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Epidemiology of gastric cancer and perspectives for prevention

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Abstract

The most recent estimates of the world-wide incidence of cancer indicate that gastric cancer was in 1990 the second most frequent cancer in the world (after lung cancer), with about 900 000 new cases diagnosed every year. Steady declines in the rates have been observed everywhere in the last few decades, but the absolute number of new cases per year is increasing mainly because of ageing of the population. The exact causes of the decline of gastric cancer are not well understood, but must include improvements in diet, food storage (e.g., refrigeration) and, possibly, the decline of *Helicobacter pylori* infection. Dietary modifications and, possibly, vitamin supplements remain one of the most important tool for the prevention of gastric cancer. Control of *H. pylori* infection, by means of eradication or immunization, is also likely to offer great potential for the prevention of this important malignancy.

Key words: stomach neoplasms/prevention & control; *Helicobacter pylori*; review

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Resumen

Las estimaciones más recientes sobre la incidencia de cáncer a nivel mundial indican que, en 1990, el gástrico fue el segundo más frecuente (después del pulmonar), con aproximadamente 900 000 casos nuevos diagnosticados cada año. Durante las últimas décadas, las tasas de incidencia de esta enfermedad han disminuido en forma constante en casi todo el mundo; sin embargo, el número absoluto de casos nuevos por año continúa en aumento debido, primordialmente, a que la población cuenta con un mayor número de personas de edad avanzada. No se sabe con exactitud a qué se debe esta disminución de casos de cáncer gástrico, pero entre las causas se mencionan: mejoras tanto en la dieta como en la conservación de los alimentos (p.e., por medio de la refrigeración) y una disminución de las infecciones por *Helicobacter pylori*. Las modificaciones a la dieta y, posiblemente, el consumo de complementos vitamínicos continúan siendo las alternativas más importantes para prevenir el cáncer gástrico. Asimismo, es probable que el control de la infección por *H. pylori*, mediante la erradicación o la inmunización, tenga grandes posibilidades de contribuir a prevenir este grave padecimiento.

Palabras clave: neoplasmas gástricos/prevención & control; *Helicobacter pylori*; revisión

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The most recent estimates of the world-wide incidence of cancer indicate that gastric cancer is the second most frequent cancer in the world after lung cancer, with over 900 000 new cases diagnosed every year.[1] Fatality rates are high (the overall mortality incidence ratio is around 85-90%) and, also as a cause of death, gastric cancer ranked second world-wide.[2] Large differences in incidence exist also within small geographical areas (e.g., north and south Italy.[3] Steady declines have been observed everywhere in the last few decades.

The exact causes of the decline of gastric cancer are not well understood, but must include improvements in the affluence of diet, food storage (e.g., refrigeration) and, possibly, the decline of *Helicobacter pylori* (HP) infection.[4,5]

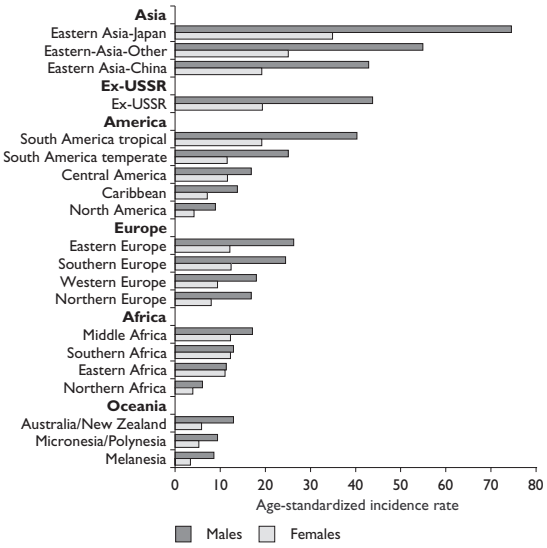
In this review, the geographical distribution and recent trends of gastric cancer will be examined. With respect to the aetiology, priority will be given to the findings concerning dietary habits and HP and their implications for the prevention of this malignancy will be assessed.

Geographical distribution

Estimated incidence rates of cancer of the stomach, standardized on the world population, ranged, in men in the mid-1980's, from below 10/100 000 in North America, Northern and Western Africa and Southern and South-Eastern Asia to very high rates (i.e., > 40/100 000) in Eastern Asia, most notably in Japan (75/100 000) and in the former Union of Soviet Socialist Republics (USSR)[6] (Figure 1).

Data from selected population-based cancer registries indicate that the highest rates (over 40/100 000) are reported from Japan, China, the ex-USSR, Portugal and certain countries in Latin America. The lowest rates (less than 15/100 000) are seen among whites in North America, in India, the Philippines, most African countries, some countries in western Europe, and Australia. Intermediate rates are seen elsewhere (Table I). Substantial variations in gastric cancer incidence can, however, be found also within countries, a good example being Italy where, for instance, male incidence rates ranged from 40.2/100 000 in Florence to 16.1/100 000 in Ragusa[3](Table I).

The mortality pattern is very similar to the incidence pattern, on account of the high fatality rates.[2] In Latin America, the highest mortality rats in males in 1985-88 are reported from Costa Rica (48.6 per 100 000) and Chile (34.4 per 100 000) and the lowest from Mexico (9.5 per 100 000) and Cuba (7.5 per 100 000).[7] The rates of stomach cancer in females are approximately half those in males, particularly in high-risk countries.



From: Parkin *et al.*, 1995[6]

FIGURE 1. ESTIMATED WORLD AGE-STANDARDIZED INCIDENCE RATES OF CANCER OF THE STOMACH IN THE WORLD IN 1985

Time trends

Mortality rates, derived from the official World Health Organization (WHO) mortality database, will be chiefly considered, since they have been available on an international scale for a longer period than incidence rates. Stomach cancer mortality declined with the last three or four decades in all European countries, but the falls were quantitatively different in absolute and in relative terms. The downward trends were more marked and started earlier in Northern and Western Europe than in Southern Europe (Figure 2).[9]

Figure 3 shows time trends in mortality rates for selected countries outside Europe. They provide examples of a general tendency to decline but also of persisting differences in the steepness of downward trends of gastric cancer in the world. Regarding to the Americas, some Central and South American countries had exceedingly high gastric cancer mortality rates that are declining.[7] Among males, for instance, Chile had an overall world standardized rate of 69.4/100 000 in 1950-1959, and of 34.4/100 000 in 1985-1989 (i.e., rates similar to the world highest ones, seen in Japan, Figure 3). Comparative figures in

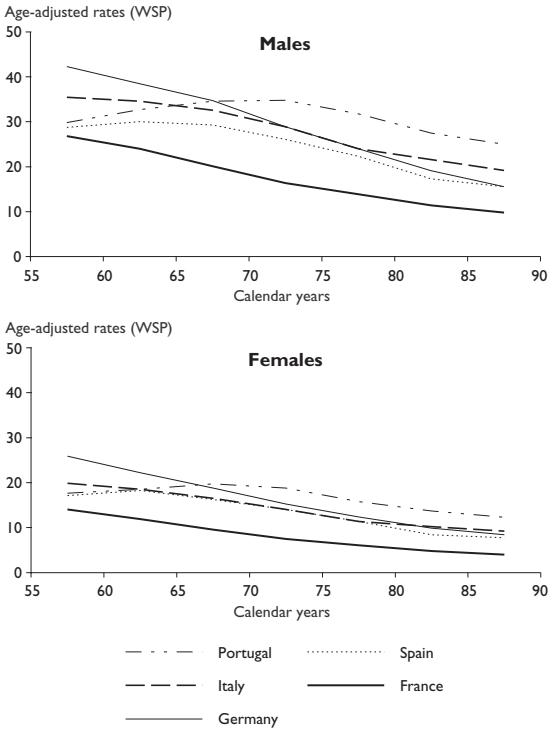
Table I

AGE-STANDARDIZED ANNUAL INCIDENCE RATES OF STOMACH CANCER BY SEX, 1983-1987*

Tumour registry	*Incidence rate per 100 000*	
	Men	*Women*
Western Europe		
Germany, Saarland	20.4	11.5
Netherlands, Eindhoven	19.9	8.8
Netherlands, Maastricht	16.6	6.3
Switzerland, Neuchatel	16.8	6.4
witzerland, Vaud	11.5	4.4
France, Doubs	15.1	5.5
France, Calvados	14.9	5.2
France, Bas Rhin	14.7	6.4
France, Isère	11.5	5.5
France, Tarn	8.3	3.4
Northern Europe		
Iceland	28.8	9.9
Finland	20.3	11.2
UK, Scotland	19.2	9.3
UK, England & Wales	16.9	6.8
Norway	15.7	8.0
Ireland, Southern	13.6	6.6
Sweden	12.7	6.5
Denmark	12.5	5.7
Southern Europe		
Portugal, V N de Gaia	47.8	23.9
Slovenia	27.9	12.8
Spain, Basque Country	27.3	10.9
Spain, Navarra	25.6	11.5
Spain, Murcia	17.6	8.3
Spain, Tarragona	15.1	7.9
Italy, Florence	40.2	19.1
Italy, Parma	38.4	17.0
Italy, Varese	32.7	15.0
Italy, Torino	20.2	8.9
Italy, Ragusa	16.1	8.2
Ex-USSR		
Russia, St. Petersburg	44.6	16.3
Kyrgyzstan	52.8	25.3
Belarus	46.7	20.1
Estonia	37.0	18.6
Latvia	34.1	15.5
Eastern Europe		
Poland, Nowy Sacz	30.8	15.1
Poland, Opole	27.4	10.1
Poland, Warsaw City	21.5	8.6
Hungary, Vas	30.6	14.3
Hungary, Szabolcz	26.4	9.3
Slovakia	27.1	12.2
Romania, County Cluj	26.1	10.7
Czech., Bov. Morav.	23.5	11.6
Germany, ex-G.D.R.	22.2	11.2
North America		
USA, Alameda, Black	16.8	7.1
USA, Alameda, White	8.8	4.1
USA, Connecticut, Black	15.0	4.1
USA, Connecticut, White	9.0	3.9
USA, SEER, Black	12.4	5.6
USA, SEER, White	8.0	3.5
Canada	12.4	5.4
Latin America		
Costa Rica	46.9	21.3
Colombia, Cali	36.3	19.9
Brazil, Porto Alegre	33.8	8.9
Brazil, Goiania	28.2	14.9
Ecuador, Quito	29.5	22.7
Peru, Trujillo	28.9	26.4
Paraguay, Asuncion	14.4	5.8
Cuba	9.8	5.0
Africa		
Mali, Bamako	19.4	10.3
Algeria, Setif	11.0	5.3
The Gambia	3.9	1.5
Asia		
Japan, Yamagata	93.3	42.9
Japan, Miyagi	85.4	36.7
Japan, Osaka	73.6	32.7
China, Shanghai	51.7	21.9
China, Tianjin	33.4	12.4
Hongkong	22.1	11.2
Singapore, Chinese	34.7	15.6
Singapore, Indian	15.9	7.5
Singapore, Malay	6.4	5.4
Philippines, Manila	13.5	8.1
Philippines, Rizal	11.1	7.4
India, Madras	15.1	6.7
India, Bombay	7.3	4.3
India, Ahmedabad	2.1	1.5
Israel, All Jews	14.6	7.5
Israel, Born Israel	9.1	6.8
Kuwait, Non-Kuwaitis	14.4	5.9
Kuwait, Kuwaitis	4.1	2.0
Oceania		
New Zealand, Maori	25.3	20.4
New Zealand, non-Maori	12.3	5.2
Australia, Victoria	14.1	6.0
Australia, N S W	11.8	5.2

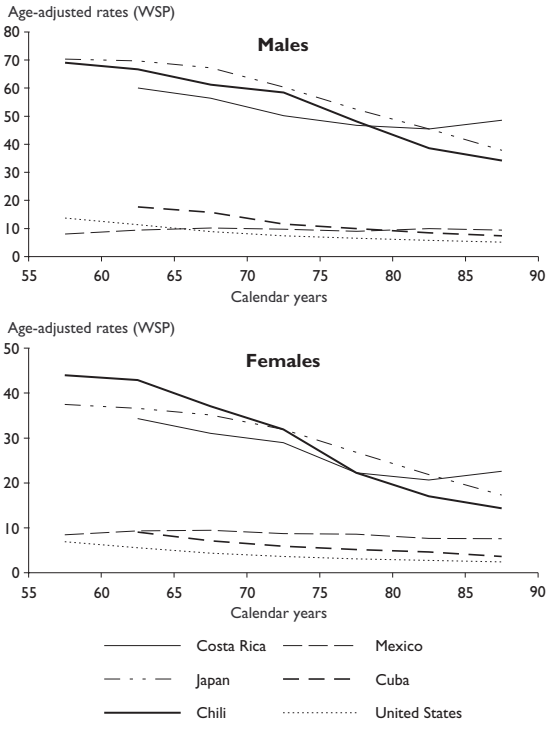
Source: Parkin *et al.*, 1992[3]

* Data do not necessarily include the whole period



From: La Vecchia *et al*., 1992[8]

FIGURE 2. STOMACH CANCER MORTALITY IN EUROPE, 1955-1989



From: La Vecchia *et al*., 1992[8]

FIGURE 3. STOMACH CANCER MORTALITY IN 1955-1989

Costa Rica were 60.3 / 100 000 males in 1960-1964 and 48.6 / 100 000 males in 1985-1989. In Mexico, no variation over the same calendar period was observed: 9.6 in 1960-64 and 9.5 per 100 000 males in 1985-89. Rates for females were lower, but the pattern of geographical differences and trends were similar (Figure 3).

Stomach cancer rates, were, and still are, high in Japan, although during the three decades considered overall age-standardized mortality declined from 71 to 38 / 100 000 males, and from 37 to 17 / 100 000 females (Figure 3). The falls were even greater, approaching 60%, in young and middle age (i.e., 35-64 years).

Mortality rates were extremely low in some African and Asian countries, including Egypt, Kuwait, the Philippines and Thailand. Such low values are at least in part, attributable to problems in case ascertainment and certification, although gastric cancer is relatively easy to diagnose. Data concerning mortality in other African and Asian countries are, unfortunately, scanty, and in most instances inaccurate.[10]

If incidence trends over the last decades, derived from population cancer registries, are examined, gastric cancer shows somewhat less marked declines than for mortality trends.[11] Incidence, however, had started to be recorded, in most countries, when the greatest fall of gastric cancer had already taken place. The greatest discrepancy between gastric cancer incidence and mortality rates can be seen in Japan. The incidence / mortality ratio in Japan, in both sexes, is presently around 2, whereas in other developed countries it is generally in the 0.8-1.5 range.[11] This high incidence / mortality ratio may partly reflect the spread of screening and early diagnosis by means of gastroscopy in Japan.[11]

It is important to bear in mind that the aforementioned downward mortality and incidence trends are dominated by the most frequent variant of gastric cancer, namely the so-called intestinal type of adenocarcinoma, usually occupying predominantly the antrum and the antrum-corpus junction. This variant is considered the endstage of a prolonged precancerous process (i.e., from chronic active gastritis, through atrophic gastritis and intestinal metaplasia and dysplasia, to frank carcinoma). The secular decline in diffuse carcinoma has been less clear, if existent, for

gastric carcinoma of the diffuse type.[12] Conversely, recent increases in incidence rates have been registered for adenocarcinoma of the gastric cardia. In United States whites, for instance, age-adjusted incidence rates of cardiac adenocarcinoma increased, from the mid-1970s to the mid-1980s, from 1.7 to 2.7 / 100 000 in men and from 0.23 to 0.45 / 100 000 in women. This increase parallels that of lower oesophageal adenocarcinoma, frequently linked with Barrett's oesophagus, reflux oesophagitis, a history of duodenal ulcer and gastric hypersecretion.[11]

Finally, it should be noted that although the gastric cancer rates are declining in most populations, the absolute number of new cases per year is increasing mainly because of ageing of the populations. This indicates that gastric cancer will still be a major public health problem in the future. The expected number of deaths from stomach cancer for the year 2000 are summarized in Table II. The first column shows the number of deaths estimated for 9 geographical areas in 1985. The second column shows the expected number of deaths for the year 2000 taking into account only the changes in the population resulting from increase and ageing. The third column is the expected number taking into account in addition to the population changes, the decreasing trends assuming that the rates will continue to decrease at the same speed as in the previous 20-30 years and in the last column the same assumptions as in column 3 are made but it is assumed that the decrease will level off (damped trend) which is probably more realistic. These estimates are derived from data published by Pisani *et al.*[2] It is of interest to note that for Latin America (as well as for the other regions), taking the more realistic projection, the number of deaths for stomach cancer in the year 2000 will be higher than those reported in 1985 both for males and females.

Risk factors

Diet

Dozens of case-control studies conducted all over the world have shown a remarkably consistent protection from fresh fruits and vegetables.[13]

Table III shows the types of vegetables and fruits which were significantly associated with gastric cancer risk in case-control investigations which included

Table II
Mortality for stomach cancer

Area	*1985*	*Expected number of deaths*		
		2000 only pop. change	*2000 pop. change + constant trend*	*2000 pop. change + damped trend*
A) Males				
China	150 900	228 600	173 400	221 900
Other Asia	44 200	66 600	58 000	65 600
Europe	58 700	71 100	45 800	67 900
ex-USSR	47 400	63 300	43 600	60 900
Latin America/Caribbean	30 500	46 200	33 300	46 100
Japan	30 300	46 600	28 400	44 300
Africa	11 400	17 800	15 300	17 500
North America	9 700	11 700	8 500	11 300
Oceania	1 200	1 600	1 100	1 600
B) Females				
China	73 800	107 000	100 000	106 000
Other Asia	26 600	45 100	30 000	46 153
Europe	42 800	49 800	29 600	47 100
ex-USSR	39 300	45 100	26 800	42 700
Latin America/Caribbean	17 600	27 400	18 700	27 200
Japan	18 900	27 100	14 400	25 400
Africa	9 800	15 200	13 400	15 000
North America	6 400	7 800	5 200	7 500
Oceania	700	900	500	800

Derived from Pisani *et al.*, 1993[2]

Table III

MAJOR FINDINGS OF CASE-CONTROL STUDIES OF VEGETABLE AND FRUIT CONSUMPTION AND GASTRIC CANCER

Author, year, study location	*Significant associations*	
	Negative	*Positive*
Graham *et al.*,1972,[14] New York, US	Raw vegetables, lettuce, coleslaw, broccoli	Potatoes
Haenszel *et al.*, 1972,[15] Hawaii, US	Tomatoes, celery, corn, onions	Pickled vegetables
Bjelke, 1974,[16] Norway	Vegetables, fruit	Canned fruit
Bjelke, 1974,[17] Minnesota, US	Tomatoes	Canned fruit
Modan *et al.*, 1974,[18] Israel	Squash, eggplant	
Haenszel *et al.*, 1976,[19] Japan	Celery, lettuce, fruit, plum, pear, pineapple	
Correa *et al.*, 1985,[20] Louisiana, US	Lettuce, tomatoes, broccoli, fruit, fruit juice	
Risch *et al.*, 1985,[21] Canada	Citrus fruit, fibrous foods	
Tajima & Tominaga, 1985,[22] Japan		Spinach, onion, cabbage, pumpkin, green pepper, pickled vegetables
Trichopoulos *et al.*, 1985,[23] Greece	Vegetables, cucumbers, onions, lettuce, lemons, oranges	
Jedrychowski *et al.*, 1986,[24] Poland	Fruit and vegetables	
La Vecchia *et al.*, 1987,[25] Italy	Green vegetable, citrus fruit, other fruit	
Hu *et al.*, 1988,[26] China	Spinach, eggplant, green beans	
You *et al.*, 1988,[27] 1989,[28] China	Fresh vegetables, sweet potatoes, fresh fruit, soybeans, vegetables, chives	
Buiatti *et al.*, 1989,[29] Italy	Raw vegetables, tomatoes, citrus fruit, other fruit	
Demirer *et al.*, 1990,[30] Turkey	Citrus fruit, raw yellow-green vegetables, cooked vegetables	
Kato *et al.*, 1990,[31] Japan	Raw vegetables	

From: Steinmetz & Potter, 1991[13] (modified)

data on the topic. Studies differed substantially from each other as concerns the type and number of vegetable and fruit items elicited in the dietary questions. However, with only two exceptions, negative associations emerged with high intake of most types of vegetables, most notably fresh green-leaf vegetables, and fruits, especially citrus fruit.

There was also a significant upward trend associated with frequent consumption of traditional foods such as polenta and stuffed pasta, with a RR of 2.4 for the highest tertile of intake in the largest study of gastric cancer published to date, conducted in seven Italian areas with different baseline incidence, and including over 1 000 cases and 1 000 controls.[29,32]

Two studies from Spain[33,34] found that an elevated risk was associated with consumption of preserved fish, salt, and pickled and smoked foods. Old-fashioned ways of food preservation (e.g. smoking of meat) seemed implicated in stomach cancer causation also in a German case-control study.[35]

Taken together, these foods may represent specific indicators of a less affluent diet, possibly the relevant factor in determining an elevated gastric cancer risk in various populations. Along this line, a Swedish study[36] suggested that various indicators of unfavourable socio-economic conditions early in life, such as short height or larger number of siblings, were positively related to subsequent gastric cancer risk. A correlate of unfavourable living conditions in the past, which may well be related to subsequent stomach cancer risk, is the availability of refrigeration, which was inversely related to gastric cancer risk in case-control studies conducted in Italy,[29,37] England,[38] and Sweden.[39]

Salt and salty foods have also been consistently incriminated as carcinogenic in relation to gastric cancer. In several studies,[27,40-42] questions were asked about taste preferences and amounts of salt usually added to foods during meals. Persons who preferred salty foods had a higher risk of developing gastric cancer, although the difficulty of assessing salt intake accurately certainly led to some underestimation of risk. One hypothesis that might explain a relationship between salt intake and gastric cancer is that excess salt acts as an irritant on the stomach wall, while nitrite and nitrate present in salt-preserved foods may induce the synthesis of N-nitrosamines in the stomach.

An increased risk of gastric cancer associated with a high consumption of chili peppers has also been reported from Mexico.[43]

Epidemiological data on the relationship between specific micronutrients and the risk of gastric cancer is scantier, but useful in the elucidation of the mecha-

nisms of dietary risk factors.[32,35,42,44-41] The main results on selected micronutrients from five European case-control studies are summarized in Table IV. The most consistent pattern of protection emerged for ascorbic acid, followed by β-carotene and α-tocopherol. The carotenoids and ascorbic acid were derived mainly from fruits and vegetables, while the a-tocopherol sources varied in different populations. While a high intake of nitrites seemed to increase gastric cancer risk, results with respect to the intake of nitrates are inconsistent. Ascorbic acid is actively concentrated in the gastric mucosa from the blood and secreted in the gastric cavity, where it can be involved in the detoxification of luminal carcinogens.[47] Various investigations have shown that in presence of HP infection, the levels of ascorbic acid in gastric juice are decreased and return to normal after eradication of the infection.[48] β-carotene may act as scavenger of the radicals and increase cell-to-cell communication, thus inhibiting the expression of malignant phenotypes in transformed cells connected to non-transformed cells.

Helicobacter pylori

Since the isolation of Helicobacter pylori in 1982, evidence for this bacterium's causal role in the pathogenesis of gastritis, duodenal ulcers and, possibly, stomach cancer has rapidly accumulated. The evidence linking HP to stomach cancer risk derives from different types of epidemiological studies.[5,49]

Ecological studies or geographical correlation studies were carried out world-wide, but revealed rather inconsistent results when the incidence or mortality rates of stomach cancer were correlated with prevalence rates of HP antibodies (i.e., the most appropriate measure of HP infection in large-scale studies). In several areas, most notably Africa, high HP prevalence went along with low gastric cancer rates. However, results of these ecological studies can easily have been distorted by variations in the accuracy of cancer registration, recent declines in HP prevalence and lack of allowance for confounding factors (e.g., dietary habits).[49]

At least ten case-control investigations on gastric cancer included data on HP prevalence (Table V). In these studies, the prevalence of antibodies to HP in patients with gastric cancer has been compared with their prevalence in a control group. Antibodies were measured in sera collected at the time of diagnosis of cancer. Table V includes four studies of this type conducted in low-risk countries for gastric cancer and six from high-risk countries. With respect to low-risk countries, a significant association was reported in the studies conducted in the United States, Finland and Sweden. However, no association was detected in a study carried out in the Netherlands. The higher HP prevalence in the controls compared with the cases and the subsequent lack of association in the Dutch study are not surprising if we consider the nature of the control group (i.e., patients undergoing upper gastrointestinal endoscopy). Although patients with peptic ulcer, gastric atrophy, intestinal metaplasia, or dysplasia were excluded from the control group, the remaining patients had non-ulcer dyspepsia that required upper endoscopy; therefore, it is possible that a considerable proportion of them had non-atrophic chronic gastritis associated with HP infection. In fact, as the authors noted, the HP prevalence in their control group (79%) was higher than that reported in healthy blood donors aged 40-59 years from the same population (47.9%). It is of interest to note that in the Swedish study the odds ratio (OR) increased with decreasing age at cancer diagnosis to reach 9.3 in subjects under 60 years of age, and that the increased risk remained after adjusting for potential confounders. The fraction of stomach cancer attributable to HP infection was about 40% in the studies from the United States and Finland and 50% in the Swedish study.

With respect to the six case-control studies carried out in high-risk countries, all but one study[54] did not show a significant positive association between HP and stomach cancer risk. The lack of a significant asso-

Table IV
SELECTED MICRONUTRIENT INTAKE AND GASTRIC CANCER RISK. ODDS RATIOS FOR HIGHEST *VERSUS* LOWEST CONSUMPTION LEVEL IN EUROPEAN STUDIES

Study	*Contry*	*β-carotene*	*Retinol*	*Ascorbic acid*	*α-tocopherol*	*Folate*	*Calcium*	*Nitrites*	*Nitrates*
Buiatti *et al.*, 1990[32]	Italy	0.9	1.0	0.5	0.6	-	0.9	1.2	0.9
Boeing *et al.*, 1991[35]	Germany	1.4	-	0.4	-	-	0.7	-	1.3
Ramon *et al.*, 1993[44]	Spain	0.5	-	0.4	0.8	-	1.9	-	-
Hansson *et al.*, 1994[45]	Sweden	0.7	0.7	0.7	0.9	-	1.1	-	1.0
La Vecchia *et al.*, 1994[46]	Italy	0.4	0.9	0.5	0.9	1.3	1.4	1.4	0.6

Table V
ODDS RATIOS OF GASTRIC CANCER BY HELICOBACTER PYLORI IN CASE-CONTROL STUDIES

	Cases		*Controls*		*OR*
	Number	*% HP+*	*Number*	*%HP+*	*(95% CI)*
Low-risk countries:					
United States[50] (Talley *et al.*, 1991)	37	65.0	252	38.0	2.7 (1.3-5.6)
Finland[51] (Sipponen *et al.*, 1992)	54	70.4	83	51.8	2.2 (1.0-4.4)
Sweden[39] (Hansson *et al.*, 1993)	112	80.4	103	61.2	2.6 (1.4-5.0)
Netherlands[52] (Kuipers *et al.*, 1993)	116	77.0	116	79.0	0.9 (0.5-1.7)
High-risk countries:					
Japan[53] (Igarashi *et al.*, 1992)	67	73.0	111	61.3	1.6 (0.8-3.1)
Japan[54] (Kikuchi *et al.*, 1995)	104	88.6	203	39.4	13.3 (5.2-35.6)
Italy[55] (Miglio *et al.*, 1992)	64	53.0	64	54.0	1.0 (0.5-1.9)
Portugal[56] (Estevens *et al.*, 1993)	80	70.0	80	81.0	0.6 (0.3-1.1)
Taiwan[57] (Lin *et al.*, 1993)	148	62.2	276	72.8	0.6 (0.4-0.9)
Venezuela (Muñoz *et al.*, unpubl.)	102	65.7	92	70.6	0.8 (0.4-1.5)

HP+= *Helicobater pylori* positive
OR= odds ratio

ciation in the Japanese study by Igarashi et al.[53] is not surprising considering that the control group comprised subjects with chronic gastritis, a condition also associated with HP. Conversely, Kikuchi et al.[54] reported a 13-fold elevated risk for early gastric cancer (i.e., below age 40 years). They suggested that the relationship between gastric carcinoma of HP may be stronger at young age, possibly due to a tendency of old cancer patients to develop severe atrophic gastritis and, hence, to lose seropositivity.

In Italy, relatively low HP prevalences were reported in both cases and controls in the Italian study considering that the study subjects came from a high-risk area for stomach cancer. Controls in this study were blood donors matched by sex and age to the cases. In the study from Portugal, controls were blood donors and subjects consulting an orthopaedic outpatient clinic and were matched to the cases by sex and age. In this study, the HP prevalence was higher in controls (81.0%) than in cases (70.0%). The gastric cancer cases from Taiwan were compared with two control groups; a random sample of 276 subjects over 40 years of age from three townships in Taiwan and 92 subjects with a mean age of 52.1 years were chosen among those undergoing a routine health check-up and found normal at endoscopy. In the first case the OR was 0.6 and in the second it was 1.0 (95% CI, 0.6-1.8). In the case-control study that we are conducting in a high-risk area for stomach cancer in Venezuela, the prevalence of HP antibodies was not significantly different in cases (65.7%) from the two control groups; it was 62.0% in the hospital controls and 70.6% in the population controls.[5]

The inherent limitation of the above case-control studies is the temporal ambiguity. In these studies HP infection and gastric cancer were diagnosed at the same time, thus impeding to determine which came first, especially if HP antibodies are considered indicators

of current or ongoing infection. In this context, case-control studies nested in cohort investigations are of particular value in assessing causality, since they document the presence of HP infection years before cancer onset.

Five nested case-control studies have reported consistent results and are summarized in Table VI. In the study conducted in the United Kingdom,[58] 29 gastric cancer cases were diagnosed in a cohort of 22 000 middle-aged men and were compared with 116 controls matched to the cases by date of birth and date of sera collection. The mean interval between sera collection and cancer diagnosis was 6 years, and the OR for gastric cancer in those with precedent HP antibodies was 2.8 (95% CI, 1.0-8.0). Limitations of this study are its size, the fact that for 13 of the 29 gastric cancer cases the diagnosis was based only on death certificates, and lack of information on other risk factors for stomach cancer.

The second study was nested in a cohort of about 6 000 Japanese-American men living in Hawaii.[59] A total of 109 cases of histologically confirmed gastric carcinoma diagnosed in this cohort were compared with 109 controls matched by age at entry and date of serum collection. The average time from serum collection to cancer diagnosis was 13.5 years and the OR of developing stomach cancer was 6.0 (95% CI, 2.1-17.3). The association with gastric cancer was significant for both intestinal and diffuse types of gastric cancer, and it became stronger with increasing antibody titers and with increasing time between serum collection and cancer diagnosis.

The study in California included 109 gastric cancers, 27 carcinomas of the gastro-oesophageal junction, and 120 000 persons.[60] The 109 gastric cancer cases included in this study were selected at random from 246 cases of stomach cancer diagnosed in the entire cohort. They were compared with an equal number of controls matched by age at serum donation, sex, race, date of serum donation, and site of recruitment. The mean interval between serum collection and the diagnosis of gastric cancer was 14.2 years. The ORs associated with the presence of preceding HP antibodies were: 3.6 (95% CI, 1.8-7.3 for stomach cancer; 0.8 (0.3-2.1) for tumours of the gastro-oesophageal junction, and 4.0 (0.5-35.8) for gastric lymphoma; only those for stomach cancer were statistically significant. The association was stronger in women and blacks and it was not confounded by either blood group or smoking history. A history of peptic ulcer was negatively associated with subsequent gastric carcinoma in this study.

The study by Lin et al.[57] consisted of the comparison of 29 patients with incident gastric cancer and 220 healthy controls, matched by age, sex and residence. They derived from a cohort of 9 777 Chinese subjects. Gastric cancer cases had a slightly higher sero-positive rate (69%) than control subjects (59%), giving an OR of 1.6 (95% CI, 0.7-2.6). The association was weak, possibly on account of the short time interval between serum collection and cancer diagnosis (mean= 3.1 years). Some years before diagnosis, many of the cases would have been likely to have severe atrophic gastritis or intestinal metaplasia. These conditions favour the loss of HP colonization, thus leading to false-negative findings in cases more frequently than in controls. A fifth prospective study is currently being conducted in Shanghai, China,[61] including a cohort of 18 244 men aged 45-64 years who provided serum samples between 1986 and 1989. The 87 cases of gastric cancer identified by September 1992 were compared with four to five controls per case, matched by year of birth, month of sample collection and residence. The mean time between sample collection and cancer diagnosis was 2.3 years. No increased risk for gastric cancer was observed (in cases OR= 0.9; 95% CI, 0.5-1.5). For cancer of the cardia the OR was 0.6 (95% CI, 0.2-1.3) and for non-cardia cancer cases it was 1.3 (95% CI, 0.6-2.9).

In conclusion, although there is an impressive body of clinical and experimental data indicating that

Table VI
ODDS RATIOS OF STOMACH CANCER BY HELICOBACTER PYLORI INFECTION IN CASE-CONTROL STUDIES NESTED WITHIN COHORTS

Study, year, country	*Follow-up years (mean)*	*No. cases*	*No. controls*	*Odds ratio*	*95% confidence interval*
Forman *et al.*, 1991 United Kingdom[58]	6	29	116	2.8	1.0-8.0
Nomura *et al.*, 1991 Hawaii, USA[59]	13	109	109	6.0	2.1-17.3
Parsonnet *et al.*, 1991 California, USA[60]	14	109	109	3.6	1.8-7.3
Lin *et al.*, 1993 Taiwan[57]	3	29	220	1.6	0.7-2.6
Webb *et al.*, 1993, China[61]	2	87	348	0.9	0.5-1.5

HP is one of the main causes of acute and chronic gastritis, firm epidemiological evidence linking HP to gastric cancer has been more difficult to obtain. From the review of the formal epidemiological studies carried out so far, the strongest evidence for a causal association is provided by case-control studies carried out in low-risk populations for gastric cancer and from the nested case-control studies in which it could be demonstrated that the HP infection preceded the gastric cancer development. However, the lack of control for potential confounders does not allow to draw definitive conclusions. Especially elevated risk derived from HP infection in younger subjects, although the rarity of gastric cancer before 40 years of age hampers the study of this age group.[54,62] The lack of association found in the case-control studies carried out in high-risk areas for stomach cancer might be due to the use of inappropriate serological assays, since assays were based on HP strains most common in Western countries.

The final proof of causality may be provided by intervention studies in which the efficacy of long-term eradication of HP in reducing gastric cancer rates is demonstrated. An important contribution can, however, come from the study of different strains of HP, with, possibly, varying oncogenic potentials. This would provide an essential tool to reassess and, possibly reconcile the aforementioned inconsistencies in the epidemiology of HP world-wide.

Other factors

Tobacco

There are forty two studies which have examined the effect of tobacco consumption as a risk factor for stomach cancer.[63] These consist of twelve cohort studies and thirty case-control studies. Ten of the cohort studies found a positive association between some aspect of tobacco use and gastric carcinoma and two did not find such an association. Eight of the cohort studies examined the presence of a dose-response relationship: three of these found a positive dose- response trend, while five others did not.

Of the thirty case-control studies, nineteen found an association between some aspect of tobacco use and stomach cancer and eleven did not. Seventeen of the studies examined a dose-response relationship between the amount of tobacco consumed and gastric carcinoma risk, and of these, six studies reported that the dose-response trend was positive; in eleven other studies a dose-response trend was not found.

From the mechanisms viewpoint, the direct carcinogenic effect of ingested tobacco or ingested tobacco smoke may include the development of precursor gastric lesions, such as gastritis, gastric peptic ulceration and intestinal metaplasia. Indirect effects of inhaled tobacco smoke in gastric carcinogenesis may involve both the nitrosamines found in smoke, as well as endogenously formed nitrosamines in smokers.

Alcohol

Alcohol drinking is strongly related to cancers of the upper digestive tract, with relative risk estimates around or over tenfold elevated among heavy drinkers as compared to non-drinkers for cancers of the oral cavity, pharynx, and oesophagus. The risk pattern with alcohol drinking is clearly different for gastric cancer,[64] but some relation is biologically plausible. Alcohol, in fact, could act as a contributory factor by causing chronic irritation of the gastric mucosa. Chronic gastritis, a disease which is thought to predispose to cancer of the stomach, is very common among alcoholics.

Social class and occupation

An inverse socio-economic gradient has been observed in most populations, the rate in lower socio-economic groups being two to three times higher than in more affluent classes.[65] An excess risk has been linked to certain occupations such as coal mining, fishing and agriculture. Since occupations are clearly related to socio-economic background, some of the excess risk observed might be attributable to patterns of lifestyle such as dietary habits.

Genetic factors

Although epidemiological evidence indicates that environmental factors play a major role in gastric carcinogenesis, a role of genetic factors is suggested by the study of blood groups and determinants of chronic gastritis.[66] Individuals of blood group A have been known for decades to show an approximately 20% excess of gastric cancer than those of group O, B or AB. They also show a similar excess of pernicious anaemia. Some data suggest that group A may be particularly associated with the diffuse type of gastric cancer.[66] A genetic aetiology has been reported for chronic atrophic gastritis, a precursor of gastric carcinoma.[67] The genetic segregation analysis showed Mendelian transmission of a recessive autosomal gene with penetrance

dependent on age and mother's chronic atrophic gastritic status. 48% of individuals with affected mothers were affected as compared to only 7% of those who mother did not have chronic atrophic gastritis.

Finally, a familial tendency to stomach cancer has long been suspected and repeatedly confirmed.[66,68,69] Better biomarkers are, however, needed to elucidate the mechanisms of familial susceptibility, including genetic and environmental interactions.

Conclusions and perspectives for prevention

Geographical distribution, time trends and the results of aetiological studies on stomach cancer are consistent in indicating a few major determinants of risk: insufficient fresh fruit and vegetable intake, excessive salt intake and gastric infection with HP, in addition, possibly, to genetic factors. Recent population-based survival data show that, even in Western countries, 5-year relative survival rates for stomach cancer are very low (around 20%) and improvement over time is small.[70] In the absence of widely available and effective screening programmes, primary prevention by decreasing exposure to the identified risk factors for the disease or by increasing protection against them might be the most effective way of controlling it. Despite clear improvements in the last decades, dietary modifications and, possibly, vitamin supplements remain the most important tool for the prevention of gastric cancer. However, no intervention trial on diet and stomach cancer is in progress and none is planned.

The main reasons for this are the logistical difficulties associated with changing the diet at a population level, especially in developing countries, and the tendency towards changes in the same direction in the placebo group as in the treatment group. This latter tendency occurs mainly in Eastern countries in which a substantial proportion of the population takes vitamin supplements, and in developing countries that are undergoing rapid economic change, such as China, which is influencing the food supply.

Two chemoprevention trials on the precancerous lesions of the stomach are in progress in high-risk areas of Colombia and Venezuela, while a third one is planned in low / intermediate-risk areas in Europe. The main features of these trials have been described in detail elsewhere.[71]

Control of HP infection, by means of eradication or immunization, is also likely to have great potential in the prevention of stomach cancer. Our ongoing studies in Venezuela suggest that prevention and / or eradication of HP infection by HP vaccines which are under development are more promising than eradication of the bacteria by antibiotics.[72]

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