

Lifestyle and dietary patterns as risk factors affect gastric cancer in Iran

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Abstract. Though the global incidence of stomach cancer (also named gastric cancer, GC) has been reduced steadily in recent decades and it is one of the most serious health problems facing Iran. The statistics show that it is the second prime reason of death in Iran, so its prevention is one of the most significant aspects of the cancer control strategy, both in Iran and across the world. The specific factors contribute to the decline in GC is uncertain, taking in account of regional disparities, racial traits, tendency of cancer incidence with time and food preservation techniques, economic-social status and so on. But GC is closely linked with some quantifiable elements, such as diet and the continual perfection of the role of nutrition and increased access of fresh fruits and vegetables. This paper aims to summarize the on-going clinical trials, future directions and some preventions of GC. And also appraise the current evidence surrounding relationship between risk factors of GC and Iran diet in terms of micro-nutrients and salt intake, smoking as well as helicobacter pylori infection.

Keywords: Gastric Cancer, risk factors, Iran.

1. Introduction

Gastric cancer has two pathological variations: intestinal type and diffuse type. Intestinal type is the consequence of the inflammatory transformation from chronic gastritis to atrophic gastritis, and finally to intestinal metaplasia and dysplasia which is more normal in the aged, while the type of diffuse is more familiar in women and individuals under the age of 50. The diffuse-type features the evolution of Gastric Helicobacter pylori infection, which is highly correlated with the intestinal type. The diagnosis of early gastric cancer is essential because it may receive endoscopic treatment with a favorable prognosis, but many patients are asymptomatic within early stages of GC and may accompany with concomitant diseases or symptoms. In a review of more than 18000 patients, the most common symptoms included weight loss and abdominal pain. Nausea, poor appetite, indigestion and mild gastric discomfort may also occur.

Studies and research from ecological, case-control, and cohort strongly believed that the risk of suffering from GC closely matched with dietary pattern. For example, high intake of various salt-preserved foods, while high intake of vegetables and fruits, especially fruits will decrease the rate of developing GC. There are three major dietary patterns in Iran, with the health dietary pattern, Western dietary pattern, and the mixed dietary pattern respectively. The health one is characterized by high intake of vegetables, dairy products, nuts, honey and so on. The Western dietary pattern mainly takes desserts, refined grains, meat and the like and the last pattern, the mixed, which is highlighted by the intake of tea, sugar and coffee.

2. Incidence of GC in Iran

In Iran, increasing cognition of health state and dietary habits, awareness of early symptoms then through in-time diagnosis so the incidence of GC decreased. Whereas due to the expand of urbanization, inadequate medical level or the diagnosis of non-curable stage will still cause the rate to rise. Due to most patients are diagnosed in end stage instead of the advanced stage, the studies

conducted in most parts in Iran carried out that GC has a high prevalence, especially marked the northern and northwest regions as high-risk while in southern and southwest parts as the moderate .

One of the highest incidence provinces of GC is Ardabil which is located in north- west of Iran and according to an active cancer surveillance institution there designed a program which collected 31% of malignancies in Ardabil from 1996- 1999, with a result of GC makes up of incidence rate of 49.1 in males and 25.4 in females , a higher incidence rate of GC in males than in females can also be observed from the result. 1732 cases have been recorded, with complete and precise data such as average age, specific incidence rates, principal cancer sites etc. in Semnan province where located in center of Iran from 1998 to 2002 illustrated GC was the highest incidence rate (39.96) among men and ranked the third highest rate (14.8) among women . During a 5-year period from 1996 to 2000, research contained 5884 cases of cancer diagnosed which consists of 3264 cases of males (55.5%) and 2620 cases of female (44.5%) in southern Iran, Kerman province. The incidence rates of GC in men (10.2) were as twice as women (5.1), while the incidence of colorectal cancer was the same (5.9) in both genders. Another research holds from 2002 to 2009 in south-west Iran, Khuzestan province showed a total case of 16,802 with 51.4% of males and 48.6% of females respectively and the result within GC is 4.31 per 100,000 women and 7.17 per 100,000 men. (Table 1)

Table 1. Overview of GC incidence rate in four provinces of Iran

province	location	men (%)	women (%)	reference
Ardabil	North-west	49.1	25.4	
Semnan	Center	40.0	14.8	
Kerman	southern	10.2	5.1	
Khuzestan	South-west	4.31	7.17	

3. Risk factors

3.1 *Helicobacter pylori* infection

Helicobacter pylori infection (*H. pylori* infection) is a gram-negative, micro aerobic *Helicobacter*, whose flagella allow it to settle in the human gastrointestinal tract. It has evolved diverse kinds of mechanisms to enhance its liability in stomach, such an acidic surrounding and improve its capacity to induce infection. One adaptation is urease which is an enzyme that hydrolyses urea and releases ammonia, neutralizing gastric acid in turns and allowing *H. pylori* to exist and colonize the gastric mucosa. Another major trait of *H. pylori* is receptor-mediated adhesion through outer membrane protein array includes lipoprotein A and B, outer inflammatory protein A, sialic acid binding adhesion and so one, in order to attach to the gastric epithelium .

H. pylori infection is the most prominent risk factor of GC and infects around half of the population worldwide. What's more, statistically 89% of non-cardia gastric cancer cases, accounting for 78% of cancer cases, were caused by *H. Pylori* infection . In Iran, *H. pylori* infection is the most salient hazard to GC and more than 80% of the population over past 40 years have a history of it . A large number of asymptomatic carriers make it demanding to eradicate *H. pylori* infection. Many factors determine the infection rate in a country such as income level, living conditions, geographical area etc. are both the determinants. Another important element is the mode of transmission. The main mode of transmission in developing countries is horizontal transmission among ordinary people, while the main mode of transmission in industrialized countries is through family members . Oral transmission seems to be the primary route of *H. pylori* infection which can explain why it usually occurs between parents and children as family members. Thus, sharing tableware during feeding seems essential for the establishment of infection. Fecal-oral transmission is another form of infection which mainly due to the intake of contaminated water due to unsatisfactory basic sanitary conditions .

A randomized trial and meta-analysis showed that after the removal of *H. pylori*, the structure of the stomach tissue in chronic gastritis and atrophic gastritis without intestinal metaplasia significantly returned to normal [12, 13]. A systematic review was confirmed that after the successful eradication

of *H. pylori*, atrophic gastritis can subside within one to two years . Population screening and eradication of *H. pylori*, which mean population testing and treatment strategy respectively can be a cost-effective method. However, this method has many potential limitations which include requests for large population participation, treatment failures because of antimicrobial resistance, and re-infections. Though the reinfection rate of *H. pylori* is often low, but it still exists. Therefore, vaccination would be a perfect intervention theoretically ; however, to date the development of preventive or therapeutic vaccines has been disappointing .

3.2 Dietary patterns

Dietary surveys found a negative correlation between GC and consumption of fruits. Citrus fruit, under the epidemiologic studies, are rich in micronutrients such as vitamin c and d b-carotene. Citrus fruit as well as vegetable rich in vitamin C, are more effective on GC prevention than normal fruit and vegetable. The mechanism of vitamin C that could prevent GC has been proven in lots of research.

In terms of red meat and dairy products, both shows positive correlation with GC. Even though neither type of foods shows enough evidence increasing the risk of GC on the molecular level, it should be attributed to the cooking process. Grilling is the main cooking method for red meat in Iran. It easily produces a compound called polycyclic aromatic hydrocarbons, a carcinogenic compound that increase the risk of GC based on many studies.

Furthermore. Dietary surveys also witness a negative association between GC and fish intake. Although the mechanism of protective role of fish is still inconsistent, it is commonly known that polyunsaturated fatty acid (PUFA), which is abundant inside fish meat, helps inhibit gastric carcinogenesis.

3.3 Micronutrients

3.3.1 Vitamin C

Diet, together with *H. pylori* infection is the two most important factors that lead to GC. Vitamin C (also known as ascorbic acid is one of the most common nutrients found in different kinds of foods. Vitamin C has various function for human body such as tissue repair and enzymatic production of neurotransmitters and improving human immune system. It has been proposed that Vitamin C is an important protective factor against GC . Gastric juice vitamin C may be protective against gastric carcinogenesis by reduction of oxidative stress at the gastric mucosal surface, vitamin C reduces the formation of N-nitroso compounds (NOCs) in gastric juice and scavenges reactive oxygen metabolites (ROMs) in gastric mucosa .

During an experiment in vitro, Vitamin C are proved to have a significant dose dependent growth inhibition on gastric AGS and MKN45 cells but this effect was significantly reduced at levels similar to those in gastric juice of *H. pylori* infected patients (<50 μ M) (table 2). Another experiment reveal that vitamin C had no prominent effect on *H. pylori* growth, hemagglutination activity, or adherence ability to gastric AGS cells compared with untreated controls, it significantly enhanced *H. pylori* associated apoptosis and induced cell cycle arrest in these cells .

Table 2. Dose dependent growth inhibition of Vitamin C on AGS and MKN45

Ascorbic acid(μ M)	AGS		MKN45	
	Protein	Proliferation	Protein	Proliferation
10	113(9)	104(3)	102(5)	101(4)
50	95(10)	89(5)	97(8)	90(2)
100	59(8)	47(5)	78(3)	83(2)
200	0*	0*	38(1)	16(3)
400	0*	0*	4(3)*	0*

*p<0.05 of demonstrated percentage untreated controls represents average

Besides, the protective role of gastric juice vitamin C against gastric carcinogenesis could also be related to a direct effect on *H. pylori*. Apart from the effect applying in on gastric AGS and MKN45

cell, vitamin C may also be capable of inhibiting H pylori growth. Jarosz et al treated H pylori positive dyspeptic patients with vitamin C 5 g daily for four weeks. To discover the relationship, Jarosz et al used 5 g of vitamin C to test their effect on H. pylori infected patients. The results reveal that 30% of patients who successfully recovered, have much higher vitamin C in gastric juice than in patients who have not eradicate the H. pylori infection. Moreover, another recently study on gerbils suggests that the H. pylori infection on gastric cells removed significantly after feeding them with 10 mg of Vitamin C every day.

3.3.2 Zinc

The mechanism by which Zinc interferes with GC is still unproved . Zinc may make some contribution for the protection of gastro-intestine tract, which is continuously exposed to loads of pathogens and toxic agents. The way in which the gastro-intestinal epithelium constitutes a barrier involves intercellular junctional complexes between neighboring cells that provide a continuous seal around the apical region of the cells. It has been reported that there is a neutrophil accumulation within epithelial crypts and in the gastro-intestinal lumen associated with gastro-intestinal disease and epithelial injury. Neutrophils accumulate within epithelial crypts as well as the gastro-intestinal lumen are correlated with several gastric injury and disease. Gut membrane injury resulted from zinc deficiency is associated with inflammatory cell infiltration. It is reasonable to find that patients with chronic intestinal permeability disorders may combine with a reduced level of mucosal zinc. Zinc deficiency may affect the intercellular junctional complexes structure of gastro-intestinal epithelial cells and therefore, allowing a more extensive migration of neutrophils. Zinc deficiency may have a devastating effect on structure and function of membrane barrier .

3.3.3 Selenium

Selenium, another highly studied micronutrients in the field of epidemiology, showed a significant negative correlation between selenium and GC risk, most likely on gastric cardia cancer. A study measured blood selenium levels in 300 Iranian adults from Ardabil with several risks of GC built a hypothesis that the high rates of GC in Ardabil may be partly attributable to selenium deficiency . 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 GC. The incident of GC in Ardabil is significantly higher than the rest of region where the serum selenium levels of healthy adults are high. Selenium is known as reducing the oxidative stress and repairing DNA and apoptosis by promoting p53 tumor suppressor gene.

3.4 High Salt Intake

In 2007, salt was classified as a risk factor for GC on molecular level. Study from Ardabil, northwest Iran, showed a positive correlation between patients who have gastric cancer and preferred food contain higher salt. Food contain high salt may help accelerate the speed of expression and translation of CagA gene. It is a gene which makes H. pylori destroy gastric epithelial cell function. Moreover, the gastric epithelial cells are easier to expose from NOCS. This is because the mucous, which is secreted by epithelial cell, become less viscous due to high salt diet. In addition, high salt diet may increase the chance of gastric epithelial cell to get inflammation, which increase cell proliferation and therefore, increase the mutation rate of cell. In experiment, H. Pylori infected gerbils show symptom of Chronic hypergastrinemia after high salt intake. Chronic hypergastrinemia can made the parietal cell loss together with H. Pylori infection and eventually become GC .

3.5 Smoking

Smoking is a one of the most common risk factors which causes different cancer. Research shows that at least 14 types of cancer, including GC, are correlated to smoking. Smoking is more common on Iranian men is common and according to the data, about 30% of men aged 25 or over smoke

regularly . A meta- analysisist points out that smoking increases risk for both cardia and non-cardia cancers with a relative risk of 1.87 and 1.60.

The cancer risk in past smokers can remain up to 14 years after quitting of smoking. Furthermore, opium has also been found to correlated to higher risk of GC. There is a striking male predominance in gastric cancer hypothesized to be the result of a greater number of male smokers, however studies suggest that this is not the case. Instead, the male predominance is related to intestinal histological subtype and is due to marked delay in the development of this type of tumor in females prior to 50–60 years of age .

While the exact mechanisms are still vague, it has been supposed that a carcinogenic substance called oxygen radicals produced when smoking. These substances increased apoptosis in the gastric epithelium, further promoting the progression of carcinogenesis.

3.6 Obesity and Physical Activity

GC is more likely to affect the needy one. Although the reason is not clear enough, some Researchers indicate that this may be in connection with an excess of physical activity, exposure to high-risk jobs and having the poor diet habits compared with the rich one. Miserable studies have studied the link between physical training and GC. More specifically, prestigious research has showed that excessive exercise will raise the relative incidence rate of GC. However, a case-control study did not support the former result and likewise, recently the larger EPIC study has found out a unobserved result in cardia-subset, which is the non-cardia distal cancer is negatively correlated with the time spent on cycling and sports activities.

The growing trend of obesity and sedentary lifestyles has attracted more and more attention in society, and many are worried about whether they will be the primary factors for many cancers . Unlike colon cancer or esophageal cancer, where obesity is a main hazardous factor, the relationship between it and GC is not direct enough and it is significative to analyze it as a subgroup. In his meta-analysis, Yang et al. has shown that the subjects who are obese and/or overweight had a around 55% ascent in danger of gastric cardia cancer . Research by Yang et al. did not indicate the additional risk of gastric non-cardia cancer for obesity group. In Asian populations, the association between obesity and GC is not obvious enough, which may be due to the higher proportion of non- cardia cancer. The mechanism of the negative correlation or non-correlation between obesity and non-cardia gastric cancer may can be explained by large- scale study which hold by Wattage et al. which showed negative correlation between body mass index and atrophic gastritis .

3.7 Virtual Factor

Viruses are one of the emerging risk factors for gastric cancer. The herpes virus acquired during child's period is known to relate to several cancers, which contain lymphoma and nasopharyngeal carcinoma. Epidemiological data declares that the overall occurrence rate of EBV-related GC is low. In addition, with a meta-analysis of total 15,952 GC cases have showed that the risk of EBV-related cancer in men has doubled, and they are more likely to appear in the heart and body. A lymphoepithelioma-like histology test indicated that more than 90% of EBV was positive .

Furthermore, one research from Japan stated that the incidence of GC is lower in patients, compared with those are seropositive for human T lymphotropic virus type 1 (HTLV1) . Unlike EBV, because of the long-term immunosuppression, the gastric environment induced by HTLV1 is not suitable for *H. pylori*. So EBV can be a cofactor for *Helicobacter pylori*-related cancer. Another virus that may be take part in the occurrence of GC is human polyoma virus, which is JC virus. About 90% of the world's population is asymptotically infected with low-level JC virus. If activated during immuno-suppression, it is related to the fatal progressive multifocal leukoencephalopathy. [33,34]

4. Clinical Therapies: Neoadjuvant chemotherapy

For GC, in addition to surgical resection and excision of lymph gland, tumor relapse and metastasis are more essential than the existence of micro metastasis and hyperplasia and proliferation . Removal of the tumor can induce the production of tumor cell growth stimulating factors, which allows the tumor cells to germinate promptly and manufacture anti-chemotherapeutic drugs . Besides, if the quantity of tumor cells is small and with a high reproduction rate, therefore the doubling time is relatively short. Whatever, advanced tumor cells with a lower proliferation rate prolong their population doubling time and reduce their sensitivity to chemotherapeutic drugs. Hence the use of chemotherapeutics that do not aim at any cell cycle can decline the size of the tumor and enhance the reproduction rate. And consequently, increase the keen sense of cell cycle- specific chemotherapeutics . what's more, removal of the tumor before chemotherapy can not only kill the primary tumor but also restrain the growth of cancer cells.

It can be found out that at population level, two main primary prevention activities for gastric cancer include: improving eating habits and reducing the incidence of H. pylori infection because it is the main cause of GC. And the secondary prevention strategy is to use existing resources, mainly endoscopic methods as the gold standard for early detection . GC is comparatively susceptible to chemotherapy drugs, but neoadjuvant chemotherapy and surgical treatment are crucial as well. We found out that neoadjuvant chemotherapy is a novel approach for the remedy of late GC. There are no exact criteria on how to choose the adjuvant chemotherapy drugs. While considering about neoadjuvant chemotherapy for GC, we should not blindly pursue the result of chemotherapy and keep delaying the plan for surgery. Regular review of treatment and testing indicators and if the tumor volume is significantly reduced, then resection is the right choice .

5. Conclusions

Overall, this paper has constructed a relationship between the incidence of Iranian gastric cancer and several risk factors cover from specific H. Pylori infection, dietary habits, viruses to intake of micronutrients, as well as lifestyles including physical activities and smoking. Through the data collected, although eradication of H. pylori infection is a prospective strategy for decreasing the incidence of GC, most factors influence it are not virus instead of dietary pattern. Taking less salted food and increasing the intake of fruits and vegetables rich in Vitamin C can have a direct effecting on inhibiting the growth of H. pylori. Apart from dietary pattern, lifestyle also plays an essential role. Regular training can reduce the risk of being attacked by GC for the obesity group. Smoking cessation can also reach the same purpose so at last, two methods are provided to prevent GC, through transforming the diet pattern and regular inspection respectively. The fundamental purpose of this review is to raise people's vigilance to GC and reduce the incidence rate.

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