Diet, *H pylori* infection and gastric cancer: Evidence and controversies

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**Abstract**

Despite decreasing incidence and mortality rates, gastric cancer (GC) still remains the fourth most common cancer and the second most common cause of cancer-related deaths worldwide. Due to the limited treatment options, at present, prevention is likely to be the only effective means of controlling this disease. The success of a prevention strategy depends upon the understanding of etiological and pathogenic mechanisms underlying gastric carcinogenesis. The etiology of GC is multi-factorial, however, in the recent years, mounting evidence suggests that environmental factors play a key role. The most important environmental factors implicated in the pathogenesis of GC are diet and *H pylori* infection. Thus, modifications in lifestyle and dietary habit associated with eradication of *H pylori* infection could hypothetically represent the most promising potential targets for GC prevention. In this review we will address the evidence and the controversies on the role of these agents in non-cardia GC by focusing on retrospective and prospective observational studies and interventional trials.

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**Key words:** Gastric cancer; *H pylori*; Diet; Observational studies; Intervventional dietary trials

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**INTRODUCTION**

Despite the decreasing incidence and mortality rates observed worldwide over the last 50 years, gastric cancer (GC) still ranks as one of the most frequent and lethal cancers worldwide[1]. Today, GC is the fourth leading cancer type in incidence accounting for almost a million new cases diagnosed annually (International Agency for the Research on Cancer-IARC 2002)[2]. At present, primary or secondary prevention are likely to be the most effective means of reducing the incidence of and mortality from this disease. However, to be successful, this strategy depends upon knowledge of the etiologic factors involved in gastric carcinogenesis.

Topographically, GC may arise in the cardia of the stomach or more distally (non-cardia cancer)[3]. Besides the individual genetic susceptibility, epidemiological data suggest that environmental factors are the predominant cause of this disease even if the etiology and possibly the pathogenesis of these two types of cancer may be completely different[2-3].

The most important factors thought to be responsible for non-cardia GC development are diet and *H pylori* infection. In this review we will address the evidence of and the controversies on the role of these agents in non-cardia GC by focusing on retrospective and prospective observational studies and interventional trials.

**DIET AND GASTRIC CANCER**

The relationship between diet and cancer has been clearly demonstrated since the 1930s, in a series of experimental classical studies in which severe caloric restriction markedly reduced the occurrence of cancer in rodents[4]. In 1982 the World Health Organization (Food & Agriculture Organization) stated that eating habits were the main factor involved in GC risk.

Numerous epidemiology studies aimed at evaluating the role of diet in gastric carcinogenesis have been carried out both in high- and low-risk geographic areas (Table 1, Table 2 and Table 3). Despite the lack of homogeneity of age, ethnicity, socio-economic status of the populations studied as well as the different methodological approaches, one of the most remarkable features emerging from these studies is the consistency with which certain foods are reported as being important in the modulation of risk of developing GC.

**Observational epidemiology studies**

The majority of the case-control epidemiological studies[5-20] have shown that high intake of salted, pickled or smoked foods, as well as dried fish and meat and refined carbohydrates significantly increases the risk of developing
Table 1  Epidemiological studies (population-based case-control) on dietary factors and gastric cancer

| Author                | Yr  | Geographic area | Case/Control | Increased risk                  | Decreased risk            |
|-----------------------|-----|-----------------|--------------|---------------------------------|----------------------------|
| Risch HA             | 1985| Canada           | 246/146      | Nitrite, chocolate, carbohydrates | Fiber, Vit. C              |
| Buatti E             | 1990| Italy            | 1016/1159    | Nitrites, protein                | Vit. C, β-carotene, α-tocopherol, vegetable fat |
| Graham S              | 1990| USA              | 295/293      | Sodium, fat, retinol             | β-Carotene, raw vegetables, onions, cucumbers |
| Ramon JM             | 1993| Spain            | 117/234      |                                | Vit. A, Vit. C              |
| Kaaks R             | 1998| Belgium          | 301/2851     | Vit. A, Vit. B12, mono, disaccharides | Polysaturated fat, fat, fiber, fiber, fiber, fiber, fiber |
| Lopez-Carrillo LD    | 1999| Mexico           | 220/2752     | Protein, saturated fat, cholesterol | Polysaturated fat, fat, fiber, fiber, fiber, fiber |
| Mathew A             | 2000| India            | 194/305      | Rice, spicy foods, chili, high-temperature food | -- |
| Palli D              | 2001| Italy            | 382/561      | Protein, nitrite, sodium          | Vit. C/B6, β-carotene, α-tocopherol, nitrates |
| Mayne ST             | 2001| USA              | 352/687      | Animal protein, cholesterol, Vit. B12, nitrite | Fiber, β-carotene, folate, Vit. C |
| Jedyrczowski W       | 2001| Poland           | 80/--        | Carbohydrates                    | Vit. E, β-carotene         |
| Hamada GS           | 2002| Brazil           | 97/192       | Beef                             | Fruits                     |
| Chen H              | 2002| Nebraska         | 124/449      | Saturated fat                    | Fiber, Vit. C              |
| Hara M              | 2003| Japan            | 149/287      |                                | Cruciferous vegetables, mushrooms |
| Nomura AM            | 2003| Hawaii           | 300/446      | Processed meat, bacon            | β-carotene, Vit. C, Vit. E, folate |
| Lagiou F             | 2004| Greece           | 110/100      |                                | Flavonone                  |
| De Stefani E         | 2004| Uruguay          | 240/960      | Salted-stewed meat, rice, tuber  | Vegetables, legumes, fruit, black tea |

Table 2  Epidemiological prospective cohort studies on association between dietary factors and GC (1990-2004)

| Author                | Yr  | Geographic area | Subjects | FU yr | Increased risk                  | Decreased risk            | No effect                  |
|-----------------------|-----|-----------------|----------|-------|---------------------------------|----------------------------|----------------------------|
| Chyoun PH            | 1990| USA (Hawaii)    | 8006     | 18    | Carbohydrates, salted-fish, bacon, cooked cereals, milk | --                        | Green/cruciferous vegetables, -- fruit |
| Kneller RW           | 1991| USA             | 17633    | 20    | Alcohol, broiling meat          | Fruit                     | --                         |
| Kato I              | 1992| Japan           | 9753     | 6     | Alcohol, broiling meat          | Fruit                     | --                         |
| Nomura A            | 1995| USA (Hawaii)    | 8006     | 25    | Fruit, vegetables               | Alcohol                   | --                         |
| Dorant E            | 1996| The Netherlands | 120852   | 3.3   | Onions                          | Leek, garlic              | --                         |
| Goldbohm RA         | 1998| The Netherlands | 120852   | 4.3   | Onions                          | Black tea                 | --                         |
| Ocke MC             | 1998| The Netherlands | 12763    | 25    | Vegetables, fruit, fiber-rich cereals | --                        | --                         |
| Terry P             | 1998| Sweden          | 11946    | 25    | Fruit                           | --                        | --                         |
| Galanis DJ          | 1998| USA (Hawaii)    | 11907    | 14.8  | Coffee                          | Pickled vegetables, dried/salted fish | --                         |
| Knekt P            | 1999| Finland         | 9985     | 24    | Nitrites, vitamins, NMHA       | Vegetables                | Whole grain, Folate, Vit. E, carotene, lycopene, fibers, BHA, BHT, Green tea |
| Jansen MC           | 1999| Netherlands     | 12000    | 25    | Refined grains                  | Fruit                     | --                         |
| Botterweck AA       | 2000| The Netherlands | 120852   | 6.3   | Retinol, carotene               | Vit. C                    | --                         |
| Tsubono Y           | 2001| Japan           | 26311    | 8     | Vegetables                      | Vegetables, citrus, fruit, whole grain | --                         |
| McCulloch ML        | 2001| USA             | 1200/000 | 14    | Vegetables                      | Vegetables, citrus, fruit, whole grain | --                         |
| Nagata CS          | 2002| Japan           | 33304    | 7     | Soy products                    | Green/yellow vegetables, fruit, -- | --                         |
| Ngoan LT           | 2002| Japan           | 13000    | 10    | Processed meat, cooking oil, pickled food, soup | -- | -- |--|
| Kobayashi M         | 2002| Japan           | 39993    | 10    | Meat pattern                    | Vegetable and fruit pattern | --                         |
| Masaki M            | 2003| Japan           | 5765     | 10    | Rice/snack pattern              | Western breakfast pattern | --                         |
| Khan MM            | 2004| Japan           | 3158     | 18    | Miso soup, Miso soup, Miso soup | -- | -- |--|
| Kim MK            | 2004| Japan           | 42112    | 10    | Traditional dietary pattern     | Healthy dietary pattern   | --                         |
| Sasaraeki S         | 2004| Japan           | 72743    | 11    | Red and processed meat, ENOC    | Green tea                 | --                         |
| EPIC                | 2006| Europe          | 521457   | 6.6   | Total vegetable intake, Onion, garlic | Dietary Vitamin C         | --                         |

Effect limited to women; Effect limited to men; FU: follow-up; NDMA: N-nitroso dimethylamine. EPIC: European prospective investigation into cancer and nutrition study; BHA: butylated hydroxyanisole; BHT: butylated hydroxyltoluene (cooking fats, oils, mayonnaise, creamy salad dressing, dried soup); ENOC: endogenous nitroso compounds.

GC while fiber, fresh vegetables and fruits were found to be inversely associated with GC risk (Table 1).

High consumption of refined carbohydrates has been shown to be associated with a significant increased risk of developing GC with an estimated odds ratio (OR) ranging from 1.5 to 8.73/100 mg of daily intake. The increased trend in risk appeared particularly high in females (OR highest quartile of consumption frequency [Q4] vs lowest quartile [Q1] 14.8). High consumption of saturated fat and cholesterol enhanced the risk of cancer for intestinal

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type GC (OR Q4 vs Q1 4.37; 95% CI 1.89-10.12 for saturated fat and OR Q4 vs Q1 2.39; 95% CI 1.23-4.64 for cholesterol)\[^8\].

The analysis of dietary micronutrients (vitamin C, vitamin E, carotenoids, fiber, flavonoids and selenium) commonly held to be protective against GC yielded conflicting results. While evidence on the protective effect of beta-carotene has been very consistent, the approximate halving risk associated with vitamin C intake, reported in some studies (OR ranging from 0.3; 95% CI 0.1-0.8 to 0.60; CI 0.41-0.88)\[^8,9,12,13\] has not been confirmed in others\[^3,8,18\].

Epidemiological approaches of case-control design could, in part, account for these contrasting results. Indeed, observational case-control studies are biased by the retrospective assessment of exposure to dietary risk factors: the onset of the symptoms affects the dietary habit and it is difficult to determine it following the diagnosis of cancer (“recall-bias”).

Observational cohort studies, in which the evaluation of diet is unaffected by symptoms, should ideally provide much more reliable evidence. Analysis of the data obtained in 21 studies involving a total of 1 651 231 individuals, followed for periods ranging between 3.3 and 25 years\[^21-44\], substantially confirmed the significant increased risk of developing GC due to high intake of total carbohydrates, salted fish, processed meat, refined grains and saturated fat\[^22,31,36\].

Two Japanese studies based on the analysis of dietary patterns failed to demonstrate an increased risk of GC in middle-aged males with a “meat” or “rice” prevalent diet (relative risk [RR] 1.00; 95% CI 0.55-1.10 and RR 1.00; 95% CI 0.52-1.19, respectively)\[^38\] while the “traditional pattern” was a risk factor for both genders (RR 2.88; 95% CI 1.76-4.72 for males and RR 2.40; 95% CI 1.32-4.35 for females)\[^40\]. A large prospective study on diet and cancer carried out on 521 457 individuals aged 35-70 years recruited in 10 European countries (EPIC-European Prospective Investigation into Cancer and Nutrition study), by analyzing 314 incident cases of GC that had occurred after 6.6 average years of follow-up, reported a significant increase of non-cardia cancer risk associated with intake of total meat (calibrated HR per 100 g/d increase 3.52; 95% CI 1.96-6.34), red meat (calibrated HR per 50 g/d increase 1.73; 95% CI 1.03-2.88), and processed meat (calibrated HR per 50-g/d increase 2.45; 95% CI 1.43-4.21). The risk of developing GC was particularly high in \textit{H pylori} antibody-positive subjects\[^42\]. Similar results were obtained for the endogenous formation of nitroso compounds (ENOC). ENOC was significantly associated with non-cardia cancer risk (HR 1.42; 95% CI 1.14-1.78 for an increase of 40 mg/d) especially in those cases with \textit{H pylori} infection (\textit{P} for interaction = 0.09)\[^43\].

Data on the protective role of fresh fruit and vegetables against stomach cancer were somewhat controversial. The analysis of 11 546 individuals included in the Swedish Twin Registry demonstrated that the lowest compared to the highest fruit and vegetable intake had a RR of developing GC of 5.5 (95% CI 1.7-18.3) with a statistically significant dose-risk trend \((\textit{P} < 0.05)\[^29\]. The Japan-Hawaii Cancer Study on 8006 Hawaiian men of Japanese ancestry reported that all types of vegetables were protective against GC. Subjects in the group of highest vegetable consumption (\(\geq\) 80 g/d) had a RR of developing GC of 0.6 (95% CI 0.3-0.9) compared to non-consumers\[^21,24\].

Green and yellow vegetables showed the highest protective effect against GC (RR 0.4; 95% CI 0.2-0.9 and 0.64; 95% CI 0.45-0.92, respectively)\[^16,17\].

On the other hand, the Seven Countries Study Research Group found no association between total vegetable intake and GC risk\[^11\]. Finally, the Cancer Prevention Study, on a cohort of 1.2 million United States individuals, demonstrated a reduced risk in males (RR 0.79; 95% CI, 0.67-0.93) and an unexpected increased risk in females (RR 1.25; 95% CI 0.99-1.58)\[^38\].

Data from EPIC study analysing the association of plasma and dietary vitamin C levels with the risk of GC, after adjustment by body mass index, total energy intake, smoking (status, duration and intensity) and \textit{H pylori} status demonstrated no association with GC risk for dietary vitamin C. In contrast an inverse GC risk was observed in the highest versus lowest quartile of plasma vitamin C (OR 0.55 95% CI 0.31-0.97). The inverse association was more pronounced in subjects consuming higher levels of red and processed meats, a factor that may increase endogenous N-nitroso compound production. The protective effect of plasma vitamin C was independent of GC anatomical sub-site (cardia \textit{vs} non-cardia) or histological sub-type (diffuse \textit{vs} intestinal) or presence of \textit{H pylori} infection\[^44\].

Several epidemiology studies specifically addressed the association of garlic consumption and risk of stomach cancer. Six case-control studies analyzing on the whole 3209 GC cases and 7600 controls, suggested a protective effect of high intake of raw and/or cooked garlic for

### Table 3  Randomised controlled dietary intervention trials for prevention of stomach cancer

| Author         | Yr   | Geographic area | Subjects | Dietary intervention | Intervention (yr) | FU (yr) | Results                                      |
|----------------|------|-----------------|----------|----------------------|-------------------|---------|---------------------------------------------|
| Wang GQ\[^a\]  | 1994 | China           | 29 584   | retinol/zinc; riboflavin/niacin; Vit. C/molybdenum; carotene/Vit.E/selenium | 5.25              | 5.25    | ↓ gastric cancer mortality                 |
| Varis K\[^a\]  | 1998 | Finland         | 29 133   | α-tocopherol 50 mg/d; β-carotene 20 mg/d; Folate 20 mg/d + Vit. B12 1 mg/mo | 5                | 5       | = gastric cancer incidence                 |
| Malila N\[^a\] | 2002 | Finland         | 29 133   | Natural β-carotene 30 mg/d | 5.8              | 8       | = gastric cancer incidence                 |
| Zhu S\[^a\]    | 2003 | China           | 216      | Synthetic β-carotene 30 mg/d | 2                | 8       | No change cancer incidence                 |
| Li H\[^a\]     | 2004 | China           | 2526     | Synthetic allitridum 200 mg + selenium 100 mg | 2                | 5       | No change cancer incidence                 |

FU: follow-up.
GC (OR ranging from 0.3 to 0.89; 95% CI 0.12-0.77 and 0.64-1.24, respectively)\(^{6,45-49}\). Only one cohort study (based on a case-cohort approach) compared the intake of garlic supplements of 152 subjects who developed GC during a 3.3 years follow-up with that of a random sample from the entire cohort who did not developed any type of cancer. Beside the expectative, garlic supplements slightly increased the risk of developing GC (RR 1.27; 95% CI 0.6-2.6)\(^{52}\).

Tea is one of the most popular beverages in the world and the consumption of tea has been hypothesized to be associated with a decreased risk of GC\(^{50}\). The catechins and their strong antioxidant and anti-angiogenic activity as well as their potential to inhibit cell proliferation and modulate carcinogen metabolism could be responsible for the biological benefits of tea\(^{51,52}\).

However, epidemiological studies analyzing the relationship between tea and GC risk yielded conflicting results\(^{57,58,53-62}\). Among the case-control studies, eight showed that high consumers of green tea (≥ 10 cups/d) had a statistically significant reduction of the risk of developing GC\(^{47,50,53,58}\), three studies failed to demonstrate any significant decrease of the GC risk\(^{59-61}\) and the remaining showed an opposite result\(^{62}\). The majority of the prospective studies did not find an inverse association between tea consumption and the risk of GC\(^{26,33,54,64}\). In contrast, three studies\(^{41,65,66}\) confirmed the protective role of tea against GC particularly for non-cardia GC (OR 0.51 95% CI 0.30-0.86) in the highest category of green tea consumption (≥ 5 cups/d \(x\) ≤ 1 cup/d)\(^{81}\). On the basis of this epidemiological evidence no convincing claims can be made with regard to the protective effect of garlic and tea on GC. However, low study power, variability in consumption categorization within studies and poor adjustment for potential confounders may limit the reliability of any conclusion regarding garlic and tea supplementation.

**Interventional dietary trials for prevention of gastric cancer**

Randomized clinical trials provide one of the most scientifically rigorous approaches for testing hypotheses emerging from epidemiological and experimental studies and represent the ideal strategic approach to evaluate inhibition of cancer development by preventive measures.

The most relevant finding reported by the observational studies analyzing the role of diet in GC development concerns the inverse association between fruit and vegetable intake and GC risk. These foods contain phytochemicals endowed with anticancer and anti-inflammatory properties and are rich in ascorbic acid, beta-carotene and other carotenoids offering many health benefits. Dietary interventional trials for stomach cancer prevention have, therefore, been based mainly on long-term supplementation with anti-oxidant micronutrients given alone or in combination (beta-carotene, vitamin A, vitamin C, vitamin E, selenium)\(^{67-71}\). However, all interventional studies but one\(^{72}\) failed to demonstrate any significant change in the risk of GC in subjects receiving anti-oxidant supplementation (Table 3). The most important study, the “General Population Trial” involving 29,584 subjects residing in Linxian, China, and followed for 5.25 years, demonstrated no statistically significant reduction in the prevalence of GC for any of the interventional arms, even though, a reduction in total mortality, total cancer mortality and stomach cancer mortality was found among those receiving beta-carotene, vitamin E and selenium\(^{67}\). Similar results were obtained in the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study conducted in Southwest Finland and involving 29,133 middle-aged male smokers observed between 1985 and 1993\(^{68,69}\). Long-term supplementation with alpha-tocopherol (50 mg/d) and/or beta-carotene (20 mg/d), both at five- and six-year follow-up, had no significant effect on the overall incidence of GC (RR 1.21 95% CI 0.85-1.74 for alpha-tocopherol and RR 1.26 95% CI 0.88-1.80 for beta-carotene). Paradoxically, a subgroup analysis according to histological type suggested an increased risk for beta-carotene on intestinal type cancer (RR 1.59 95% CI 0.99-2.56)\(^{68,69}\). Finally, another study involving 216 atrophic gastritis patients treated with folic acid and/or beta-carotene supplementation and followed for a period of 8 years failed to demonstrate any significant reduction in the incidence of GC. However, folic acid significantly improved gastric mucosa lesions by reversing gastric atrophy, inflammation and intestinal metaplasia and dysplasia at the end of follow-up\(^{73}\).

On the other hand, a double-blinded interventional study involving 2,526 subjects at risk of developing GC and 2,907 controls from a Chinese province, demonstrated, in the first five years of follow-up, a significant reduction in the morbidity rates of malignant gastric tumours in the intervention group treated with large doses of synthetic allitridium associated with microdoses of selenium for a period of 3 years (RR 0.48; 95% CI 0.21-1.06 for the entire population and RR 0.36; 95% CI 0.14-0.92 for male group)\(^{74}\).

**H pylori infection and GC risk**

Since the incidental discovery in 1983, the association of H pylori with GC has become a hot topic of gastroenterological studies. Just a decade later, a large cross-sectional study (the EUROGAST study) involving 17 populations from 13 different countries (United States, Japan and 11 European countries), concluded that H pylori-infected patients had six-fold increased risk of GC compared with uninfected subjects\(^{75}\). In 1994, despite some controversial opinion, the International Agency for Research on Cancer declared H pylori to be a group I human carcinogen for gastric adenocarcinoma\(^{76}\). The statement was mainly based on epidemiological investigations since no experimental studies had been performed at that time to prove the causal link between H pylori and GC. Currently, although substantial evidence supports the role of H pylori infection in GC development, the magnitude of the risk of GC associated with infection remains unclear.

Many epidemiological studies have been conducted in an attempt to address this issue (Tables 4 and 5). Retrospective case-control studies analyzing on the whole 8,306 GC cases and 15,884 controls reported an increased risk of developing GC for patients with H pylori infection.
Table 4  Epidemiological studies (case/control) on association between H. pylori infection and GC risk (1990-2005)

| Author | Yr | Geographic area | Case/Control n | OR (95% CI) | Detection of infection |
|--------|----|-----------------|----------------|-------------|------------------------|
| Leffeld R11 | 1990 | The Netherlands | 91/401 | 2.04 (1.07-3.91) | Serology |
| Caruso ML12 | 1990 | Italy | 44/22 | 1.42 (0.79-2.63) | Serology |
| Talley NJ13 | 1991 | USA | 69/252 | 1.63 (1.00-2.67) | Serology |
| Sipponen P14 | 1992 | Finland | 54/84 | 2.21 (1.01-4.49) | Serology, histology |
| Kuipers EJ15 | 1993 | The Netherlands | 114/116 | 0.86 (0.44-1.69) | Serology |
| Estevens J16 | 1993 | Portugal | 80/80 | 0.54 (0.24-1.19) | Serology |
| Blaser MJ17 | 1993 | Japan | 29/58 | 2.14 (0.72-6.40) | Serology |
| Tatsuta M18 | 1994 | Japan | 41/19 | 2.62 (0.98-6.86) | Biopsy culture |
| Buruk F19 | 1995 | Turkey | 46/40 | 1.89 (0.69-5.21) | Serology |
| Hansson LE20 | 1995 | Sweden | 112/103 | 2.60 (1.35-5.02) | Serology |
| Archimandritis A21 | 1995 | Greece | 47/50 | 1.23 (0.51-2.95) | Serology |
| Lin JT22 | 1995 | China, Taiwan | 143/823 | 1.42 (0.97-2.18) | Serology |
| Hu HY23 | 1994 | China | 51/102 | 5.10 (1.70-15.5) | Serology, histology |
| Sipponen P24 | 1994 | Finland | 243/1408 | 3.11 (1.99-4.74) | Histology |
| Asaka M25 | 1994 | Japan | 213/213 | 2.55 (1.44-4.44) | Serology |
| Kikuchi S26 | 1995 | Japan | 105/102 | 13.3 (5.3-35.6) | Serology |
| Rud J27 | 1995 | Germany | 111/111 | 1.39 (0.82-2.36) | Serology |
| Fukuda H28 | 1995 | Japan | 282/767 | 1.13 (0.81-1.58) | Serology |
| Menegatti M29 | 1995 | Italy | 307/162 | 3.66 (2.33-5.74) | Serology, histology |
| Asaka M30 | 1995 | Japan | 109/109 | 2.40 (1.30-4.80) | Serology |
| Hata RA31 | 1996 | Japan | 95/95 | 1.03 (1.05-3.12) | Serology |
| Shibata T32 | 1996 | Japan | 50/50 | 1.10 (0.42-2.86) | Serology |
| Kato S33 | 1996 | Japan | 82/151 | 1.12 (0.60-2.07) | Serology |
| Kokkola A34 | 1996 | Finland | 50/22 | 3.27 (1.42-7.52) | Histology |
| Menegatti M35 | 1996 | Italy | 148/54 | 4.02 (1.99-8.17) | Serology, histology |
| Sivaparakash R36 | 1996 | India | 75/77 | 1.91 (1.00-3.67) | Serology, biopsy culture |
| Kim HY37 | 1997 | Korea | 160/160 | 1.39 (0.89-2.17) | Serology |
| Mielikle S38 | 1997 | Germany | 215/215 | 16.7 (9.6-28.1) | Serology, histology |
| Shi Y102 | 1997 | China | 110/125 | 3.30 (1.90-5.59) | Serology |
| Barreto-Zuniga R11 | 1997 | Japan | 58/75 | 3.00 (1.69-5.33) | Serology |
| Martin-de-Arjila C104 | 1997 | Spain | 48/50 | 3.91 (1.02-8.86) | Serology |
| Azuma T105 | 1998 | Japan | 82/167 | 2.97 (0.54-1.75) | Serology |
| Komoto K106 | 1998 | Japan | 105/105 | 4.50 (2.33-13.4) | Serology, histology |
| Wu MS107 | 1998 | Taiwan | 135/135 | 2.43 (1.29-4.65) | Serology |
| Whiting JL108 | 1998 | UK | 154/154 | 1.67 (1.01-2.75) | Serology |
| Lee BM109 | 1998 | Korea | 175/113 | 5.20 (3.10-8.70) | CLO test |
| Kikuchi S110 | 1999 | Japan | 103/101 | 15.0 (4.84-55.2) | Serology |
| Zhang Ze111 | 1999 | USA | 134/65 | 11.2 (2.5-50.3) | Histology |
| Cai L112 | 2000 | China | 101/101 | 3.45 (0.90-13.2) | Serology |
| Enroth H113 | 2000 | Sweden | 72/324 | 2.1 (1.1-3.9) | Serology, histology |
| Chang WK114 | 2001 | Korea | 136/136 | 1.82 (1.10-3.30) | Serology |
| Ekstrom AM115 | 2001 | Sweden | 298/244 | 5.0 (1.10-23.6) | Serology |
| Fujokatu N116 | 2001 | Brazil | 93/186 | 0.80 (0.47-1.36) | Serology |
| Konturek SJ117 | 2002 | Poland | 337/337 | 2.59 (1.64-4.22) | Serology |
| Sriamporn S118 | 2002 | Thailand | 111/232 | 0.60 (0.40-1.0) | Serology |
| Wu AH119 | 2003 | USA | 127/356 | 1.85 (1.03-3.32) | Serology |
| Brenner H120 | 2004 | Germany | 68/360 | 18.3 (2.4-136.7) | Serology |
| Machida-Montani A121 | 2004 | Japan | 122/235 | 8.20 (3.70-18.2) | Serology |
| Kato M122 | 2004 | Japan | 2503/6578 | 2.47 (2.19-2.97) | Serology |
| Nomura AM123 | 2005 | Hawaii | 299/336 | 4.86 (5.90-8.13) | Serology |

1Japanese Brazilian; 2non-Japanese Brazilian.

(OR ranging from 1.10; 95% CI 0.43-2.86 to 18.3; 95% CI 2.4-136.7). However, five studies failed to demonstrate any significant risk associated to previous or concurrent H pylori infection.10,10-115,116,117 Retrospective case-control studies are limited “per se” by several biases. In GC patients (cases) H pylori infection is usually assessed after the development of cancer, but advanced gastric diseases can be characterized by the loss of infection resulting in a fall of the circulating anti-H pylori antibodies. In addition, the type of control population and the absence of adjustment for confounding factors (age, sex, smoking, and dietary habit) can hamper the statistical evaluation leading, to over- or underestimation of the real risk linked to H pylori infection.

Prospective studies, by contrast, should be more informative because they use internal control “nested” within a cohort. The infection is assessed by examining blood samples taken years before the onset of clinical disease, so that the enrollment of the studied population did not suffer of selection bias. All cohort studies111-113 reported an increased risk of developing GC associated to H pylori infection (OR ranging from 1.06; 95% CI 0.80-1.40 to 6.0; 95% CI 2.1-17.3) (Table 5). Only one study conducted in a high-risk population from Shanghai,
China, failed to demonstrate an association between *H. pylori* infection and the subsequent risk of GC[132]. However, an update of the results at longer follow-up and by using an enzyme-linked immunosorbent assay (ELISA) based on strains validated among the Shanghai residents showed a statistically significant association between *H. pylori* seropositivity and GC risk (OR 1.84; 95% CI, 1.08-3.11 raising to 3.74; 95% CI 1.51-9.30 among subjects followed for 5 or more years after enrolment)[134].

A meta-analysis of cohort and case-control studies evaluated that the summary OR for GC in *H. pylori* infected patients was 1.92 (95% CI 1.32-2.78), 2.24 (95% CI 1.15-4.4), and 1.81 (95% CI, 1.16-2.84) for all studies, cohort, and case-control studies, respectively. The risk of developing GC was greatest in younger patients (OR 9.29 at age < 29 years) and was equally associated with the intestinal or diffuse type GC[144]. A combined analysis of 12 case-control studies (6 from Europe, 4 from Asia, 2 from the United States) nested with prospective cohorts and involving 1228 GC cases and 3406 controls, revealed that the association of *H. pylori* infection with GC was restricted to non-cardia cancers (OR 2.97; 95% CI 2.3-3.7), and was stronger when blood samples for *H. pylori* serology were collected ten years or more before cancer diagnosis (OR 5.9; 95% CI 3.4-10.3)[145]. However, the most powerful evidence comes from a prospective study on 1526 Japanese patients followed for approximately 7.8 years. GC developed in 36 out of 1246 *H. pylori*-positive patients (2.9%) in contrast to none of the 280 non-infected subjects[146].

Infection with cagA-positive strains further increases the risk of developing GC. According to a recent meta-analysis of 2284 cases and 2770 controls, infection with cagA-positive strains increased the risk of developing GC up to 1.64-fold (95% CI 1.21-2.24) for all sites GC and 2.01-fold (95% CI 1.21-3.32) for non-cardia GC[147].

The close relationship between *H. pylori* infection and GC leads to the critical question of whether antimicrobial therapy can be considered for GC chemoprevention. A prospective, randomized, placebo-controlled, population study carried out in a high-risk area of China involving 1630 subjects observed from 1994 to 2002 reported a comparable incidence of GC in the subjects receiving *H. pylori* eradication treatment and those receiving placebo. However, eradication of *H. pylori* significantly decreased the development of GC in a subgroup of *H. pylori* carriers not presenting precancerous lesions[148]. On the other hand, a randomized, controlled chemoprevention trial conducted in subjects with confirmed histological diagnoses of multifocal, non-metaplastic atrophy and/or intestinal metaplasia, assigned to receive anti-*H. pylori* triple therapy and/or dietary supplementation (ascorbic acid, beta-carotene, or their corresponding placebos), demonstrated a significant regression rate of the lesions for all three basic interventions (RR 4.8 95% CI 1.6-14.2 for anti-*H. pylori* treatment; 5.1, 95% CI 1.7-15.0 for beta-carotene treatment, and 5.0, 95% CI 1.7-14.4 for ascorbic acid treatment in subjects with atrophy and 3.1, 95% CI 1.0-9.3; 3.4; 95% CI 1.1-9.8, and 3.3; 95% CI 1.1-9.5 in subjects with intestinal metaplasia)[149].

### INTERPLAY BETWEEN *H. PYLORI* INFECTION AND DIET

A synergistic interaction between *H. pylori* infection and diet in GC has been suggested[150]. One possible mechanism by which *H. pylori* exerts its “carcinogenic” potential is the greater likelihood of malignant transformation due to inflammatory responses of the gastric epithelium. The generation of reactive oxygen species (ROS) and the increased level of nitric oxide (NO) synthase associated with the mucosal colonization by *H. pylori* cause DNA mutations which may be the initial step in the genetic alterations of gastric epithelial cells[151-153]. Another possible explanation is that the *H. pylori*-related inflammation

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**Table 5 Epidemiological studies (cohort nested case-control study) on association between *H. pylori* infection and GC risk**

| Author          | Yr   | Geographic area | Case/Control n | OR (95% CI) | Mean follow-up (yr) |
|-----------------|------|-----------------|----------------|-------------|---------------------|
| Nomura AM[131]  | 1991 | USA             | 109/109        | 6.0 (2.1-17.3) | 12                  |
| Parsonnet J[132]| 1991 | USA             | 109/109        | 3.6 (1.8-7.3)  | 14.2                |
| Forman D[133]   | 1991 | England         | 116/484        | 2.7 (1.0-7.9)  | 15                  |
| Parsonnet J[134]| 1993 | USA             | 136/136        | 2.62 (1.47-4.69)| 21                  |
| Blaser MJ[135]  | 1995 | USA             | 102/102        | 1.45 (0.76-2.80)| 3                   |
| Lin YT[136]     | 1995 | China, Taiwan   | 29/220         | 1.13 (0.81-1.58)| 13                  |
| Annema A[137]   | 1996 | Finland         | 80/146         | 1.50 (0.70-3.22)| 6                   |
| Webb PM[138]    | 1996 | China           | 87/261         | 0.93 (0.57-1.54)| 40                  |
| Siman J[139]    | 1997 | Sweden          | 56/224         | 5.00 (2.20-11.5)| 5.7                 |
| Watanabe Y[140]| 1997 | Japan           | 45/225         | 1.84 (1.54-5.72)| 8                   |
| 'Yuan JM[141]   | 1999 | China           | 188/548        | 1.84 (1.08-3.11)| 12                  |
| Hansen S[142]   | 1999 | Norway          | 208/208        | 5.15 (2.83-9.37)| 13                  |
| You WC[143]     | 2000 | China           | 34/2594        | 1.18 (1.20-2.60)| 4.5                 |
| Tullius H[144]  | 2001 | Iceland         | 23/128         | 1.16 (1.05-1.28)| 20                  |
| Siman J[145]    | 2001 | Sweden          | 56/224         | 5.00 (2.2-11.2)| 5.7                 |
| Limburg P[146]  | 2001 | China           | 92/192         | 2.29 (1.26-4.14)| 15                  |
| Nomura AM[147]  | 2002 | Hawaii          | 261/261        | 2.70 (1.30-5.6) | 25                  |
| Kosunen TU[148] | 2005 | Finland         | 363/4854       | 2.49 (1.86-3.34)| 24                  |
| Shin A[149]     | 2005 | Korea           | 86/344         | 1.06 (0.80-1.40)| 2.6                 |
| Knell P[150]    | 2006 | Finland         | 225/435        | 3.12 (1.97-4.95)| 15                  |

1 Re-evaluation of the Webb study with ELISA developed and validated among Shanghai residents.
induces predisposing morphological changes in the gastric mucosa such as atrophy and intestinal metaplasia[134]. These latter conditions decrease the acidity in the stomach increasing the endogenous formation of nitrosamides, the main subset of N-nitroso compounds[130]. Nitrosamides, spontaneously formed in the stomach from the nitrite and amides, do not require enzymes but depend on the presence of nitrates and are favored by a high pH. Thus, the ability of the host to reduce nitrate to nitrite and the dietary intake of nitrate and amine are critical for the onset of the gastric carcinogenic process. This hypothesis links the theory of “N-nitroso compounds-mediated GC risk” with that of the “H pylori-related GC risk” suggesting an “integrated model” of gastric carcinogenesis. However, even if the synergistic interaction between diet and H pylori infection is biologically plausible, only a few epidemiological studies have simultaneously evaluated the role of H pylori infection and dietary habits in relation to GC risk. Furthermore, the results of these studies were conflicting (Table 6)[118,121,156,157]. A case-control study conducted in Thailand analyzing both the effect of dietary pattern and H pylori infection found an increased risk of GC associated with a high intake of salt (OR 1.8; 95% CI 1.1-3.0) and fermented foods (OR 1.9; 95% CI 1.1-3.3)[118]. In contrast, a weak negative association was found between GC risk and vegetable and fruit intake and no association between H pylori infection and GC risk (OR 0.6; 95% CI 0.4-1.0)[118]. Likewise, a study evaluating the role of H pylori infection and capsaicin consumption on the risk of GC demonstrated an increased risk (OR 1.71; 95% CI: 0.76-3.88) in high-level consumers of capsaicin (90-200 mg/d) as compared to low-consumers (0-29.9 mg/d). However, this effect was independent of H pylori status and was higher for diffuse type GC (OR 3.64; 95% CI 1.09-12.2) compared to the intestinal type (OR 1.36; 95% CI 0.31-5.89)[123]. Lastly, Machida-Montani et al[32] found a close correlation between GC and H pylori infection (OR 8.2; 95% CI 3.7-18.2), frequent intake of fermented soybean soup (OR 2.1; 95% CI 0.9-5.1), and rice (OR 2.5; 95% CI 1.0-6.1) but no significant interaction between diet and H pylori infection. In contrast, in a Korean hospital-based case-control study, subjects with H pylori infection and high salt intake had a 10-fold higher risk of developing GC than subjects without H pylori infection and low salt intake (P = 0.047)[106].

**DISCUSSION**

GC develops through a multistage process which may span ≥ 20 years[154]. The long latency period hypothetically provides wide opportunities for intervention to prevent cancer development. However, several questions need to be answered before the results of epidemiological and interventional studies can be extended to the clinical setting.

Firstly, GC comprises at least two main entities, the intestinal and the diffuse type, which differ considerably from an epidemiological, clinical and molecular point of view[155]. Based on epidemiological evidence, the intestinal type, preceded by precancerous lesions, seems more closely influenced by environmental factors while the latter recognizes mainly a “genetic” substrate. However, only a few studies have focused on the nutritional pattern in relation to the histotype of GC[150-161]. Even hampered by the small number of cases studied, the results strongly suggest that the dietary risk factors are common to both types of GC while the protective factors play a more important role in preventing the intestinal type. Secondly, trials directly evaluating cancer development as target require very large numbers of subjects to be followed for decades. Trials with smaller groups of subjects followed for shorter periods and focusing on the intermediate steps of the gastric carcinogenic process may hypothetically obtain information on the possible inhibition of cancer development. However, only the “intestinal type” cancer recognizes a precancerous “cascade” of events and only a small subset of patients with precancerous lesions develop GC[155]. Thus, very large number of subjects for many years would need to be followed to obtain conclusive results. Finally, due to the “synergistic” interplay between diet and H pylori infection, H pylori should always be properly considered.

In conclusion, although GC is a disease of genes, mainly triggered by H pylori-related mucosal inflammation, overwhelming evidence suggest that diet and lifestyle factors are important causes leading to cancer. Indeed, the progressive decline in GC incidence observed between 1930s and 1980s, before the discovery of H pylori, can be, without doubt, related to improvement of diet and spread use of refrigerators. On the other hand, data suggesting that H pylori eradication may reduce the risk of developing GC need still to be confirmed by large-scale population studies[162]. One study that economically modelled the cost of screening per year of life saved estimated that in selected populations such as Japanese American, serological screening for H pylori at age 50 years was more beneficial than breast cancer screening[163]. However, there are insufficient data to recommend general screening for H pylori of asymptomatic patients to prevent GC. The decision to screen should be based on individual risk factors such as race, and family history of GC[164].

At present, even if foods and food components acting as risk or protective factors for GC still remain to be fully

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**Table 6** Epidemiological studies (hospital-based case-control) on association between dietary factors and H pylori infection and gastric cancer risk

| Author                  | Yr  | Geographic area   | Case/Control n | Increased risk                              | Decreased risk                              | H pylori risk       |
|-------------------------|-----|-------------------|----------------|---------------------------------------------|---------------------------------------------|---------------------|
| Sritamporn S[155]       | 2002| Thailand          | 131/262        | Salt, fermented foods                       | Vegetables, fruit                           | Independent         |
| Lee SA[156]             | 2003| Korea             | 69/199         | Salt, kimchi, salt-fermented fish           | Vegetables, fruit, soybean curds, broth     | Increased           |
| Lopez-Carrillo L[157]   | 2003| Mexico            | 234/468        | Capsaicin                                   | --                                          | Independent         |
| Machida-Montani A[158]  | 2004| Japan             | 122/235        | Fermented soy bean, rice                   | --                                          | Independent         |
defined, a diet rich in fruit, vegetables and cereals and poor in meat, fat and salt has a good prophylactic potential for cancer and many other chronic diseases of lifestyle i.e. coronary heart disease, hypertension, obesity and diabetes. Thus, “diet for cancer prevention” can be proposed as a general role of well-being and can represent the basis for a rational health policy.

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