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Review Article

EPIDEMIOLOGIC EVIDENCE OF GASTRIC CANCER PROGNOSIS: ROLE OF DIETARY FACTORS

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ABSTRACT

There are geographic and ethnic differences in the incidence of gastric cancer around the world as well as with its trends for each population over time. The incidence patterns observed among immigrants change according to where they live. All of these factors indicate the close association of gastric cancer with diet. This review presents epidemiological evidence on the association between dietary factors and gastric cancer. Infection with Helicobacter pylori is a strong risk factor of gastric cancer however smoking, alcohol, diet, genetics and epigenetic factors may also play a role in the occurrence of this disease. The risk may be increased with a high intake of various traditional salt-preserved foods and decreased with a high intake of fruit and vegetables. Among them, vitamin C is a probable candidate supported by a relatively large group of epidemiological evidence. Consumption of green tea is possibly associated with a decreased risk of gastric cancer. In contrast, processed meat and N-nitroso compounds may be positively associated with the risk of gastric cancer. In conclusion, dietary modification by reducing salt and salted food intake, as well as by increasing intake of fruit and vitamin C, represents a practical strategy to prevent gastric cancer.

Keywords: Dietary habits, Gastric Cancer, Helicobacter pylori.

INTRODUCTION

Gastric cancer, a malignant tumour arises from the lining of the stomach. It is considered as one of the most prevalent cancers throughout the world, and ranks second in terms of cancer related deaths[1]. Worldwide it causes approximately 700,000 deaths every year[2]. In most of the cases it is either asymptomatic or may cause only nonspecific symptoms in its early stages. So, by the time symptoms occur, carcinogenesis process often reaches an advanced stage and may also metastasize which is one of the main reasons for its relatively poor prognosis. Infection with Helicobacter pylori is an established cause; however smoking, alcohol, diet, genetics and epigenetic factors may also play a role in the occurrence of this disease[3,4]. Various worldwide epidemiological studies have shown that there is a close correlation between diet and gastric cancer development. Dietary factors like pickled food, food rich in nitrite and high salt concentration and smoked food are reported to increase the risk. On the other hand it has been reported that black tea reduces the risk of gastric cancer due to its antioxidant properties[5]. In this review, we present epidemiological evidence for the association between dietary factors and gastric cancer, with particular reference to our recent work in our lab.

Dietary habit and gastric cancer in India

Gastric Cancer is considered as one of the most prevalent cancer throughout the world, and ranks second in terms of cancer related deaths (WHO). In India, the incidence of gastric cancer is overall less compared to the world. However, in Kashmir valley, it is amongst the first five cancers with a male dominance (Male: Female - 3.17:1). Studies show that dietary factors are probably the main reason for

its high incidence. Consumption of high salt content including salted tea and food along with Helicobacter pylori infection may be the possible reasons for the high incidence of gastric cancer in the Kashmiri population. Drinking of salted tea is a typical habit among this population. Green tea is boiled in water for long along with a pinch of sodium bicarbonate. It is then subjected to brewing until a reddish brown coloured extract is obtained. This salted alkaline solution is stored for a long period and used over for many days. Later it is mixed with water, salt and milk and taken in hot condition. Consumption of even more than 10 cups of this tea a day is a common phenomenon. In a study on Kashmiri population, Qurieshi et al showed that more than 2/3rd of the gastric cancer patients consumed more than 4 cups of salted tea per day[6]. A study from North India carried out on Kashmiri population between 2009 and 2011 recorded 776 gastric cancer patients (590 males and 186 females) having a median age of 55 and 60 years for males and females respectively. The age-adjusted rate (AAR) of gastric cancer among urban areas of India is (3.0–13.2) compared to the worldwide AAR (4.1–95.5).Worldwide, there has been a decline in the incidence of gastric cancer in the developed countries and this has been attributed to improved food hygiene, sanitation, and food preservation techniques. But, this declining trend has not been seen in certain parts of India[7].The regional variation in incidence of gastric cancer can be ascertained by the fact that gastric cancer in South Indian males has been reported to be more common than their North Indian counterparts[8]. Differences in dietary pattern along with use of alcohol and tobacco are considered to be potential risk factors. In a case–control study from Trivandrum, excess consumption of rice and chili, together with the consumption of high-temperature food were found to be independent risk factors for gastric cancer in multivariate analysis[9]. The incidence of gastric cancer in Mizoram has been reported to be the highest in India. The AAR in males and females are reported at 50.6 and 23.3, respectively [Indian Council of Medical Research (ICMR), First Report of the Population Based Cancer Registries Under North Eastern Regional Cancer Registry 2003-2004].In Mizoram, gastric cancer accounts for 30% of all cancer cases with a male-to-female ratio being 2.3:1; the median age for males and females was 58 years and 57 years respectively[10].The high prevalence of gastric cancer in Mizoram has mainly been attributed to dietary and unknown genetic interactions.

Dietary Risk Factors for Gastric Cancer

Epidemiologic studies throughout the world have shown a relationship between diet and gastric cancer risk. The diets that are most commonly linked to high gastric cancer risk are those that are rich in salted, pickled, smoked or poorly preserved foods, those with high meat content and those with low fruit and vegetable content[3]. A link between high salt consumption and increased gastric cancer risk has been reported in numerous studies[3]. Dietary salt intake varies widely among humans, and in some populations with a high incidence of gastric cancer, median dietary salt intakes of 46 g per day have been reported[11].In Colombia, the consumption of high levels of salt (as measured by high urinary sodiumto- creatinine ratios) was associated with an increased risk for precancerous gastric lesions (chronic atrophic gastritis, intestinal metaplasia and dysplasia) compared with what is observed in persons who consume lower levels of salt[12]. Additionally, a prospective study of a Japanese population, conducted over a 14 y period, reported that H. pylori-infected subjects consuming a high-salt diet had an increased risk of gastric cancer when compared with H. pylori-infected subjects who consumed lower levels of salt[13].Vitamin C has also been studied as a potential protective factor against the development of gastric cancer, likely through its antioxidant effects. Higher plasma levels of vitamin C have been associated with a lower risk for gastric cancer, irrespective of anatomic site[14].Epidemiological evidence supports the premise that both H. pylori and obesity are independent risk factors for gastric cancer[15].Obesity induced inflammation underlies increasingly common diseases, such as type II diabetes and atherosclerosis[16]. Importantly, several studies employing mouse models and focusing on the direct effect of adipose-derived factors on established tumors, have shown that obesity promotes cancers (e.g. colorectal and pancreatic cancer) and implicate systemic inflammation as an important component of the tumorigenic process[17]. Studies have supported the protective role of dietary folic acid against specified cancers[18]. A recent study also found that high dietary folate increased survival rates in gastric cancer

patients compared with low folic acid intake in advanced gastric cancer[19]. Green tea contains polyphenols, more commonly known as catechins. Antioxidant activities and the ability to inhibit the nitrosation of polyphenols have been isolated from green tea in both in vitro and in vivo studies[20]. In addition, recent research has proposed many other possible mechanisms for the cancer inhibitory effects of green tea, including modulation of signal transduction pathways, leading to the inhibition of cell proliferation and transformation, induction of apoptosis and cell cycle arrest, and inhibition of tumor invasion and angiogenesis[21]. Fruit and vegetables are rich sources of vitamin C. Vitamin C acts as an antioxidant and can quench reactive oxygen species produced in the gastric environment. It is also known to inhibit production of carcinogenic N-nitroso compound in the stomach (Fig 1)[22] .

Diet and *Helicobacter pylori*-induced gastric cancer

CagA affects multiple signaling pathways within gastric epithelial cells[23]. CagA is translocated into host epithelial cells by the *cag* type IV secretion system and activates β-catenin, leading to transcriptional up regulation of genes implicated in cancer. The CagA protein of certain *H. pylori* strains also can induce NFκB activation. Thus, the entry of CagA into host cells activates multiple signaling pathways that may increase the risk for malignant transformation (Fig 2)[23].

Iron Deficiency and Gastric Cancer Risk

Iron deficiency is associated with an increased risk for gastric cancer, as well as neoplasms that arise elsewhere in the gastrointestinal tract[24]. There are multiple mechanisms through which iron deficiency may arise, including blood loss and dietary deficiency of iron. Among the many possible

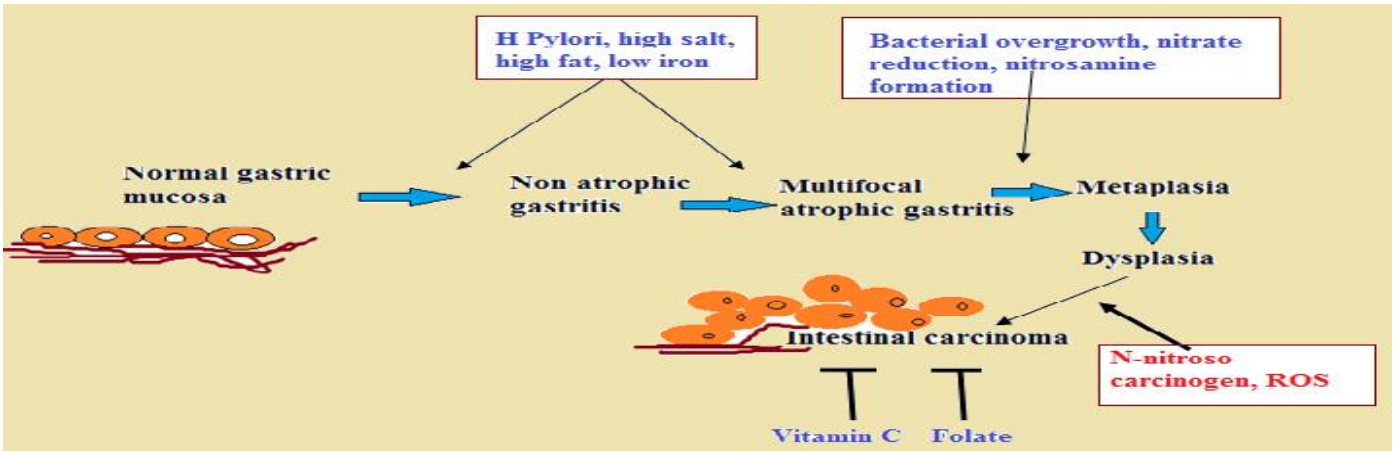

Figure 1: inhibition of production of carcinogenic N-nitroso compound in the stomach

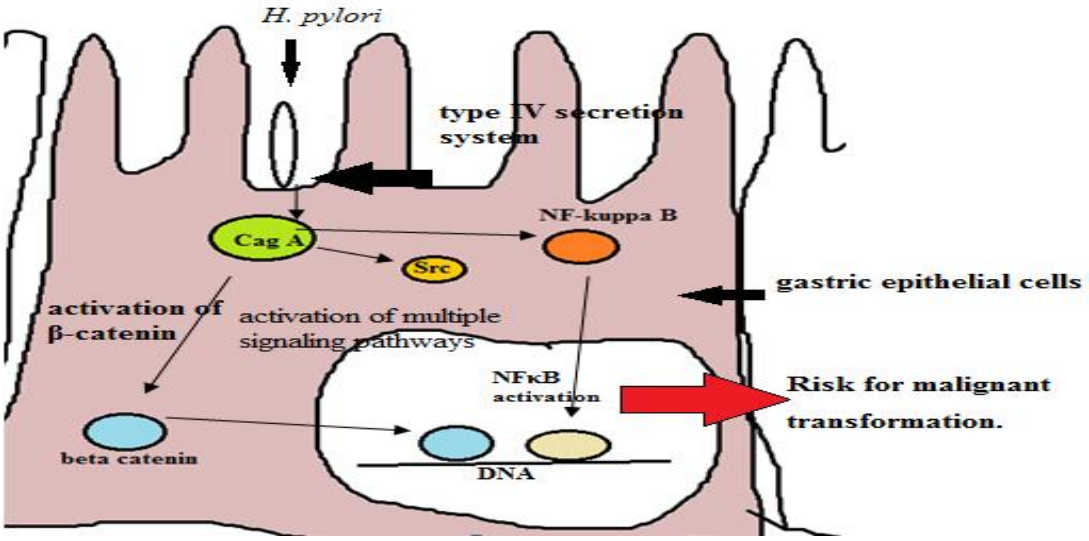

Figure 2: *Helicobacter pylori*-induced gastric cancer pathway

causes of blood loss, colonization by certain H. pylori strains has been associated with hemorrhagic gastritis and a resulting loss of iron[25].A recent study analysed the effect of dietary iron depletion on the development of H. pylori-induced cancer in gerbils infected with a cagA+ H. pylori strain[26] .H. pylori infection induced more severe gastritis in iron-depleted gerbils than in iron-replete gerbils. Gastritis also developed earlier in H. pylori-infected iron depleted gerbils compared with infected iron-replete gerbils[26].

CONCLUSION

Direct effects of several dietary constituents on the gastric epithelium might either raise or lower the threshold for malignant transformation. Also dietary components might damage the gastric mucosa, allowing increased entry of potent carcinogens inside the gastric tissue. Some dietary components are known to interact with immune receptors in the intestine thereby regulating intestinal immunity. Dietary composition might influence the composition of the gastric micro biota, or favour the proliferation of Helicobacter pylori variants. The composition of the diet may also influence epigenetic alterations, as shown in a recent study which reported that dietary folic acid supplementation protected against loss of global DNA methylation and markedly reduced the development of gastric inflammation. Dietary modification to reduce salt and salted food intake and to increase intake of fruit, particularly vitamin C as well as quitting smoking represents an effective, practical, low-cost means of preventing gastric cancer. In our laboratory, we are screening gastric cancer patients for ADH1B, ALDH2, CYP2E1, GSTM1, GSTT1, GSTP1, XRCC1 and TP53 genes polymorphisms where dietary habits of patients are also taken into account. This is done to find whether specific food habits actually modulate the risk of gastric cancer by interacting with the polymorphisms of study genes. In our study population, we have observed a tendency of excessive intake of certain food types like animal fat, high salt, pickle and salted tea among the patient group. Chili pepper intake may also be a risk factor for gastric cancer[27]. Capsaicin, the active part of the chili can participate in the carcinogenic process. It may act as an irritant to the mucosal layer of the stomach. However, its erosive role in gastric mucosa remains controversial[28]. Although not statistically significant, yet we observed the tradition of excessive intake of chili among some of our patients. Gastric cancer is a multifactorial disease where various genetic, epigenetic and environmental factors may interact in the prognosis of the carcinogenic progression. In our recently published review, we have tried to assess whether excessive consumption of alcohol contributes to the risk of cancer burden[4]. Thus our study also corroborates with the previously reported findings that suggest certain dietary factors aggravate the progression of gastric cancer.

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