H. pylori: foe or friend?

Martin J Blaser

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New York University School of Medicine
Department of Biology, NYU
H. pylori: a tale of two (three?) stomachs

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Gastric mucosa in an *H. pylori*+ person

**Curved bacilli on gastric epithelium.**
Section is cut at acute angle to show bacteria on surface, forming network between epithelial cells. (Warthin-Starry silver stain; bar = 10 μm.)

Probability that a Duodenal Ulcer would remain in remission during a 56-week follow-up period.

Week after Treatment

Probability of remaining in remission (%)

Placebo
Antibiotics

P<0.001

E Hentschel et al. NEJM 1993; 328:308-12
The Nobel Prize in Physiology or Medicine 2005

"for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease"

Barry J. Marshall
1/2 of the prize
Australia
NHMRC Helicobacter pylori Research Laboratory, QEII Medical Centre; University of Western Australia
Nedlands, Australia
b. 1951

J. Robin Warren
1/2 of the prize
Australia
Perth, Australia
b. 1937
Current view of the causation of peptic ulcers

Remaining problems:
Why do males get peptic ulcers so much more than females?
Why does PUD express at ages 20-50?
Why does PUD burn out?
Location: Why do some people get either DU or GU or both?
Ethnicity: African enigma?
*H. pylori* populations have a geographic structure

>100,000 years in humans
Cosmopolitan
Early life ➔ Persistent
Highly prevalent
CagA translocation and phosphorylation

H. pylori

Pilus

Y

Y

SH2

SHP

Grb2

Sos

Ras

Raf

Mek

MAPK (ERK)

Scattering (AGS)

Proliferation (MDCK)

Cortactin

Src

Csk

SH2

PTPases

F-actin

Cytoskeleton

Hummingbird phenotype (AGS)

Apoptosis

Effect of *H. pylori* on cyclinD1 expression

**Gastric epithelial cell**

**cagA+/babA2+**

**H. pylori**

**CagA**

**BabA**

**Cell scattering**

(hummingbird phenotype)

**Src kinases**

**p-Y**

**CagA**

**MAPK**

**ERK1/2**

**p38**

**JNK**

**Transcription factor**

**c-Fos**

**c-Jun**

**ATF-2**

**CREB-1**

**Cell cycle progression**

**Cyclin D1 protein**

**Cyclin D1 mRNA**

**Cyclin D1**

**Promotor**

**AP1 CRE**

**YJ Chang et al. Cell Microbiol 2006; 8:140.**
*H. pylori* prevalence in the United States, by age and by year of birth

Disappearance of *Helicobacter pylori* in Japanese families

% decline in prevalence

- Grandmothers (244/355)
- Mothers (251/578)
- Children (101/808)

Approximate year of birth

1940 1970 2000

12.5 43.4 68.7

Adapted from Y. Urita et al. *J Ped Child Health* 2013; 49:394-8
Effects of *H. pylori* loss on the gastric microbiome

- **Skin**: Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Spirochaetes
- **Mouth**: Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Spirochaetes
- **Esophagus**: Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Spirochaetes
- **Colon**: Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Spirochaetes

**References**

- PNAS 2006; 103:732.
- ISMEJ 2011; 5:574.
Association of *H. pylori* seropositivity with peptic ulcer disease

<table>
<thead>
<tr>
<th>Type of ulcer</th>
<th>Cases (patients/controls)</th>
<th>Matched-pair status +/-/-</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Ulcer</td>
<td>150</td>
<td>+/+ 32 +/− 10 −/− 1</td>
<td>3.2</td>
<td>1.7-6.5</td>
</tr>
<tr>
<td>Duodenal Ulcer</td>
<td>65</td>
<td>+/− 12 +/− 3 −/− 2</td>
<td>4.0</td>
<td>1.1-14.2</td>
</tr>
<tr>
<td>Either GU or DU</td>
<td>215</td>
<td>+/+ 44 +/− 13 −/− 3</td>
<td>3.4</td>
<td>1.8-6.3</td>
</tr>
</tbody>
</table>

The path to gastric cancer

Adapted from Pelayo Correa (1970’s)
Association of *H. pylori* with developing gastric cancer, in prospective studies

<table>
<thead>
<tr>
<th>Locale</th>
<th>Cases (%+)</th>
<th>Controls (%+)</th>
<th>Odds ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>29 (69)</td>
<td>116 (47)</td>
<td>2.8 (1.0-8.0)</td>
</tr>
<tr>
<td>US (California)</td>
<td>109 (84)</td>
<td>109 (61)</td>
<td>3.6 (1.8-7.3)</td>
</tr>
<tr>
<td>US (Hawaii)</td>
<td>109 (94)</td>
<td>109 (76)</td>
<td>6.0 (2.1-17.3)</td>
</tr>
<tr>
<td><strong>Meta analysis</strong></td>
<td></td>
<td></td>
<td>3.8 (2.3-6.2)</td>
</tr>
<tr>
<td><strong>Adjusted meta analysis</strong>*</td>
<td></td>
<td></td>
<td>8.7 (2.7-44.7)</td>
</tr>
</tbody>
</table>

* For patients with cancer developing ≥ 15 years after serum obtained

Association of *H. pylori* and *cagA* status with development of gastric adenocarcinoma

<table>
<thead>
<tr>
<th><em>H. pylori</em></th>
<th><em>cagA</em></th>
<th>Number of</th>
<th>Adjusted OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>Case patients</td>
<td>16</td>
<td>46</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>41</td>
<td>43</td>
<td>2.7</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>141</td>
<td>108</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Two models for *H. pylori*-induced gastric cancer risk

Host responses

Strain, host, or co-factor differences

Atrophic gastritis

Effects on epithelial cells (cell cycle, mutation)

Changes in gastric microecology (new organisms)

Adenocarcinoma
Important “historical” diseases of the upper gastrointestinal tract

- Squamous cell cancer
- Gastric ulcer
- Maltoma
- Duodenal ulcer
- Gastric cancer
Important “historical” diseases of the upper gastrointestinal tract

- Squamous cell cancer
- Maltoma*
- Gastric ulcer*
- Duodenal ulcer*
- Gastric cancer*

*Associated with *H. pylori*
“The only good \textit{H. pylori} is a dead \textit{H. pylori}”

Lancet 1997
Death rates for cancer of the stomach, by gender and year of death, 1930-1998, United States

Rate per 100,000

Year of Death


Males, rates adjusted to 2000 U.S. standard population

Males, rates adjusted to 1970 U.S. standard population

Females, rates adjusted to 2000 U.S. standard population

Females, rates adjusted to 1970 U.S. standard population

Cancer 2003; 97:3250
Important “new” diseases* of the upper GI tract

- Duodenal ulcer (iatrogenic)
- Gastric ulcer (iatrogenic)
- Reflux esophagitis*
- Barrett’s esophagus*
- Eosinophilic esophagitis*
- Esophageal Adenocarcinoma*

*Newly recognized or substantially increasing in mid-late 20th century
Relative incidence of esophageal adenocarcinoma and 5 other cancers in the USA, 1975-2001

Hypothetical pathway for development of adenocarcinoma of the lower esophagus

- Reflux esophagitis
- Barrett’s esophagus
- Dysplasia
- Adenocarcinoma
Rates of 3 upper GI diseases in USA Veterans, 1970-1995

El-Serag & Sonnenberg *Gut* 1997;41:594.
Schematic of 20th century trends in USA incidence of esophageal disease and *H. pylori* colonization

Relative incidence of event


10 8 6 4 2 0

Reflux esophagitis

Barrett’s esophagus

Adenocarcinoma of the esophagus

*H. pylori* colonization

*J Infect Dis* 1999:179;1523.
Association of GE-junction adenocarcinoma with carriage of *H. pylori*, by *cagA* status

<table>
<thead>
<tr>
<th>Subject status</th>
<th>Number of controls</th>
<th>Number of cancer cases</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em></td>
<td><em>cagA</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>138</td>
<td>91</td>
<td>1.0</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>40</td>
<td>26</td>
<td>1.1</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>46</td>
<td>12</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**H. pylori** status and development of gastric adenocarcinoma by site in ATBC study, Finland*

<table>
<thead>
<tr>
<th>Site</th>
<th>Case-control pairs</th>
<th>% <strong>H. pylori</strong>-positive$^+$</th>
<th>Adjusted matched OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardia</td>
<td>173</td>
<td>93</td>
<td>7.92 (3.02-20.90)</td>
</tr>
<tr>
<td>Cardia</td>
<td>61</td>
<td>59</td>
<td>0.31 (0.11-0.89)</td>
</tr>
</tbody>
</table>

* Nested case-control study from cohort of 29,133 men, 50-69 years old

$^+$ Positive in either whole cell or CagA serologic assay

Association of three upper GI tract cancers with *H. pylori* seropositivity

<table>
<thead>
<tr>
<th><em>H. pylori</em> serostatus</th>
<th>Controls</th>
<th>Cases</th>
<th>Fully adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1036 (74)</td>
<td>225 (84)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>310 (22)</td>
<td>35 (13)</td>
<td>0.45</td>
<td>0.30-0.67</td>
</tr>
<tr>
<td>EGJAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1036 (74)</td>
<td>261 (85)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>310 (22)</td>
<td>37 (12)</td>
<td>0.41</td>
<td>0.27-0.60</td>
</tr>
<tr>
<td>ESCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1036 (74)</td>
<td>154 (71)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>310 (22)</td>
<td>54 (25)</td>
<td>1.04</td>
<td>0.71-1.50</td>
</tr>
</tbody>
</table>

Proposed reciprocal relationship between adenocarcinomas of the lower stomach and of the esophagus and upper stomach

\[ H. pylori^+ (cag^+); \]
- Cellular infiltration
- Atrophic gastritis
- CA
- Non-cardia Stomach

40-80 years

CA
- Barrett’s
- Esophageal reflux

\[ H. pylori^- (Acagia); \]
- Esophagus and Cardia Stomach

*J Infect Dis* 1999; 179:1523-30
Gastric effectors of extra-gastric processes

- Squamous cell cancer
- Eosinophilic esophagitis
- Barrett’s esophagus
- Reflux esophagitis
- Maltoma
- Gastric ulcer
- Duodenal ulcer
- Gastric cancer

Peptide hormones

Lymphocytes
Gastric mucosa in an *H. pylori*+ person

Any immunologic effects?

*Lancet* 1983; i;1273-5.
Expression of IL-10, FOXP3, and TGF-b1 mRNA in gastric tissue, by H. pylori status


T-regs protect against asthma and allergies?
Immune responses to live typhoid vaccine in 74 volunteers, by *H. pylori* status

<table>
<thead>
<tr>
<th>IgG seroconversion to <em>S. typhi</em> antigens</th>
<th><em>H. pylori</em>⁺ (n=24)</th>
<th><em>H. pylori</em>⁻ (n=50)</th>
<th>p-value</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS (O–antigen)</td>
<td>63</td>
<td>32</td>
<td>0.01</td>
<td>3.8 (1.1 – 12.6)</td>
</tr>
<tr>
<td>Flagella (H–antigen)</td>
<td>38</td>
<td>22</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

Relationship between history of diarrhea and *H. pylori status* among 2477 German children

<table>
<thead>
<tr>
<th>H. pylori carriage</th>
<th>Crude OR (95% CI)</th>
<th>Partially adjusted(^a) OR (95% CI)</th>
<th>Fully adjusted(^b) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>0.37 (0.28-0.49)</td>
<td>0.56 (0.41-0.75)</td>
<td>0.56 (0.42-0.76)</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for nationality of children.

\(^b\)Adjusted for nationality, sex, education of father, education of mother, number of siblings, and history of antibiotic treatment within past six months.

Immune responses to *M. tuberculosis* in 342 African subjects, by *H. pylori* status

*M. tuberculosis* challenge in 41 cynomolgus macaques: outcome according to *H. pylori* positivity

<table>
<thead>
<tr>
<th>H. pylori</th>
<th>No. of monkeys</th>
<th>6-8 month outcome (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>30</td>
<td>Active TB 17</td>
<td>Latent TB 83</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
<td>Active TB 55</td>
<td>Latent TB 45</td>
</tr>
</tbody>
</table>

Relative risk of active TB in *H. pylori*-positive hosts: $p = 0.04$ (Fisher’s exact test). OR = 0.31 (0.12-0.80)

Changes in the prevalence of diagnosed asthma, 1965-2005

W. Eder et al.  
NYC Asthma Study Design

Bellevue Hospital Center Asthma Clinic

Eligible cases

Case definition and ascertainment

Cases (n = 318)

Indeterminant (n = 12)

Controls (n = 208)

Spirometry, Allergy testing

Assessment of *H. pylori* and CagA status

Community

Eligible controls
Association between *H. pylori* serostatus and asthma in 318 asthma cases and 208 non-asthma controls

<table>
<thead>
<tr>
<th>Status</th>
<th>Asthma N (%)</th>
<th>Controls N (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- -</td>
<td>171 (53.8)</td>
<td>108 (51.9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>+ -</td>
<td>68 (21.4)</td>
<td>35 (16.8)</td>
<td>1.23 (0.74-2.03)</td>
<td>0.94 (0.57-1.57)</td>
</tr>
<tr>
<td>+ +</td>
<td>79 (24.8)</td>
<td>65 (31.3)</td>
<td>0.77 (0.50-1.18)</td>
<td>0.63 (0.41-0.98)</td>
</tr>
</tbody>
</table>

*Adjusted for income and race (white, black, other) via logistic regression

Asthma-free survival among 296 New York City adults with asthma, according to *H. pylori* status.
**H. pylori and asthma risk, by age at onset**

<table>
<thead>
<tr>
<th>Subject status</th>
<th>Never</th>
<th>Ever, Age at onset ≤ 15</th>
<th>Ever, Age at onset &gt; 15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>OR</td>
</tr>
<tr>
<td>H. pylori</td>
<td>CagA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>3613</td>
<td>149</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>1330</td>
<td>34</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>2115</td>
<td>38</td>
</tr>
</tbody>
</table>

ORs adjusted for race-ethnicity, age, sex, BMI, smoking status, and educational attainment


Yu Chen
**H. pylori** and allergic rhinitis risk, by age at onset

<table>
<thead>
<tr>
<th>Subject status</th>
<th>Odds Ratio (95% CI) for ever having allergic rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>H. pylori CagA</strong></td>
<td>n</td>
</tr>
<tr>
<td>- -</td>
<td>3613</td>
</tr>
<tr>
<td>+ -</td>
<td>1330</td>
</tr>
<tr>
<td>+ +</td>
<td>2115</td>
</tr>
</tbody>
</table>

ORs were adjusted for race-ethnicity, age, sex, BMI, smoking status, and educational attainment.

# H. pylori status and skin sensitization

<table>
<thead>
<tr>
<th>Allergen</th>
<th>H. pylori-</th>
<th>Hp+ cagA- (95% CI)</th>
<th>Hp+ cagA+ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ragweed</td>
<td>1.0</td>
<td>0.77 (0.57-1.03)</td>
<td>0.73 (0.57-0.94)</td>
</tr>
<tr>
<td>Bermuda Grass</td>
<td>1.0</td>
<td>0.81 (0.57-1.15)</td>
<td>0.85 (0.64-1.14)</td>
</tr>
<tr>
<td>Rye grass</td>
<td>1.0</td>
<td>0.87 (0.65-1.17)</td>
<td>0.73 (0.57-0.94)</td>
</tr>
<tr>
<td>White oak</td>
<td>1.0</td>
<td>0.82 (0.53-1.27)</td>
<td>0.84 (0.59-1.20)</td>
</tr>
<tr>
<td>Russian thistle</td>
<td>1.0</td>
<td>0.97 (0.67-1.42)</td>
<td>0.69 (0.49-0.97)</td>
</tr>
<tr>
<td>Alternaria</td>
<td>1.0</td>
<td>0.68 (0.43-1.08)</td>
<td>0.69 (0.47-0.99)</td>
</tr>
</tbody>
</table>

ORs adjusted for race-ethnicity, age, sex, BMI, smoking status, and educational attainment
Does *H. pylori* infection in early childhood prevent asthma?

**SENSITIZATION + CHALLENGE = Asthma-like signs**

- **C57BL/6**
- Sensitization: House dust mite (HDM) antigen
- **Uninfected**
- **Infected-neonatal (iN)**
- **Infected-adult (iA)**
- Day 0: HDM/PBS+ Alum i.p.
- Day 14: HDM aerosol
- Day 28-30: Sacrifice
- Day 32: Sacrifice

Are neonatally infected mice protected from asthma-like symptoms induced by house dust mite allergen?

H. pylori reprograms DCs towards tolerogenicity

The re-programmed genes are in the \textit{H. pylori}^{+} \textit{human} stomach

Gastric mucosa in an *H. pylori*+ person

Any metabolic benefits?

*Lancet* 1983; i;1273-5.
Gastric expression of satiety hormones

Leptin

Ghrelin

M Gronberg, J Histochem Cytochem 2008, 56:793-801
Effect of *H. pylori* eradication on fasting and post-meal serum ghrelin levels in 21 patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline (pre-eradication)</th>
<th>Follow-up (post-eradication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-meal</td>
<td>6000</td>
<td>2000</td>
</tr>
<tr>
<td>Post-meal</td>
<td>4000</td>
<td>2000</td>
</tr>
</tbody>
</table>

Pair-wise Wilcoxon Signed-rank test

- Pre-meal:
  - Baseline: p=0.04
  - Follow-up: p=0.21

- Post-meal:
  - Baseline: p=0.016

F Francois et al. *BMC Gastroenterol* 2011;11:37
Changes in physiology: from the *H. pylori*-colonized stomach to the *H. pylori*-free stomach

Ancient

Post-modern

Gastric cancer

GEJ adenocarcinoma
Changes in physiology: from the *H. pylori*-colonized stomach to the *H. pylori*-free stomach

**Consequences**
- PUD
- Gastric cancer
- GERD → cancer
- Asthma
- Infections?
- Celiac disease?

**Ancient → Post-modern**
- Somatostatin production $\uparrow$
- Gastrin release $\downarrow$
- Gastric acidity $\uparrow$
- Leptin production $+/-$
- Ghrelin production $\uparrow$
- T-regulatory cell populations $\downarrow$

*Updated from Gut 2008;57:561*
Gastric cancer subsite-specific trends among Whites, age 25-84 Years, 1977-2006

WF Anderson et al. *JAMA* 2010
Noncardia gastric cancer in Whites by age group, 1977-2006

WF Anderson et al. JAMA 2010
 ARTICLE

The Changing Face of Noncardia Gastric Cancer Incidence Among US Non-Hispanic Whites


Affiliation of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

Correspondence to: M. Constanza Camargo, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6E-338, Bethesda, MD 20892-9780 (e-mail: camargomc@mail.nih.gov).

Abstract

Background: The initial step for noncardia gastric carcinogenesis is atrophic gastritis, driven by either Helicobacter pylori infection or autoimmunity. In recent decades, the prevalence rates of these two major causes declined and increased, respectively, with changes in Western lifestyles. We therefore assessed gastric cancer incidence trends for US race/ethnic
EDITORIAL

A New Gastric Cancer Among Us

Martin J. Blaser, Yu Chen

In 1900, gastric cancer was the leading cause of cancer death in the United States and in many countries (1). This cancer, nearly all of which is attributable to decades-long gastric colonization by Helicobacter pylori (2), has been declining with the progressive disappearance of these bacteria (3). This has been very much a triumph (1), and the trends began long before we discovered in 1983, with cohorts born in the late 19th century (1). What is causing this new and rising epidemic?

“CYF gastric cancers”
Corpus-dominant
Young-dominant (<age 50 years)
Female-dominant
Deaths in NHANES III among all participants

H. pylori IgG ELISA in 1988
6+ years
(n=10,168)

H. pylori IgG ELISA and
CagA IgG ELISA in 1988
Adults (≥ 20 years) (n=7,384)

Mortality in 2006: Probabilistic matching with National Death Index (NDI) death certificate records

Follow-up person years: 147796
Deaths observed:
All-cause: 2055
CVD: 875
CHD: 512
Stroke: 159
All cancer: 459
Lung cancer: 135
GI cancer: 104

Follow-up person years: 105930
Deaths observed:
All-cause: 2023
CVD: 873
CHD: 512
Stroke: 159
All cancer: 457
Lung cancer: 135
GI cancer: 103

H. pylori status and risk of all-cause mortality in NHANES III among subjects ≥40 years old

HRs were adjusted for age and sex, educational attainment (years), BMI (<25, >25, missing), race/ethnicity, and smoking status (never/past/current).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1898 total cases</td>
<td></td>
</tr>
<tr>
<td>H. pylori-</td>
<td>594</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>H. pylori+</td>
<td>1304</td>
<td>1.00 (0.84, 1.18)</td>
</tr>
</tbody>
</table>
**H. pylori** status and risk of all-cause mortality in NHANES III among subjects ≥40 years old

HRs were adjusted for age, sex, educational attainment, BMI, race/ethnicity, and smoking status.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1898 events</td>
<td></td>
</tr>
<tr>
<td><strong>H. pylori+</strong></td>
<td>1304</td>
<td>1.00 (0.84, 1.18)</td>
</tr>
<tr>
<td><strong>H. pylori+ cagA-</strong></td>
<td>513</td>
<td>1.03 (0.83, 1.29)</td>
</tr>
<tr>
<td><strong>H. pylori+ cagA+</strong></td>
<td>791</td>
<td>0.97 (0.80, 1.18)</td>
</tr>
</tbody>
</table>
**H. pylori** status and risk of CVD mortality in NHANES III among subjects ≥40 years old

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em> +</td>
<td>571</td>
<td>0.89 (0.71, 1.11)</td>
</tr>
<tr>
<td><em>H. pylori</em> + <em>cagA</em> -</td>
<td>241</td>
<td>0.96 (0.68, 1.34)</td>
</tr>
<tr>
<td><em>H. pylori</em> + <em>cagA</em> +</td>
<td>330</td>
<td>0.83 (0.67, 1.04)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em> +</td>
<td>328</td>
<td>0.92 (0.72, 1.19)</td>
</tr>
<tr>
<td><em>H. pylori</em> + <em>cagA</em> -</td>
<td>138</td>
<td>0.94 (0.67, 1.33)</td>
</tr>
<tr>
<td><em>H. pylori</em> + <em>cagA</em> +</td>
<td>190</td>
<td>0.91 (0.68, 1.22)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em> +</td>
<td>107</td>
<td>0.69 (0.44, 1.08)</td>
</tr>
<tr>
<td><em>H. pylori</em> + <em>cagA</em> -</td>
<td>49</td>
<td>1.05 (0.59, 1.85)</td>
</tr>
<tr>
<td><em>H. pylori</em> + <em>cagA</em> +</td>
<td>58</td>
<td>0.45 (0.27, 0.76)</td>
</tr>
</tbody>
</table>

HRs were adjusted for age, sex, educational attainment, BMI, race/ethnicity, and smoking status.
**H. pylori** status and risk of cancer mortality in NHANES III among subjects ≥40 years old

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. pylori +</td>
<td>288</td>
<td>0.91 (0.71, 1.16)</td>
</tr>
<tr>
<td>H. pylori cagA-</td>
<td>106</td>
<td>0.93 (0.65, 1.33)</td>
</tr>
<tr>
<td>H. pylori cagA+</td>
<td>182</td>
<td>0.89 (0.67, 1.17)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. pylori +</td>
<td>80</td>
<td>0.61 (0.35, 1.05)</td>
</tr>
<tr>
<td>H. pylori cagA-</td>
<td>32</td>
<td>0.67 (0.35, 1.29)</td>
</tr>
<tr>
<td>H. pylori cagA+</td>
<td>48</td>
<td>0.55 (0.31, 0.98)</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. pylori +</td>
<td>74</td>
<td>1.07 (0.57, 2.00)</td>
</tr>
<tr>
<td>H. pylori cagA-</td>
<td>25</td>
<td>0.87 (0.41, 1.87)</td>
</tr>
<tr>
<td>H. pylori cagA+</td>
<td>49</td>
<td>1.22 (0.58, 2.59)</td>
</tr>
</tbody>
</table>

HRs were adjusted for age, sex, educational attainment, BMI, race/ethnicity, and smoking status.
$H.\ pylori$ status and risk of GI cancer mortality in NHANES III among subjects $\geq$40 years old

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H.\ pylori^+$</td>
<td>31</td>
<td>1.08 (0.42, 2.81)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA-</td>
<td>11</td>
<td>0.59 (0.25, 1.39)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA+</td>
<td>20</td>
<td>1.46 (0.50, 4.28)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H.\ pylori^+$</td>
<td>16 (total events)</td>
<td>40.95 (4.19, 399.92)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA-</td>
<td></td>
<td>40.37 (3.55, 458.54)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA+</td>
<td></td>
<td>41.41 (4.09, 419.48)</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H.\ pylori^+$</td>
<td>6 (total events)</td>
<td>0.33 (0.04, 3.01)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA-</td>
<td></td>
<td>0.44 (0.05, 3.84)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA+</td>
<td></td>
<td>0.24 (0.02, 2.43)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H.\ pylori^+$</td>
<td>15</td>
<td>0.63 (0.28, 1.40)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA-</td>
<td>23 (total events)</td>
<td>0.21 (0.05, 0.91)</td>
</tr>
<tr>
<td>$H.\ pylori^+$ cagA+</td>
<td></td>
<td>0.95 (0.43, 2.11)</td>
</tr>
</tbody>
</table>

HRs were adjusted for age and sex.
The discovery of *H. pylori* as a pathogen, 1980’s-1990’s

The biphasic nature of *H. pylori* interactions with humans: now

Infections

Asthma

IBD?

Celiac disease?

Obesity?

Stroke?

Reflux → Adenocarcinoma

Eosinophilic esophagitis

Other cancers?

Ulcer disease

Metabolic syndromes

Gastric cancer

The future of *H. pylori*, based on current trends

![Graph showing the prevalence of *H. pylori* over age in different regions](graph.png)
An alternative future of *H. pylori*

Prevalence (%)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
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<tbody>
<tr>
<td>Developed</td>
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<tr>
<td>Developing</td>
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<tr>
<td>Post-modern</td>
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<td>100</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Post-post-modern</td>
<td></td>
<td>50</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Introduction Eradication
Cancer risk in Japanese immigrants to the US