

The *Helicobacter pylori* Genome Project and Gastric Cancer Research at the US National Cancer Institute.

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Gastric Cancer Research at NCI

- NCI is a very large research institution and here I will focus on the intramural work in the **Division of Cancer Epidemiology and Genetics**
- A full report on NCI's support of gastric and esophageal cancer can be had here:
 - <https://deainfo.nci.nih.gov/advisory/ctac/workgroup/ctacsupport/mat.htm>

Gastric Cancer Research in DCEG

- **Gastric cancer prevention trials**
- Descriptive epidemiology
- Etiologic research
- H. pylori Genome Project (HpGP)

NCI-sponsored gastric cancer prevention trials

- Two separate trials conducted in different parts of China
 - **Nutrition Intervention Trial**
 - Prevention of esophageal and gastric cancer
 - **Shandong Intervention Trial**
 - Prevention of progression of preneoplastic lesions

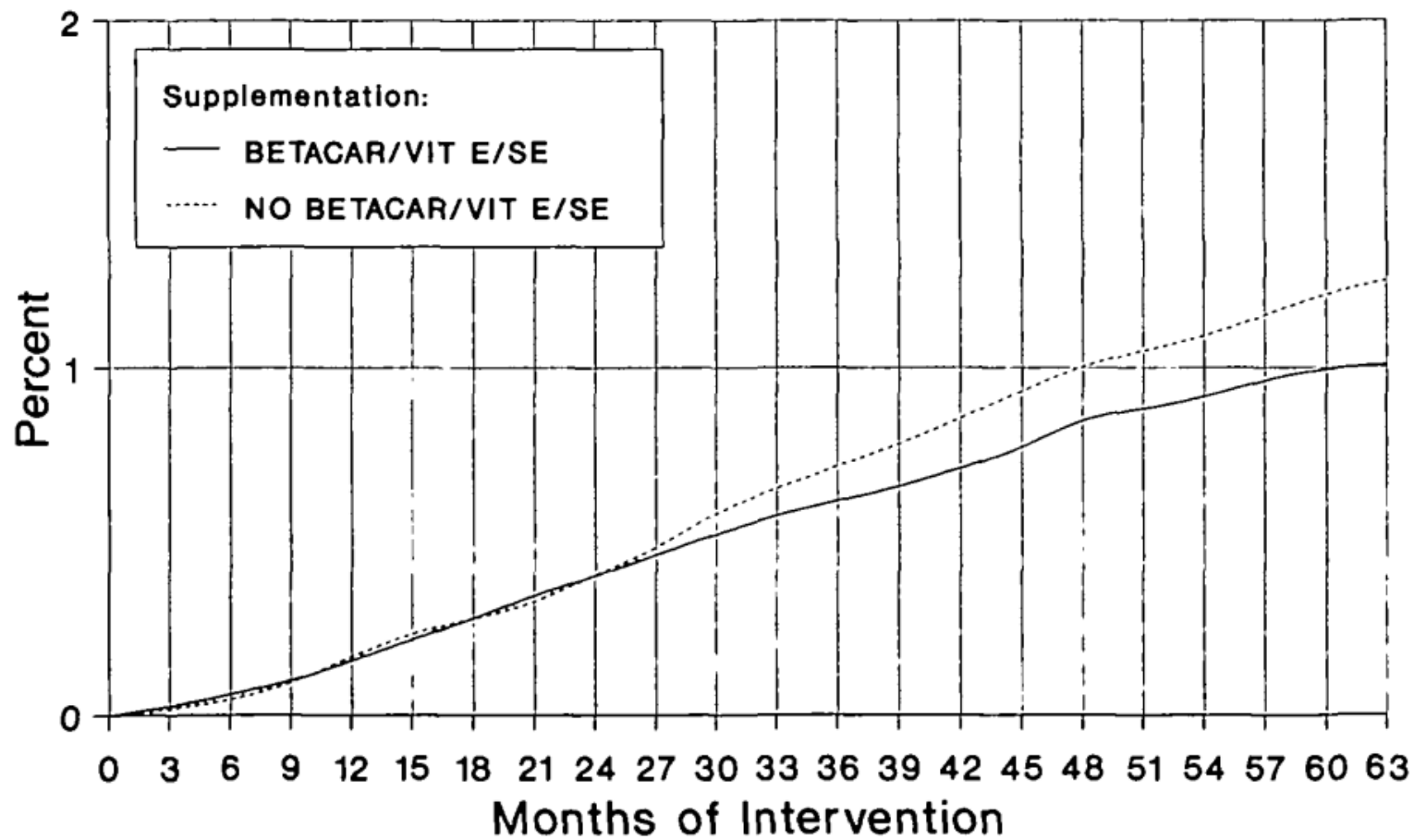
Nutrition Intervention Trials in Linxian, China: Supplementation With Specific Vitamin/Mineral Combinations, Cancer Incidence, and Disease- Specific Mortality in the General Population

*William J. Blot, Jun-Yao Li, Philip R. Taylor, Wande Guo,
Sanford Dawsey, Guo-Qing Wang, Chung S. Yang, Su-Fang Zheng,
Mitchell Gail, Guang-Yi Li, Yu Yu, Buo-qi Liu, Joseph Tangrea,
Yu-hai Sun, Fusheng Liu, Joseph F. Fraumeni, Jr., You-Hui
Zhang, Bing Li**

Journal of the National Cancer Institute, Vol. 85, No. 18, September 15, 1993

Table 1. Types and daily doses of micronutrients by treatment factor

Factor	Micronutrients	Dose per day
A	Retinol (as palmitate)	5000 IU
	Zinc (as zinc oxide)	22.5 mg
B	Riboflavin	3.2 mg
	Niacin	40 mg
C	Ascorbic acid	120 mg
	Molybdenum (as molybdenum yeast complex)	30 μ g
D	Beta carotene	15 mg
	Selenium (as selenium yeast)	50 μ g
	Alpha-tocopherol	30 mg



Effects of Nutrition Intervention on Total and Cancer Mortality: 25-Year Post-trial Follow-up of the 5.25-Year Linxian Nutrition Intervention Trial

Shao-Ming Wang*, Philip R. Taylor, Jin-Hu Fan*, Ruth M. Pfeiffer, Mitchell H. Gail, He Liang, Gwen A. Murphy, Sanford M. Dawsey, You-Lin Qiao, Christian C. Abnet

JNCI J Natl Cancer Inst (2018) 110(11): djy043

Randomized Double-Blind Factorial Trial of Three Treatments To Reduce the Prevalence of Precancerous Gastric Lesions

Wei-cheng You, Linda M. Brown, Lian Zhang, Ji-you Li, Mao-lin Jin, Yun-shen Chang, Jun-ling Ma, Kai-feng Pan, Wei-dong Liu, Yuanreng Hu, Susan Crystal-Mansour, David Pee, William J. Blot, Joseph F. Fraumeni Jr., Guang-wei Xu, Mitchell H. Gail

Year, treatment group	Dysplasia or gastric cancer		Severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer		Average severity score			
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	Active	Placebo	Difference (95% CI)	<i>P</i> †
1999								
<i>H. pylori</i> treatment	1.13 (0.89 to 1.44)	.32	0.77 (0.62 to 0.95)	.016	4.14	4.22	-0.08 (-0.21 to 0.05)	.22
Vitamins	1.10 (0.89 to 1.37)	.39	1.32 (1.12 to 1.57)	.001	3.97	3.87	0.10 (-0.01 to 0.21)	.068
Garlic	0.98 (0.79 to 1.22)	.86	0.99 (0.84 to 1.18)	.94	3.93	3.92	0.01 (-0.10 to 0.12)	.84
2003								
<i>H. pylori</i> treatment	1.07 (0.88 to 1.31)	.49	0.60 (0.47 to 0.75)	<.001	4.45	4.69	-0.24 (-0.40 to -0.09)	.002
Vitamins	1.03 (0.87 to 1.23)	.71	1.14 (0.96 to 1.37)	.14	4.29	4.23	0.06 (-0.08 to 0.20)	.38
Garlic	1.02 (0.86 to 1.21)	.83	1.08 (0.90 to 1.29)	.40	4.26	4.25	0.01 (-0.12 to 0.15)	.83

Effects of *Helicobacter pylori* treatment and vitamin and garlic supplementation on gastric cancer incidence and mortality: follow-up of a randomized intervention trial


Wen-Qing Li,¹ Jing-Yu Zhang,¹ Jun-Ling Ma,¹ Zhe-Xuan Li,¹ Lian Zhang,¹ Yang Zhang,¹ Yang Guo,¹ Tong Zhou,¹ Ji-You Li,¹ Lin Shen,¹ Wei-Dong Liu,² Zhong-Xiang Han,² William J Blot,^{3,4} Mitchell H Gail,⁵ Kai-Feng Pan,¹ Wei-Cheng You¹

Table 2 | Odds ratios (95% confidence intervals) for incidence of gastric cancer by *Helicobacter pylori* treatment, and vitamin and garlic supplementation

Interventions	Adjusted for baseline histology				Fully adjusted*			
	Placebo (No with event/No in group)	Treatment (No with event/No in group)	Odds ratio (95% CI)	P value	Placebo (No with event/No in group)	Treatment (No with event/No in group)	Odds ratio (95% CI)	P value
<i>H pylori</i> treatment	78/1123	40/1119	0.48 (0.33 to 0.72)	<0.001	76/1086	40/1086	0.48 (0.32 to 0.71)	<0.001
Vitamin supplementation	90/1679	60/1665	0.66 (0.47 to 0.92)	0.02	89/1627	58/1610	0.64 (0.46 to 0.91)	0.01
Garlic supplementation	82/1678	68/1666	0.82 (0.58 to 1.14)	0.23	81/1631	66/1606	0.81 (0.57 to 1.13)	0.22

Number of participants and number of gastric cancer cases is lower than in table 1 because of missing information on baseline histology or other covariates.

*Adjusted for baseline histology (moderate chronic atrophic gastritis or less severe gastric lesions, severe chronic atrophic gastritis or superficial intestinal metaplasia, deep intestinal metaplasia, or dysplasia), age, sex, history of ever using alcohol, and history of ever smoking.

Fully adjusted*				
Placebo (No with event/No in group)	Treatment (No with event/No in group)	Odds ratio (95% CI)	P value	
76/1086	40/1086	0.48 (0.32 to 0.71)	<0.001	
89/1627	58/1610	0.64 (0.46 to 0.91)	0.01	
81/1631	66/1606	0.81 (0.57 to 1.13)	0.22	

Gastric Cancer Research in DCEG

- Gastric cancer prevention trials
- **Descriptive epidemiology**
- Etiologic research
 - The role of *Helicobacter pylori* in gastric cancer by subsite and geographic location
- H. pylori Genome Project (HpGP)

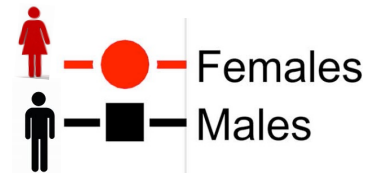
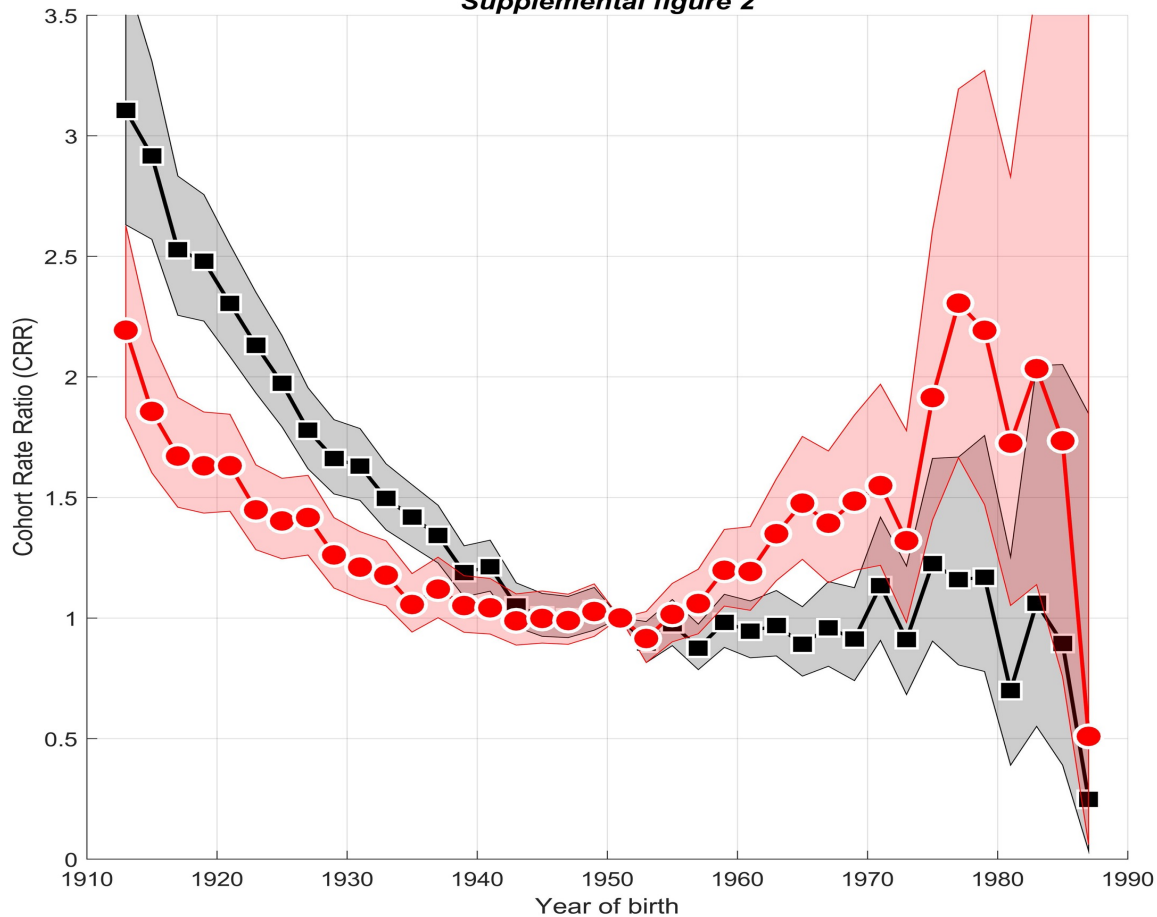
ARTICLE

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

William F. Anderson, Charles S. Rabkin, Natalie Turner,
Joseph F. Fraumeni Jr., Philip S. Rosenberg, M. Constanza Camargo

JNCIJ Natl Cancer Inst (2018) 110(6): djx262

Supplemental figure 2



Sex and age differences in mortality trends of gastric cancer among Hispanic/Latino populations in the United States, Latin America, and the Caribbean

J. Smith Torres-Roman,^{a,b,} Christian S. Alvarez,^c Pedro Guerra-Canchari,^{b,d} Bryan Valcarcel,^b José Fabián Martínez-Herrera,^{b,e} Carlos A. Dávila-Hernández,^f Camila Alves Santos,^{b,g} Samara Carollyne Mafra Soares,^{b,g} Dyego Leandro Bezerra de Souza,^{b,g,h} and M. Constanza Camargo^c*

**The Lancet Regional
Health - Americas
2022;16: 100376**

Published online 7

October 2022

<https://doi.org/10.1016/j.lana.2022.100376>

lana.2022.100376



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Gastric Cardia cancer and *Helicobacter pylori*

- Gastric cardia tumors
 - occur in the top few centimeters of the stomach
 - clinically and histologically, they are difficult to separate from esophageal adenocarcinomas
- Mistakenly thought to be primarily a tumor of White men of European origin

Global burden of oesophageal and gastric cancer by histology and subsite in 2018

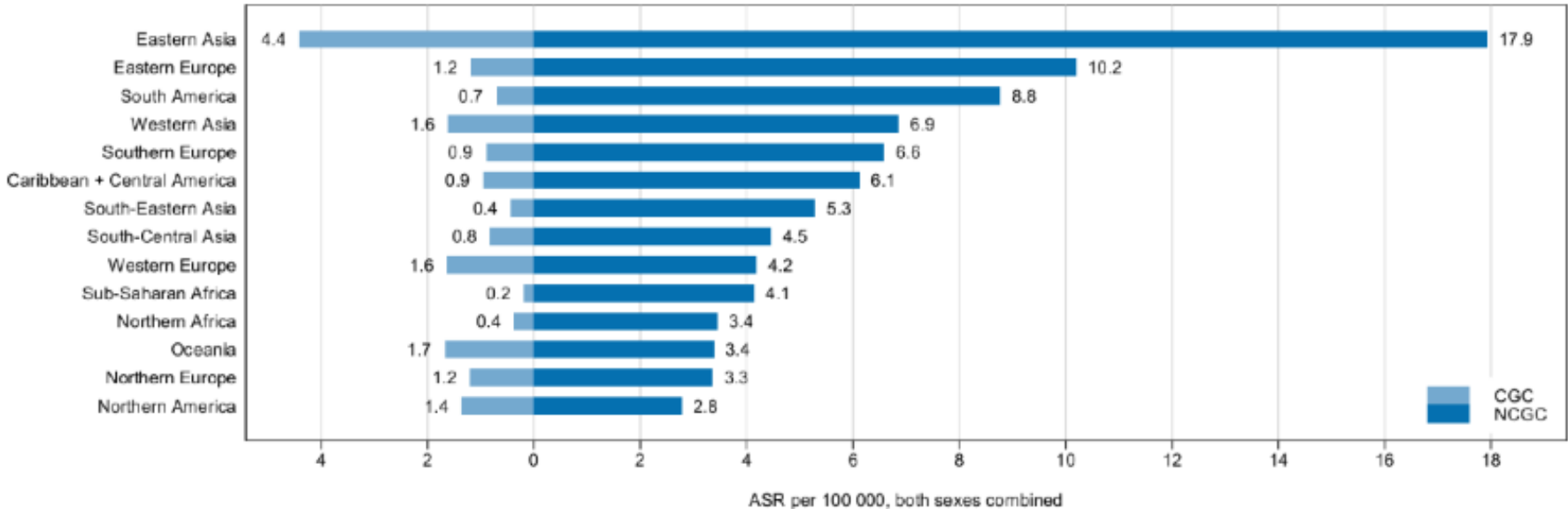
Melina Arnold ,¹ Jacques Ferlay,¹ Mark I van Berge Henegouwen ,²
Isabelle Soerjomataram¹

Arnold M, *et al.* *Gut* 2020;**69**:1564–1571. doi:10.1136/gutjnl-2020-321600

For both CGC and NCGC, the vast majority of cases occurred in Asia, together representing over 70% of the global case burden of both subsites ([figure 1](#)). In the case of CGC, about 121 000 cases (67%) occurred in Eastern Asia (whereof 110 000 in China), followed by South Central Asia (14 000 cases, 8%) and Northern America (9 000 cases, 5%).

Gastric Cardia cancer and *Helicobacter pylori*

Gastric cancer



Gastric Cardia cancer and *Helicobacter pylori*

Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts

Gut 2001;**49**:347–353

Helicobacter and Cancer Collaborative Group

Gastric cancer and *H pylori*

Gut 2002;**51**:455–458

S M Dawsey, S D Mark, P R Taylor
National Cancer Institute, Bethesda, MD, USA

P J Limburg
Mayo Clinic, Rochester, MN, USA

Gastric Cardia cancer and *Helicobacter pylori*

Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China

F Kamangar^{*,1}, Y-L Qiao^{*,2}, MJ Blaser^{3,4}, X-D Sun², H Katki¹, J-H Fan², GI Perez-Perez^{3,4}, CC Abnet¹, P Zhao², SD Mark⁵, PR Taylor¹ and SM Dawsey¹

British Journal of Cancer (2007) 96, 172–176

Gastric Cardia cancer and *Helicobacter pylori*

	Number tested	Adjusted HR ^a (95% CI)
Subcohort	992	—
Oesophageal squamous cell cancer	335	1.17 (0.88–1.57)
Gastric cardia cancer	582	1.64 (1.26–2.14) ←
Gastric non-cardia cancer	343	1.60 (1.15–2.21) ←

Gastric Cardia cancer and *Helicobacter pylori*

Multiplex *H. pylori* Serology and Risk of Gastric Cardia and Noncardia Adenocarcinomas

Ramin Shakeri¹, Reza Malekzadeh¹, Dariush Nasrollahzadeh^{1,2}, Michael Pawilta³, Gwen Murphy⁴, Farhad Islami^{1,5}, Masoud Sotoudeh¹, Angelika Michel³, Arash Etemadi^{1,4}, Tim Waterboer³, Hossein Poustchi⁶, Paul Brennan⁷, Paolo Boffetta⁸, Sanford M. Dawsey⁴, Farin Kamangar^{1,9}, and Christian C. Abnet⁴

Cancer Res; 75(22) November 15, 2015

Gastric Cardia cancer and *Helicobacter pylori*

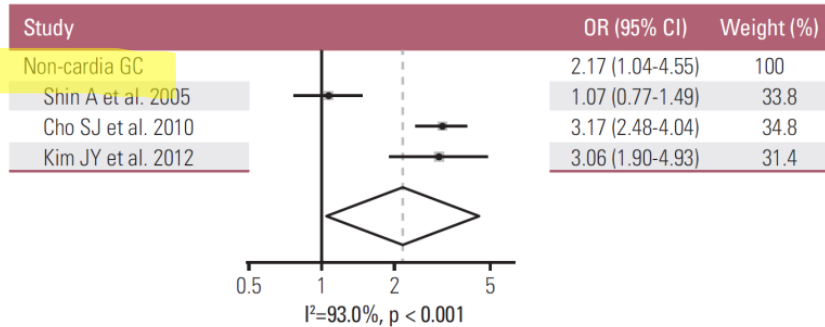
	Gastric cardia adenocarcinoma				Gastric noncardia adenocarcinoma			
		Controls	Unadjusted	Adjusted ^a		Controls	Unadjusted	Adjusted ^a OR
	<i>N</i> (%)	<i>N</i> (%)	OR (95% CI)	OR (95% CI)	<i>N</i> (%)	<i>N</i> (%)	OR (95% CI)	(95% CI)
	142	276			103	195		
Whole cell ELISA	11 (7.7) 131 (92.3)	20 (7.2) 131 (92.8)	1 0.9 (0.4-1.9)	1 1.3 (0.5-3.1)	6 (5.8) 97 (94.2)	19 (9.7) 176 (90.3)	1 1.7 (0.6-4.3)	1 1.3 (0.4-3.7)
CagA	17 (12.0) 125 (88.0)	56 (20.3) 220 (79.7)	1 1.9 (1.1-3.4)	1 2.1 (1.1-4.1)	9 (8.7) 94 (91.3)	47 (24.1) 148 (75.9)	1 3.1 (1.4-6.5)	1 3.5 (1.4-8.2)

Gastric Cardia cancer and *Helicobacter pylori*

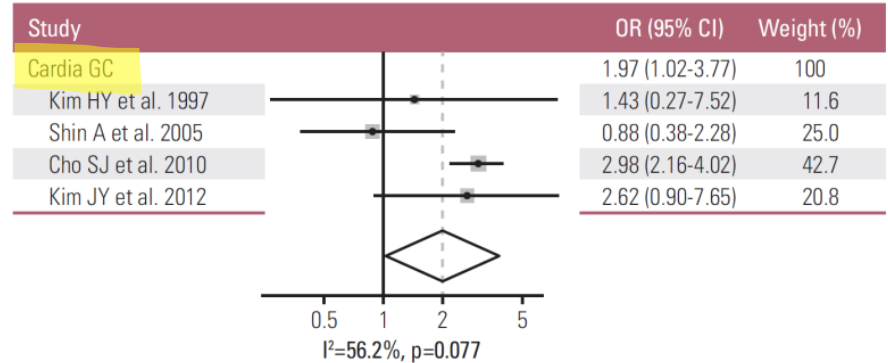
Original Article

Population Attributable Fraction of *Helicobacter pylori* Infection–Related Gastric Cancer in Korea: A Meta-Analysis

Yoon Park, Moran Ki



2.17 (1.04-4.55)



1.97 (1.02-2.22)

Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis

Catherine de Martel, Damien Georges, Freddie Bray, Jacques Ferlay, Gary M Clifford

www.thelancet.com/lancetgh Vol 8 February 2020

	Men		Women		Total	
	New cases	New cases attributable to infectious pathogens	New cases	New cases attributable to infectious pathogens	New cases	New cases attributable to infectious pathogens
<i>Helicobacter pylori</i>						
Non-cardia gastric cancer	550 000	490 000	300 000	270 000	850 000	760 000
Cardia gastric cancer	130 000	27 000	46 000	8900	180 000	36 000
Non-Hodgkin lymphoma of gastric location	12 000	8700	10 000	7600	22 000	16 000

Noncardia Gastric Cancer = 89%
Cardia Gastric Cancer = 20%

www.thelancet.com/lancetgh Vol 8 February 2020

Gastric Cancer Research in DCEG

- Gastric cancer prevention trials
- Descriptive epidemiology
- Etiologic research
- Genome Wide Association Studies (GWAS)
- **H. pylori Genome Project (HpGP)**









The *Helicobacter pylori* Genome Project: insights into *H. pylori* population structure from analysis of a worldwide collection of complete genomes

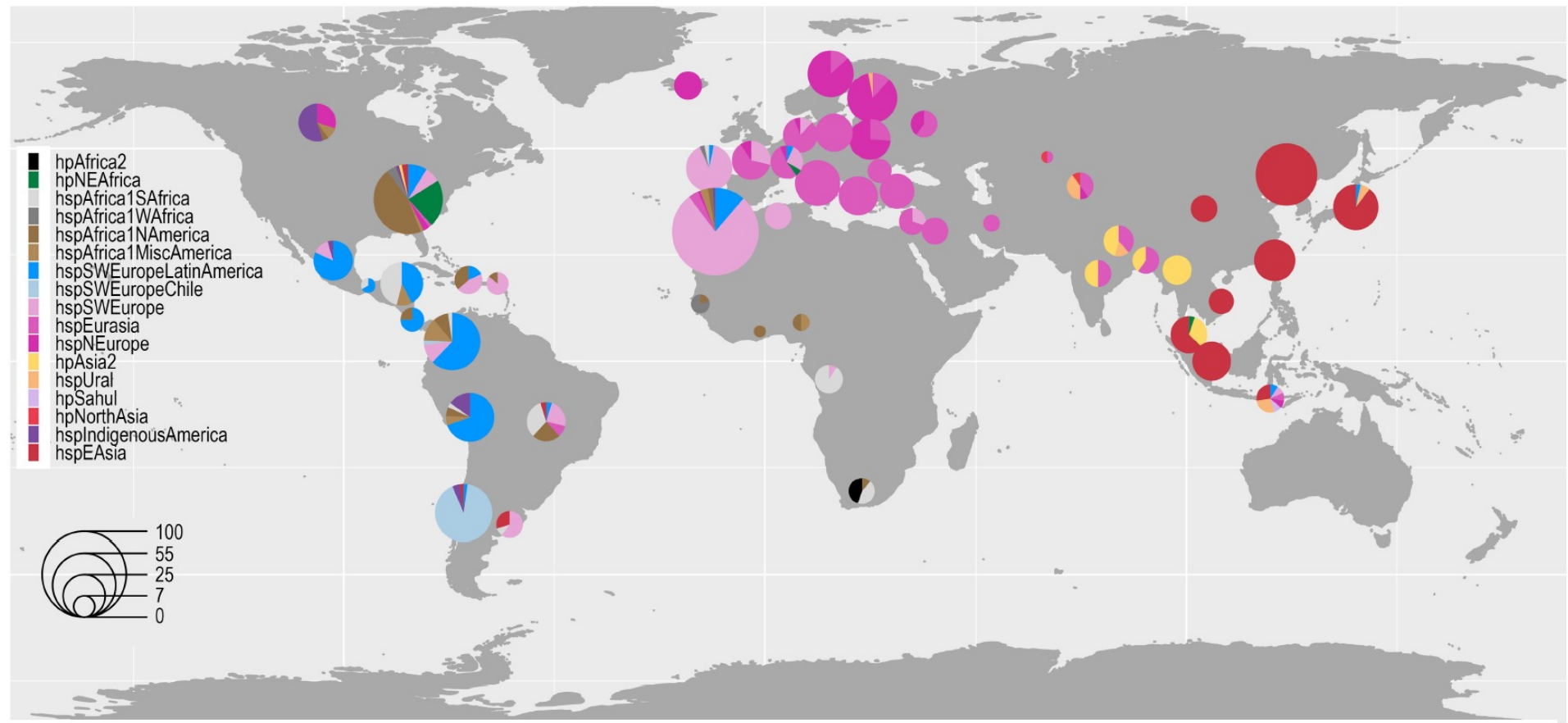
Received: 5 September 2023

Accepted: 13 November 2023

Published online: 11 December 2023

Kaisa Thorell ^{1,204} , Zilia Y. Muñoz-Ramírez ^{2,204}, Difei Wang^{3,4},
Santiago Sandoval-Motta^{5,6,7}, Rajiv Boscolo Agostini⁸, Silvia Ghirotto⁸,
Roberto C. Torres ⁹, HpGP Research Network*, Daniel Falush ⁹,
M. Constanza Camargo ^{4,205} & Charles S. Rabkin^{4,205}


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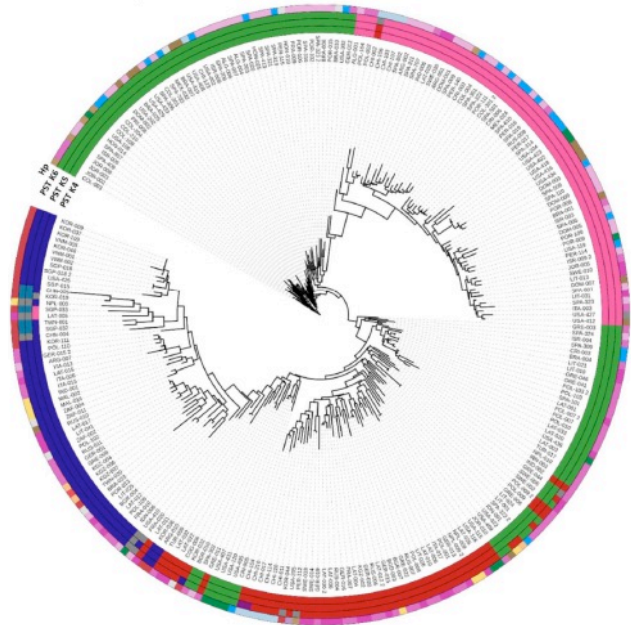


***H. pylori* Genome Project**

- **1011 *H. pylori* strains collected from people with:**
 - **Non-atrophic gastritis (N=606)**
 - **Advanced intestinal metaplasia (N=172)**
 - **Gastric cancer (N=233)**
- **Primary manuscripts in preparation:**
 - ***H. pylori* resistance to antibiotics**
 - **Characterization of plasmids**
 - **GWAS of gastric cancer and intestinal metaplasia**
- **Epigenomes of 1011 Hp strains still in process**

Gene content, phage cycle regulation model and prophage inactivation disclosed by prophage genomics in the *Helicobacter pylori* Genome Project

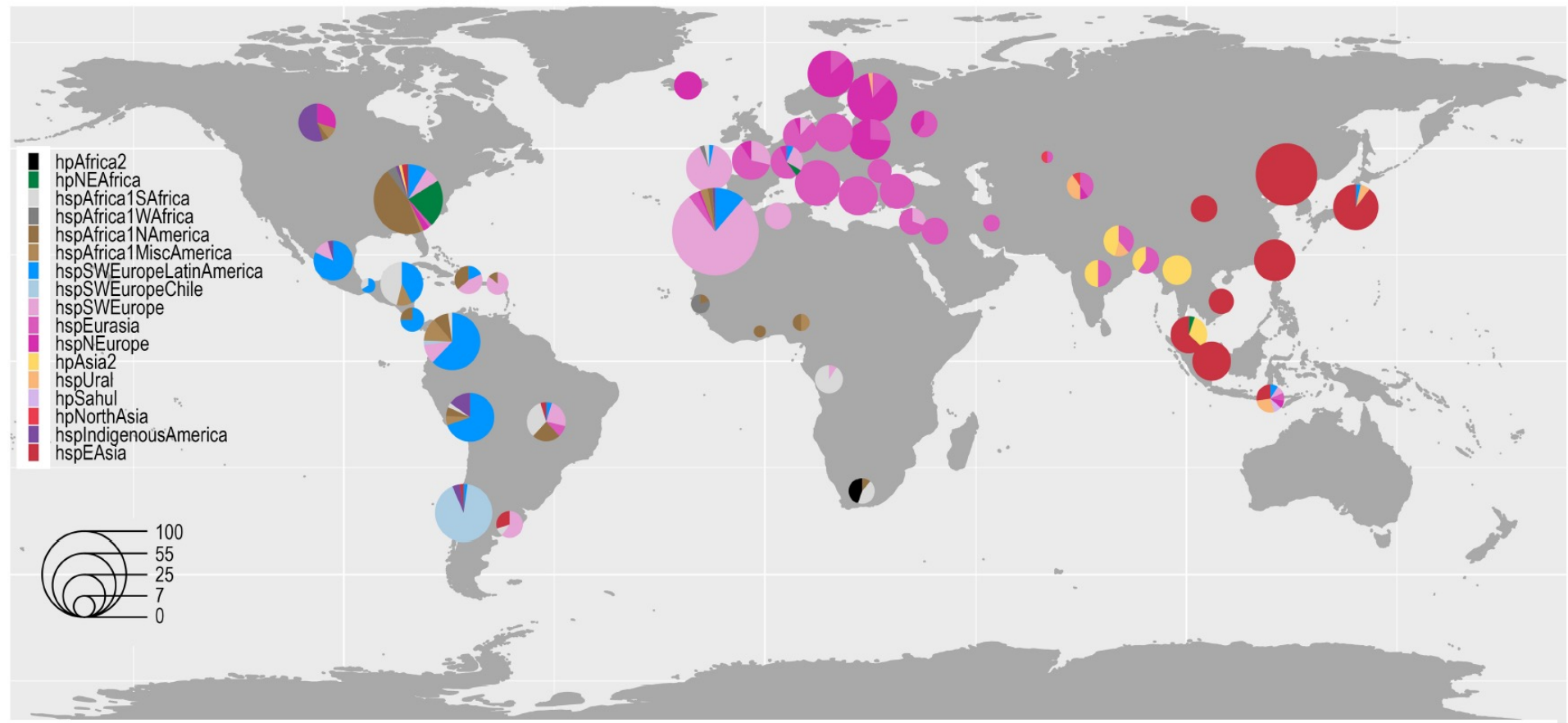
Filipa F. Vale ^{a,b}, HpGP Research Network*, Richard J. Roberts^c, Ichizo Kobayashi^{d,e,f,g}, M. Constanza Camargo^{h#}, and Charles S. Rabkin^{h#}



GUT MICROBES

2024, VOL. 16, NO. 1, 2379440

<https://doi.org/10.1080/19490976.2024.2379440>



African *Helicobacter pylori* Genome Project



- At least 80% of the continent (n=1000 individuals) using mainly string test (EnterTrack)
- Collaboration with the African *Helicobacter* and Microbiota Study Group
- Microbiome component

Novel Device to Sample the Esophageal Microbiome— The Esophageal String Test

Sophie A. Fillon^{1,9,*}, J. Kirk Harris^{2,9}, Brandie D. Wagner³, Caleb J. Kelly¹, Mark J. Stevens², Wendy Moore¹,
Rui Fang³, Shauna Schroeder¹, Joanne C. Masterson¹, Charles E. Robertson⁴, Norman R. Pace⁴,
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September 2012 | Volume 7 | Issue 9 | e42938

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