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REVIEW

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.

Key words: Gastric cancer; *H pylori*; Diet; Observational studies; Interventional 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 2and 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 *n*	Increased risk	Decreased risk
Risch HA[5]	1985	Canada	246/146	Nitrite, chocolate, carbohydrates	Fiber, Vit. C
Buiatti E[6]	1990	Italy	1016/1159	Nitrites, protein	Vit. C, β-carotene, α-tocopherol, vegetable fat
Graham S[7]	1990	USA	293/293	Sodium, fat, retinol	β-Carotene, raw vegetables, onions, cucumbers
Ramon JM[8]	1993	Spain	117/234	--	Vit. A, Vit. C
Kaaks R[9]	1998	Belgium	301/2851	Vit. A, Vit. B12, mono, disaccharides	Polyunsaturated fat, Vit. C/B1-B2-B6, C/A
Lopez-Carrillo L[10]	1999	Mexico	220/752	Protein, saturated fat, cholesterol	Polyunsaturated fat, fiber, Vit. E
Mathew A[11]	2000	India	194/305	Rice, spicy foods, chili, high-temperature food	--
Palli D[12]	2001	Italy	382/561	Protein, nitrite, sodium	Vit. C/B6, β-carotene, α-tocopherol, nitrates
Mayne ST[13]	2001	USA	352/687	Animal protein, cholesterol, Vit. B12, nitrite	Fiber, β-carotene, folate, Vit. C
Jedrychowski W[14]	2001	Poland	80/--	Carbohydrates	Vit. E, β-carotene
Hamada GS[15]	2002	Brazil	97/192	Beef	Fruits
Chen H[16]	2002	Nebraska	124/449	Saturated fat	Fiber, Vit. C
Hara M[17]	2003	Japan	149/287	--	Cruciferous vegatables, mushrooms
Nomura AM[18]	2003	Hawaii	300/446	Processed meat, bacon	β-carotene, Vit. C, Vit. E, folate
Lagiou P[19]	2004	Greece	110/100	--	Flavanone
De Stefani E[20]	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 *n*	FU yr	Increased risk	Decreased risk	No effect
Chyou PH[21]	1990	USA (Hawaii)	8006	18	--	Green/ cruciferous vegetables, fruit	--
Kneller RW[22]	1991	USA	17633	20	Carbohydrates, salted-fish, bacon, cooked cereals, milk	--	--
Kato I[23]	1992	Japan	9753	6	Alcohol, broiling meat	Fruit	--
Nomura A[24]	1995	USA (Hawaii)	8006	25	--	Fruit, vegetables	Alcohol
Dorant E[25]	1996	The Netherlands	120852	3.3	--	Onions	Leek, garlic
Goldbohm RA[26]	1996	The Netherlands	120852	4.3	--	--	Black tea
Ocke MC[27]	1998	The Netherlands	12763	25	--	Vegetables, fruit, fiber-rich cereals	--
Terry P[28]	1998	Sweden	11946	25	--	Fruit, vegetables	--
Galanis DJ[29]	1998	USA (Hawai)	11907	14.8	Coffee	Fruit, raw vegetables	Pickled vegetables, dried/salted fish
Knekt P[30]	1999	Finland	9985	24	--	--	Nitrates, nitrites, NDMA
Jansen MC[31]	1999	Netherlands	12000	25	Refined grains	Fruit	Vegetables Whole grain
Botterweck AA[32]	2000	The Netherlands	120852	6.3	Retinol, carotene	Vit. C	Folate, Vit. E, carotene, lycopene, fibers, Vit. A, BHA, BHT
Tsubono Y[33]	2001	Japan	26311	8	--	--	Green tea
McCullough ML[34]	2001	USA	1200000	14	Vegetables[1]	Vegetables, citrus fruit, whole grain[2]	--
Nagata C[35]	2002	Japan	33304	7	--	Soy products	--
Ngoan LT[36]	2002	Japan	13000	10	Processed meat, cooking oil, pickled food, soup	Green/yellow vegetables, fruit, cuttle-fish, tofu, potatoes	--
Kobayashi M[37]	2002	Japan	39993	10	--	Fruit, vegetables	--
Masaki M[38]	2003	Japan	5765	10	Meat pattern Rice/snack pattern	Vegetable and fruit pattern Western breakfast pattern	--
Khan MM[39]	2004	Japan	3158	18	Carbonated drink/juice[1]	Miso soup[2]	--
Kim MK[40]	2004	Japan	42112	10	Traditional dietary pattern	Healthy dietary pattern[1]	--
Sasazuki S[41]	2004	Japan	72743	11	--	Green tea[1]	--
[1]EPIC[42-44]	2006	Europe	521457	6.6	Red and processed meat, ENOC	Plasma vitamin C Total vegetable intake Onion, garlic	Dietary Vitamin C

[1]Effect limited to women; [2]Effect limited to men; FU: follow-up; NDMA: N-nitrosodimethylamine. EPIC: European prospective investigation into cancer and nutrition study; BHA: butylated hydroxyanisole; BHT: butylated hydroxytoluene (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[5] to 8.73/100 mg of daily intake[14]. The increased trend in risk appeared particularly high in females (OR highest quartile of consumption frequency [Q4] *vs* lowest quartile [Q1] 14.8)[28]. High consumption of saturated fat and cholesterol enhanced the risk of cancer for intestinal

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

Author	Yr	Geographic area	Subjects *n*	Dietary intervention	Intervention (yr)	FU (yr)	Results
Wang GQ[67]	1994	China	29584	retinol/zinc; riboflavin/niacin; Vit. C/molybdenum; carotene/Vit.E/selenium	5.25	5.25	↓ gastric cancer mortality
Varis K[68]	1998	Finland	29133	α-tocopherol 50 mg/d; β-carotene 20 mg/d;	5	5	= gastric cancer incidence
Malila N[69]	2002	Finland	29133	α-tocopherol 50 mg/d; β-carotene 20 mg/d Folate 20 mg/d + Vit. B12 1 mg/mo	5-8	8	= gastric cancer incidence No change cancer incidence
Zhu S[70]	2003	China	216	Natural β-carotene 30 mg/d Synthetic β-carotene 30 mg/d	2	8	↓ precancerous lesions
Li H[71]	2004	China	2526	Synthetic allitridum 200 mg + selenium 100 mg	2	5	No change cancer incidence

FU: follow-up.

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)[10].

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[5,18,19].

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 *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 *H pylori* infection (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 ($P < 0.05$)[28]. 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 ($\geqslant$ 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)[36,37].

On the other hand, the Seven Countries Study Research Group found no association between total vegetable intake and GC risk[31]. 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)[34].

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 *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 *vs* non-cardia) or histological sub-type (diffuse *vs* intestinal) or presence of *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

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)[25].

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[47,50,53-62]. 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[26,33,63,64]. 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 ($\geqslant$ 5 cups/d *vs* $\leqslant$ 1 cup/d)[41]. 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 concerned 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[70] 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[70].

On the other hand, a double-blinded interventional study involving 2526 subjects at risk of developing GC and 2507 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 allitridum 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)[71].

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 (Unites States, Japan and 11 European countries), concluded that *H pylori*-infected patients had six-fold increased risk of GC compared with uninfected subjects[72]. 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[73]. 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 8306 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
Loffeld RJ[74]	1990	The Netherland	91/401	2.04 (1.07-3.91)	Serology
Caruso ML[75]	1990	Italy	44/22	4.72 (1.32-19.04)	Histology
Talley NJ[76]	1991	USA	69/252	1.63 (0.79-3.37)	Serology
Sipponen P[77]	1992	Finland	54/84	2.21 (1.01-4.91)	Serology, histology
Kuipers EJ[78]	1993	The Netherlands	116/116	0.86 (0.44-1.68)	Serology
Estevens J[79]	1993	Portugal	80/80	0.54 (0.24-1.19)	Serology
Blaser MJ[80]	1993	Japan	29/58	2.14(0.72-6.40)	Serology
Tatsuta M[81]	1993	Japan	41/19	2.42 (0.69-8.66)	Biopsy culture
Buruk F[82]	1993	Turkey	46/40	1.89 (0.69-5.21)	Serology
Hansson LE[83]	1993	Sweden	112/103	2.60 (1.35-5.02)	Serology
Archimandritis A[84]	1993	Greece	47/50	1.23 (0.51-2.95)	Serology
Lin JT[85]	1993	China, Taiwan	143/823	1.42 (0.97-2.08)	Serology
Hu PJ[86]	1994	China	51/102	5.10 (1.70-15.5)	Serology, histology
Sipponen P[87]	1994	Finland	243/1408	1.31 (0.99-1.74)	Histology
Asaka M[88]	1994	Japan	213/213	2.55 (1.48-4.44)	Serology
Kikuchi S[89]	1995	Japan	105/102	13.3 (5.3-35.6)	Serology
Rudi J[90]	1995	Germany	111/111	1.39 (0.82-2.36)	Serology
Fukuda H[91]	1995	Japan	282/767	1.13 (0.81-1.58)	Serology
Menegatti M[92]	1995	Italy	307/162	3.66 (2.33-5.74)	Serology, histology
Asaka M[93]	1995	Japan	109/109	2.40 (1.20-4.80)	Serology
Hatz RA[94]	1996	Germany	95/93	2.03 (1.05-3.92)	Serology
Shibata T[95]	1996	Japan	50/50	1.10 (0.43-2.86)	Histology
Kato S[96]	1996	Japan	82/151	1.12 (0.60-2.07)	Serology
Kokkola A[97]	1996	Finland	50/22	3.27 (1.42-7.52)	Histology
Menegatti M[98]	1996	Italy	148/54	4.02 (1.99-8.17)	Serology, histology
Sivaprakash R[99]	1996	India	75/75	1.91 (1.00-3.67)	Serology, biopsy culture
Kim HY[100]	1997	Korea	160/160	1.39 (0.89-2.17)	Histology
Miehlke S[101]	1997	Germany	215/215	16.7 (CI 9.6-29.1)	Histology, ^{13}C-UBT
Shi Y[102]	1997	China	110/125	3.30 (1.90-5.9)	Serology
Barreto-Zuniga R[103]	1997	Japan	55/75	3.00 (1.69-5.33)	Serology
Martin-de-Argila C[104]	1997	Spain	48/50	3.01 (1.02-8.86)	Serology
Azuma T[105]	1998	Japan	82/167	0.97 (0.54-1.75)	Serology
Komoto K[106]	1998	Japan	105/105	5.60 (2.33-13.4)	Serology, histology
Wu MS[107]	1998	Taiwan	135/135	2.43 (1.29-4.65)	Serology
Whiting JL[108]	1998	UK	154/154	1.67 (1.01-2.75)	Serology
Lee BM[109]	1998	Korea	175/113	5.20 (3.10-8.70)	CLO test
Kikuchi S[110]	1999	Japan	103/101	15.0 (6.4, 35.2)	Serology
Zhang ZF[111]	1999	USA	134/65	11.2 (2.5-50.3)	Histology
Cai L[112]	2000	China	101/101	3.45 (0.90-13.2)	Serology
Enroth H[113]	2000	Sweden	72/324	2.1 (1.1-3.9)	Serology, histology
Chang WK[114]	2001	Korea	136/136	1.82 (1.10-3.00)	Serology
Ekstrom AM[115]	2001	Sweden	298/244	5.0 (1.10-23.6)	Serology
Fujioka N[116]	2001	Brazil	93/186[1]	0.80 (0.47-1.36)	Serology
			228/226[2]	0.84 (0.54-1.30)	
Konturek SJ[117]	2002	Poland	337/337	2.59 (1.61-4.22)	Serology
Sriamporn S[118]	2002	Thailand	111/232	0.60 (0.40-1.0)	Serology
Wu AH[119]	2003	USA	127/356	1.85 (1.03-3.32)	Serology
Brenner H[120]	2004	Germany	68/360	18.3 (2.4-136.7)	Serology
Machida-Montani A[121]	2004	Japan	122/235	8.20 (3.70-18.2)	Serology
Kato M[122]	2004	Japan	2503/6578	2.47 (2.19-2.79)	Serology
Nomura AM[123]	2005	Hawaii	299/336	4.86 (5.90-8.13)	Serology

[1]Japanese Brazilian; [2]non-Japanese Brazilian.

(OR ranging from 1.10; 95% CI 0.43-2.86 to 18.3; 95% CI 2.4-136.7)[74-123]. However, five studies failed to demonstrate any significant risk associated to previous or concurrent *H pylori* infection[78,79,105,116,118]. 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 studies[124-143] 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,

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[124]	1991	USA	109/109	6.0 (2.1-17.3)	12
Parsonnet J[125]	1991	USA	109/109	3.6 (1.8-7.3)	14.2
Forman D[126]	1991	England	116/484	2.7 (1.0-7.9)	15
Parsonnet J[127]	1993	USA	136/136	2.62 (1.47-4.69)	21
Blaser MJ[128]	1995	USA	102/102	1.45 (0.76-2.80)	3
Lin JT[129]	1995	China, Taiwan	29/220	1.13 (0.81-1.58)	13
Aromaa A[130]	1996	Finland	80/146	1.50 (0.70-3.22)	6
Webb PM[131]	1996	China	87/261	0.93 (0.57-1.54)	40
Siman JH[132]	1997	Sweden	56/224	5.00 (2.20-11.5)	5.7
Watanabe Y[133]	1997	Japan	45/225	1.84 (1.54-5.72)	8
[1]Yuan JM°[134]	1999	China	188/548	1.84 (1.08-3.11)	12
Hansen S[135]	1999	Norvay	208/208	5.15 (2.83-9.37)	13
You WC[136]	2000	China	34/2594	1.8 (1.20-2.60)	4.5
Tulinius H[137]	2001	Iceland	23/128	1.16 (1.05-1.28)	20
Siman JH[138]	2001	Sweden	56/224	5.0 (2.2-11.2)	5.7
Limburg P[139]	2001	China	92/192	2.29 (1.26-4.14)	15
Nomura AM[140]	2002	Hawaii	261/261	2.70 (1.30-5.6)	25
Kosunen TU[141]	2005	Finland	363/4854	2.49 (1.86-3.34)	24
Shin A[142]	2005	Korea	86/344	1.06 (0.80-1.40)	2.6
Knekt P[143]	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.

China, failed to demonstrate an association between *H pylori* infection and the subsequent risk of GC[131]. 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 cag-A-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

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
Sriamporn S[118]	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[121]	2004	Japan	122/235	Fermented soy bean, rice	--	Independent

induces predisposing morphological changes in the gastric mucosa such as atrophy and intestinal metaplasia[154]. These latter conditions decrease the acidity in the stomach increasing the endogenous formation of nitrosamides, the main subset of N-nitroso compounds[155]. Nitrosamides, spontaneously formed in the stomach from the nitrite and amides, do not require enzymes but depend on the presence of nitrites 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)[157]. Lastly, Machida-Montani *et al*[121] found a close correlation between GC and *H pylori* infection (OR 8.2; 95% CI 3.7-18.2), frequent intake of fermented soy bean 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 ($P = 0.047$)[156].

DISCUSSION

GC develops through a multistage process which may span $\geqslant$ 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[158]. 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[6,159-161]. 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[154]. 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

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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