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Epidemiology of gastric cancer

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Summary. - Despite a dramatic reduction in incidence and mortality rates, gastric cancer (GC) was still recently the second most common neoplastic cause of death worldwide. GC treatment has not been substantially improved and screening programmes have not proven feasible outside Japan. On the other hand, primary prevention of GC is hampered by the lack of a single specific causal factor, even if diet has been shown to play a relevant role in its etiology. A large number of studies have indicated that salted/smoked and pickled/ preserved foods (rich in salt, nitrites and preformed nitrosocompounds) are associated with an increased risk of GC. In contrast, a high consumption of fresh fruit and raw vegetables and a high intake of antioxidants have been shown to reduce the risk of GC. Domestic refrigeration and a reduced use of salt contribute to explain the decreasing temporal trend and the geographical patterns of GC. Results of human chemoprevention trials are encouraging but have not been confirmed. Evidence of an association between *Helicobacter pylori* infection and GC has been recently provided, even if several aspects of GC epidemiology do not fit in this hypothesis. Studies on *H. pylori* eradication and its effects on GC risk represent a priority for future research in view of the potential preventive applications.

Key words: gastric cancer, diet, nutrients, N-nitrosocompounds, *Helicobacter pylori*.

Riassunto *(Epidemiologia del carcinoma gastrico)*. - Nonostante la notevole riduzione dei tassi di incidenza e mortalità il carcinoma gastrico (CG) rappresentava ancora recentemente la seconda causa di morte per tumore a livello mondiale. Il trattamento del CG non ha subito sostanziali modifiche ed i programmi di screening non si sono dimostrati ripetibili al di fuori del Giappone. D'altra parte, la prevenzione primaria del CG è resa difficile dalla assenza di un singolo ben definito fattore causale, anche se è dimostrato che la dieta svolge un ruolo rilevante. Numerosi studi hanno indicato che cibi salati, affumicati, conservati o in salamoia (ricchi in sale, nitriti e nitroso-composti preformati) sono associati con un aumentato rischio di CG. Alti consumi, invece, di frutta fresca e verdure crude ed una elevata assunzione di anti-ossidanti riducono il rischio di CG. La refrigerazione a livello domestico ed il conseguente ridotto uso del sale contribuiscono a spiegare il trend temporale e la distribuzione geografica del CG. I risultati dei trial di chemioprevenzione sono incoraggianti ma non sono stati ancora confermati. Recentemente è stata dimostrata l'associazione del CG con l'infezione con *Helicobacter pylori*, anche se diversi aspetti dell'epidemiologia del CG non risultano spiegati da questa ipotesi. Studi sulla eradicazione dell'*H. pylori* ed i suoi effetti sul rischio di CG rappresentano una priorità per la ricerca in considerazione delle possibili ricadute a livello dei programmi di prevenzione.

Parole chiave: carcinoma gastrico, dieta, nutrienti, N-nitrosocomposti, *Helicobacter pylori*.

Introduction

Despite the long-standing and widespread reduction in incidence and mortality rates, in 1985 gastric cancer (GC) was still the second most common neoplastic cause of death worldwide [1]. The surgical and medical treatments of GC have not been substantially modified in the last decade and large scale early diagnosis programmes have proven to be difficult to carry out outside Japan [2]. On the other hand, primary prevention of GC is hampered by the lack of a single well defined causal factor; the dramatic decline of GC cannot be considered the direct result of public health interventions but a spontaneous temporal trend related to the modifications in life-style and diet.

Dietary factors have actually been shown to play a relevant role in the etiology of GC. A large number of studies, overall, have indicated that salted/smoked fish and meats and pickled/preserved foods (rich in salt, nitrites and preformed nitroso-compounds) are associated with an increased risk of GC; risk factors, however, tend to show a great variability in different populations. On the other hand, protective factors have been identified more consistently. A high consumption of fresh fruit and raw vegetables and a high intake of antioxidants and carotenoids have been shown to reduce the risk of GC. Domestic refrigeration and the associated reduced use of salt contribute to explain the decreasing temporal trend and the geographical patterns of GC. Interaction between dietary factors and metabolic polymorphisms currently

appears as a promising research approach for further investigations. Preliminary results of human chemoprevention trials are encouraging but have not been confirmed so far.

A major contribution to the understanding of several gastric diseases, including GC, has been the identification of *Helicobacter pylori*, a spiral shaped bacterial organism able to survive in the acid environment of the stomach. Epidemiological evidence of an association between *H. pylori* infection and GC has been provided, even if several aspects of GC epidemiology do not fit in this hypothesis. Studies on *H. pylori* eradication represent a priority for future research on GC in view of the potential preventive applications.

The most recent results of epidemiologic reasearch on GC are discussed in this review with particular attention to diet and *H. pylori*. Methodology and biological plausibility are also briefly reviewed.

Diet and related factors

The identification of the dietary factors causally related to GC has represented a particularly difficult task because of the methodological problems in collecting reliable and specific dietary information that generally impair all types of nutritional epidemiology studies. A long time interval has been postulated between dietary exposure to (pro-)carcinogenic chemicals, initiating a multi-step process during infancy or early adulthood, and GC diagnosis. In contrast, a typical dietary interview is focused on foods consumed in a recent period (usually a 12-month period before diagnosis/interview), in order to avoid recall problems. Recent dietary habits are thus utilized as indicators of the "stable" diet of adult life.

The decreasing temporal trend of GC is so strong and persistent [3, 4] that the relevant association with a causally-related group of foods or contaminants, which were consumed frequently in the past but rarely in the more recent period, might have been easily missed by most studies, particularly if poorly designed or of small size.

On the other hand, the pathogenetic model currently suggested for GC [5] has become more and more complex and is clearly multifactorial. Dietary and other risk factors (including *H. pylori*) must fit in such a wide cascade of events occurring over a long period of time in the life of individuals at risk.

Correlation and cross-sectional studies

National or regional data on dietary habits (based on food disappearance statistics or dietary surveys) available at the level of the general population for different areas have been correlated with specific GC incidence and mortality rates, usually for the same time period [6]. Overall, because of the low quality of nutritional and other indicators and the lack of temporal latency, results have been inconsistent. Similar studies, for instance, have suggested that the average concentration of nitrates in drinking water and that of nitrites in the soil were linked to GC distribution in high risk countries. In contrast, a high intake of nitrate is now considered an indicator of high consumption of fresh vegetables; comparisons between different populations using biomarkers of the intake of nitrates showed higher levels in low-risk areas [7, 8]. Recently a large cooperative european study, EUROGAST, has been carried out in order to correlate blood levels of micronutrients and other biomarkers in a series of random samples of different populations at varying GC risk [9,10].

In cross-sectional studies, a group of subjects (sampled from the general population) are offered a gastroscopy examination and evaluated in terms of prevalence of precancerous gastric lesions; blood levels of micronutrients and other diet-related factors are then compared across different histologic categories [11].

Cohort studies

In a cohort or prospective study, a large group of healthy subjects is followed over time after an initial assessment of exposure at the individual level (usually a self-administered questionnaire on diet and other life-style factors; biologic samples may be collected and stored away); new cases of the disease of interest are then identified during the follow-up period (with the exclusion of those occurring in the first 6-12 months). In order to increase the efficiency, those subjects who will develop the disease in the study period will be compared to a sample of those who will remain free of GC (this study design is known as a "case-control study nested in a cohort"). Dietary information is collected well before any symptom of GC (for cases) and is referred to a time period before enrollment. GC, however, as most of the other cancers, is a rare event with incidence rates in the order of 10 to 100 new cases per 100,000 person-years (100,000 subjects followed per one year or 10,000 per ten years), depending on the population at risk, and these studies are extremely expensive and time consuming. Large cooperative cohorts are necessary because most of available studies are of small/moderate size and their results are difficult to interpret, being typically based on small numbers of GC cases. Standardised dietary assessment procedures (thousands of subjects are usually involved) and adequate storing of biologic samples for future measurement of diet-related parameters are now considered essential and, for instance, have been implemented in the most recent large scale research projects [12]. These studies are expected to shed new light on GC etiology in a few years.

Up to now, only one japanese cohort focused on diet [13] reached a large size (with thousands of cases in a recent updated analysis); its results have confirmed previous findings but blood samples were not available. Other studies suffered from a limited amount of dietary information because, at enrollment, only a 24-hour recall was collected [14]. An ecologic analysis of the 16 cohorts assembled in the Seven Countries Study reported a strong inverse association of vitamin C with 25-year GC mortality [15].

Case-control studies

Most of the available evidence on the association between diet and GC has been provided by case-control studies [16]: more than 50 of them have been published so far, after the first seminal papers in the early 1960, ranging in size between less than a hundred and over one thousand GC cases [17]. The main findings of the studies published in the last decade with more than 200 GC cases are presented in Table 1. This popular, although often incorrectly used, study design tends to be efficient and relatively rapid. The dietary habits (and other socio-demographic characteristics) of a series of GC cases are compared to those of a group of subjects (defined as controls), randomly sampled from the same population from which the case series has been expressed. A food frequency questionnaire is generally used in a face to face interview. The association between dietary habits in the past (childhood or early adulthood) and the risk of GC has been investigated only in a few studies so far and results have been quite disappointing [17-19]. The group of cases should include a very high proportion of all GC patients identified as eligible during the study period in the study population in order to avoid selections. The choice, identification and interview of the control group is, however, the real methodological problem, particularly when considering that dietary habits are strongly associated with other socio-economic determinants. In the so called hospital-based studies, controls are actually sampled among other patients admitted to the same hospital(s) of the cases, usually for a group of minor health problems, *a priori* considered "unrelated" to dietary factors suspected to play a role in the etiology of GC. This apparently simple formula is in fact difficult to be applied for most diet-related diseases and trade-offs are common in the enrollment of hospitalised controls, with problems in the interpretability of results. Low cost and convenience (both GC cases and controls are interviewed in the same hospital) are, however, very attractive features. In contrast, population based case-controls have more clearly defined criteria and their results are certainly more reliable, in particular for diet-related factors. These studies, however, need more resources and are difficult to carry out.

Food consumption

Fruit and vegetables

A high consumption of fresh fruit has been consistently reported as a strong protective factor for GC [17, 20-27] and also for chronic atrophic gastritis (CAG), either histologically or serologically defined [28, 29]. A particularly strong effect has been reported for the consumption of citrus fruit [17, 30-34]. Consumption of nuts and other types of dried fruit has been reported as either negatively [35-37] and positively associated [31]. Canned fruit has been reported as positively associated to GC [26].

A high consumption of raw vegetables, particularly if yellow-green, has been consistently reported as a protective factor by many studies worldwide [17, 21, 22, 24, 26, 27, 31-33, 37-40]. Specific protective effects have been reported for several single vegetables, consumed alone or in mixed salads (tomatoes, lettuce, cucumber, carrots, celery, sweet peppers, onions). A chinese study reported a strong effect for onions and other local allium vegetables [41], used as the main ingredients of raw salads.

An inverse association with cooked vegetables has also been reported in several studies [21, 24, 26, 35, 42]. In one large study no effect was specifically shown for the consumption of cooked vegetables while at the same time a negative association was evident with raw vegetables [17], thus suggesting a stronger role for thermolabile compounds.

Pickled and fermented vegetables, in contrast, have been consistently identified as risk factors for GC [34, 37], possibly because of the high content in nitrates and salt and low levels of antioxidants.

Beans and other dry legumes represented a staple food for many populations in the past and have been reported to be associated with GC risk [26, 31], together with fava beans [43], in which a precursor of a mutagenic compound has been identified. Soybean products as tofu have been sometimes reported as protective [40].

Fish and meat

The consumption of salted/smoked fish has been consistently reported as a risk factor in many countries [17, 35, 44]. One study found a negative association [45]. In an Italian study salted fish has also been associated with the risk of serologically defined severe CAG [46].

Smoked and cured meats have been repeatedly identified as associated with an increased risk of GC [17, 20, 33, 44, 47, 48]. More recently, several studies from western countries reported a positive association with the consumption of fresh meats [17, 25, 31, 47, 49]. A correlation study of GC mortality [49] also suggested a positive association with meat consumption in different

Table 1. - Selected case-control studies on dietary factors and gastric cancer (with at least 200 GC cases) published in the last decade (1986-1995)

Reference	Country	Type *(a)*	GC cases/ controls	Risk factors	Protective factors
Middleton *et al.* 1986 [125]	USA	H	262/2,918	NS	NS
La Vecchia *et al.* 1987 [32]	Italy	H	206/474	Pasta and rice Polenta Ham	Green vegetables Fresh fruit Citrus fruit
Hu *et al.* 1988 [42]	China	H	241/241	Salted/fermented foods Potatoes	Cooked vegetables
You *et al.* 1988-1989 [22, 41]	China	P	564/1,131	Fermented sour pancakes Salted foods	Fresh vegetables Fruit Vitamin C Carotene Garlic Onions
Tuyns 1988 [71]	Belgium	P	293/2,914	Salt	
Buiatti *et al.* 1989 [17]	Italy	P	1,016/1,159	Traditional soups Meat Salted/dried fish Cold cuts Seasoned cheese Salt	Raw vegetables Fresh fruit Citrus fruit Olive oil Garlic Refrigeration
Buiatti *et al.* 1990 [56]	Italy	P	1,016/1,159	Protein Nitrite	Vitamin C Carotene α-tocopherol Vegetable fats
De Stefani *et al.* 1990 [47]	Uruguay	H	210/630	Meat Salted meat Hot mate	Vegetables Fruit
Graham *et al.* 1990 [39]	USA	P	293/293	Fat Retinol Sodium	Raw vegetables Carotene Refrigeration
Kato *et al.* 1990 [50]	Japan	H	427/3,014	Salted fish	Western style breakfast
La Vecchia *et al.* 1990 [75]	Italy	H	526/1,223		Refrigeration
La Vecchia *et al.* 1990 [126]	Italy	H	563/1,501	Foods at very high temperature	
Lee *et al.* 1990 [44]	Taiwan	H	217/820	Salted/cured meats Smoked/fried foods Fermented beans Green tea	Milk

Table 1 (continued)

Reference	Country	Type *(a)*	GC cases/ controls	Risk factors	Protective factors
Boeing *et al.* 1991 [48]	Poland	H	741/741	Salt Sausages	Fruit Vegetables Non white bread Cheese
Gonzàlez *et al.* 1991 [35]	Spain	H	354/354	Cold cuts Preserved fish	Cooked green vegetables Fresh/dried fruit
Agudo *et al.* 1992 [127]	Spain	H	354/354	NS	NS
Hoshiyama *et al.* 1992 [36]	Japan	P/H	294/ (294+202)	Salt Rice Fish	Raw vegetables Fruit Nuts
Hoshiyama *et al.* 1992 [37]	Japan	P	(216+35)/ 483	Salty foods Rice Pickled vegetables	Raw vegetables Fruit Nuts Potatoes
Jedrychowski *et al.* 1992 [77]	Poland	H*(*)*	741/741	Fried/stewed meats	Whole meal bread Fresh vegetables/fruit
Tuyns *et al.* 1992 [26]	Belgium	P	301/2,851	White bread Flour products Added sugar Whole-milk Fatty meats	Fresh fruit Cooked/raw vegetables Lean meats
Hansson *et al.(**)* 1994 [19]	Sweden	P	338/679	Milk	Fruit/vegetables Whole bread Fish Cheese Tea Refrigeration
Hansson *et al.(**)* 1994 [57]	Sweden	P	338/679	Fat	Vitamin C/ vitamin E β-carotene Nitrates
Lopez-Carrillo *et al.* 1994 [51]	Mexico	P	220/752	Chili pepper	NS
Gonzales *et al.* 1994 [18]	Spain	P	354/354	Nitrosamines Nitrites Fat	Vitamin C Fiber Carotene Nitrates
La Vecchia *et al.* 1994 [128]	Italy	H	273/2,024	Nitrites Methionine Calcium	β-carotene Ascorbic acid Folate Nitrates
Guo *et al.* 1994 [82]	China	N	539/2,695	Low BMI	NS
Lee *et al.* 1995 [40]	Korea	H	213/213	Broiled fish Stews Salt	Vegetables Soybean tofu Refrigeration

Modified from Palli 1994 [16]
(a) H: hospital-based case-control study; P: population-based case-control study; N: nested case-control study
(*) Household dietary practices
(**) 20 years before interview
NS: no significant result

Italian regions. Negative associations have been reported from high-risk areas and developing countries, where meat consumption is still very rare or associated with a western life-style. One study has reported opposite effects for the consumption of lean versus fatty meats [26].

Dairy products

A high consumption of cheese and other dairy products has been reported as protective in northern european studies [33, 45, 48], while, in contrast, a moderate positive association was found for seasoned [17] and soft cheese [26].

Overall, milk has not been consistently related to GC risk, although two recent studies suggested a positive association [26,45]. A protective effect has been reported in studies carried out in Far Eastern populations, possibly because of the association between milk and a western-style diet [44, 50].

Cereals and starchy foods

No relevant effect has, overall, been shown for the consumption of bread, pasta and other starchy foods. Cereal products rich in carbohydrates, however, have been positively associated with GC risk [26, 31, 37]. A strong positive association has been reported in high risk areas in Italy for a group of traditional dishes including meat soups, home-made stuffed pasta, rice and a sort of mais porridge, sharing preparation and storing practices established decades ago [17, 32].

Wholemeal bread and bran cereals have been repeatedly related to a decrease in GC risk [19, 25, 32, 33, 48], suggesting a nitrite-trapping role for fiber.

No consistent association has been identified with the consumption of sweets and cookies, but simple sugars, chocolate and other desserts have been reported as positively associated in some study [27, 30].

Spices and condiments

Garlic has been reported as inversely associated with GC in several studies in different countries including China and Italy [17, 39, 41, 48]. These results are in agreement with experimental data suggesting that garlic may play a role in the inhibition of CYP2E1, an enzyme acivating N-nitroso compounds.

Chili pepper and other spices showed a protective effect in Italy [17], possibly due to the association with a low-risk dietary pattern typical of the southern part of the country; recently, however, chili has been reported as a strong risk factor in a mexican study [51], in agreement with the mutagenic properties of capsaicin.

Olive oil has been associated with a decreased risk of GC in mediterranean countries [17, 27], possibly for its content in antioxidants but also for its typical use with raw salads.

Coffe and tea

No consistent association has been found between coffee consumption and GC risk. Several studies evaluated the role of tea drinking: for black tea most results are inconclusive, with a few studies suggesting positive [52] or negative associations [19]. For green tea, two Asian studies reported a protective effect [23, 53], in agreement with some laboratory experiments and the high content in polyphenols, but one showed a positive association [44].

Isolated reports

Several studies have sporadically reported the protective role of the consumption of a single well identified food or vegetable, including, for instance, grapes in Italy [17] and borage in Spain [54]. Some of these foods are particularly rich in specific naturally occurring substances which could explain the reported effects but the statistical problems related to the multiple comparisons (just by chance 5% of all the investigated food items could reach a level of significance) must be taken into account. On the other hand, the meaning of these isolated findings can be better interpreted considering wider groupings of foods (fresh fruit) or chemicals (polyphenols).

Other single food items have been associated with an increased GC risk mostly because heavily consumed by that particular population; fermented sour pancakes, for instance, are a staple food in a chinese high-risk area [22], while fava beans are heavily consumed in colombian villages [43]. Contamination of milk with bracken fern carcinogenic compounds has been suggested as a possible explanation of high GC risk in a rural area of North Wales [55]. In contrast, a food may simply be an indicator of a traditional dietary pattern or life-style (even in terms of ethnic or social group), actually responsible for the reported positive association with GC risk.

Nutrient intake

The estimated dietary intakes of several macro- and micronutrients have been related to GC risk in many case-control studies while blood levels have been evaluated in prospective and cross-sectional studies. Overall, the available evidence clearly supports a strong protective role for vitamin C and, to a minor degree, for alpha-tocopherol and beta-carotene. Nitrite intake has been consistently reported as a risk factor, together with total energy intake. This association with a high caloric intake is in agreement with other well known determinants of GC (risk is highest among manual unskilled workers) and has to be kept in mind when considering the role of individual nutrients.

Vitamin C

Virtually all studies have reported a strong protective effect for a high ascorbic acid intake, possibly because of its role in the inhibition of nitrosation reactions in the water compartment of gastric microenvironment. As an alternative mechanism, vitamin C could also function as free-radical scavenger. In one study [56] this effect persisted after adjusting for the intake of other protective nutrients. Experimental and cross-sectional studies (but not human intervention trials) have repeatedly confirmed this protective effect.

Vitamin E

Two well designed studies [56, 57] have reported a clear protective effect for alpha tocopherol, possibly because of its role as anti-nitrosating agent in the lipid compartment of gastric microenvironment (in analogy with that of vitamin C). A prospective study [58] and preliminary results of a chemoprevention trial [59] also confirmed this role. Another more recent trial, in contrast, reported no effect of the supplementation in heavy smokers [60].

Carotenoids

The estimated dietary intake of beta-carotene (or more in general of carotenoids because most food tables and many laboratories were unable to make a clear distinction between different carotenes and related compounds), has been consistently associated with a decreased risk of GC in several studies [30, 56, 57]. Prospective [61], cross-sectional [11, 62] and intervention studies [59] have confirmed this protective effect. Also CAG has been negatively associated with carotene intake [46]. Similar associations have not been observed with preformed vitamin A intake (except one poorly-designed study [63]) and thus conversion of beta-carotene to retinol is not considered the relevant mechanism. Carotene may act as an antioxidant and a free radical-trapping compound.

Minerals

Serum or toenail selenium levels have been reported as negatively associated with GC risk in two prospective studies [58, 64] but not in others [65]. No association has been found among serum levels and intestinal metaplasia, a pre-cancerous gastric lesion [11].

A convincing evidence has linked low body iron deposits as measured by serum ferritin levels to increased GC risk [66, 67], but this association seems more likely due to a long term condition of achlorydria, causing a reduced absorption of dietary iron, than to a real nutritional deficiency.

Nitrates, nitrites and nitrosable compounds

The relationship between estimated dietary intakes of nitrates and nitrites and GC risk has been repeatedly evaluated in case-control studies, often with inconclusive results; overall, however, a negative association is evident for nitrates [18, 30, 57]. Nitrite has been, in contrast, more often positively associated with GC risk [18, 30, 56]. These findings are in agreement with the results of most, but not all, correlation studies. When fresh vegetables are the main source of nitrates in the diet, as in western countries, it is of course difficult to disentangle their effect from that of all the antioxidants present at the same time.

A large study in Italy [56], reported a strong positive association with dietary protein intake, particularly from animal sources, which could provide specific secondary and tertiary amines for gastric nitrosation when combined with high levels of nitrite. Similar results have been reported by other studies [21, 39], but not adequately discussed, possibly because apparently in contrast with the general pattern of GC epidemiology. It is interesting the fact that traditional GC risk factors include smoked/salted fish and meats, the main sources of animal proteins in the diet of many populations in the past. Also fat (and in particular animal fat) has been reported as positively associated with GC risk [18, 27, 56, 57].

The intake of preformed N-nitroso-compounds (dymethyl-nitrosamine or NDMA) has been estimated in three case-control studies, one with inconclusive results [30], while recently two others reported a positive association [18, 68]. These estimates are based on average values and do not take into consideration the wide variability of actual food concentrations. It is also possible, therefore, that reported associations are grossly underestimated.

Cytochrome P450IIE1 enzymes (also known as CYP2E1) are responsible for the activation of many carcinogenic compounds, including N-nitrosamines: ethnic differences identified on the basis of restriction fragment length polymorphisms could be related to the increased genetic susceptibility for GC of high-risk populations. Rare alleles associated with increased gene expression were reported as significantly more frequent among Japanese than among caucasians [69]. A recent large study, however, found no association between a CYP2E1 specific genotype and GC at the individual level [70].

Salt consumption, food storage and refrigeration

A high intake of salt, as reported at interview by study subjects, has been consistently associated with an increased risk of GC [17, 37, 38, 48, 71, 72]. These

results are in agreement with some correlation study [73] and the decreasing temporal trend of GC. Only one nested case-control study reported a negative association on the basis of a self adminestered questionnaire [74]. GC risk has been consistently reported as positively associated with the age at which one started using an electric refrigerator for food storing [17, 19, 38, 75]. Early availability of a domestic refrigerator is clearly related to social class in most countries, and GC risk is inversely associated with socioeconomic level [76].

Food preparation and cooking

Consumption of grilled meats or fish is a potential source of polycyclic aromatic hydrocarbons and has been reported as positively associated with GC risk [17, 25, 40], although a study reported a negative association [19]. A positive association has also been found with the frequency of consumption of fried foods in two studies in Taiwan and Poland [44, 77].

The glutathione S-transferase family is a group of enzymes involved in the detoxification of chemical carcinogens catalysing the conjugation of several hydrophobic compounds with reduced glutathione. A higher proportion of the null phenotype was identified in a small group of GC patients (14/19 or 74%), in comparison to that of a control group (about 50%), suggesting a possible association between this phenotype and increased GC risk [78]. These results have been confirmed recently [70].

Alcohol and smoking

A large number of cohort and case-control studies have, overall, provided evidence that alcohol consumption has no substantial effect on GC risk [79, 80]. Positive findings can be interpreted as the result of confounding due to the association between drinking patterns, diet and social class. Evidence of a causal role of tobacco smoking in gastric carcinogenesis has been provided by several but not all studies [80, 81]. Again, it is difficult to disentangle the effects of different dietary patterns among smokers from the direct effect of the many chemical compounds (including N-nitrosamines) present in smoke. The declining temporal trend of GC is not fitting with the increasing rates of lung and other smoke-related cancers in the last four decades.

Chemoprevention trials

A significant reduction in stomach cancer incidence and mortality has been reported among participants receiving daily supplementation with beta carotene, vitamin E and selenium in a nutrition intervention trial in a rural county in northern China [59], where only a low body mass index was found associated with GC risk [82]. Modest effects or inconclusive results were reported by the same study group when pre- cancerous lesions or early gastric neoplasia were considered in an endoscopic survey [83, 84].

A negative result has been recently reported by a Finnish trial in heavy smokers [60].

Viral infections

The Epstein-Barr virus, causally linked to two different tumors, has been described in GC cells [85], particularly in lympho-epithelioma-like carcinomas [86]. Recently a case-control study nested in a cohort of Japanese Americans reported a 2-4 fold increase risk of GC in subjects with elevated antibody titers to EBV [87]. The biologic meaning of this finding is uncertain and could simply represent a marker of immune disregulation.

Reproductive and hormonal factors

The reasons for the twofold sex ratio (M/F) which is observed worldwide for GC rates are not well understood. A large Italian case-control study showed that post-menopausal women with GC had a significantly earlier menopause and shorter fertile life [88]. These findings have been confirmed [89] and suggest that female hormones or some hormone-related factor could play a protective role.

H_2 receptor antagonists

The widespread utilization of histamine H_2 receptor antagonists has been suggested as one of the possible explanations of the increasing trend observed for the cardia GC in several western countries. This hypothesis has not been confirmed [90]. Other studies had previously reported an increased risk of GC in the first year after beginning use of cimetidine, possibly because of misdiagnosis [91].

Helicobacter pylori infection

Since the identification of *Helicobacter pylori* in 1982 its causal role in specific types of acute and chronic gastritis and possibly duodenal ulcer has clearly emerged from an impressive number of clinical, epidemiological and laboratory studies. Other studies have also provided the evidence of a positive association with GC (with the exclusion of cardia cancers) and gastric lymphoma [92, 93]; extensive reviewes are available [94, 95].

If a causal link between *H. pylori* infection and GC could be confirmed a specific strategy for primary prevention of this cancer (large-scale eradication or, possibly, vaccination programmes) would be available, although its feasibility is debatable and its impact still unclear. The definite confirm of the causal role of *H. pylori* has proven difficult to obtain.

The working group of the IARC monograph series met in June 1994 and considered the available evidence already sufficient to classify *H. pylori* as "carcinogenic to humans (Group 1)" [94]. More recently, however, additional well designed studies have reported inconsistent results in terms of GC risk and randomized trials on the effect of eradication are needed.

Several mechanisms through which *H. pylori* could increase the risk of GC have been suggested and include increased cell replication during acute and chronic gastritis, alteration of the mucus barrier, increased *in situ* synthesis of carcinogens, decreased gastric juice levels of L-ascorbic acid and induction of DNA damage, resulting from the production of oxygen and nitrogen radicals [94]. On the other hand, *H. pylori* has been shown to be strongly related to socio-economic characteristics [96] and the possibility of confounding has to be taken into account, particularly in view of the moderate strenght of the association (overall, approximately a 2-3 fold crude risk) reported by analytical studies.

Correlation studies

Several studies have correlated *H. pylori* seroprevalence with GC incidence and/or mortality rates in different countries (Table 2): both negative [97-100] and positive results [9, 101, 102] have been reported. One large study in China [102] was able to take into account the dietary habits of participants: the correlation was no longer significant after adjustment for the levels of selected micronutrients [103]. Another large survey, known as EUROGAST, compared 17 population random samples, mostly from European countries; other groups from Japan and USA were later included to extend the range of GC risk [9]. The study, overall, reported a strong and statistically significant association which, however, weakened and lost its significance when all these additional groups were excluded and only the original European populations were considered in the analysis [104]. The GC incidence rates in Florence, the Italian center in the EUROGAST study, were much higher than would be predicted from the regression on the current *H. pylori* prevalence, thus confirming a previous population-based study showing no difference between areas in Italy at low and high risk of GC [98]. In a related paper the same Italian populations showed a significant 5-fold difference in terms of severe CAG, serologically defined

Table 2. - Ecological studies on the seroprevalence of *Helicobacter pylori* infection in different populations with contrasting gastric cancer rates

Reference	Year	Country	no. of subjects	Ratio(*)		P
				H. pylori infection	Gastric cancer rates	
Correa *et al.* [101]	1990	Colombia	78	1.5	5.8	< 0.01
Forman *et al.* [102]	1990	China	1,882	3.4	23	0.02
Sierra *et al.* [97]	1992	Costa Rica	282	1.1	2.5	NS
Palli *et al.* [98]	1993	Italy	930	1.1	2.5-3	NS
Fukao *et al.* [99]	1993	Japan	1,815	1.2-1.5	2.8-2.9	NS
Tsuguane *et al.* [100]	1993	Japan	624	1.4	2.6	NS
EUROGAST [9]	1993	13 countries (**)	3,194	2.8-8.8	9.5-13.3	0.002

Modified from Munoz & Pisani 1994 [95]
(*) Ratio between the maximum and the minimum value
(**) 11 European countries, Japan and USA
NS: no significant result

on the basis of a low level of Pepsinogen I [46]. The specific geographical distribution of *H. pylori* prevalence in Italy did not fit with observed GC rates when symptomatic subjects undergoing a first endoscopic examination have been considered in a large recent survey [105].

A well known example of lack of correlation is the so called "African enigma": most African countries have a very high *H. pylori* prevalence and, at the same time, a low incidence of GC. It is unlikely that this inconsistency can be simply explained by underreporting of GC.

In all the reported studies seroprevalence is very similar in the two sexes while, in contrast, GC shows a strong male predominance.

Case-control studies

Several case-control studies have been carried out and have, overall, reported an association between *H. pylori* infection and GC [106-110]; however, several inconsistent results are also available [111-113]. Most of these studies are of small size, except one with 213 GC case [109] and used hospitalised or symptomatic controls, causing serious problems in the interpretation of results. Adjustment for dietary or demographic factors is rarely performed and only in one study the association with GC persisted after such adjustment [108]. The risk of GC appears increased particularly in younger subjects [108, 110].

Infection is usually assessed at the same time of GC diagnosis and this represents a serious limitation of this study design, requiring the assumption of current seroprevalence being a reliable indicator of infection in the past. Progression from chronic gastritis to atrophic gastritis (and then to intestinal metaplasia and dysplasia, the pathogenetic sequence of intestinal-type GC) is considered to occurr only over a period of several years. The reported association between *H. pylori* and GC, in order to be considered causal, should respect this temporal latency. It is clear that *nested case-control studies* represent the most reliable study design to address this issue because infection can be assessed in blood samples collected (for both GC cases and control subjects) in a prospective study well before the diagnosis.

Only six such studies have been reported so far (Table 3) and none was able to present results adjusted for potential confounders as dietary or socio-economic characteristics. Three of these were already available for the IARC evaluation and have been also used for a pooled analysis showing an increase in the estimated risks of GC with an increasing time interval between blood collection and analysis [114]. The British study reported an increased risk for *H. pylori*-positive subjects, based on 29 GC cases diagnosed in a large cohort [115]. The second study was carried out in California [116], including 109 GC cases identified within a larger group of cases diagnosed in a cohort of over 120,000 members of a health insurance; the effects were stronger among

Table 3. - Nested case-control studies of *Helicobacter pylori* infection and gastric cancer

Author	Country	Year [Ref.]	GC cases		Matched controls		Mean follow-up (years)	Odds ratio	(95% CI)
			no.	*H. pylori* positive (%)	no.	*H. pylori* positive (%)			
Forman *et al.*	UK	1991 [115]	29	(69.0)	116	(46.6)	6	2.8	(1.0-8.0)
Parsonnet *et al.*	Ca, USA	1991 [116]	109	(84.4)	109	(60.6)	14.2	3.6	(1.8-7.3)
Nomura *et al.*	Hawaii, USA	1991 [117]	109	(94.5)	109	(76.1)	13.5	6.0	(2.1-17.3)
Hansen *et al.*	Norway	1994 [118]	201	(NA)	402	(NA)	12.4	1.8	(1.2-2.6)
Lin *et al.*	Taiwan	1995 [119]	29	(69.0)	220	(59.0)	3.1	1.6	(0.7-2.6)
Webb *et al.*	China	1995 [120]	87	(54.0)	348	(56.0)	2.3	0.9	(0.6-1.5)

NA: not available.

women and blacks. Another study from Hawaii identified 109 GC cases in a small cohort of Japanese American males and found a 6-fold risk of GC for those *H. pylori*-positive at the enrollment; the risk was particularly high among younger subjects [117]. Overall, the association was similarly strong for the intestinal and diffuse histological types of GC.

Another study from Norway, available only in abstract form [118], identified 201 GC in a large cohort of over 100,000 men and women with a median time interval between blood collection and diagnosis of 12 years. Strongly increased risks were evident for GC of the pylorus region and in previously resected patients; the risk was also increased for GC of the body and antrum while, in contrast, an inverse association was evident with tumors of the cardia and the gastroesophageal junction. Two more recent nested case-control studies have been carried out in Taiwan [119] and China [120] and showed a non- significant increase in GC risk or no increase at all, respectively.

The role of *cagA*-positive *H. pylori* strains (encoding for a high molecular weight protein) has been assessed in a recent analysis of a previous nested case-control study [117], in which infected GC cases have been compared to infected controls; results showed some increase in risk for cagA+ subjects, especially for intestinal-type GC of the distal stomach [121].

An increased *H. pylori* seroprevalence has also been recently described in small clinical series of patients affected with other cancers and cardiovascular diseases [122-124]; the meaning of these findings is not clear.

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