> Theoretically, active immunization of young children against *H.pylori* is ideal to prevent infection and its chronic consequences including peptic ulcer disease and gastric cancer; but currently there is no commercial vaccine for clinical use.

Eradication of the current *H.pylori* infection in children and young adults may be an alternative way of cancer prevention. This can be done in the earlier stages of infection, before development of severe atrophic gastritis and intestinal metaplasia, but current evidence does not support this strategy. Massive public eradication of *H.pylori* in

populations with high infection rate i.e. Iran, is impractical for several reasons including the high expenses of diagnostic tests, therapy on a national scale and the danger of development of multi-drug resistant microorganisms.

### Secondary prevention of gastric cancer

At least 80% of Iranian patients with gastric cancer are being diagnosed in advanced stages of the disease and they do not gain any survival benefit from conventional surgical, chemotherapeutic or radiotherapeutic methods.<sup>71-73</sup> Therefore early cancer detection using an efficient surveillance program is a justified way to reduce gastric cancer mortality. These methods of population screening for gastric cancer are being adopted in Japan, South Korea and a part of Taiwan.<sup>69</sup>

Perhaps one of the most practical methods of secondary prevention is to detect early gastric cancer in a group of high risk population defined by a set of criteria. Apart from age and high regional incidence; the rate of gastric cancer and severe atrophic gastritis, especially its body predominant form, would be an acceptable

selection criterion in high incidence areas.<sup>74,75</sup> In our population based study in Ardabil, 37% of randomly selected persons aged 40 or more had some degree of gastric body atrophy.<sup>25</sup> As histological detection of atrophic gastritis through endoscopic examination is not feasible in large screening programs, serologic tests for serum pepsinogen I (PG I) and pepsinogen II (PG II) would be a reliable alternative. Low serum PG I and PG I/II has been shown to be acceptable markers of atrophic gastritis and cancer risk.<sup>76-78</sup> Therefore selection of a high risk group based on age, low serum PG I and PG I/II in a high risk area, i.e. Ardabil, for screening programs may reduce mortality and morbidity from gastric cancer through early detection of cancer and high grade gastric precancerous lesions. These strategies may not reduce the incidence rate of gastric cancer in the community, but it could be a justified preventive process along with other primary prevention programs, including reduction of *H.pylori* infection rate in young generations, improvement of food production and preservation methods, decrease of salt intake, cessation of smoking and adapting a healthy life style.

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