[Frontiers in Bioscience 17, 1640-1647, January 1, 2012]

The role of diet in gastric cancer: still an open question

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TABLE OF CONTENTS

1. ABSTRACT

The risk of gastric cancer is often related to lifestyle and diet. There have been several studies on correlation between Nutrition and the risk of gastric cancer with different and sometimes contradictory results. Here we reviewed the role of nutrition as risk/protective factor in the development of gastric cancer.

2. INTRODUCTION

Gastric carcinoma (GC) was the leading cause of cancer-related death worldwide through most of the twentieth century. It still remains the fourth most common type of cancer worldwide with 943,000 estimated new cases per year (1). In many parts of world, however, the incidence of GC has gradually decreased, principally because of changes in diet, food preparation and other environmental factors.

Moreover it is important to discern between adenocarcinoma of the proximal stomach (cardia, GCC) and adenocarcinoma arising in other parts of the stomach (body, GNCC). In fact, whereas GCC is often related to diet and lifestyle while the GNCC is mainly related to *Helicobacter pylori* infection (2, 3). The prognosis of proximal cancers may be even worse than those of distal cancers (4).

Despite the incidence of GNCC has sharply declined in the past decades, the incidence of GCC has increased quite rapidly over the past thirty years in many Western countries (5).

The etiology of GC is likely multifactorial. A list of factors associated with an increased risk of GC is outlined in Table 1.

Table 1. Factors associated with increased risk of developing GC

ACQUIRED FACTORS
Nutritional
• High salt consumption • High nitrate consumption • Low dietary vitamin A and C • Poor food preparation (smoked, salt cured) • Lack of refrigeration • Poor drinking water • Obesity • High caloric consumption
Occupational
• Rubber workers • Coal workers
Others
• Cigarette smoking • *Helicobacter Pylori* infection • Epstein-Barr virus • Radiation exposure • Prior gastric surgery for benign gastric ulcer disease
GENETIC FACTORS
• Type A blood • Pernicious anemia • Family history • Hereditary nonpolyposis colon cancer • Li-Fraumeni syndrome
PRECURSOR LESIONS
• Adenomatous gastric polyps • Chronic atrophic gastritis • Dysplasia • Intestinal metaplasia • Menetrier's disease

Dietary factors and Western lifestyle are also thought to have an important role in gastric carcinogenesis, but evidence from cohort studies for such a role, particularly among Western populations, is lacking.

Many questions are still open especially about the role of diet in the development of GC. Here we review the overall findings from various epidemiological studies regarding the role of diet in the etiology of GC. We will base our discussion as much as possible on published reviews and meta-analyses, and evidence from prospective studies.

3. FRUITS AND VEGETABLES

The role of fruits and vegetables in the reduction of the risk for GC is also controversial, even if many studies have been published.

Fruits and vegetables are a rich source of carotenoids, vitamin C, folate, and phytochemicals, which may have a protective role in the carcinogenesis process. It is likely that modulation of xenobiotic-metabolizing enzymes, in particular phase II enzymes, contributes to this putative preventive mechanism. The mechanisms of antioxidant activity may be also possible. In 2007, an expert panel assembled by the World cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) demonstrated that diets high in fruits and vegetables protect against GC (6). This evaluation was based mainly on reports of case-control studies. Since then, however, several cohort studies have reported conflicting results. The joint WHO/FAO Expert Consultation in 2003 concluded that fruit and vegetables "probably", but not "convincingly", decrease the risk of GC (7). Successively, a report by the International Agency for Research on Cancer (IARC) concluded from the case-control studies comparing subjects from high fruit intake categories with subjects from low intake categories, that the mean OR was 0.63 (95% CI, 0.58-0.69), range 0.31-1.39 (8). Regarding vegetables, IARC arrived for the available case-control studies at a mean OR of 0.66 (95% CI, 0.61-0.71), range 0.30-1.70. The five cohort studies on vegetables and GC showed a mean RR of 0.94 (95% CI, 0.84-1.06), range 0.70-1.25 comparing high to low intakes. For both fruits and vegetables, the IARC analyses showed significant heterogeneity between the ORs from case-control studies, but not from cohort studies (8). In contrast, most of the 20 evaluable case-control studies provided statistically significant ORs below 1.0 and a summary value of 0.66 (95% CI, 0.61-0.71) (9). The reason why case-control studies were more likely to show an inverse association is not clear, although one explanation might be the recall bias. Furthermore, people with preclinical symptoms of GC or stomach disorders may have changed their dietary habits months or years before diagnosis. A meta-analysis of cohort studies published up to 2004, reported non-significant summary estimates (RR for the highest *versus* the lowest consumption category) of 0.89 (95% CI, 0.78-1.02) for fruit (13 studies) and 0.98 (95% CI, 0.86-1.13) for vegetables (8 studies) (10). However, the inverse association became more clear when the studies were limited to those with incidence data (seven studies for fruit: RR = 0.82, 95% CI, 0.73-0.93; five studies for vegetables: RR=0.88, 95% CI, 0.69-01.13) and with follow-up periods of 10 years or longer (three studies for fruit: RR=0.66, 95% CI, 0.52-0.83, two studies for vegetables: RR=0.71, 95% CI, 0.53-0-94).

Subsequent to the evaluation by the IARC and the meta-analysis of Lunet *et al.*, several cohort studies have reported the association with fruit and vegetables (8, 10). In a Swedish study (139 GC cases among 70.000 men and women) subjects who consumed 2.5 servings of vegetables or more per day had a HR of 0.56 (95% CI, 0.34-0.93) compared with those who consumed less than 1.0 serving per day (11). The respective HR for fruit consumption was 0.86 (95% CI, 0.52-1.43). In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, conducted among 521,457 men and women living in 10 European countries, it was showed no significant association between the consumption of fresh fruits, total vegetables, or specific groups of vegetables and risk for GC regardless of anatomic site, although a non-significant inverse association was observed for citrus or onion and garlic and risk for GCC only (12).

Another large European cohort study reported the results on fruit and vegetable consumption and GC by anatomic site. In the prospective analysis of the Alpha-tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, among 29,133 male smokers, the high consumption of fruits was associated with a lower risk of GNCC, but not with GCC (13). However, consumption of vegetables was

not associated with risk for GCC or GNCC in the ATBC Cancer Prevention Study (13).

In a Japanese study (400 GC cases among 40,000 men and women) the RR associated with intake 1 day or more per week compared with less than 1 day per week was 0.64 (95% CI, 0.45-0.92) for yellow vegetables, 0.48 (95% CI, 0.25-0.89) for white vegetables, and 0.70 (955 CI, 0.40-1.00) for fruit (9). RRs associated with the quintile of total vegetable consumption were 1.00, 0.86, 0.75, 0.90 and 0.75 (for trend, P=0.17). Moreover this association became clearer for the differentiated type of GC, at 1.00, 0.96, 0.78, 0.88 and 0.53 (for trend, p = 0.03). This study suggests that vegetable and fruit intake, even in relatively low amounts, is associated with a lower risk of GC.

Recently, an Iranian case-control study, conducted among a total of 635 cases (231 cases of GC), demonstrated a reduced risk for consumption of fresh fruits overall, and citrus fruits in particular, those who ate citrus fruits more than 3 times per week had about 70% lower risk than those who never or infrequently ate this group of fruits (OR = 0.28; p for trend <0.01) (14).

In summary, the consumption of fruits and vegetables, particularly fruits, is probably protective against GC. Nevertheless, it remains unknown which constituents in fruits and vegetables play a significant role in GC prevention.

Noteworthy the role of Allium vegetables, that was investigated in a total of 2 cohort studies, 27 case-control studies and 2 ecological studies; and 1 cohort study, 16 case control studies, and 2 ecological studies investigated garlic (6). There was also one relevant intervention study that combined allitridium (a garlic extract containing triallysulphides) and selenium supplements. Most of the studies showed decreased risk with increased intake (6). Meta-analysis of cohort data showed a 23% decreased risk per 50 g Allium vegetables per day (6). Meta-analysis of case-control data showed a 20% decreased risk per 50 g Allium vegetables per day and a 59% decreased risk per serving of garlic per day (6). A single study of combined selenium and allitridium supplements showed a statistically significant decreased risk in men but not women, after 5 years of follow-up. In conclusion, though not copious and mostly from case-control-studies, is consistent, with a dose-response relationship, so Allium vegetables probably protect against gastric cancer.

4. SALT AND SALTED FOODS

In experimental studies in rats, ingestion of salt is known to cause gastritis and, on co-administration, to enhance the carcinogenic effects of known gastric carcinogens such as *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) (15, 16). A high salt concentration in the stomach destroys the mucosal barrier and leads to inflammation and damage such as diffuse erosion and degeneration. Further more, the induced proliferative change may act to promote the fact of food-derived carcinogens. It is therefore biologically plausible that high salt intake increases the risk of gastric cancer in humans.

The INTERSALT study, in which were randomly selected 24-h urine samples from 39 populations from 24 countries (n = 5756), Joossens and colleagues analyzed median sodium levels in samples from subjects aged 20-49 years in relation to the national gastric cancer mortality rates (17). For the 24 countries the Pearson correlation of gastric cancer mortality with sodium was 0.70 in man and 0.74 in women (both P < 0,001). In an ecological study of 65 rural counties in China, the consumption of salt-preserved vegetables was correlated with gastric cancer mortality (r = 0.26 in men, 0.36 in women) (18).

A Japanese ecological study of five selected areas in Japan showed an almost linear correlation between the cumulative mortality rate of gastric cancer in subjects up to 75 years of age and the urinary salt excretion level in 24-h urine samples (19, 20).

Many but not all case-control studies have found a positive association between gastric cancer and they take of highly salted foods such as salted fish, cured meat, and salted vegetables or the use of tables salt (21). Several studies have quantitatively estimated the total salt intake and found a strong positive association with the risk of gastric cancer, and several other studies evaluated its associations with the intake of salted food such as salted fish and vegetables. In an evaluation performed by the WCRF and the American Institute for Cancer Research (AICR) in 2007, 3 cohort studies, 21 case-control studies and 12 ecological studies reported an association between salt or salted food and risk of gastric cancer (6).

Moreover, several recent case-control studies have also revealed an association between salted food and the risk of gastric cancer (22-25).

Four recent studies, between 2002 and 2006, reported the association between the consumption of salted foods (slated fish pickled foods) and the increased risk of gastric cancer (26-29).

These findings imply that either the intake of highly salted food increases the risk of gastric cancer or that it is merely a good marker of a preference for salted food or salt intake in general. An alternative explanation for the strong association between highly salted food and gastric cancer might involve the presence of chemical carcinogens as N-nitroso compounds, which are formed by reacting nitrate or nitrite during the process of preservation and during digestion in the stomach. Recent meta-analysis based on six prospective studies and nine case-control studies showed that the consumption of processed meat was associated with an increased risk of gastric cancer (30). Of note, processed meat often contains chemical carcinogens such as the N-nitroso compounds as well as high amounts of salt.

5. VITAMINS AND MINERAL

Intake of several other micronutrients has been associated with decreased gastric cancer risk, though specific interventional trials are limited. The majority of studies have shown vitamin C intake to be protective, and low serum levels of vitamin C have been associated with increased

risk of GC in Northern China and South Korea (31-36). Ecologic, case-control, and cohort studies have shown that increased serum levels and intake of carotenoids are associated with decreased gastric cancer risk (31, 33, 34, 37). Correa *et al.* state in their review then low serum levels of beta-carotene and alpha-tocopherol, but not of vitamin C, are associated with gastric dysplasia, and that *Helicobacter pylori* infection is associated with lower levels of vitamin C in the gastric juice (38). Several studies have found a significant prospective effect of selenium intake, and a study by Scieszka *et al.* showed that patients with gastric cancer had lower plasma concentrations of selenium than dead healthy age-matched control subjects (39). Limonene, the oil found in citrus fruit peel, has shown a prospective effect in several animal studies (40, 41). Flavonoids and kaempferol, widely distributed in plant foods, may afford protection as well (42).

Blot *et al.* performed a study in Linxian, China, were stomach cancer mortality rates are among the highest in the world and intake level of several micronutrients is chronically low (43). Their results showed the supplementation with beta-carotene, vitamin E, and selenium reduced gastric cancer mortality by 21% and the supplementation with retinol and zinc reduced gastric cancer prevalence by 62%. These results suggest that a combination of micronutrients may confer protection in micronutrient-deficient populations.

A chemoprevention trial of gastric dysplasia in which 2 g vitamin C or 30 mg beta-carotene supplements (as antioxidants) and anti-*Helicobacter pylori* therapy were tested singly or in combination for 6 years in Columbia, demonstrated that all three treatments were successful regarding lesion regression rates, with no additional benefit from combining treatments (44). However, *Helicobacter pylori* treatment seemed to be only effective when given singly; some indications of adverse effects were seen when it was administered together with beta-carotene or vitamin C. The effects of the treatments on lesion progression were less clear.

A recent case-control study conduced in Northern Italy between 1997 and 2007 (including 230 patients with incident, histologically confirmed gastric cancer and 547 frequency-matched controls) showed protective effect of the vitamins and fiber dietary pattern against gastric cancer risk (45).

6. ALCOHOL

Data from epidemiologic studies provide little support for harmful effect of alcohol on the development of gastric cancer. The relationship between alcohol consumption and gastric cancer risk remains controversial. An early meta-analysis of 14 case-control studies and two cohort studies reported that alcohol consumption was associated with a modest increase in risk of gastric cancer; the summary relative risk for an increase of 25 g per day of alcohol was 1.07 (95% CI 1.04-1.10) (46). However, recent data from four large prospective cohort studies and prospective analysis of data from and automated database provide little support for the association between total alcohol consumption and gastric cancer risk (47, 48). Data from the Norwegian cohort suggests that alcohol may interact with smoking to increase gastric cancer risk. In that study, smoking doubled the risk for gastric cancer, and alcohol consumption had no significant association with the risk, but combined high exposure to cigarettes (>20/day) and alcohol (>5 occasions/14 days) increased the risk of gastric non-cardia cancer 4.9-fold (95% CI 1.90-12.62) in comparison with nonusers of both cigarettes and alcohol (47). Findings have also been mixed regarding the relation of alcoholic beverage type to gastric cancer risk (47, 49, 50).

7. NITRATE, NITRITE AND NITROSAMINE

There are two sources of nitrosamines that humans are exposed to, namely performed exogenous nitrosamines and nitrosamines produced endogenously from nitrate and nitrite (51, 52). Performed nitrosamines are present mainly in nitrite-cured meat and fish and other foods, smoked, pickled and salty preserved foods, and alcoholic beverages (beer and whiskey) (51, 52). Nitrate, a natural compound, is present in vegetables and drinking water[51,52] and is used as a food additive in cheese and cured meat (53). N-nitroso compounds are also found in tobacco products, drugs, and industrial material (51). Dietary nitrate can be reduced to nitrite by oral bacteria and then to N-nitroso compounds (e.g. nitrosamines) by acid-catalyzed and bacterial nitrosation in the stomach through the reaction with compounds such as amines, amides and amino acids (51, 53).

N-nitroso compounds have been found to be carcinogenic in animal studies (51). Two nitrosamines (N-nitrosodiethylamine and N-nitrosodimethylamine) are classified as probably carcinogenic to humans (group 2A) by the IARC (54). Epidemiologic studies suggest a positive association between nitrosamines and gastric cancer risk, but the data are still inconclusive (52). Most epidemiologic investigations on nitrosamine and related food intake and gastric cancer risk have been case-control investigation, which support a positive association of nitrite, nitrosamine, processed meat and fish, preserved vegetables and smoked food intake with risk of gastric cancer (52).

Only a few prospective cohorts have evaluated the association between intake of nitrate, nitrite or nitrosamine and risk of gastric cancer, and the findings are not entirely consistent. In the Netherlands Cohort Study, intake of nitrate was associated with gastric cancer risk whereas intake of nitrite was non-significantly but positively associated with the risk (44, 53). There was no association with intakes of nitrate, nitrite or N-nitrosodimethylamine and risk of gastric cancer in a Finnish cohort study (55). The EPIC cohort study found no association between dietary intake of N-nitrosodimethylamine and gastric cancer risk, but endogenous formation of N-nitroso compounds was significantly associated with risk for gastric non-cardia cancer (relative risk 1.42, 95% CI 1.14-1.78 for an increase of 40 microg/day) but not with gastric cardia cancer (relative risk 0.96, 95% CI 0.69-1.33) (56). Data from the EPIC cohort also suggested a possible interaction of endogenous of nitrous compounds with *Helicobacter pylori*

infection or plasma vitamin C levels; the positive association between endogenous formation of nitrous compounds and risk for gastric non-cardia cancer was present only in those who were infected with Helicobacter pylori or those who had reduced plasma vitamin C levels (56).

Processed meat, an important source of N-nitroso compounds, refers to those preserved by adding nitrate, nitrite or salt, or by smoking (30). In a meta-analysis that summarized available evidence from six prospective cohort studies and nine case-control studies published from January 1996 through March 2006, the summary relative risks for an increment in processed meat consumption of 30 g per day (approximately half of an average serving) were 1.15 (95% CI 1.04-1.27) for the cohort studies and 1.38 (95% CI 1.90-1.60) for the case-control studies (30). In the EPIC cohort, when the association between processed meat and gastric cancer was evaluated by anatomic site, each 50 g per day increase in processed meat was associated with a significant 2.45-fold increase in GNCC but not with GCC (57).

8. MISCELLANEA

Other foods are investigated with contradictory and little significant evidences. Many authors have investigated the correlation between the consumption of green tea and risk of GC. There was no data from case-control studies nested within prospective cohort studies that showed significant associations between the consumption of green tea and the risk of GC (58-61). However, the results from Galanis DJ *et al*. suggested a higher risk of GC in men consuming green tea, whereas those of Sasazuki S *et al*. suggested a decreased risk in women consuming green tea (58, 61). The number of retrospective case-control studies which found no association between the risk of GC and the consumption of green tea nearly equals that which reported a positive association (62-72). More recently Kuriyama S *et al*. found that green tea consumption was not related to GC-specific mortality (73).

9. CONCLUSIONS AND PERSPECTIVES

Overall, prevention of GC is not dependent on supplementation with a single food or nutrient but instead is associated with an increase in a variety of nutrients and phytochemical rich plant foods, as well as attention to salting and cooking of meat.

Probably more information about lifestyle and dietary habits could reduce the risk of GC. Azevedo LF *et al*. suggest that simply increasing vegetable consumption by 100g/person/d could reduce the GC mortality rate by one third (37).

10. ACKNOWLEDGMENTS

M. Berretta, A. Cappellani and A. Lleshi contributed equally to the paper. The authors would like to thank Paola Favetta for her expert assistance in the revision of language and preparation of the manuscript.

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Key Words: Gastric cancer, Risk, Foods, Salt, Alcohol, Micronutrients, Review

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