Gastric Cancer Epidemiology and Prevention in the Low Resource Settings

Douglas Morgan, MD MPH
Gastroenterology, Hepatology, & Nutrition
Vanderbilt Institute for Global Health (VIGH)
Vanderbilt University

IOM Workshop in Cancer Care in Low Resource Areas
October 26, 2015
Gastric Cancer Prevention in Low Resource Areas

Gastric cancer epidemiology
• The altitude enigma in Latin America

The biology of *H. pylori* and gastric cancer
• The role of the microbiome

Context: Central America

Opportunities for prevention
• Biomarker development
• *H. pylori* eradication
• Chemoprevention
• Novel endoscopy technologies
Gastric Cancer: Provocative Themes

- The “other” infection-associated cancer
  - Chronic bacterial infection, \textit{H. pylori}

- \textit{H. pylori} eradication (antibiotics) to prevent cancer

- Geography as a “biomarker” for risk
  - Implications for immigrant populations

- Role of the human microbiome
  - Carcinogenesis and homeostasis

- Partnering of cancer screening programs
New Cancer Cases Attributable to Infection

Total infection-attributable in 2008:
- 23% in LMICs
- 7.4% in HICs

*H. pylori*: 6.2% of cancers
Gastric cancer: Epidemiology Summary 2015

The third leading cause of cancer mortality
Annual incidence over one million
Leading cause of infection-associated cancer mortality
*H. pylori* is a WHO Class I Carcinogen
All-cause mortality worldwide: 14th
Will rise to 10th, given growing & aging populations
Consistent 2:1 male to female ratio
Significant geographic variability offers the opportunity for scientific discovery & focused prevention
High incidence regions include:
Latin America, Eastern Asia, Eastern Europe

In the U.S., incidence rates are double in minorities
# Risk Factors for Gastric Cancer by Subsite

## Worldwide Data

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Risk factor</th>
<th>DISTAL</th>
<th>Cardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convincing</td>
<td>Chronic <em>H. pylori</em> infection&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>↑</td>
<td>↓ or null</td>
</tr>
<tr>
<td></td>
<td>Smoking&lt;sup&gt;3&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Probable</td>
<td>High consumption of fruits and vegetables&lt;sup&gt;4-6&lt;/sup&gt;</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Excessive salt consumption&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>High consumption of processed meat&lt;sup&gt;9&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Excess weight&lt;sup&gt;10&lt;/sup&gt;</td>
<td>null</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Reflux&lt;sup&gt;11&lt;/sup&gt;</td>
<td>?</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus infection&lt;sup&gt;12&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Suggestive</td>
<td>High consumption of fiber&lt;sup&gt;13&lt;/sup&gt;</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>High consumption of alcohol&lt;sup&gt;14&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Estrogens&lt;sup&gt;15&lt;/sup&gt;</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>Some genetic variants&lt;sup&gt;16, 17&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Gastric cancer “Rim of Fire” ?
Gastric Cancer Mortality in the Americas

Torres J & Morgan DR, Cancer Causes Control 2013
IARC 2010, GLOBOCAN 2010
Colombia GC mortality variation by municipio
Costa Rica GC incidence variation by canton
Gastric Cancer “Correa” Cascade

Premalignant lesions

Polk DB, Nature Rev Cancer 2010;
Correa P, Gastro 2007
Correa P, Cancer Res 1992
Pathogenesis Triangle for Gastric Cancer

Host Genetic Factors & Host Response
Cytokine polymorphisms (IL1B, IL-10, TNFa)

H. Pylori
Virulence factors (cagA, vacA, babA2)

Gastritis
Atrophy
Intestinal metaplasia
Dysplasia
Adenocarcinoma

Dietary & Environmental Factors
Diet: Antioxidants & Insults
Co-infection: EBV
Other: Tobacco, Alcohol, Fogón
Four Molecular Subtypes of Gastric Adenocarcinoma

Four Molecular Subtypes of Gastric Adenocarcinoma

- **CIN**
  - Intestinal histology
  - TP53 mutation
  - RTK-RAS activation

- **EBV**
  - PIK3CA mutation
  - PD-L1/2 overexpression
  - EBV-CIMP
  - CDKN2A silencing
  - Immune cell signalling

- **GS**
  - Diffuse histology
  - CDH1, RHOA mutations
  - CLDN18–ARHGAP fusion
  - Cell adhesion

- **MSI**
  - Hypermutation
  - Gastric-CIMP
  - MLH1 silencing
  - Mitotic pathways

Four Molecular Subtypes of Gastric Adenocarcinoma

Four Molecular Subtypes of Gastric Adenocarcinoma

**Key Features of Four Molecular Classes of Gastric Cancer**

- **Epstein-Barr virus positive (9\% of cancers)**
  - High levels of EBV genome
  - PIK3CA mutation in 82\%, cell survival and growth
  - MET mutation in 32\%, growth factor signalling
  - ERBB2 mutation in 18\%, growth factor signalling

- **Microsatellite instability (22\% of cancers)**
  - Hypermutation (> 11.4 mutations/ Mb)
  - PIK3CA mutation in 64\%, cell survival and growth
  - ERBB3 mutation in 55\%, growth factor signalling
  - B2M mutation in 36\%, HLA class 1 antigen presentation

- **Genomically stable (20\% of cancers)**
  - CDH1 mutation in 38\%, cell adhesion defects
  - MET mutation in 29\%, growth factor signalling
  - RHOA mutation in 15\%, GTP-ase activity
  - Diffuse +/- signet ring cell histology

- **Chromosome instability (50\% of cancers)**
  - TP53 mutation in 71\%, DNA repair
  - ERBB2 mutation in 38\%, growth factor signalling
  - CDKN2A mutation in 29\%, cell cycle regulation
  - PIK3CA mutation in 26\%, cell survival and growth

---

Genes commonly mutated (any molecular class)

<table>
<thead>
<tr>
<th>TP53</th>
<th>KRAS</th>
<th>RNF43</th>
<th>RASA1</th>
<th>PTPRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH1</td>
<td>MUC6</td>
<td>ABCA10</td>
<td>FAM46D</td>
<td></td>
</tr>
<tr>
<td>SMAD4</td>
<td>APC</td>
<td>CTNNB1</td>
<td>PLB1</td>
<td></td>
</tr>
<tr>
<td>PIK3CA</td>
<td>BCOR</td>
<td>MACF1</td>
<td>CNGA4</td>
<td></td>
</tr>
<tr>
<td>RHOA</td>
<td>EYA4</td>
<td>SMAD2</td>
<td>EIF2C4</td>
<td></td>
</tr>
<tr>
<td>ARID1A</td>
<td>BNC2</td>
<td>SOHLH2</td>
<td>ERBB2 (HER2)</td>
<td></td>
</tr>
</tbody>
</table>
THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.

YOU CALL THIS LIVING?
Gastric Cancer Cascade and the Microbiome

Gastritis  Atrophy  Metaplasia  Dysplasia

Plottel and Blaser, *Cell Host and Microbe*
**H. Pylori: Phylogenetics**
Falush D, Science 2003

[Map showing historical migrations and events related to H. Pylori.]
Nariño, Colombia
Human and *H. pylori* co-evolution
Kodaman N, PNAS 2014

![Graph showing the co-evolution of human and *H. pylori* in different regions.](image)

- **Coast**
  - African
  - African (AA1)

- **Mountain**
  - European
  - Amerindian
  - East Asian (AEA)
  - European (AE2)
  - European (AE1)
Human and *H. pylori* co-evolution

Kodaman N, PNAS 2014; Kodaman N, Front Genetics 2014
Atherton JC, J Clin Invest 2009
The Central America Four region (CA-4)

**Central America Four (CA-4)**
- Region united by history, politics, language, culture, and poverty
- Regional integration with open borders in 2006, affecting health and economic systems, is in process (~European Union)
- Core LMIC region of Latin America with a population of 35 million
  - Account for a significant U.S. Hispanic immigrant population (4M)
  - Total at-risk population: >40 million

**Conclusion**: A regional approach to global health and cancer control is efficient and imperative
Western Honduras Gastric Cancer Initiative
Western Honduras Gastric Cancer Initiative

Western Honduras
- Mountainous coffee region
- Hispanic Mestizo (Mayan)

Hospital de Occidente:
- District Hospital for region
- Referral population: ~1M
- Significant clinical & research infrastructure improvements
  • ”Watershed” (cuenca) for epidemiology research
Gastric cancer incidence estimation in a resource-limited nation: use of endoscopy registry methodology

Ricardo L. Dominguez · Seth D. Crockett · Jennifer L. Lund · Lia P. Suazo · Paris Heidt · Christopher Martin · Douglas R. Morgan

Cancer Causes Control (2013)

• Incidence 2000-09, mean ASRs:
  ➢ Males 36 (29-43), Females 14.5 (11-20)

• Patient population
  ➢ Male : Female ratio, 2.1 : 1
  ➢ Median age: 58 (youngest patient, 17)
  ➢ Age distribution: <25 <35 <49
    5% 12% 25%

• Endoscopy yield: 1 cancer / 7-10 endoscopies
  ➢ Pyloric obstruction: 30-40% with high mortality

• Pathology: 60% poor, 30% moderate, <10% well
Western Honduras Gastric Cancer Initiative

Gastric cancer incidence, Males
per 100,000 person years

- 9.42 - 10.49
- 10.50 - 13.00
- 13.01 - 16.33
- 16.34 - 22.29
- 22.30 - 52.48
Gastric Carcinogenesis Triangle: Honduras

**Host Genetic Factors & Host Response**
- IL-1B-511T* 82%
- IL-10-1082* 93%
- TNFα-308A* 7%

**H. Pylori**
- Population: 87%
- CagA: 71%
- VacA: 71%

**Dietary & Environmental Factors**
- Diet: +Salt, -Selenium
- Co-infections: EBV
- Other: Fogón

Gastric Carcinogenesis Triangle:
- Gastritis
- Atrophy
- Intestinal metaplasia
- Dysplasia
- Adenocarcinoma
Wood stove (fogón) association with gastric cancer
Rifkin S, Digestive Disease Week 2015
Gastric Cancer Prevention Program

- *H. pylori* eradication (age<40, NAG)
- Endoscopy Surveillance (age>40, IM)
- Chemoprevention (Nutrition)

Chronic Gastritis risk populations
- Intervention

Precancerous risk populations
- Screening Program

Precancerous risk populations
- Intervention (Antioxidants)
Gastric cancer prevention: Needed research

Biomarkers: There are no proven serum biomarkers for gastric cancer, gastric premalignant lesions, nor for the risk of progression of premalignant lesions. *H. pylori*, CagA and/or pepsinogen testing lack sensitivity and specificity.

Chemoprevention: There are no existing agents for patients with precancerous lesions. *H. pylori* eradication may be helpful in patients with chronic gastritis, but is insufficient for atrophy or IM.

Endoscopy technology. Endoscopy screening programs have a significant impact (Japan, Korea). Needed: Novel imaging & cost-effective strategies.
Gastric Cancer Prevention Program

H. pylori eradication
(age < 40, NAG)

Endoscopy Surveillance
(age > 40, IM)

Chemoprevention (Nutrition)

Precancerous risk populations
Defined by Biomarkers

Chronic Gastritis risk populations

Precancerous risk populations

Intervention

Screening Program

Intervention (Antioxidants)
Prevention of Gastric Cancer

This year, it is estimated that more than 700,000 people will die of gastric cancer, making this disease the third most common cause of cancer death globally. Although gastric cancer rates have been declining by approximately 2% per year, the numbers of cases and deaths are expected to increase in coming years, reflecting increasing numbers of older (and thus, higher-risk) individuals in the world. Despite its importance, gastric cancer receives little attention from research funding agencies or public health organizations. For example, the National Cancer Institute annually spends approximately $12 million on programs directly related to gastric cancer, just 0.2% of its budget, and only 10% of this amount is allocated for prevention research. In contrast, the annual cost of treating gastric cancer in the United States, a lower-risk country, is estimated at approximately $2 billion.

Of the 989,000 gastric cancer cases in the world in 2008, an estimated 770,000 could be attributed to Population-based *H. pylori* treatment could select for antibiotic-resistant pathogens in the community, although in many countries, such an effect might be overshadowed by indiscriminate use of antibiotics for other human and veterinary purposes. Treating *H. pylori* will alter the overall composition of the intestinal flora; the health consequences are unknown.

Screening and treatment for *H. pylori* is generally acceptable and affordable. An inexpensive serological test can determine who may be infected, with a sensitivity and specificity that could be sufficient for population-based prevention programs. Low-cost treatment regimens using 2 or 3 generic antibiotics plus a proton pump inhibitor for 7 to 14 days can eradicate the infection in more than 80% of cases, depending on the antibiotic resistance patterns of *H. pylori* within the population. Economic modeling studies indicate that *H. pylori* screening and treatment strategies are cost-effective under a large range of assumptions about effectiveness and
Randomised controlled trials of *H pylori* eradication therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>H pylori eradication</th>
<th>Control</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correa 2000</td>
<td>3/437</td>
<td>2/415</td>
<td>1.42 (0.24 to 8.48)</td>
<td>4.0</td>
<td>1.42 (0.24 to 8.48)</td>
</tr>
<tr>
<td>Wong 2004</td>
<td>7/817</td>
<td>11/813</td>
<td>0.63 (0.25 to 1.63)</td>
<td>14.2</td>
<td>0.63 (0.25 to 1.63)</td>
</tr>
<tr>
<td>Leung 2004-Zhou 2008</td>
<td>2/276</td>
<td>7/276</td>
<td>0.29 (0.06 to 1.36)</td>
<td>5.2</td>
<td>0.29 (0.06 to 1.36)</td>
</tr>
<tr>
<td>Saito 2005</td>
<td>2/379</td>
<td>3/313</td>
<td>0.55 (0.09 to 3.27)</td>
<td>4.0</td>
<td>0.55 (0.09 to 3.27)</td>
</tr>
<tr>
<td>You 2004-Ma 2012</td>
<td>34/1130</td>
<td>52/1128</td>
<td>0.65 (0.43 to 1.00)</td>
<td>70.2</td>
<td>0.65 (0.43 to 1.00)</td>
</tr>
<tr>
<td>Wong 2012</td>
<td>3/255</td>
<td>1/258</td>
<td>3.04 (0.32 to 28.99)</td>
<td>2.5</td>
<td>3.04 (0.32 to 28.99)</td>
</tr>
<tr>
<td>Total</td>
<td>51/3294</td>
<td>76/3203</td>
<td>0.66 (0.46 to 0.95)</td>
<td>100.0</td>
<td>0.66 (0.46 to 0.95)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau^2=0.00$, $\chi^2=3.62$, df=5, $P=0.60$, $I^2=0\%$
Test for overall effect: $z=2.27$, $P=0.02$
Prevention of Gastric Cancer

This year, it is estimated that more than 1 million people will die of gastric cancer, making this the third most common cause of cancer death globally. Although gastric cancer rates have been declining at approximately 2% per year, the numbers of deaths are expected to increase in coming years, driven by increasing numbers of older (and thus, healthier) individuals in the world. Despite its importance, cancer receives little attention from research agencies or public health organizations. For example, the National Cancer Institute annually spends approximately $12 million on programs directly related to gastric cancer, just 0.2% of its budget, and only a small amount is allocated for prevention research. In contrast, the annual cost of treating gastric cancer in the United States, a lower-risk country, is estimated at approximately $2 billion.  

Of the 989,000 gastric cancer cases in 2008, an estimated 770,000 could be attributed to Helicobacter pylori infection. This number is likely to increase as the population ages. The infection also leads to an increased risk of other gastrointestinal conditions, such as peptic ulcer disease and gastric adenocarcinoma. Additionally, there is growing evidence that smoking, obesity, and other risk factors, such as diet and lifestyle, play a role in the development of gastric cancer. The prevention of gastric cancer is therefore a complex and multi-faceted issue.
Latin America *H. pylori* and Gastric Cancer Consortium

México, northern & southern
  Ciudad Obregón, Sonora
  Tapachula, Chiapas

Honduras, Copán
  Western Regional Hospital

Nicaragua, León
  University of Nicaragua, León

Costa Rica, Guanacaste
  INCIENSA Fundación

Colombia, Pasto
  Universidad de Valle

Chile, Santiago
  Pontificia Universidad Católica
Study Schema

Community-based recruitment (n=1859)

13C Urea Breath Test (79% positive)

Randomization (n=1463)

- Triple
- Sequential
- Concomitant

6-8 weeks: UBT + evaluation (n=1414)

- Hp positive
- Hp negative
- Hp unknown

Quadruple

1 year: UBT + evaluation (n=1340)
Risk of Recurrent *Helicobacter pylori* Infection 1 Year After Initial Eradication Therapy in 7 Latin American Communities

<table>
<thead>
<tr>
<th></th>
<th>Total Subjects (n / N)</th>
<th>Recurrence Rate (%)</th>
<th>95% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>125 / 1091</td>
<td>11.5</td>
<td>9.9 – 13.3</td>
</tr>
<tr>
<td>Antibiotic regimens p-value</td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Triple, 14 days</td>
<td>47 / 389</td>
<td>12.1</td>
<td>8.8 – 15.3</td>
</tr>
<tr>
<td>Sequential, 10 days</td>
<td>36 / 356</td>
<td>10.1</td>
<td>7.0 – 13.2</td>
</tr>
<tr>
<td>Concomitant, 5 days</td>
<td>42 / 346</td>
<td>12.1</td>
<td>8.7 – 15.6</td>
</tr>
</tbody>
</table>

Importance The long-term effectiveness of *Helicobacter pylori* eradication programs for preventing gastric cancer will depend on recurrence risk and individual and community factors.

Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial

Ming Zeng*, Xu-Hu Mao*, Jing-Xin Li, Wen-De Tong, Bin Wang, Yi-Ju Zhang, Gang Guo, Zhi-Jing Zhao, Liang Li, De-Lin Wu, Dong-Shui Lu, Zhong-Ming Tan, Hao-Yu Liang, Chao Wu, Da-Han Li, Ping Luo, Hao Zeng, Wei-Jun Zhang, Jin-Yu Zhang, Bo-Tao Guo, Feng-Cai Zhu, Quan-Ming Zou
Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial

Ming Zeng*, Xu-Hu Mao*, Jing-Xin Li, Wen-De Tong, Bin Wang, Yi-Ju Zhang, Gang Guo, Zhi-Jing Zhao, Liang Li, De-Lin Wu, Dong-Shui Lu, Zhong-Ming Tan, Hao-Yu Liang, Chao Wu, Da-Han Li, Ping Luo, Hao Zeng, Wei-Jun Zhang, Jin-Yu Zhang, Bo-Tao Guo, Feng-Cai Zhu, Quan-Ming Zou

**Overview**
- Large phase III trial (n= 4464)
- Performed in children (ages 6-15)
- Follow-up, 1-3 years
- Outcome, natural infection
- Efficacy 71.8%

**Challenges**
- Administration, 2hr fast & bicarbonate
- Fusion protein with E.coli LTB (Bell’s)
- Waning efficacy at 3 years
- Therapeutic vaccine?
Gastric Cancer Prevention Program

H. pylori eradication (age<40, NAG)

Endoscopy Surveillance (age>40, IM)

Chemoprevention (Nutrition)

Precancerous risk populations

Precancerous risk populations

Screening Program

Intervention (Antioxidants)

Nutrition
H. pylori infection results in increased levels of polyamines, natural polycations, synthesized by the enzyme ornithine decarboxylase (ODC).

Infection also increases the level of spermine oxidase (SMOX), which catabolizes spermine and produces hydrogen peroxide (H2O2), and leads to DNA damage in gastric epithelial cells.

DFMO has been shown to inhibit ODC.
Gastric Cancer Prevention Program

H. pylori eradication (age<40, NAG)

Endoscopy Surveillance (age>40, IM)

Chemoprevention (Nutrition)

Chronic Gastritis risk populations

Precancerous risk populations

Precancerous risk populations

Intervention

Screening Program

Intervention (Antioxidants)
Ultra low-cost endoscopy for UGI and gastric cancer screening in low resource settings
Caprara R, IEEE BME 2015
Gastric Cancer: LMIC Case Study in Prevention

Gastric cancer is a common cancer affecting LMICs

• A marked health disparity in the U.S.

The marked geographic variability permits scientific discovery and focused prevention & PBCRs

Opportunities for prevention

• Biomarker development
• *H. pylori* eradication
• Role of diet and environment
• Chemoprevention
• Novel endoscopy technologies
¡Mil Gracias!