SECCIÓN: SOCIAL DETERMINANTS OF HEALTH
DOI: 10.22267/rus.2628s1.10484
REVIEW ARTICLE
REVISTA UNIVERSIDAD Y SALUD

Correa's Model of gastric carcinogenesis: Integrative evidence from Nariño, Colombia

El Modelo de Correa en la carcinogénesis gástrica: Evidencia integradora desde Nariño, Colombia

Modelo de Correa na carcinogênese gástrica: Evidências integrativas de Nariño, Colômbia

ABSTRACT

Introduction: The Correa cascade model has been fundamental to understanding gastric carcinogenesis. A substantial portion of the evidence supporting its development was generated in Nariño, Colombia, a region characterized by marked contrasts in gastric cancer risk. **Objetive:** To describe and synthesize the development of Correa's gastric carcinogenesis model based on studies conducted in Nariño, integrating epidemiological, histopathological, experimental, and evolutionary evidence, and to discuss its implications for gastric cancer prevention. **Materials and methods:** Review article integrating population- and hospital-based observational studies, serial histopathological assessments of gastric biopsies, randomized clinical trials of chemoprevention, molecular and genetic studies of *Helicobacter pylori* and the human host, conducted between 1960 and 2015 in Andean and coastal populations of Nariño. **Results:** The accumulated evidence supports a sequential histopathological progression of precursor lesions, with the possibility of partial regression at early stages. *H. pylori* is identified as a major etiological determinant of non-cardia gastric cancer, whose effect is modulated by diet, immune response, and population context; however, gastric cancer may occur in the absence of infection. Its early eradication is associated with sustained regression of precancerous lesions. In addition, evolutionary discordance between human ancestry and bacterial lineages is associated with greater inflammation and risk of progression. **Conclusion:** This review expands the classical Correa model by incorporating environmental, immunological, and evolutionary modulators and proposes an integrative conceptual framework to guide prevention and chemoprevention strategies tailored to populations at high risk of gastric cancer.

Keywords: Gastric carcinogenesis; Correa model; *Helicobacter pylori*; chemoprevention; evolutionary biology. (Source: DeCS, Bireme).

Sustainable development goals: Good health and well-being. (Source: SDG, WHO).

RESUMEN

Introducción: El modelo de la cascada de Correa ha sido fundamental para comprender la carcinogénesis gástrica. Parte sustancial de la evidencia que lo sustentó se generó en Nariño, Colombia, una región con contrastes marcados de riesgo. **Objetivo:** Describir y sintetizar el desarrollo del modelo de carcinogénesis gástrica propuesto por Correa a partir de estudios realizados en Nariño, integrando evidencia epidemiológica, histopatológica, experimental y evolutiva, y discutir sus implicaciones para la prevención del cáncer gástrico. **Materiales y métodos:** Artículo de revisión que integra estudios observacionales poblacionales y hospitalarios, evaluaciones histopatológicas seriadas de biopsias gástricas, ensayos clínicos aleatorizados de quimioprevención, estudios moleculares y genéticos de *Helicobacter pylori* y del huésped humano, entre 1960 y 2010 en poblaciones andinas y costeras Nariñenses. **Resultados:** La evidencia acumulada respalda una progresión histopatológica secuencial de lesiones precursoras, con posibilidad de regresión parcial en etapas tempranas. *H. pylori* se identifica como un determinante etiológico mayor del cáncer gástrico no cardial, su efecto está modulado por la dieta, la respuesta inmune, el contexto poblacional, aunque el cáncer gástrico puede presentarse en ausencia de la infección. Su erradicación temprana se asocia con regresión sostenida de lesiones precancerosas. Además, la discordancia evolutiva entre la ancestría humana y los linajes bacterianos se relaciona con mayor inflamación y riesgo de progresión. **Conclusión:** Esta revisión amplía el modelo clásico de Correa al incorporar moduladores ambientales, inmunológicos y evolutivos, propone un marco conceptual integrador que orienta estrategias de prevención y quimioprevención adaptadas a poblaciones de alto riesgo.

Palabras clave: Carcinogénesis gástrica; modelo de Correa; *Helicobacter pylori*; quimioprevención; biología evolutiva. (Fuente: DeCS, Bireme).

Objetivos de desarrollo sostenible: Salud y bienestar. (Fuente: ODS, OMS).

Luis Eduardo Bravo [1]
Monica L. Quijano-Lievano [2,3]
Pelayo Correa [4]

1. *Emeritus Professor*, Facultad de Salud, Universidad del Valle. Cali, Colombia.
2. Programa de Doctorado en Salud, Universidad del Valle. Cali, Colombia.
3. Registro Poblacional de Cáncer de Cali, Departamento de Patología, Universidad del Valle. Cali, Colombia.
4. Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Vanderbilt University Medical Center. Nashville, Tennessee, United States of America. RIP.

Citation:
Bravo LE, Quijano-Lievano ML, Correa P. Correa's model of gastric carcinogenesis: Integrative evidence from Nariño, Colombia. Univ. Salud [Internet]. 2026; 28(Suppl 1):e10484. DOI: 10.22267/rus.2628s1.10484

Received:	August	21 - 2026
Revised:	August	31 - 2026
Accepted:	September	04 - 2026
Published:	October	05 - 2026

CC BY NC SA

ISSN: 0124-7107 - ISSN (Online): 2389-7066
Univ. Salud 2026 - Vol 28 - Suppl 1
https://doi.org/10.22267/rus
https://revistas.udenar.edu.co/index.php/usalud

Acknowledgments:
This manuscript was originally conceived as a tribute to Pelayo Correa and to the scientific program he built around the study of gastric carcinogenesis. The authors acknowledge the sustained support of the National Cancer Institute through Program Project Grant P01 CA028842, "Etiological Studies of Gastric Carcinoma". Professor Correa did not have the opportunity to read the final version of the manuscript

Funding sources:
This work is based on research conducted within the framework of the National Cancer Institute Program Project Grant P01 CA028842, "Etiological Studies of Gastric Carcinoma," originally led by Pelayo Correa.

Conflict of interests:
None declared.

Responsibility statement:
The authors declare that they are responsible for the content and accuracy of the information presented.

Consent for publication:
All authors reviewed and approved the final version for publication in the journal.

RESUMO

Introdução: O modelo em Cascata de Correa tem sido fundamental para a compreensão da carcinogênese gástrica. Uma parte substancial das evidências que o sustentam foi gerada em Nariño, Colômbia, uma região com marcantes contrastes de risco. **Objetivo:** Descrever e sintetizar o desenvolvimento do modelo de carcinogênese gástrica proposto por Correa com base em estudos conduzidos em Nariño, integrando evidências epidemiológicas, histopatológicas, experimentais e evolutivas, e discutir suas implicações para a prevenção do câncer gástrico. **Materiais e métodos:** Artigo de revisão que integra estudos observacionais populacionais e hospitalares, avaliações histopatológicas seriadas de biópsias gástricas, ensaios clínicos randomizados de quimioprevenção, estudos moleculares e genéticos do Helicobacter pylori e do hospedeiro humano, entre 1960 e 2010 em populações andinas e costeiras de Nariño. **Resultados:** As evidências acumuladas apoiam uma progressão histopatológica sequencial das lesões precursoras, com possibilidade de regressão parcial nos estágios iniciais. O H. pylori é identificado como um importante determinante etiológico do câncer gástrico não-cárdico; seu efeito é modulado pela dieta, resposta imune e contexto populacional, embora o câncer gástrico possa ocorrer na ausência de infecção. A erradicação precoce está associada à regressão sustentada das lesões pré-cancerosas. Além disso, a discordância evolutiva entre a ancestralidade humana e as linhagens bacterianas está relacionada ao aumento da inflamação e ao risco de progressão. **Conclusão:** Esta revisão expande o modelo clássico de Correa ao incorporar moduladores ambientais, imunológicos e evolutivos, propondo uma estrutura conceitual integrativa que orienta estratégias de prevenção e quimioprevenção adaptadas a populações de alto risco.

Palavras-chave: Carcinogênese gástrica; modelo de Correa; *Helicobacter pylori*; quimioprevenção; biologia do desenvolvimento. (Fonte: DeCS, Bireme).

Objetivos de desenvolvimento sustentável: Saúde e bem-estar. (Fonte: MDS, ONU).

https://doi.org/10.22267/rus.2628s1.10484

INTRODUCTION

The Cali Population-Based Cancer Registry, the oldest in Latin America, identified gastric cancer as the most common cancer in its first publication, which covered the years 1962–1964[1]. At that time, approximately two-thirds of Cali's inhabitants were immigrants from other regions of Colombia or from abroad. The 1964 National Census, which recorded each resident's place of birth, made it possible to calculate incidence rates specific to the different immigrant groups.

Immigrants from Nariño had the highest gastric cancer incidence rate, more than three times higher than that of native residents of Cali and five times higher than that of individuals born in the coastal regions[2]. These differences are illustrated in Panel A of Figure 1, which shows gastric cancer incidence rates according to place of birth.

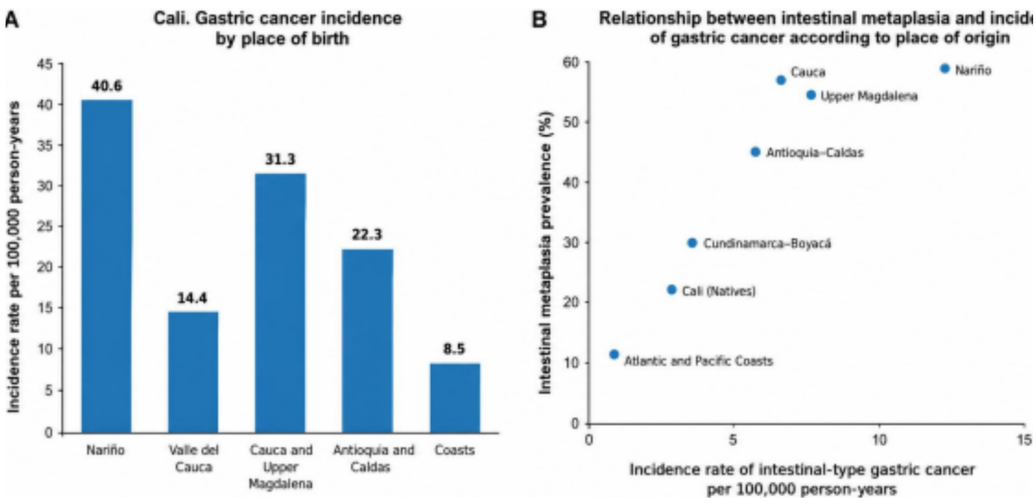

Figure 1. (**Panel A**) Gastric cancer incidence rates among men residing in Cali, according to place of birth, 1962–1966. (**Panel B**) Relationship between the frequency of intestinal metaplasia and the incidence of intestinal-type gastric cancer according to region of origin[2,3]

Previous studies, conducted mainly in Europe, had established an association between intestinal metaplasia of the gastric mucosa and the development of gastric cancer. At that time, more than 30 % of adults who died in Cali underwent autopsy at the University Hospital, San Juan de Dios Hospital, or forensic medicine services. Taking advantage of this circumstance, a detailed study was conducted to document the presence of intestinal metaplasia in the gastric mucosa based on 1500 adult autopsies.

The highest prevalence of intestinal metaplasia was found among immigrants from Nariño (58%), again approximately three times higher than that observed among native residents of Cali (19%) or individuals born in the coastal regions (21%). In addition, the extent of metaplasia was greater among immigrants from Nariño than among the other groups[2]. This relationship—greater extent of metaplasia and higher gastric cancer incidence—is shown in Panel B of Figure 1, where regions with a higher proportion of metaplasia are located farther to the right on the X-axis, demonstrating a positive association between the two indicators.

These findings led the investigators to focus their studies on the department of Nariño. The research base was established at the Departmental Hospital, with the support of its administrators. During that period, virtually all documented cases of gastric cancer were evaluated at hospitals with X-ray and surgical services, primarily the Departmental Hospital of Pasto, San Pedro Hospital in Pasto, and the general hospitals of Ipiales and Túquerres.

A total of 276 gastric cancer cases were recorded at these centers between 1968 and 1972. By comparing the birthplaces of cancer patients with those of controls without the disease, identified from hospital discharge records, two high-risk areas were identified: area A, in the northern part of the department, and area B, in the south, separated by a lower-risk area around the Guáitara River. Very few cases were recorded among patients born in areas at lower elevations above sea level, including the Pacific coast.

This pronounced geographic contrast in gastric cancer risk is clearly illustrated in Figure 2, where the higher-altitude Andean areas stand out as high-incidence foci compared with coastal and lower-elevation regions.

Figure 2.
High- and low-risk areas for gastric cancer in the department of Nariño, Colombia

Note: The higher-altitude Andean areas show two main high-risk foci (Areas A and B), separated by a lower-risk area around the Guáitara River, whereas low-altitude regions, including the Pacific coast, have lower incidence[2,3].

https://doi.org/10.22267/rus.2628s1.10484

The Precancerous Cascade

The next step in the search for the causes of gastric cancer was to compare individuals with cancer with individuals without the disease (controls). However, obtaining reliable data required hundreds of patients, which was difficult to achieve. Given the previously documented association between intestinal metaplasia and gastric cancer, research in Nariño focused on characterizing precancerous lesions. For this purpose, an initial gastroscopic examination was performed in 463 residents of Nariño by Dr. Luis Carlos Burbano. Subsequently, the survey was expanded to a total of 1788 endoscopic examinations after Dr. Guillermo Zarama joined the study as an endoscopist.

Detailed examination of gastric biopsies made it possible to characterize the stages of the precancerous process, referred to as the "precancerous cascade". The histopathological lesions represent an ordered sequence of changes that includes chronic active gastritis, multifocal atrophy with glandular loss, intestinal metaplasia (complete and incomplete), and dysplasia[3,4].

Of this initial group (cohort), 1422 patients underwent a second endoscopy after an average period of five years. This made it possible to describe the dynamics of the precancerous process, characterized by slow progression, with multiple partial episodes of progression toward more advanced lesions and regression toward less advanced lesions, a phenomenon described as a *steady state*[4].

The progression rate from non-atrophic gastritis to atrophic gastritis was 7.5 per 100 person-years, and the progression rate from atrophy to metaplasia was 6.7, both higher than the regression rates from atrophy to non-atrophic gastritis[1,5] and from metaplasia to atrophy[3]. At the most advanced stage of the process, regression from dysplasia to metaplasia[4,5] was greater than progression from metaplasia to dysplasia[2,6]. The data corresponding to these advanced stages are less reliable because of the small number of dysplasias diagnosed.

This sequential process was synthesized into a histopathological model known as the "Correa cascade", which is presented in Figure 3.

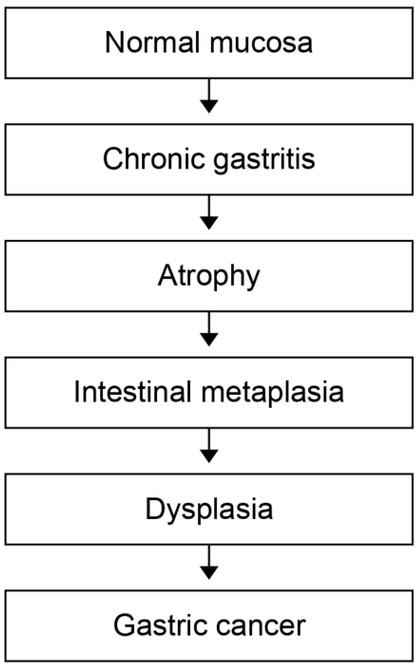

Figure 3.
Gastric precancerous model, the "Correa Cascade"

Note: Histopathological sequence proposed by Correa describing the orderly transition from normal gastric mucosa to chronic gastritis, glandular atrophy, complete intestinal metaplasia, incomplete intestinal metaplasia, and finally dysplasia. This model illustrates the slow and cumulative progression of the precancerous process and provides the conceptual basis for understanding *Helicobacter pylori*-associated gastric carcinogenesis[6].

In parallel, biological factors that could modulate the precancerous process were evaluated. Among these was vitamin C, known for its ability to inhibit the endogenous formation of nitrosated compounds. Vitamin C concentrations in gastric juice and plasma showed a progressive decline across the different stages of the precancerous cascade, from normal mucosa to dysplasia, together with a progressive decrease in the gastric juice/plasma ratio, suggesting a gradual loss of protective mechanisms as the process advanced.

Diet

Before the association between *Helicobacter pylori* and gastric cancer was established, epidemiological studies had indicated that certain dietary characteristics influence the development of this malignancy. Populations at high risk of gastric cancer shared two main characteristics: excessive salt intake and low consumption of fresh, unprocessed fruits and vegetables.

Dietary surveys conducted between 1968 and 1972 confirmed these findings in the population of Nariño[7]. For example, lettuce consumption was 36 % in high-risk areas and 55.7% in low-risk areas. Even within the general high-risk areas, the epidemiological survey showed differences between populations: municipalities such as Guaitarilla had a higher risk than others such as Guachucal, where fruit consumption, including oranges, was more frequent.

In high-risk areas, meat was more frequently salted for preservation, and additional salt was added to food at the table. These populations were estimated to consume an average of 24 grams of salt per person per day. In other countries, such as Japan and Belgium, public health campaigns succeeded in reducing daily salt intake from approximately 24 grams to 11 grams per person.

Helicobacter pylori

In 1994, the International Agency for Research on Cancer (IARC), part of the World Health Organization, classified *Helicobacter pylori* infection as a primary cause of gastric cancer.

In Nariño, the carbon-13 urea breath test documented that infection could begin during the first months of life, reaching a prevalence of 50 % by two years of age and nearly 90% by nine years of age. In adults, serological studies showed that infection persists in more than 90 % of individuals throughout life. Studies of transmission mechanisms in the population of Aldana concluded that initial infection was associated with the presence of infected older siblings in the household[5].

In the high-risk area of Nariño, *Helicobacter pylori* infection in adults frequently leads to multifocal atrophic gastritis, a lesion that increases the risk of gastric cancer. In contrast, in other populations where infection is primarily associated with duodenal peptic ulcer disease, the induced gastritis is non-atrophic and is not associated with an increased risk of cancer.

The consequences of infection during childhood are less well understood and remain under investigation. In this context, *Helicobacter pylori*-induced gastritis in children has been observed to be much more severe in Nariño than in New Orleans, a region at low risk of gastric cancer[8].

Mountain versus coast

Previous surveys had shown that the risk of gastric cancer and precancerous lesions is lower in Tumaco than in the Andean region of Nariño. The initial hypothesis proposed to explain this difference was a lower prevalence of *Helicobacter pylori* infection on the coast.

To evaluate this hypothesis, the research team from the Center for Health Studies of the University of Nariño (CESUN), led by Professor María Clara Yépez, joined the investigation. Surveys using the urea breath test unexpectedly demonstrated that *Helicobacter pylori* infection is as prevalent and begins as early in Tumaco as in the Andean region[9].

This phenomenon—high prevalence of infection accompanied by low cancer risk—has been described in other countries and is known as the "African enigma". Analysis of bacterial virulence factors showed that these were more frequent in strains isolated in the Andean region than in those from Tumaco. The *CagA*-positive genotype was found in 90% of strains from the Andean region, compared with 81% in patients from Tumaco. The *VacA* s1 genotype was observed in 93.2% in the Andean region and 83.7% in Tumaco, and *VacA* m1 in 83.3% and 70.2%, respectively[10].

Although these differences were statistically significant, they probably do not, by themselves, explain the marked differences in gastric cancer risk between the two populations.

Intestinal parasitism

Epidemiological and experimental observations have described a possible protective effect of helminthiasis against the development of gastric cancer. This effect has been attributed to the fact that helminth infection induces a Th2-type immune response, also described as allergic or anti-inflammatory, whereas *Helicobacter pylori* infection predominantly induces a proinflammatory Th1-type response.

A survey of intestinal parasitism among children from Tumaco and the Andean region showed that intestinal parasitism, particularly helminthiasis, was significantly more prevalent on the coast (85%) than in the Andean region (30%).

https://doi.org/10.22267/rus.2628s1.10484

Immunoglobulin E (IgE), a marker of an allergic-type immune response, was seven times higher in the serum of children from the coastal region than in those from the Andean region[11]. This difference is illustrated in Figure 4, which compares total serum IgE levels in children and adults from high-risk Andean areas and low-risk coastal areas.

A *Helicobacter pylori* **and bacterial virulence**

Factor	Pasto (%)	Tumaco (%)
Helicobacter pylori	High	High
*cagA**	90.4	81.1
vacA s1*	93.2	83.7
vacA m1*	83.3	70.2

* p value < 0.05

B **Intestinal parasitism and immune response**

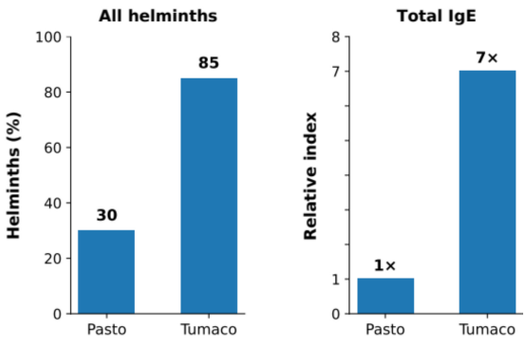

Figure 4.
Helicobacter pylori, bacterial virulence, and immune response in mountain and coastal populations of Nariño

Note: Panel A. *H. pylori* infection is high in both Pasto (mountain) and Tumaco (coast), but the bacterial virulence factors cagA, *vacA* s1, and *vacA* m1 are more frequent in Pasto. Panel B. In contrast, intestinal parasitism is higher in Tumaco (85 % vs. 30 %), accompanied by total IgE levels approximately seven times higher than in Pasto. Taken together, the panels illustrate differences in *H. pylori* virulence and in the host immune context between mountain and coastal populations. $p < 0.05$ for comparisons indicated by an asterisk.

The above findings do not exclude the involvement of other factors that may explain the different outcomes of *Helicobacter pylori* infection on the coast and in the mountains. Among these, diet remains of particular interest. Fresh fish, rich in omega-3 fatty acids known for their antioxidant and antineoplastic properties, is widely consumed on the coast. Genetic susceptibility to gastric cancer also warrants further investigation. The −511T polymorphism of the interleukin-1β (IL-1β) gene is particularly frequent in the high-risk population of Nariño and requires more detailed study, together with the identification of other potential susceptibility factors.

Chemoprevention of gastric cancer precursor lesions

Although gastric cancer incidence rates have been declining[1,2], recent estimates indicate that it remains the fourth most common cancer and the second leading cause of cancer death worldwide[6]. Among etiological factors, high salt intake has been considered an important causal factor[3], whereas adequate consumption of fresh fruits and vegetables is associated with a reduced risk[4,7]. It is now widely accepted that *Helicobacter pylori* infection plays a prominent causal role[5].

H. pylori infection is acquired during childhood and persists for decades if not treated with antibiotics[8]. The clinical outcome of infection is variable[9]. In most individuals, it is asymptomatic; symptomatic patients generally fall into two categories: non-atrophic gastritis and multifocal atrophic gastritis. The former is located mainly in the antrum, is associated with hyperacidity and duodenal ulcer, and does not confer an increased risk of gastric cancer[10]. In the latter, chronic gastritis involves the antrum and corpus in multiple foci characterized by glandular loss (atrophy), usually followed by replacement with glands exhibiting an intestinal phenotype (intestinal metaplasia).

Before the development of neoplasia, a series of sequential changes occurs in the gastric mucosa (Figure 3)[11]. Each of these lesions has been well characterized and may occur with varying degrees of severity. In the early stages, metaplasia displays a phenotype resembling that of the small intestine and is referred to as type I or complete metaplasia[12]. At more advanced stages, the metaplastic cells acquire a colonic phenotype, referred to as type III or incomplete metaplasia, which is associated with a higher risk of gastric cancer than complete metaplasia[13]. In general, the precancerous process progresses slowly toward more advanced lesions; however, under certain circumstances, regression toward less advanced stages may occur[14].

Subsequent studies focused on the hypothesis that oxidative stress constitutes a crucial mechanism in the chain of preneoplastic events[15]. *H. pylori* infection induces inflammation of the gastric mucosa, with increased expression of inducible nitric oxide synthase (iNOS) and increased production of nitric oxide[16,17]. Antioxidant enzymes, such as catalase and superoxide dismutase, may prevent cellular damage induced by oxidative stress. Thus, opposing forces of oxidation and antioxidation interact to promote or prevent neoplastic transformation.

H. pylori strains exhibit a high degree of genetic diversity. Two bacterial genes, *cagA* and *vacA*, are important determinants of virulence. The presence of the *cagA* gene is associated with a stronger proinflammatory response and greater oxidative stress in the gastric mucosa[11], and *cagA*-positive genotypes predominate among patients with gastric cancer. Variants of the *vacA* gene, particularly the s1 and m1 genotypes, are also associated with an increased risk of cancer[18].

Human polymorphisms associated with an increased risk of gastric cancer involve cytokines expressed during the inflammatory process, including interleukin-1β and its receptor antagonist, interleukin-10, and tumor necrosis factor-α[19]. The combination of highly virulent bacterial genotypes with high-risk, proinflammatory host polymorphisms results in a marked increase in gastric cancer risk[20]. These findings suggest the possibility of identifying individuals at high risk of developing this malignancy within the general population.

Chemoprevention clinical trial

Several clinical trials have shown a reduction in the progression of preneoplastic lesions following eradication of *H. pylori* [14,21]. In China, a clinical trial demonstrated a reduction in gastric cancer mortality among subjects with non-atrophic gastritis who received antioxidant supplements[22].

A clinical trial was conducted at the Departmental Hospital of Nariño to evaluate the effects of anti-*H. pylori* treatment and dietary antioxidant supplementation[22]. A total of 630 participants were recruited in Pasto and Túquerres, including men and women aged 29 to 69 years. All participants underwent medical history assessment, blood sampling, physical examination, and upper gastrointestinal endoscopy with gastric biopsies. Participants with a histological diagnosis of atrophic gastritis, with or without intestinal metaplasia, and dysplasia, who were otherwise in good health, were randomly assigned to one of eight treatment regimens using a stratified, double-blind design (Figure 5).

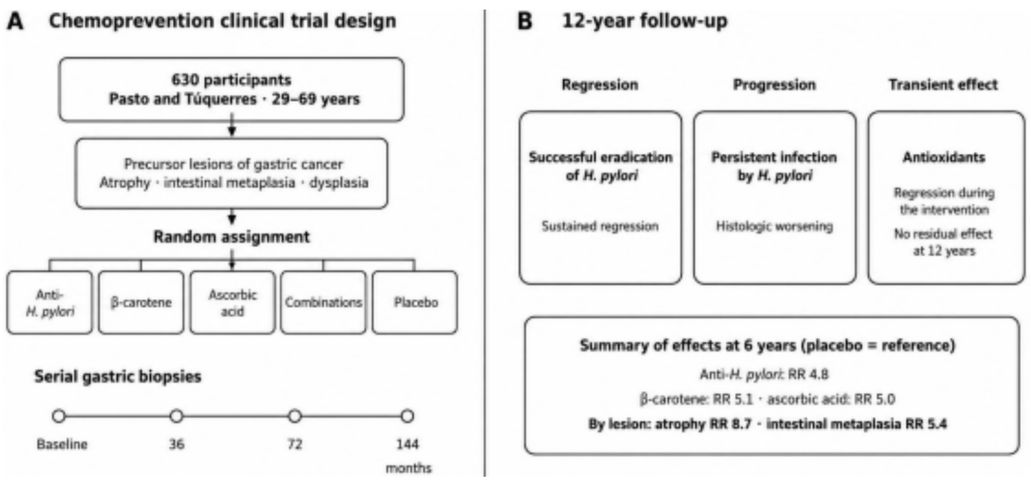

Figure 5.
Design of the chemoprevention clinical trial and 12-year follow-up

Note: Panel A. Random assignment of 630 participants with gastric cancer precursor lesions to anti-*H. pylori* treatment, β-carotene, ascorbic acid, combinations of these interventions, or placebo, with serial gastric ((biopsies. **Panel B.** Classification of outcomes during follow-up and summary of the effects observed at 6 years, using placebo as the reference group. RR: relative risk[12].

https://doi.org/10.22267/rus.2628s1.10484

Assignment to β-carotene (30 mg once daily), ascorbic acid (1 g twice daily), and their respective placebos was carried out using identical formulations supplied by Hoffmann-La Roche. After an initial unsuccessful eradication attempt with amoxicillin and furazolidone, a bismuth-based triple-therapy regimen was adopted, consisting of amoxicillin (500 mg three times daily), metronidazole (375 mg three times daily), and bismuth subsalicylate (524 mg three times daily) for 14 days. At enrollment, the prevalence of *H. pylori* infection in the study population was 95%.

Gastric biopsies were collected at baseline and at 36, 72, and 144 months of follow-up. At each evaluation, four biopsies were obtained from standardized sites in the gastric antrum and corpus. Disease progression or regression was assessed by comparing histological findings before and after the intervention.

At six years of follow-up, eradication of the infection and dietary supplementation with β-carotene, ascorbic acid, or both agents resulted in significant regression of the lesions compared with placebo (RR 5.1; 95% CI: 1.7–15.0). No significant differences were observed among the different treatment groups, nor were additive effects found when *H. pylori*eradication was combined with antioxidant supplementation.

H. pylori eradication was associated with significant lesion regression, with a relative risk of 8.7 (95% CI: 2.7–28.0) among patients with atrophy and 5.4 (95% CI: 1.7–17.6) among those with intestinal metaplasia. These results support the hypothesis that oxidative stress represents a common final pathway in *H. pylori*-induced gastric carcinogenesis.

After antioxidant supplementation was discontinued, the cohort remained under observation without additional intervention. At 12 years of follow-up, a strong and sustained effect of *H. pylori* eradication on healing of precursor lesions was documented. The regression rate was proportional to the square of the time that patients remained free of infection, showing a cumulative effect: the longer the period without infection, the faster and more sustained the healing process, particularly among subjects with less advanced lesions at baseline (Figure 5).

In contrast, subjects with persistent *H. pylori* infection showed worsening of the histological score at the end of follow-up. The beneficial effect of antioxidants observed during the first six years disappeared after supplementation was discontinued, and no residual effect was detected thereafter.

The course of infected patients differed according to whether they had received antibacterial treatment. Those who had never received antibiotics showed an average increase of 0.18 in the histological score compared with baseline[5,6]. In contrast, those

who received anti-*H. pylori* treatment but remained infected showed an average decrease of 0.19 compared with their baseline score. One possible explanation is the selective survival of less virulent strains following antibiotic treatment.

It has been documented that many patients harbor multiple *H. pylori* genotypes, and strains that survive treatment tend to be less virulent, with a higher prevalence of *cagA*-negative and *vacA* s2m2 genotypes.

These findings not only deepened understanding of the interplay among *H. pylori*, bacterial virulence, and the host response, but also consolidated the model of gastric carcinogenesis that had guided decades of research (Figure 6). It was at this point of significant scientific progress that Professor Pelayo Correa's career took an unexpected turn that would challenge the continuity of this research program.

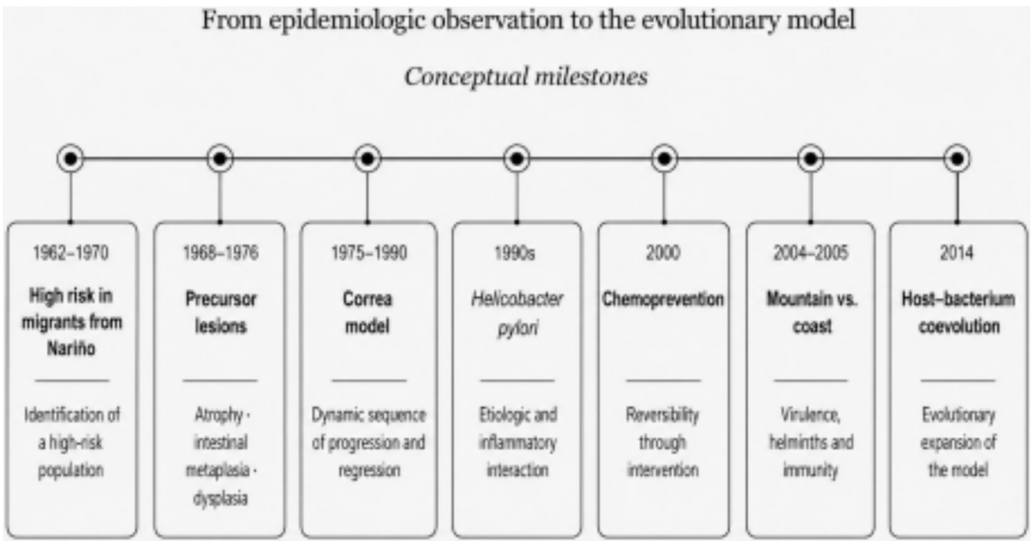

Figure 6.
From epidemiological observation to an evolutionary model of gastric carcinogenesis

Note: **Panel A.** Design of the chemoprevention clinical trial conducted in Pasto and Túquerres, which translated epidemiological observations on gastric cancer precursor lesions into an experimental intervention targeting *Helicobacter pylori* and antioxidants, with serial histological follow-up. **Panel B.** The 12-year follow-up showed that successful *H. pylori* eradication was associated with sustained regression of precursor lesions, whereas persistent infection was associated with histological progression; the effect of antioxidants was transient and did not persist over the long term. Taken together, these findings helped consolidate a dynamic and evolutionary model of gastric carcinogenesis in which progression and regression of lesions depend on modifiable exposures over time.

The results of these studies provided the basis for expanding the Correa model by incorporating an evolutionary perspective on the interaction between *H. pylori* and the host.

Expanding the Correa Model in light of evolutionary biology

The interdisciplinary work that revitalized Correa's original proposal helped elucidate key mechanisms of oxidative damage induced by *Helicobacter pylori* and led to a fundamental finding: an abrupt disruption of long-standing coevolution between the bacterium and the human host may represent a stronger risk factor than bacterial virulence itself. This evolutionary perspective expands the original histopathological model—the Correa cascade—and provides an integrative framework linking ancestry, chronic inflammation, and gastric cancer risk.

https://doi.org/10.22267/rus.2628s1.10484

As shown in Figure 7A, concordance or discordance between human ancestry and bacterial lineages modulates the intensity of gastric damage. Stable coevolution, such as that observed between African populations and the hpAfrica1 bacterial lineage, is associated with relatively balanced host–pathogen interactions, possibly as a result of prolonged reciprocal adaptation. Evolutionary compatibility may help regulate the inflammatory response and limit persistent tissue damage. In contrast, evolutionary discordance—for example, between populations with Amerindian ancestry and European bacterial lineages—promotes a more intense and sustained inflammatory response, with a greater risk of progression along the precancerous cascade. As summarized in Figure 7B, these relationships make it possible to distinguish among processes of historical coevolution, evolutionary discordance, and recent non-coevolved associations, whose differences may help explain the population-level variability observed in gastric cancer risk.

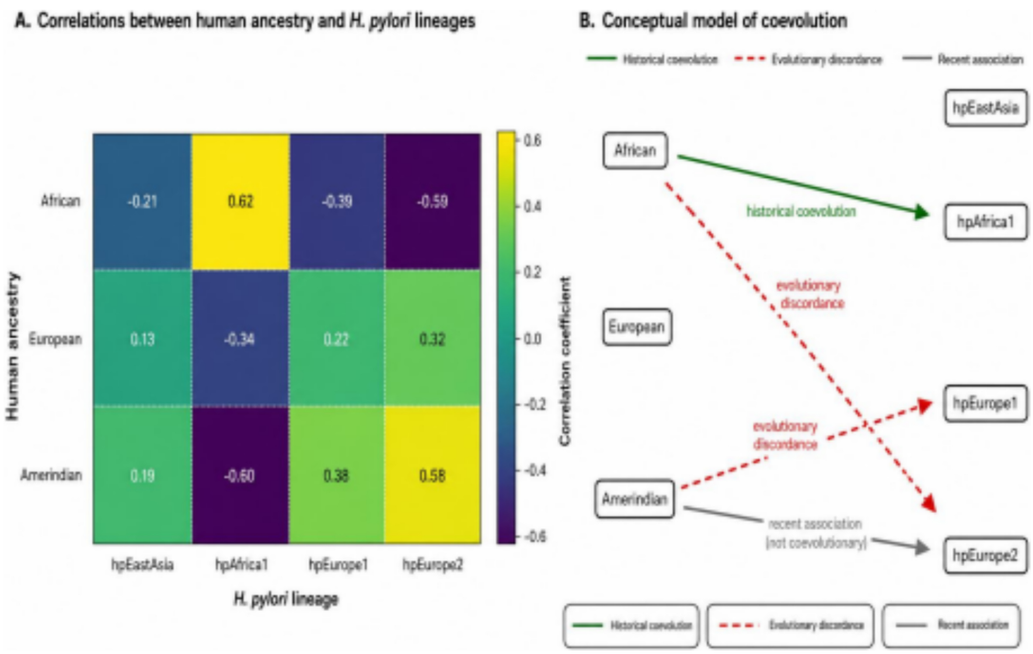

Figure 7.
Association between human ancestry and *Helicobacter pylori* lineages

Note: Panel A. Heat map of the correlation coefficients between the human ancestry components and the bacterial lineages analyzed. Positive and negative values indicate direct and inverse associations, respectively. **Panel B.** Conceptual model of the proposed relationships between human ancestries and *H. pylori* lineages. The green arrow represents historical coevolution; the dashed red arrows, evolutionary discordance; and the gray arrow, a recent non-coevolved association[16].

CONCLUSIONS

Interventions aimed at preventing gastric cancer often require long periods of follow-up, because many of their effects—particularly those mediated by the host response—develop gradually and may not be detectable in short-term studies. The benefits of antioxidant supplementation appear to be limited to the period of use, and the effectiveness of any intervention depends largely on the initial stage of the precancerous lesion: the earlier the intervention, the greater its potential impact.

The contemporary understanding of host–*Helicobacter pylori* interactions, particularly the recognition of disrupted coevolution as an important determinant of inflammation and progression, makes it possible to reconsider preventive approaches from a more contextual and biologically informed perspective. Within this framework, it is essential to advance the development of rapid, accessible, and low-cost diagnostic tools capable of identifying bacterial genotypes and host characteristics associated with increased risk, in order to guide screening and prioritize tailored interventions. These may include selective eradication of *H. pylori*, the rational use of antioxidants, and targeted endoscopic surveillance of individuals at higher biological risk.

Recognition and significance of his work

After a scientific career of broad impact, Professor Pelayo Correa retired from Vanderbilt University in 2015. On the occasion of his retirement, the institution held an academic meeting at which collaborators and researchers from different regions of the Americas reviewed and discussed the major contributions of his work and its influence on epidemiology and the biological understanding of gastric cancer.

In 2016, Universidad del Valle awarded him the degree of *Doctor Honoris Causa* in Health in recognition of the significance of his scientific work in Colombia and his contribution to the study of gastric cancer in high-risk populations. These honors reflect the impact of a career that not only expanded the understanding of gastric carcinogenesis, but also made a decisive contribution to the epidemiology of gastric cancer worldwide, consolidating an integrative research approach that brings together pathology, epidemiology, molecular biology, microbiology, and evolutionary biology.

https://doi.org/10.22267/rus.2628s1.10484

REFERENCES

1. Correa P, Llanos G. Morbidity and mortality from cancer in Cali, Colombia. J Natl Cancer Inst [Internet]. 1966 [citado 2025 Dic 21]; 36(4):717-745. Disponible en: https://pubmed.ncbi.nlm.nih.gov/5935516
2. Correa P, Cuello C, Duque E. Carcinoma and Intestinal Metaplasia of the Stomach in Colombian Migrants. J Natl Cancer Inst [Internet]. 1970 Feb 1 [citado 2025 Dic 21]; 44(2):297-306. DOI: 10.1093/jnci/44.2.297
3. Haenszel W, Correa P, Cuello C, Guzman N, Burbano L, Lores H, et al. Gastric cancer in Colombia. II. Case-control epidemiologic study of precursor lesions. J Natl Cancer Inst [Internet]. 1976 [citado 2025 Dic 21]; 57(5):1021-1026. Disponible en: https://pubmed.ncbi.nlm.nih.gov/1003538
4. Correa P, Haenszel W, Cuello C, Zavala D, Fontham E, Zarama G, et al. Gastric precancerous process in a high risk population: cohort follow-up. Cancer Res [Internet]. 1990 Ago 1; 50(15):4737-4740
5. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 61. Schistosomes, Liver Flukes and Helicobacter pylori, IARC Publications editor. IARC; 1994 [citado 2025 Dic 21]. Disponible en: https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Schistosomes-Liver-Flukes-And-Em-Helicobacter-Pylori-Em--1994
6. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. Lancet [Internet]. 1975 Jul 12 [citado 2025 Dic 21]; 2(7924):58-60. Disponible en: https://pubmed.ncbi.nlm.nih.gov/49653
7. Cuello C, Correa P, Haenszel W, Gordillo G, Brown C, Archer M, et al. Gastric cancer in Colombia. I. Cancer risk and suspect environmental agents. J Natl Cancer Inst [Internet]. 1976 [citado 2025 Dic 21]; 57(5):1015-1020. Disponible en: https://pubmed.ncbi.nlm.nih.gov/1003537
8. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med [Internet]. 2001 Sep 13 [citado 2025 Dic 21]; 345(11):784-789. Disponible en: https://pubmed.ncbi.nlm.nih.gov/11556297
9. Camargo MC, Yepez MC, Ceron C, Guerrero N, Bravo LE, Correa P, et al. Age at acquisition of Helicobacter pylori infection: comparison of two areas with contrasting risk of gastric cancer. Helicobacter [Internet]. 2004 [citado 2025 Dic 21]; 9(3):262-270. Disponible en: https://pubmed.ncbi.nlm.nih.gov/15165263
10. Pignatelli B, Bancel B, Estève J, Malaveille C, Calmels S, Correa P, et al. Inducible nitric oxide synthase, anti-oxidant enzymes and Helicobacter pylori infection in gastritis and gastric precancerous lesions in humans. Eur J Cancer Prev [Internet]. 1998 [citado 2025 Dic 21]; 7(6):439-447. Disponible en: https://pubmed.ncbi.nlm.nih.gov/9926291
11. Li CQ, Pignatelli B, Ohshima H. Increased oxidative and nitrative stress in human stomach associated with cagA+ Helicobacter pylori infection and inflammation. Dig Dis Sci [Internet]. 2001 [citado 2025 Dic 21]; 46(4):836-844. Disponible en: https://pubmed.ncbi.nlm.nih.gov/11330421
12. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. J Natl Cancer Inst [Internet]. 2000 Dic 6 [citado 2025 Dic 21]; 92(23):1881-1888. Disponible en: https://pubmed.ncbi.nlm.nih.gov/11106679
13. Sung JJY, Lin SR, Ching JYL, Zhou LY, To KF, Wang RT, et al. Atrophy and intestinal metaplasia one year after-cure of H. pylori Infection: A prospective, randomized study. Gastroenterology [Internet]. 2000 [citado 2025 Dic 21]; 119(1):7-14. Disponible en: https://pubmed.ncbi.nlm.nih.gov/10889149
14. Wong B, Lam S, Wong R, Feng R, Zheng T, Yuen S, et al. Conference Paper: Eradication of Helicobacter pylori infection significantly slows down the progression of precancerous lesions in high risk population: a 5-year prospective randomized study. WB Saunders Co; 2002. Disponible en: http://www.elsevier.com/locate/gastro

15. Whary MT, Sundina N, Bravo LE, Correa P, Quinones F, Caro F, et al. Intestinal helminthiasis in Colombian children promotes a Th2 response to Helicobacter pylori: possible implications for gastric carcinogenesis. Cancer Epidemiol Biomarkers Prev [Internet]. 2005 Jun [citado 2025 Dic 21]; 14(6):1464-1469. Disponible en: https://pubmed.ncbi.nlm.nih.gov/15941957
16. Kodaman N, Pazos A, Schneider BG, Blanca Piazuelo M, Mera R, Sobota RS, et al. Human and Helicobacter pylori coevolution shapes the risk of gastric disease. Proc Natl Acad Sci U S A [Internet]. 2014 Ene 28 [citado 2025 Dic 21]; 111(4):1455-1460. Disponible en: https://pubmed.ncbi.nlm.nih.gov/24474772
17. Correa P, Miller M, Mannick E. Oxidative damage during the gastric precancerous process. En: Eiichi T, editor. Molecular Pathology of Gastroenterological Cancer. 1st edition. Tokio (JPN): Springer Japan; 1997. p. 23-29. Disponible en: https://link.springer.com/chapter/10.1007/978-4-431-65915-0_3
18. Parsonnet J, Friedman GD, Orentreich N, Vogelman H. Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. Gut [Internet]. 1997 [citado 2025 Dic 21]; 40(3):297-301. Disponible en: https://pubmed.ncbi.nlm.nih.gov/9135515
19. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology [Internet]. 2003 May 1 [citado 2025 Dic 21]; 124(5):1193-1201. Disponible en: https://pubmed.ncbi.nlm.nih.gov/12730860
20. Figueiredo C, Machado JC, Pharoah P, Seruca R, Sousa S, Carvalho R, et al. Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. J Natl Cancer Inst [Internet]. 2002 Nov 20 [citado 2025 Dic 21]; 94(22):1680-1687. Disponible en: https://pubmed.ncbi.nlm.nih.gov/12441323
21. Sung JJY, Lin SR, Ching JYL, Zhou LY, To KF, Wang R Ten, et al. Atrophy and intestinal metaplasia one year after-cure of H. pylori Infection: A prospective, randomized study. Gastroenterology [Internet]. 2000 [citado 2025 Dic 21]; 119(1):7-14. Disponible en: https://pubmed.ncbi.nlm.nih.gov/10889149
22. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst [Internet]. 1993 Sep 15 [citado 2025 Dic 21]; 85(18):1483-1491. Disponible en: https://pubmed.ncbi.nlm.nih.gov/8360931

https://doi.org/10.22267/rus.2628s1.10484