Etiology of stomach cancer (C16) in Central and South America

Patricia Cueva[1], Mónica S. Sierra[2], Luis Eduardo Bravo[3], David Forman[2]
[1] Registro Nacional de Tumores de Quito, Hospital Solón Espinosa Ayala SOLCA Núcleo de Quito, Ecuador.
[2] Section of Cancer Surveillance, International Agency for Research on Cancer, France.
[3] Registro Poblacional de Cancer de Cali, Departamento de Patología, Universidad del Valle, Colombia.

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Stomach cancer develops from a multistep process that evolves from a series of changes in the gastric mucosa that progress from normal gastric mucosa to non-atrophic gastritis, multifocal gastric atrophy (without intestinal metaplasia), intestinal metaplasia, dysplasia (low- and high-grade), and finally to cancer [1, 2]. Similarly to most malignancies, stomach cancer is a multifactorial disease that involves several environmental and genetic factors at different stages of the carcinogenic process [3, 4]. This section focuses on *Helicobacter pylori* infection and briefly reviews other known factors related to this malignancy.

Helicobacter pylori

Helicobacter pylori, a gram negative bacterium that colonizes the human stomach, is usually acquired during early childhood and can be transmitted through direct person-to-person contact by either oral–oral or feco–oral pathways [5, 6]. The prevalence of *H. pylori* infection varies widely between and within countries and has been reported to range among adults from 10% to 95% in the developed world [7], from 50% to 90% in the developing world and from 50% to 95% in the South American region [8, 9]. The prevalence of infection also differs according to age, race/ethnicity, migration from high-prevalence areas, and indicators of low socioeconomic status (crowding, level of education, lack of proper sanitation and safe drinking-water, and poor diet) [6, 7].

Although many people are infected with *H. pylori*, less than 20% of infected individuals develop a gastroduodenal disease [6]. Chronic *H. pylori* infection is nearly always accompanied by chronic active gastritis and occasionally leads to duodenal ulcers, gastric ulcers, and more rarely, in the presence of certain additional factors, gastric adenocarcinoma [3, 10, 11]. The International Agency for Research on Cancer classified *H. pylori* as a human carcinogen in 1994 [3] and it is now considered to be one of the most common etiological agents of infection-related cancers [12, 13]. The mechanisms by which *H. pylori* contributes to the development of stomach cancer are complex. The pathogenic process of *H. pylori* involves relationships between the effects of chronic gastric inflammatory responses, bacterial products that affect cell signalling and cell biology, and cell homeostasis [14]. Such responses are in fact interrelated with the host-determined modulation of inflammatory responses, specific factors of *H. pylori* virulence (i.e., cytotoxin-

associated gene product A (CagA) and vacuolating cytotoxin A), and altered gastric secretory function [3].

An analysis of 12 case–control studies nested within prospective cohorts (from China, Finland, Iceland, Japan, Norway, Sweden, Taiwan, China, the United Kingdom, and the USA) revealed that individuals who were found to be *H. pylori*-seropositive 10 years or more before diagnosis had approximately 6 times the risk of developing non-cardia gastric cancer than *H. pylori*-negative individuals, but no association was found between *H. pylori* and cardia cancer [15]. Furthermore, *H. pylori* has been associated with an increased risk of gastric carcinoma in seven meta-analyses (risk ratio [RR], 2.0–2.9) [3, 4].

In a recent meta-analysis of 34 studies, Cavaleiro-Pinto et al. [16] evaluated the association between *H. pylori* infection and gastric cardia cancer and found that *H. pylori* infection was inversely related to cardia carcinoma (summary RR, 0.78; 95% confidence interval [CI], 0.63–0.97; I^2 = 11.6% in 16 studies) in countries with a low incidence of gastric cancer (Australia, Finland, Germany, Norway, Sweden, and the USA), whereas it was positively associated with cardia carcinoma (RR, 1.98; 95% CI, 1.38–2.83; I^2 = 18.4% in 14 studies) in countries with a high incidence of gastric cancer (China, Japan, and the Republic of Korea). A strong positive association was found between *H. pylori* infection and non-cardia carcinoma in areas with both a high and low incidence of gastric cancer (RR, 3.02; 95% CI, 1.92–4.74; I^2 = 90.7% for high incidence in 14 studies; RR, 2.56; 95% CI, 1.99–3.29; I^2 = 46.6% for low incidence in 15 studies). Cavaleiro-Pinto et al. [16] also compared the risk of cardia and non-cardia gastric cancer from CagA-positive and -negative strains of *H. pylori* in high- and low-incidence areas. No clear association was found between CagA-positive *H. pylori* strains and cardia gastric cancer in either area (RR, 1.47; 95% CI, 0.44–4.87] for high incidence in 4 studies; RR, 0.74; 95% CI, 0.51–1.08 for low incidence in 10 studies). However, a positive association between CagA-positive *H. pylori* strains and non-cardia gastric cancer was found in countries of with a low incidence (RR, 4.59; 95% CI, 2.79–7.57 in 9 studies) but not in those with a high incidence (RR, 2.08; 95% CI, 0.40–10.69 in 4 studies).

de Martel et al. [13] estimated that 74.7% (650 000) of all new non-cardia gastric cancer cases (870 000) diagnosed worldwide in 2008 were attributable to *H. pylori* infection, indicating that infection with *H. pylori* could be responsible for 470 000 new cancer cases in less developed regions and for 190 000 new cases in more developed regions of the world. Recently, Plummer et al. [17] estimated that 89% (774 000) of the non-cardia gastric cancer cases that occurred in 2008 were attributable to *H. pylori* infection. These estimations were based in a prevalence of *H. pylori* of 94.6% (as measured by immunoblot and western blot) in gastric cancer cases and a relative risk of 17.0, which resulted in a population attributable fraction of 89.0%. Applying the same population attributable fraction to the most recent global estimates for stomach cancer from 2012 [18], 89% (734 000) of the non-cardia gastric cancer cases (823 000) would be attributable to *H. pylori* infection with the major burden falling in Asia, eastern Europe, and South America (Table 1) [19].

Geographical distribution of H. pylori *infection and stomach cancer*

There is an inconsistent relationship between the prevalence of *H. pylori* infection and the geographical distribution of gastric cancer. In Africa, the prevalence of infection is high but the incidence of gastric cancer is low. Similar differences have been reported in China, Colombia, Costa Rica, India, and Malaysia [20]. Four major etiological factors have been proposed to explain this geographical enigma: a) *H. pylori* strains with different oncogenic potential; b) immunomodulation of *H. pylori* infection by co-infections, with marked polarization towards Th2 cell responses; c) diet (abundance of foods rich in micronutrient antioxidants); and d) genetic susceptibility [20]. In Central and South America, some or a combination of these factors may be particularly relevant (i.e., the immune modulation by co-infection probably with helminths).

Striking differences in gastric cancer incidence rates exist among populations within Colombia that are separated by distances of only 200 km despite the high prevalence of *H. pylori* infection (~90%). The incidence rates are approximately 25 times higher among inhabitants from the Andes Mountains who are mainly of Amerindian ancestry (Tuquerres) than among those from the Pacific coast who mostly have African ancestors (Tumaco). An analysis of *H. pylori* isolates revealed that all isolates had multiple ancestries; however, a European ancestral *H. pylori* cluster predominated in Tuquerres, a high-risk area, while an African cluster predominated in Tumaco, a low-risk area [21]. These results indicate that populations from the high-risk mountain region have lost their Amerindian ancestral *H. pylori* while those from the low-risk region still carry their African *H. pylori* strains [21]. Those carrying *H. pylori* of European ancestry were reported to be infected with more virulent strains (phosphatidylinositol 4,5-biphosphate binding protein and CagA) and had more severe gastritis and DNA damage than those carrying *H. pylori* of African ancestry [22, 23].

The virulence of *H. pylori* and the severity of disease appear to depend on a co-evolution between the human hosts and their *H. pylori* strains. The interaction between individuals of Amerindian descendant in the mountain regions infected with *H. pylori* strains of African origin have been shown to have more severe lesions than those infected with CagA strains. Thus, it can be hypothesized that the risk profile of a population depends on the ancestry of the host and that of the *H. pylori*. In a prediction model using gastric histopathology scores based on a continuous scale of increasing severity from 2 (gastritis) to 6 (cancer), hosts of mainly Amerindian ancestry (i.e. 95th percentile) and *H. pylori* of mainly African descent (73.1%) predicted a histopathology score of 4.8 while hosts of the same ancestry infected with a strain of low-virulence *H. pylori* of African descent (5.6%) predicted a histopathology score of 3.1. The risk profile differed if the ancestry of the host was within the 5th percentile of Amerindian ancestry infected mainly with *H. pylori* of African descent (73.1%) and resulted in a histopathology score of only 2.4. The interaction between host and pathogen ancestry is strong, having an effect that is 5 times higher than that of phosphatidylinositol 4,5-biphosphate binding protein-CagA or CagA, which is recognized as the most virulent *H. pylori* factor in the pathogenesis of precursor lesions and gastric cancer [23]. Consequently, the genetics of both the human host and the *H. pylori* strain may cluster differently across populations and may explain the observed differences in the risk of stomach cancer.

Other factors

Smoking

In the evaluations of tobacco smoke and involuntary smoking (2004) and personal habits and indoor combustions (2012), the International Agency for Research on Cancer concluded that there is sufficient evidence for a causal association between cigarette smoking and gastric cancer. The risk of developing gastric cancer increased with increased duration and intensity (number of cigarettes) of smoking and decreased with increasing duration of successful quitting. The evaluations ruled out potential confounding or effect modification by *H. pylori* infection and confounding by alcohol consumption and diet [24, 25]. In a recent meta-analysis of 32 studies (27 cohort and 5 nested case–control), Ladeiras et al. [26] found that current smokers had an increased risk of developing gastric cancer compared with never-smokers (RR, 1.62; 95% CI, 1.50–1.75 for men; RR, 1.20; 95% CI, 1.01–1.43 for women) and the risk increased as the intensity of smoking increased (RR, 1.3 for the lowest consumption; RR, 1.7 for smokers of ≥ 30 cigarettes per day in the trend estimation analysis). Current smokers had a higher risk of both cardia (RR, 1.87; 95% CI, 1.31–2.67 with substantial heterogeneity) and non-cardia (RR, 1.60; 95% CI, 1.41–1.80) cancers than never-smokers. Similarly, the meta-analysis of Bonequi et al. [27] in Central and South America found that smokers had an greater risk of gastric cancer than non-smokers (odds ratio [OR], 1.47; 95% CI, 1.19–1.81) and current smokers had a greater risk than former smokers (OR, 1.41; 95% CI, 1.05–1.89 in 5 studies). The dose–response meta-analysis showed that the gastric cancer risk increased by 12% (95% CI, 6–18%) every 10 pack–years of exposure to cigarette smoking [27].

Alcohol

Alcohol consumption maybe associated with an increased risk of stomach cancer [28, 29], but the relevant epidemiological studies had several methodological problems, including a lack of stratification by *H. pylori* infection status and proper control of important confounding factors such as socioeconomic status, smoking, and dietary habits [28].

In a meta-analysis of 44 case–control and 15 cohort studies that included 34 557 cases of gastric cancer, Tramacere et al. [30] found a moderate association between alcohol drinking and stomach cancer (pooled RR, 1.07; 95% CI, 1.01–1.13 vs non-drinkers); however, the association was stronger when heavy alcohol drinkers (≥ 4 drinks per day) were compared with non-drinkers (RR, 1.20; 95% CI, 1.01–1.44). Heavy drinkers also had a higher risk of non-cardia gastric carcinomas than non-drinkers (RR, 1.17; 95% CI, 0.78–1.75) but no association was found with cardia adenocarcinoma (RR, 0.99; 95% CI, 0.67–1.47). After adjustment for smoking and fruit and vegetable consumption, the association between alcohol consumption and gastric cancer was independent of sex and geographical area.

Similarly, in a meta-analysis of 16 case–control studies conducted in Brazil, Chile, Colombia, Mexico, Uruguay, and Venezuela, Bonequi et al. [27] found that ever-drinkers had a 61% increased risk of gastric cancer compared with never-drinkers (pooled OR, 1.61; 95% CI, 1.26–2.05), although between-study heterogeneity was

high. The positive association remained after excluding five case–control studies included in the main analysis because of their extreme values (sensitivity analysis summary OR, 1.45; 95% CI, 1.24–1.70).

Diet

Evidence from epidemiological studies suggests that dietary factors may play an important role in the etiology of stomach cancer [31]. The World Cancer Research Fund/American Institute for Cancer Research recently summarized the scientific evidence on the effect of food and nutrients and the risk of stomach cancer and concluded that (i) non-starchy vegetables (allium vegetables) and fruit probably protect against stomach cancer; (ii) salt and salt-preserved foods probably cause stomach cancer; and (iii) there is limited evidence to reach a conclusion regarding the association between the consumption of legumes (including soya products), chili pepper, foods containing vitamin C or selenium, meat, or grilled, barbequed, or smoked animal foods and stomach cancer [31]. However, a recent report indicated that the consumption of processed meat increases the risk of stomach cancer [32].

In the Central and South American meta-analysis, Bonequi et al. [27] found that the use of table salt increased the risk of stomach cancer compared with no use (OR, 1.98; 95% CI, 1.40–2.82 in 6 studies). They also found moderate positive associations between “total meat”, “processed meat”, and “red meat” consumption and the risk of stomach cancer (OR, 1.53; 95% CI, 0.91–2.57 in 2 studies; OR, 1.62; 95% CI, 1.25–2.10 in 4 studies; OR, 1.47; 95% CI, 1.13–1.90 in 4 studies); the consumption of chili peppers was also positively associated with the risk of gastric cancer (OR, 1.94; 95% CI, 1.40–2.68 for often to > 9 jalapenos per day vs never to < 3 jalapenos per day in 3 studies) [27].

Increased body weight and attained height

Increased body weight

Body fatness affects several metabolic, hormonal, inflammatory, genetic, and immune factors that may contribute to the initiation and progression of some cancers, including gastrointestinal cancers [31, 33]. Overweight and obesity have been consistently associated with oesophageal and gastric cardia adenocarcinomas, but the biological mechanism is uncertain [34]. Results from three recent meta-analyses revealed weak to moderate associations between increased body mass index (BMI) and the risk of stomach cancer with noticeable differences after stratification of studies by cardia and non-cardia subsites [35–37].

Kubo and Corley [35] evaluated the association between BMI and the risk of cardia adenocarcinoma in 2504 cases from 14 studies (2 cohort and 12 case–control) and found that overweight (BMI, 25–28 kg/m^2) was associated with an increased risk of cardia adenocarcinoma compared with normal (BMI, 18.5–25 kg/m^2) weight (OR, 1.5; 95% CI, 1.3–1.8 in 4 studies). In contrast, Chen et al. [36] found that overweight (BMI, 25–30 kg/m^2) and obesity (BMI > 30 kg/m^2) were not associated with the risk of gastric cancer in a meta-analysis of 24 prospective studies (41 791 cases). However, results differed when the studies were stratified by cardia and non-cardia gastric cancers. Compared with normal weight (BMI, 18.5–24.9 kg/m^2), overweight

and obesity were positively associated with the risk of gastric cardia cancer (RR, 1.21; 95% CI, 1.03–1.42 for overweight; RR, 1.82; 95% CI, 1.32–2.49 for obesity) but not with non-cardia gastric cancer (RR, 0.93; 95% CI, 0.82–1.05 for overweight; RR, 1.0; 95% CI, 0.87–1.15 for obesity). Similarly, in a meta-analysis of 16 studies, Lin et al. [37] found that obesity (BMI > 30 kg/m^2) was associated with an increased risk of gastric cancer when compared with normal weight (BMI, 18.5–25 kg/m^2), whereas overweight (BMI > 18.5–30 kg/m^2) was not (OR, 1.13; 95% CI, 1.03–1.24 for obesity; OR, 1.04; 95% CI, 0.96–1.12 for overweight). However, overweight and obesity were associated with an increased risk of gastric cardia cancer compared with normal weight (OR, 1.22; 95% CI, 1.05–1.42 for overweight; OR, 1.61; 95% CI, 1.15–2.24 for obesity).

Attained height

The relationship between attained height and stomach cancer remains controversial; while several studies have shown no relationship (as cited in [38]), others have identified an inverse relationship between greater attained height and the risk of stomach cancer [39–42].

Use of non-steroidal anti-inflammatory drugs

Current evidence suggests that non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, decrease the risk of gastric cancer [43–45]. NSAIDs have been shown to inhibit the production of the cyclooxygenases 1 and 2 (COX-1 and COX-2) through prostaglandin-dependent and independent-pathways. COX-2 is also involved in cell proliferation, apoptosis, and angiogenesis. This is relevant to the carcinogenic process in the stomach because the *COX-2* gene is overexpressed in several gastrointestinal malignancies [45, 46].

In a dose–response meta-analysis, Ye et al. [45] found that long-term (≥ 4 years) and low-frequency (1–4.5 times per week) aspirin use was associated with an approximately 10–29% lower risk of gastric cancer. Stratification by geographical region, study design, sample source, cancer site, and *H. pylori* infection status showed a non-statistically significant difference between subgroups. However, aspirin use was inversely related to the risk of non-cardia gastric cancer (RR, 0.59; 95% CI, 0.44–0.74) but was not associated with the risk of cardia gastric cancer (RR, 0.81; 95% CI, 0.60–1.03). Aspirin use was also inversely related to *H. pylori*-positive status (RR, 0.49; 95% CI, 0.28–0.70) but not with *H. pylori*-negative status (RR, 0.81; 95% CI, 0.43–1.18).

Epstein–Barr virus

Approximately 5–10% of the gastric cancers diagnosed worldwide are associated with Epstein–Barr virus (EBV) [3]. EBV-positive gastric cancer has been suggested to belong to a different entity because it develops early in life and has different histopathology. EBV-DNA and virus monoclonality have been identified in gastric tumour cells [3]. Although strong mechanistic evidence links EBV to the development of stomach cancer, the epidemiological evidence is weak because of the difficulty in controlling for the effects of *H. pylori* infection [12].

Pernicious anaemia

Pernicious anaemia is an autoimmune disorder that has been strongly associated with an increased risk of developing gastric adenocarcinoma independent of *H. pylori* infection (although this potential interaction has not yet been evaluated carefully) [12].

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Table 1. Estimated annual burden of gastric cancer and non-cardia gastric cancer by world region, 2012

World region	All gastric cancer cases	Non-cardia gastric carcinoma[a]	*H. pylori*-associated cancers[b,c]
Sub-Saharan Africa	18 000	18 000	16 000
North Africa and West Asia	23 000	20 000	18 000
Central Asia	96 000	86 000	76 000
East Asia	587 000	504 000	449 000
South America	61 000	57 000	51 000
North America	25 000	17 000	16 000
Eastern Europe	70 000	62 000	55 000
North-western Europe	40 000	30 000	27 000
Southern Europe	30 000	27 000	24 000
Oceania	3000	2000	2000
World	**954 000**[d]	**823 000**	**734 000**

[a] Estimated using proportions of non-cardia cancers within all microscopically verified gastric cancers within Cancer in Five Continents, Volume X registries stratified by region, sex, and age group [18].
[b] Applying the population attributable fraction of 89% from [17].
[c] Numbers differ slightly due to rounding errors.
[d] The number for the world is slightly larger than the sum of the individual numbers, due to rounding errors.
Source: Data compiled from [19].

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