

COMMENTARY

## Gastric cancer epidemiology and risk factors

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### Abstract

We performed a detailed analysis of the epidemiology of gastric carcinoma, based upon a review of the literature in English. The analysis reveals many puzzling features. There has been a steady fall in the incidence of gastric carcinoma in most societies studied, but a more recent steady rise in the incidence of adenocarcinoma of the cardia and lower esophagus, largely confined to White males. Although the evidence for a major role for *Helicobacter pylori* (*H. pylori*) in the etiology of gastric corpus cancer is compelling; in Western society, it probably accounts for fewer than half the cases. The relative roles of dietary constituents such as salt and nitrites and the phenotyping of *H. pylori* in causation and the beneficial effects of a high fruit and vegetable diet and an affluent lifestyle, for all of which there is some evidence, are yet to be quantified. © 2003 Elsevier Science Inc. All rights reserved.

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### 1. Introduction

The second half of the 20th century has seen a sharp worldwide decline in both the incidence and mortality of gastric cancer. Despite this, the condition remains the world's second leading cause of cancer mortality behind lung cancer. It has been estimated that there will have been more than 870,000 deaths from the disease in the year 2000, accounting for approximately 12% of all cancer deaths [1–3].

Gastric cancer has attracted much attention from epidemiologic investigators over recent years, particularly with the emergence of *H. pylori* as a risk factor for the condition. This has led to an improved understanding of the etiology and pathogenesis of gastric cancer and raised the possibility of active prevention of the disease. Differences in exposures to *H. pylori* and a range of other environmental factors probably account for much of the variations seen in the incidence of gastric cancer over time and between populations.

We begin with a discussion of the pathology of gastric cancer, then consider descriptive epidemiology, and finally review the evidence concerning possible etiologic factors. The evidence described in this report was identified from the English language literature by searching the Medline database.

### 2. Pathology

Approximately 90% of stomach cancers are adenocarcinomas. Non-Hodgkin's lymphomas and leiomyosarcomas make up most of the remaining 10%.

Adenosquamous, squamous, and undifferentiated carcinomas also occur but are rare. Other very rare malignant primary tumors of the stomach include choriocarcinomas, carcinoid tumors, rhabdomyosarcomas, and hemangiopericytomas. Kaposi's sarcoma, in association with the acquired immunodeficiency syndrome, has also been reported [4].

Adenocarcinomas may be subdivided histologically into two categories: (1) a well-differentiated or intestinal type, with cohesive neoplastic cells forming gland-like structures that frequently ulcerate; and (2) a diffuse type in which cell cohesion is absent, resulting in infiltration and thickening of the stomach wall without the formation of a discrete mass. The intestinal type is more common in males and older age groups. Diffuse carcinomas are relatively more common in younger age groups and have a more equal male-to-female ratio [5].

### 3. Descriptive epidemiology

One of the notable features of the descriptive epidemiology concerning gastric cancer is that it establishes some clear distinctions between cancer localized to the gastric cardia and cancer of the rest of the stomach, as discussed below.

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### 3.1. International variations

There is marked geographic variation in the incidence of gastric cancer. International Agency for Research on Cancer data for 1996 (Table 1), demonstrate age-standardized incidence rates in males ranging from 95.5/10<sup>5</sup> in Yamagata, Japan, to 7.5/10<sup>5</sup> in Whites in the United States. High-risk areas include China and large parts of central and South America [6]. Most of the geographic variation is accounted for by differences in the incidence of noncardia cancer. Cancer localized to the cardia has a more uniform distribution (Table 2). Gastric cardia cancer accounts for only 4% of total gastric cancer cases in males in Osaka, Japan, compared to 39% in white males in the United States [7]. On a histologic level, the incidence of diffuse adenocarcinomas is reported to be similar in most populations, while the intestinal type predominates in the high-risk geographic regions and is the type that has declined significantly in incidence in many countries [8,9].

Ethnic groups who have migrated from high- to low-incidence countries have an overall risk intermediate between that of their homeland and that of their new country (Table 3). First generation migrants tend to maintain their high-risk while subsequent generations have risk levels approximating that of the host country [10].

### 3.2. Time trends

Both incidence and mortality rates for gastric cancer have declined sharply over the latter half of this century in many countries around the world [1]. In Australia, the age-standardized mortality rate for gastric cancer in men has fallen steadily from 25.9/10<sup>5</sup> in 1950 to 6.7/10<sup>5</sup> in 1994. In Japan, over the same period the mortality rate has more than halved, but the decline did not become apparent until the early 1970s [11]. In contrast to the trend for an overall decrease in gastric cancer rates, in developed countries there has been a rapid increase in the incidence of gastric cancer localized to the cardia [12–14].

Such changes began in the United States in the 1970s and 1980s, with a very high M:F ratio (largest for any cancer except lip cancer) and a higher incidence in Whites than in Blacks [14,15]. Blot et al. have argued cogently that these changes are real, and not due to misclassification or coding errors. Endoscopy with its increased ability to localize tumors is not the explanation for the increase in cardia tumors for this would imply a reciprocal fall in esophageal adenocarcinoma whose incidence has risen also. A U.S. report has clearly demonstrated a parallel five- or sixfold rise in adenocarcinoma of the gastric cardia and of the lower esophagus in recent decades [16]. A rising incidence of adenocarcinoma around the cardia has also been reported from the UK [12], Sweden [17], Australia [18], and Switzerland [19]. Recent investigations of the cause suggest that two factors are of importance. For decades Barrett's Esophagus, a complication of reflux esophagitis, has been regarded as having unquantified malignant potential with a recent Swedish

Table 1

International comparison of age-adjusted incidence rates (/100,000) of gastric cancer in selected countries

Country, region	Male	Female	Ratio
Japan, Yamagata	95.5	40.1	2.4
Japan, Hiroshima	83.1	35.9	2.3
Korea, Kanwha	65.9	25.0	2.6
Japan, Osaka	65.0	27.3	2.4
Costa Rica	51.5	22.7	2.3
China, Shanghai	46.5	21.0	2.2
Italy, Florence	36.3	15.9	2.3
Columbia, Cali	33.3	19.3	1.7
Peru, Trujillo	31.1	20.1	1.5
Yugoslavia, Vojvodina	20.8	9.4	2.2
Hong Kong	19.4	9.5	2.0
Germany, Saarland	18.5	9.0	2.1
Italy, Genoa	17.6	8.3	2.1
United Kingdom	16.1	6.3	2.6
Spain, Granada	15.5	7.0	2.2
US, SEER <sup>a</sup> (Black)	14.5	5.9	2.5
Norway	13.6	6.4	2.1
Switzerland, Geneva	12.3	5.4	2.3
France, Bas Rhin	12.2	4.9	2.5
Australia, Victoria	11.7	4.9	2.4
Philippines, Manila	11.1	6.4	1.7
Canada	10.6	4.5	2.4
Australia, NSW	10.1	4.2	2.4
Singapore (Malay)	8.7	5.5	1.6
India, Bombay	7.7	3.8	2.0
Thailand, Chiang Mai	7.5	4.9	1.5
US, SEER* (White)	7.5	3.1	2.4
Highest/lowest ratio	12.7	12.9	

Data taken from *Cancer Incidence in Five Continents, Volume VII, 1996* [9]

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study showing a strong link between reflux symptoms and adenocarcinoma of the lower esophagus. Among those with frequent long-term and severe symptoms the OR was 43.5 (18.3–103.5) for adenocarcinoma of the esophagus and 4.4 (1.7–11.0) for carcinoma of the cardia but no link between esophageal squamous carcinoma and reflux was demonstrated [20]. In view of the association between obesity and reflux and esophagitis there is a strong suggestion that obesity is the underlying factor in the reflux and esophageal problems [21,22]. How this relates to cardia carcinoma is

Table 2

Comparison of age-adjusted incidence rates (/100,000) of gastric cardia cancer and noncardia cancer in selected countries

Country, region	Cardia			Non-Cardia		
	Male	Female	Ratio	Male	Female	Ratio
China, Shanghai	8.1	2.0	4.1	38.5	19	2.0
Japan, Hiroshima	4.6	1.5	3.1	78.6	34.4	2.3
Japan, Osaka	2.4	0.8	3.0	62.6	26.5	2.4
United Kingdom	2.9	0.6	4.8	13.1	5.6	2.3
Singapore (Chinese)	2.4	0.6	4.0	27.0	13.0	2.1
Australia, NSW	2.1	0.4	5.3	8.1	3.8	2.1
New Zealand (Non-Maori)	2.9	0.6	4.8	8.1	3.8	2.1
New Zealand (Maori)	1.5	0.5	3.0	26.4	13.3	2.0
US, SEER (White)	2.9	0.5	5.8	4.6	2.5	1.8
US, SEER (Black)	1.8	0.5	3.6	12.7	5.4	2.4

Data taken from *Cancer Incidence in Five Continents, Volume VII, 1996* [7].

Table 3  
Migrant comparison of age-adjusted incidence rates (/100,000) of gastric cancer

Ethnicity	Region	Male	Female
Chinese	China, Shanghai	46.5	21.0
	Singapore	29.3	13.6
	Hong Kong	19.4	9.5
	Hawaii	12.3	5.2
	Los Angeles	11.7	7.6
	Highest/lowest ratio	4.0	2.8
Japanese	Yamagata	95.5	40.1
	Osaka	65.0	27.3
	Hawaii	21.5	10.6
	Los Angeles	21.2	12.0
	Highest/lowest ratio	4.5	3.8

Data taken from *Cancer Incidence in Five Continents, Volume VII, 1996* [7]

unclear. However, there are two threads relative to diet that may be relevant. A further report from the Swedish study has shown a strong inverse relationship between cardia cancer and dietary fibre intake (P trend <.0001) [23]. It has been hypothesized that this effect may be mediated by the ability of cereal fiber to neutralize salivary nitrite, a recognized gastric carcinogen. It has also been shown that Omeprazole administration is followed by a dramatic rise in gastric juice nitrite, both fasting and postprandial [24]; Proton Pump Inhibitors (PPIs) such as Omeprazole<sup>®</sup> are now widely prescribed for reflux symptoms since their introduction in the 1980s.

### 3.3. Age, sex, and race

The incidence of gastric cancer rises progressively with age, with most patients being between the ages of 50 and 70 years at presentation. Cases in patients younger than 30 years are very rare.

Noncardia cancer is more common in males than females by a ratio of approximately 2:1. Gastric cardia cancer has a higher male-to-female ratio, of up to nearly 6:1 in U.S. Whites (Table 2) [7].

There are significant variations in the overall incidence of gastric cancer between different ethnic groups living in the same region (Table 4). [6] The ethnic distribution for cardia cancer is different, with a preponderance in Whites over Blacks in the United States and non-Maoris over Maoris in New Zealand (Table 2) [7].

### 3.4. Socioeconomic status

Low socioeconomic status has been consistently shown to be associated with an increased risk of gastric cancer overall [1]. Remarkably, the increase in incidence of cardia cancer has been predominantly in professional classes [12].

## 4. Possible causes of gastric cancer

### 4.1. *H. pylori*

Since *H. pylori* was first reported by Marshall in 1983, a wealth of evidence has been gathered concerning this organ-

Table 4  
Ethnic difference in age-adjusted incidence rates (/100,000) of gastric cancer

Country, region	Ethnicity	Male	Female
Singapore	Chinese	29.3	13.6
	Indian	10.3	7.9
	Malay	8.7	5.5
	Highest/lowest ratio	3.4	2.5
	US, Los Angeles	Korean	35.5
US, Los Angeles	Japanese	21.2	12.0
	Black	13.6	5.9
	Hispanic White	11.8	6.9
	Chinese	11.7	7.6
	Other white	7.6	3.2
	Filipino	6.8	4.0
	Highest/lowest ratio	5.2	5.1
	New Zealand	Maori	27.9
Non-Maori	11.0	4.8	
Highest/lowest ratio	2.5	2.9	

Data taken from *Cancer Incidence in Five Continents, Volume VII, 1996*

ism and its role in the etiology of gastric cancer [25]. In 1994, the International Agency for Research on Cancer classified *H. pylori* as carcinogenic to humans [26]. Evidence supporting a causal association between *H. pylori* and gastric cancer can be found in ecologic studies, case–control studies, and prospective cohort studies.

An international population study performed by the Eurogast study group found that countries with high gastric cancer rates typically have a high prevalence of *H. pylori* infection [27]. The prevalence of *H. pylori* infection has declined in developed countries over recent decades, paralleling the fall in gastric cancer incidence. Similarly, the excess of gastric cancer seen in those of lower socioeconomic status is matched by a similar excess of *H. pylori* infection in these groups [28,29]. Some case–control studies have reported significant associations between *H. pylori* positivity on serology and overall gastric cancer risk [30–32], others no association [33,34], while two studies have reported significantly increased risks for noncardia cancer, but not for cancer of the cardia [35,36]. *H. pylori* infection may be lost with the development of atrophic gastritis and atrophy that are present in many gastric cancer patients so retrospective studies need to be interpreted with caution [29].

Prospective studies provide the strongest support for the association [37–40].

Forman et al. undertook a pooled analysis of data from three such prospective studies. The risk of gastric cancer following *H. pylori* infection increased significantly with the length of follow-up, with an almost ninefold risk observed after 15 years or more (Table 5) [41]. Meta-analyses of prospective studies suggest that the risk of gastric cancer is increased two- or threefold in those chronically infected with *H. pylori* [42,43]. A further prospective nested case–control study reported a significant association between prior *H. pylori* infection and gastric adenocarcinoma overall, but no association with cancer of the cardia [44]. *H. pylori* contributes to the causation of gastric cancer via mechanisms that include the development and pro-

gression of chronic gastritis. The infection causes chronic gastritis in almost all infected individuals, and accounts for nearly all cases of chronic gastritis [45,46]. *H. pylori* gastritis may progress over time from an initially superficial nonatrophic form to more severe forms, including severe atrophic gastritis with intestinal metaplasia in a small proportion of cases [47,48]. Chronic gastritis is present in the great majority of cases of gastric cancer, and is associated with an increased risk for the condition [49]. That risk increases with the severity of the gastritis, with reported risks in excess of 10-fold for severe atrophic antral gastritis [49,50]. Intestinal type gastric cancer appears to be more strongly associated with severe atrophic gastritis, whereas the diffuse type is more common in nonatrophic gastritis [49]. There is now strong evidence for a role for virulence factors in *H. pylori* carcinogenesis. The Cag A virulence factor is strongly associated with the risk of adenocarcinoma, whereas its absence carries, at most, a low risk of diffuse adenocarcinoma [51,52].

#### 4.2. *H. pylori* and gastric non-Hodgkin's lymphoma

Almost all non-Hodgkin's lymphomas arising in the stomach are B-cell tumors. These may be high-grade, or low-grade lymphomas of mucosa-associated lymphoid tissue (MALT). These two subtypes are probably parts of the spectrum of the same disease [53,54]. An association between *H. pylori* infection and gastric non-Hodgkin's lymphoma has been shown by a series of studies. Wotherspoon et al. (1991) found *H. pylori* infection in 92% of 110 cases of gastric MALT lymphoma [55], and Parsonnet et al. that prior *H. pylori* infection conveyed a statistically significant sixfold increased risk of gastric non-Hodgkin's lymphoma overall, with the association being slightly stronger for high-grade lymphomas [56]. A complete regression of low-grade MALT lymphoma following eradication of *H. pylori* infection was reported in five of six patients [57], and the same outcome in 23 of 33 patients, with partial regression in a further four patients [58]. A complete regression of low-grade MALT lymphoma for 16 months following *H. pylori* eradication, with subsequent relapse of the lymphoma following reinfection with *H. pylori* has also been reported [59].

Table 5  
Risk of gastric cancer following *H. pylori* infection

Interval (years)	Cases	%Hp +	Controls	%Hp +	OR	(95% CI)
0–4	25	80.0	58	58.6	2.1	(0.6–8.7)
5–9	46	80.4	85	54.1	2.3	(0.9–6.5)
10–14	78	89.7	93	62.4	4.4	(1.8–13.0)
>14	98	89.8	98	66.3	8.7	(2.7–45.0)
All	247	87.0	334	60.8	3.8	(2.3–6.2)

Combined analysis of three prospective studies, stratified by time intervals between blood donation and cancer diagnosis.

%HP +, percentage positive for *H. pylori* infection; OR, odds ratio; 95% CI, 95% confidence interval.

Adapted from Forman et al. [31].

#### 4.3. Gastric surgery

Since a possible association between gastric surgery and subsequent gastric cancer was first noted in 1922, there have been numerous reports on the subject [60]. Many studies, including large long-term follow-up studies, point to an increased risk of gastric cancer particularly 15 years or more after gastric surgery [61–64]. The association is strongest for gastrectomy performed for gastric ulcer and less persuasive for vagotomy or for gastrectomy performed for duodenal ulcer. The link does not extend to cancer of the gastric cardia [64]. A possible linkage is with gastritis, a recognized antecedent of cancer. Gastritis localized to the antrum related to *H. pylori* colonization is characteristic of duodenal ulcer; gastric resection leaves a normal mucosa, whereas gastritis of the body of the stomach and so of the gastric stump is characteristic of gastric ulcer; thus sparing of the cardia from active carcinoma would be expected after partial gastrectomy for duodenal ulcer.

#### 4.4. Peptic ulcer disease

Gastric ulcer, duodenal ulcer, and gastric cancer all have *H. pylori* infection as a common risk factor. An association between prior peptic ulcer and increased gastric cancer risk might therefore be expected. However, duodenal ulceration has been inversely associated with gastric cancer risk [64–66]. Although earlier studies have failed to demonstrate any increased long-term risk in patients with gastric ulcers, recent evidence supports a moderate association with gastric cancer that arises other than in the cardia [64–67]. In seeking to explain this apparent paradox, Parsonnet has argued that *H. pylori* infection can progress to gastric cancer or duodenal ulcer, but seldom to both [68]. She suggested factors other than *H. pylori* infection must foster one disease while militating against the other, nominating genetic characteristics of the host and the organism, exogenous elements and, particularly, the time of life when *H. pylori* infection was acquired as important influences. Early infection predisposes to atrophic gastritis and the risk of cancer, but reduces duodenal ulcer risk due to decreased acid production associated with the gastritis. With later infection, atrophic gastritis is less likely and gastric cancer risk is reduced. Whether the risk of gastric carcinoma is altered by duodenal ulcer is vexed. The only firm data compare duodenal ulcer and gastric ulcer, both characterized by an accompanying gastritis. A key issue is whether the adenocarcinoma rate following duodenal ulcer is different to that found with a normal gastric mucosa; no data are available nor likely on this issue. However, the absence of gastritis implies absence of *H. pylori*, and there are good data indicating that those without *H. pylori* colonization have a minimal risk of gastric carcinoma [69].

#### 4.5. Dietary factors

Distinct variations in the incidence and mortality of gastric cancer, over time, between and within countries, in dif-

fering socioeconomic groups, and in migrants and their offspring suggest that diet may be etiologically important and its role has been extensively investigated with inconclusive results.

#### 4.6. Fruit and vegetables

The dominant dietary hypothesis is that fresh fruits and vegetables, or contained micronutrients, are protective against gastric cancer. Numerous studies have shown, almost uniformly, a protective association with fresh fruits and vegetables, independent of other dietary factors. The association has been less pronounced in limited cohort studies [70].

Possible protective micronutrients include vitamins C (ascorbate) and E (alpha-tocopherol), carotenoids (particularly beta carotene), and selenium [70]. The evidence is strongest for vitamin C, with an approximate halving of risk associated with high intake vs. low intake demonstrated in case-control studies [71]. However, a 5-year intervention trial, involving 30,000 40 to 69 year olds in China, did not show any change in risk of gastric cancer in subjects receiving supplemental vitamin C [72].

#### 4.7. Salt

The hypothesis that excess salt intake could be involved in the etiology of stomach cancer was first presented in 1965. It was postulated that the continuous use of high doses of salt would result in early atrophic gastritis, thereby increasing the later risk of stomach cancer [73]. Since that time high salt consumption has been reasonably consistently associated with an increased risk of gastric cancer in ecologic and analytical studies, although good quantitative data are lacking [73–80].

#### 4.8. Nitrite and nitrate

Many *N*-nitroso compounds have been shown to be carcinogenic in animal experiments. Such compounds may be formed in the human stomach from dietary nitrite or nitrate. Hence, the hypothesis that a diet high in nitrite or nitrate may predispose to gastric cancer. The major sources of nitrate and nitrite are vegetables and preserved meats, respectively. Drinking water is an additional source of nitrate, but usually contains negligible nitrite.

In general, daily nitrate intake is approximately 100 times that of nitrite. Small quantities of pre-formed *N*-nitroso compounds may also be contained in some foods including cured meats [70–82]. Case-control studies examining dietary intake of nitrate and the risk of gastric cancer have consistently found a negative association. In such studies, vegetable intake has been consistently related to a decreased risk of gastric cancer. Nitrate intake was probably an index of vegetable intake and the negative association is not surprising in that context [70]. Recent case-control studies have all reported a weak, statistically nonsignificant increased risk of gastric cancer (relative risks from 1.12 to 1.28) for high vs. low nitrite intake [80,81,83,84]. Nitrite in-

take probably reflects consumption of preserved meats, typically high-salt foods so isolating an effect of nitrite consumption is difficult. Further evidence suggests that the interaction of the above dietary components is important. For example, a diet high in nitrite does not appear to confer an increased risk if that diet is also high in antioxidants from fruit and vegetables [81].

#### 4.9. Other dietary factors

The collective literature on diet and gastric cancer provides data for a comprehensive array of food groups, nutrients, micronutrients, and food-storage methods. Difficulties in gathering and interpreting this evidence limit the conclusions that can be drawn. The advent of widely available refrigeration, the consequent availability of fresh food and the decreased consumption of preserved foods may have contributed to the decline in gastric cancer incidence in the second half of this century.

Dixon has pointed out how virulent strains of *H. pylori* release reactive oxygen metabolites that could destroy neighboring glandular tissue leading to gastric glandular atrophy, hastened by factors such as bile reflux or a high-salt intake but retarded by antioxidants such as ascorbic acid, alpha tocopherol, beta carotene, and cysteine [85].

#### 4.10. Ionizing radiation

The best evidence concerning the role of ionizing radiation in the etiology of gastric cancer comes from the study of survivors of the atomic bombings of Hiroshima and Nagasaki. In a prospective incidence study of this cohort of approximately 80,000, Thompson et al. identified more than 2,600 cases of gastric cancer [86]. A linear dose-response effect ( $P < .001$ ) was observed between radiation dose and risk of gastric cancer, although the excess risk was small (0.32 at one Sievert, 95% CI, 0.16 to 0.50) and the attributable risk was low (6.5%), in the setting of a high background rate of gastric cancer in this Japanese population.

Studies of patients undergoing therapeutic radiation to the region of the stomach for peptic ulcer disease [87] (a treatment modality used from the late 1930s to the mid-1960s) and for testicular cancer [88,89], also provide significant support for this association. These studies suggest a two- to fourfold increased risk in patients exposed to radiation doses of 15 to 30 Gy.

Studies of occupational radiation exposure in radiographers [90] and radiologists [91,92] have not demonstrated increased risks, presumably due to the much lower radiation doses involved compared to the atomic bomb survivors and the therapeutically irradiated. Differentiation of risk based on the type of gastric cancer is not possible from the available evidence.

#### 4.11. Pernicious anemia

An association between pernicious anemia and gastric cancer has long been recognized. In the most recent and

largest study of this topic, Hsing et al. observed a threefold increase in the risk of gastric cancer in a cohort of 4,517 pernicious anemia patients, followed for up to 20 years [93].

#### 4.12. Smoking

The relationship between smoking and gastric cancer has been extensively examined yet remains unclear; while most studies have reported a weak to moderate association, a few have found none [40,94–102]. In the positive studies the increased relative risks reported have generally been less than twofold, and only a few studies have found a dose–response relationship [94,98,99]. A particular limitation of the available studies has been a lack of control for confounding, particularly by *H. pylori* infection, which is positively correlated with smoking, and by fruit and vegetable intake, which is inversely associated.

Most of the evidence does not allow any differentiation of risk by anatomic subsite or by histologic type. One case–control study found a stronger association for gastric cardia cancer than for other gastric cancer across multiple categories of smoking, whereas another did not [99,103,104].

#### 4.13. Alcohol

A 1994 review of the experimental, descriptive, and analytical evidence relating to alcohol and gastric cancer found little to support an association [105]. After examining over 50 mostly negative cohort and case–control studies, the authors concluded that alcohol consumption was unlikely to be materially involved in the etiology of gastric cancer. Subsequently, studies have not challenged that conclusion [40,94,99]. Five case–control studies showed no association between alcohol consumption and cancer of the gastric cardia [99,104,106–108] and one a doubling of risk in drinkers vs. nondrinkers. [101]

#### 4.14. Epstein-Barr virus infection

Epstein-Barr virus has been isolated from gastric adenocarcinomas and poorly differentiated carcinomas with lymphoid infiltrate by a number of investigators. Epstein-Barr virus infection may contribute to the development of gastric carcinoma, but the data are limited.

#### 4.15. Asbestos

Several studies of workers with occupational exposure to asbestos have reported limited evidence of an association [109–112]. However, methodologic problems cast doubt on the association. A case–control study of heavily exposed asbestos miners and millers in Western Australia found no association between gastric cancer mortality and intensity of exposure, duration of employment, or time since employment began [113].

#### 4.16. Other risk factors

The risk of gastric cancer is increased in first-degree relatives of patients with the disease by approximately two-

threefold [114–116]. Familial clustering of *H. pylori* infection may contribute to this risk; other suggested risk factors include blood group A and gastric polyps. However, the final word on heredity in gastric cancer may well be the Scandinavian Twin Study of 44,788 pairs of twins in the Swedish, Danish, and Finnish twin registries [117]. This found an increased risk of gastric cancer in the twin of an affected person. Model fitting to assess the contribution of hereditary and environmental factors found that inherited genes contributed 28% (95% C.I. 0–51%), shared environmental factors 10% (95% CI, 0–34%), and environmental factors 62% (95% CI, 0–76%). The statistical model used provided a perfect fit ( $P = 1.0$ ). This may be significant in the role of *H. pylori*. A recent review outlines our developing knowledge of the almost limitless possibilities for an hereditary basis to resistance to pathogenic organisms [118], allowing a role for *H. pylori* in both the hereditary and shared environmental causes of gastric cancer.

## 5. Conclusions

Although much is known about the causes of gastric cancer, much still is shrouded in mystery. Particularly puzzling is the recent rise in adenocarcinoma around the cardia, largely confined to White males in affluent societies. One thing is clear. Contrary to a developing view that *H. pylori* is a major cause of gastric cancer, simple epidemiologic analysis shows that it is probably a minority cause in Western societies. If chronic *H. pylori* infection increases the risk of cancer by a factor of about 2.5 [42] in a population with a prevalence in older persons of about 50%, then the Population Attributable Risk or Etiologic Fraction is only about 40% [119]. Given the evidence for an increase in reflux symptoms on eradication of *H. pylori* [120] and the links between longstanding reflux symptoms [20] and obesity [21] with lower esophageal adenocarcinoma, we may be seeing the ultimate irony. As society grows more affluent and hygienic, it diminishes its risk of gastric adenocarcinoma, but, in males at least, it simultaneously increases its risk of adenocarcinoma around the cardia.

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