III JORNADA CIENTÍFICA TEMAS DE ACTUALIDAD EN CÁNCER DIGESTIVO

CÁNCER GÁSTRICO Y DE LA UNIÓN ESÓFAGO-GÁSTRICA (UEG)

Málaga, 23 de febrero 2017

Organizado por: Universidad Francisco de Vitoria UFV Madrid

¿Es la erradicación de *H. pylori* un modo de prevenir el Cáncer gástrico?

Ana Fernández Montes
Complexo Hospitalario Universitario de Ourense
Málaga, 23 de febrero de 2017

Planteamiento del Problema

- ¿Porqué estamos hablando de esto?
- ¿Está asociado *H.pylori* con Cáncer Gástrico?
- ¿Cómo causa Cáncer gástrico *H.pylori*?
- **¿Prevendríamos el Cáncer gástrico?**
- **Cuestiones objeto de debate**
- **¿Qué hacer?**
- **Conclusiones**

1

¿Porqué estamos hablando de esto hoy?

¿Porqué estamos hablando de esto hoy?

Incidencia y Mortalidad

GLOBOCAN 2012:

951.000 casos (6,8% de todos los casos)

5º cáncer más frecuente a nivel mundial

3º causa de muerte por cáncer a nivel mundial (723.000 casos / 8,8% de todos los casos)

70% en países en desarrollo y la mitad en ASIA (mayormente China:43%)

La mayoría de la evidencia "obviamente " procede de estudios Asiáticos

Ferlay et al.Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.

¿Porqué estamos hablando de esto hoy?

…Incidencia diferente según regiones

Incidencia	Hombres	Mujeres
Mundial	631,1	320,3
Países en vías desarrollo	456,2	220,2
Países desarrollados	175,1	99,4
Asia	480,4	219,6
Europa	84,2	55,4

Ferlay et al, GLOBOCAN 2012, Int J Cancer 2015

¿Porqué estamos hablando de esto hoy?

Cáncer e Infección

GLOBOCAN 201

14 millones de

2,2 millones so

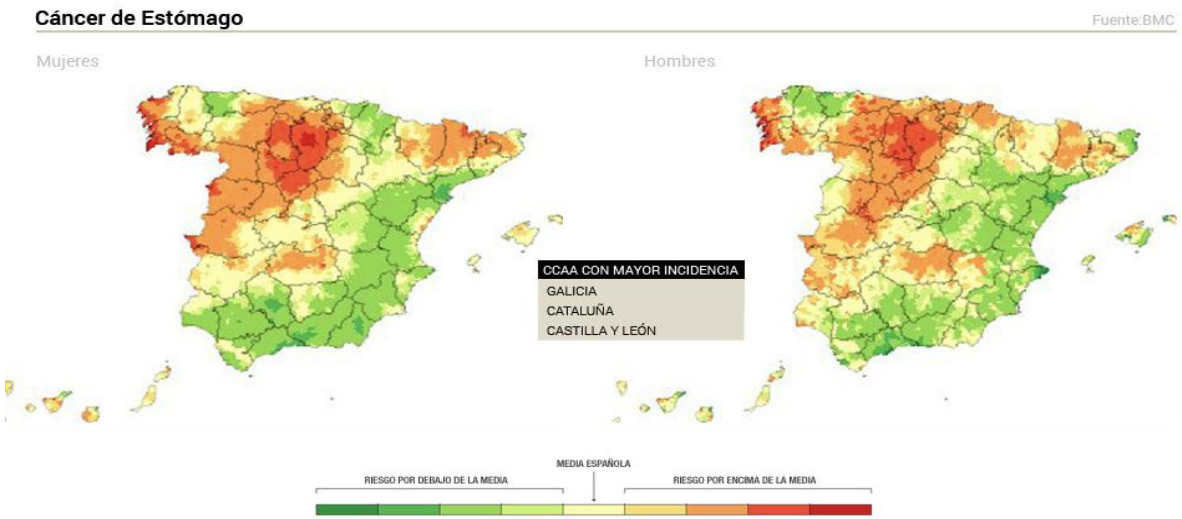
Mayoría en paí

Agentes causale

- *Helicobacter*
- Virus del Pap
- VHB: 420.00
- VHC:170.000
- VEB:120.000 casos

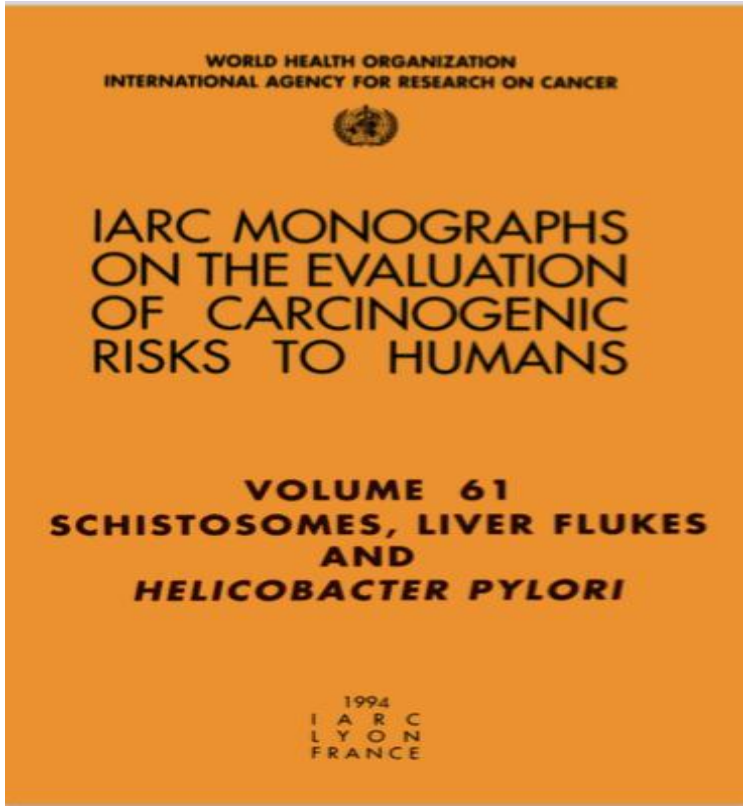
Plummer et al. Global burden of cancers attributable to infections in 2012: a syntheticanalysis. Lancet Glob Health. 2016 Sep;4(9):e609-16.

Tumor	Incidencia			Mortalidad			Prevalencia 5 años		
	Total	%	ASR	Total	%	ASR	Total	%	ASR
Estómago	7810	3,6	7,8	5389	5,2	4,9	12611	2,2	31,8



2 ¿Está asociado *H.pylori* con Cáncer Gástrico?

…Catalogado como carcinógeno desde 1994



¿Está asociado *H.pylori* con C. Gástrico?

Evidencia

 # Metanálisis de estudios observacionales epidemiológicos (n:42 estudios)

"La infección por *H.pylori* se asocia con un incremento x 2 del desarrollo de cáncer gástrico"

RR 2,04 (IC 95% 1,69-2,45)

Eslick GD et al. Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis.Am J Gastroenterol. 1999.

#Revisión sistemática de 32 estudios retrospectivo:

"Es más frecuente 2-3 veces tener un cáncer gástrico si hay infección por *H.pylori*".

Danesh et al. Alimente Pharmacol Ther 1999

 # Estudio EUROGAST(13 países):

"Principal factor de riesgo de cáncer gástrico, incremento x 6 el riesgo de cáncer gástrico entre infectados."

An international association between Helicobacter pylori infection and gastriccancer. The EUROGAST Study Group.Lancet 1993.

 # Metanálisis de estudios de casos- control o de cohortes (n:19)

Mayor riesgo de C.gástrico si hay infección a edades jóvenes y asociación igualmente con intestinales y difusos.

Fundamentalmente gástricos no cardias.

Huang et al.Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer.Gastroenterology 1998.

¿Está asociado *H.pylori* con C. Gástrico?

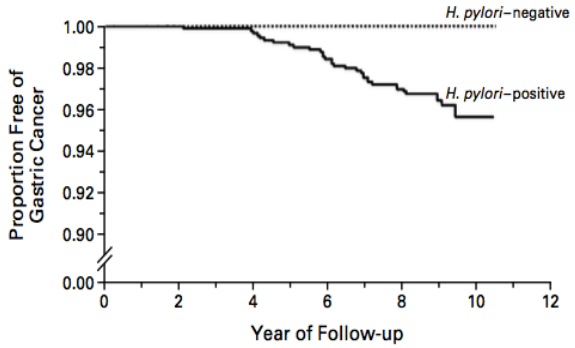
Evidencia

Estudio prospectivo Japonés con 1526 pacientes con úlceras duodenales, úlceras gástricas, pólipos hiperplásicos y dispepsia no ulcerosa.

Se evaluaba *H.pylori* (histológicamente: ureasa y test serológico) y se seguían mediante EDA cada 1-3 años.

1246 *H.pylori+* y 280 *H.pylori-* (todos dispepsia no ulcerosa).

Desarrollan cáncer 36 pacientes de los infectados y ninguno de los no infectados
(2,9%)
Riesgo 5% a los 10 años.



No. at Risk						
H. pylori–negative	280	272	251	245	213	57
H. pylori–positive	1246	1219	1086	907	782	258

Figure 1. Kaplan–Meier Analysis of the Proportion of *H. pylori*–Positive and *H. pylori*–Negative Patients Who Remained Free of Gastric Cancer.

During follow-up, gastric cancer developed in 36 of the 1246 *H. pylori*–infected patients (2.9 percent) but in none of the 280 uninfected patients (P<0.001).

Uemura et al,NEJM 2001

3 ¿Cómo causa Cáncer gástrico *H. pylori*?

Dos mecanismos

Directo: cambios epigenéticos por parte de H.pylori en las células epiteliales gástricas

Indirecto: por respuesta inflamatoria 2º a H.pylori en la mucosa gástrica.

Sobretodo cag A y o vac A.

Ishaq et al.Gastroenterol Hepatol Bed Bench 2015.

La carcinogénesis gástrica es multifactorial…

Producción ureasa : hace resistente a HCl.

Bacilo flagelado (FlaA):movilidad

Factores de virulencia (cepas con):

- Vac A …vacuoliza
- Cag A...inhibe p53..

Ambas mayor riesgo de desarrollo de lesion premalignas y de cáncer

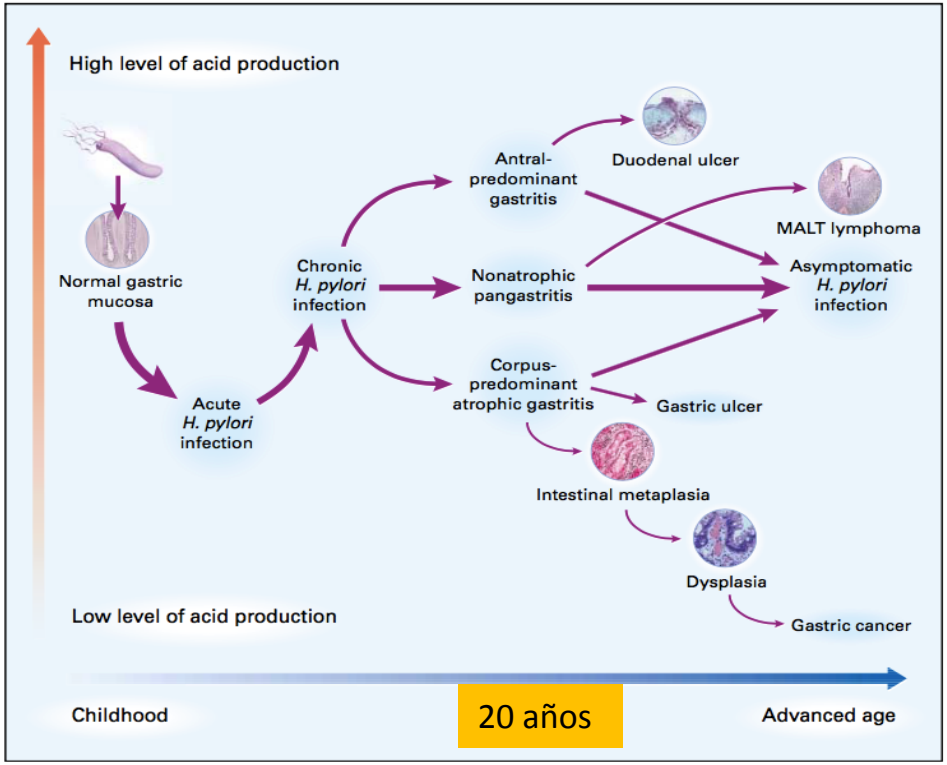


Figure 3. Natural History of *Helicobacter pylori* Infection.

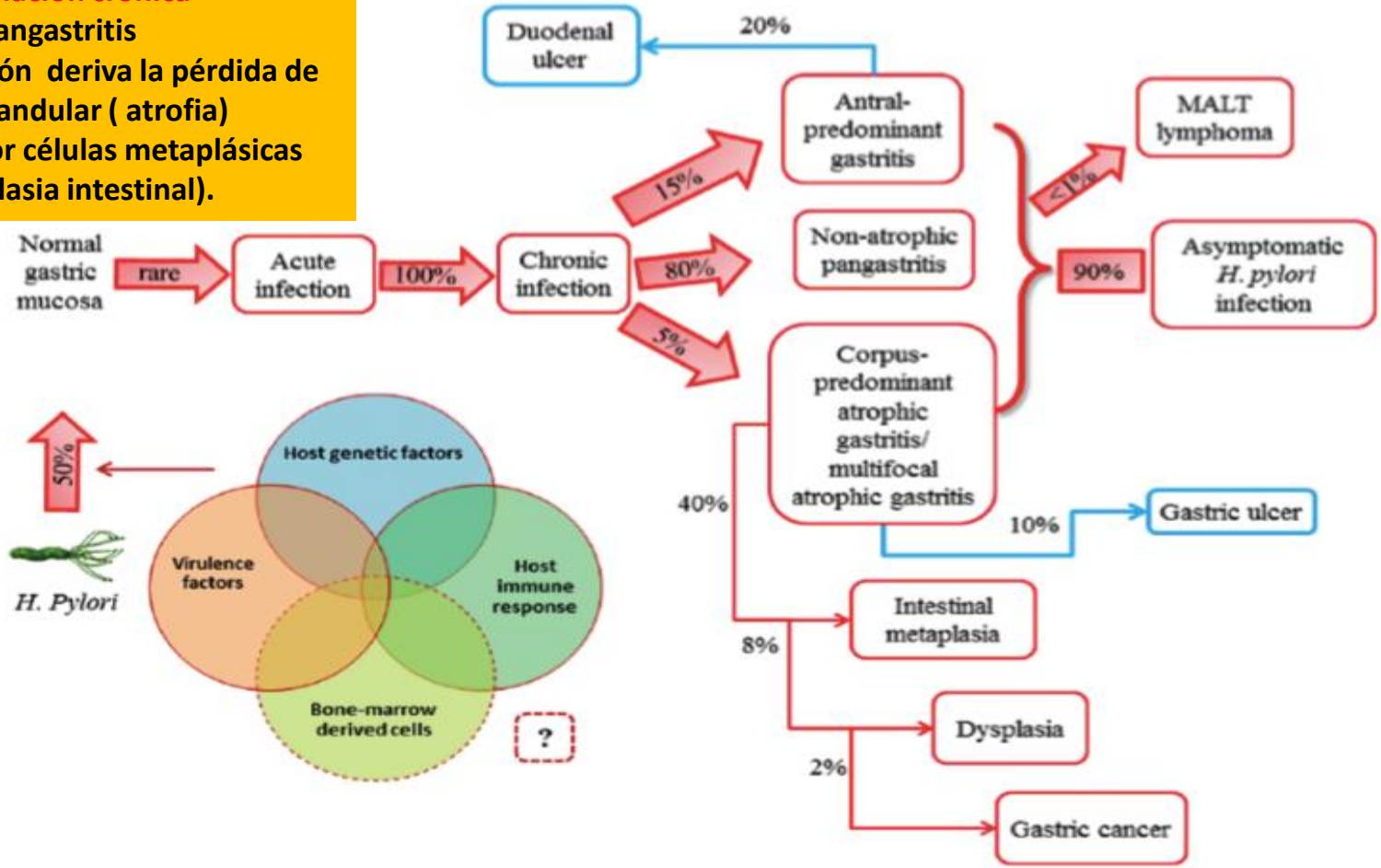
Suerbaum et al,NEJM 2002

Inflamación crónica

Pangastritis

De la inflamación deriva la pérdida de tejido glandular (atrofia)

Reemplazo por células metaplásicas (metaplasia intestinal).



Conteduca et al.In J Clin Oncol, 2013.

¿Qué otros factores están implicados en la carcinogénesis?

1) **H.pylori: cepas más agresivas aquellas cagA y Vac A.**

Huang et al. Gastroenterology 2003
Peek et al-Int J Camcer 1999

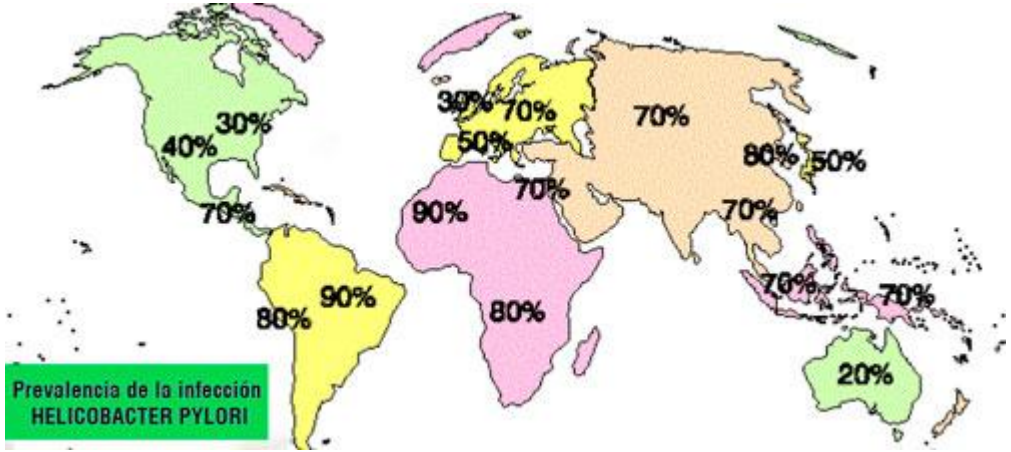
2) Ambiente:
Sal y ahumados
Baja ingesta de frutas y vegetales.
Fumar y consumo de alcohol.

Wiseman et al.Proc Nutr Soc 2008.

3) Factores individuales:
Polimorfismos IL-1B….promueve la inflamación.

Kamangar et al.Cancer Epidemiol Biomarquer Prev 2006.

Distribución de la Infección por *H.Pylori*



20-50% desarrollados
80% en desarrollo
Ingesta oral…infancia

Conteduca et al. Int J Oncol. 2013 H. pylori infection and gastric cancer: state of the art (review).Int J Oncol 2013.

Cáncer gástrico y *H.pylori*

- *Cáncer gástrico 3º tumor en mortalidad, 5º en incidencia*
- *Diferente incidencia según regiones*
- *H.pylori: riesgo de cáncer gátrico x2-6*
- *H.pylori se asocia a intestinales y difusos. No cardiales.*
- *H.pylori (directo y mediante inflamación crónica)*
- *A) Pangastritis…difusos*
- *B) Gastritis atrófica, metaplasia intetsinal y displasia gástrica…intestinales*

4

¿Qué evidencia tiene la erradicación de *H.pylori* como medida de prevención de C.gástrico? (Prevención Primaria)

…Dado que hemos demostrado que el principal causante de pangastritis y de otras lesiones premalignas (gastritis atrófica, metaplasia intestinal y displasia)

Annals of Internal Medicine | REVIEW

Meta-analysis: Can *Helicobacter pylori* Eradication Treatment Reduce the Risk for Gastric Cancer?

Lorenzo Fuccio, MD; Rocco Maurizio Zagari, MD; Leonardo Henry Eusebi, MD; Liboria Laterza, MD; Vincenzo Cennamo, MD; Liza Ceroni, MD; Diego Grilli, PhD; and Franco Bazzoli, MD

Table 1. **Gastric Cancer Cases in Groups Treated for *Helicobacter pylori* and Control Groups**

Author, Year (Reference)	Enrollment Period	Format	Province, Country	Gastric Cancer Incidence in General Population (Reference)*	Primary Outcome	Randomly Assigned Patients, *n*	
						Treatment Group	Control Group
Correa et al, 2000 (23)	1991	Full text	Nariño, Colombia	160 (31)	Progression of preneoplastic lesions	491	485
Leung et al, 2004 (30)	1996	Full text	Shandong, China	50 (30)	Progression of preneoplastic lesions	295	292
Wong et al, 2004 (25)	1994	Full text	Fujian, China	99 (32)	Incidence of gastric cancer	817	813
Saito et al, 2005 (28)	Not available	Abstract	Japan	62 (33)	Progression of preneoplastic lesions	379	313
You et al, 2006 (26)	1994	Full text	Shandong, China	50 (30)	Progression of preneoplastic lesions	1130	1128
Fukase et al, 2008 (27)	April 2001 to July 2003	Full text	Japan	62 (33)	Incidence of gastric cancer	272	272
Zhou, 2008 (29)	1996	Abstract	Shandong, China	50 (30)	Progression of preneoplastic lesions	276	276

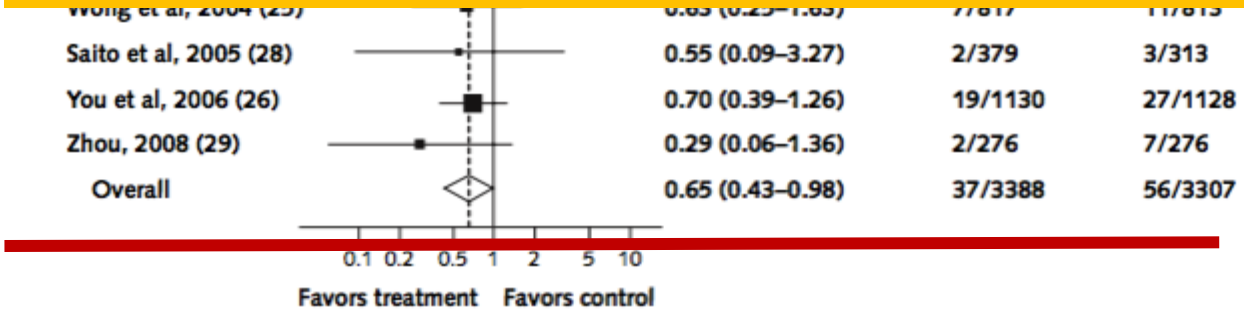
* Incidence rates are cases per 100 000 ... of >20 cases per 100 000 persons per year. In Western Europe and North Americ... 31).
† Information provided by the authors

Zonas de alta incidencia (> 20 casos /100.000 habitantes)
Asiáticos
Seguimiento mediano 6 años
Tasas erradicación del 73%-88,9%
La mayoría ya lesiones preneoplásicas

Ann Internal Medicine, 2009

Figure 2. Forest plot of 6 studies reporting gastric cancer in treated and nontreated groups.

Desarrollo de C.gástrico 1,1% brazo de tratamiento vs 1,7% en rama control.
Recalcar que tiene lesiones premalignas y desaparecen.
La mayor magnitud de la quimioprevención es antes de desarrollar lesiones premalignas.
Claramente la erradicación previene el C.gástrico.



The area of the boxes corresponds to the weight of each study. RR = relative risk.

Matices:

- ✓ **Los estudios están infradimensionados y fallan para mostrar efecto quimioprevención…deberíamos seguirlos 10 años.**
- ✓ **Solo 7 estudios. Asiáticos la mayoría …la validez externa es dudosa.**
- ✓ **Solo dos estudios doble ciego.**

LETTERS | 6 OCTOBER 2009

Redundant Data in the Meta-analysis on *Helicobacter pylori* Eradication

Alexander C. Ford, MBChB, MD; Paul Moayyedi, MBChB, PhD

Article, Author, and Disclosure Information

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TO THE EDITOR:

We read with interest the recent meta-analysis by Fuccio and colleagues (1). There is an ongoing Cochrane review on this subject; its protocol is published (2), and its results have been reported in abstract form (3). Fuccio and colleagues report that eradication therapy for *Helicobacter pylori* reduces the subsequent incidence of gastric cancer. However, we have serious doubts about the accuracy of their analysis. In the Methods section of their article, Fuccio and colleagues state that when they found multiple articles for a single study, they used the latest publication from each eligible study. However, the meta-analysis erroneously incorporated data from the same randomized, controlled trial (RCT) twice (4, 5). Tables 1 and 2 (1) showed "2" studies that were conducted in the Shandong province of China, commenced in 1996, had very similar numbers of participants, and used identical eradication regimens of the same duration. We contacted the original investigators of these studies (2, 3) directly when collecting data for our review. Those investigators confirmed that the 2 publications were in fact 5-year (4) and 10-year (5) follow-up studies from the same RCT.

Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials

Objetivo 1º:

Efecto de la erradicación de *H.pylori e*n individuos asintomáticos comparado con placebo en la aparición de Cáncer gástrico.

Objetivos 2ºs:

Aparición de Cáncer esófago, mortalidad de Cáncer gástrico ,efectos en todas las causas de mortalidad y efectos 2º de la terapia erradicadora.

CRITERIOS:

- ✓ Ensayos randomizados
- ✓ Individuos sanos
- ✓ Erradicación vs placebo/no tratamiento
- ✓ Duración mínima de tratamiento 7 días
- ✓ Seguimiento mínimo de dos años
- ✓ Al menos 2 cánceres gástricos durante el seguimiento
- ✓ Valoración dicotómica de la incidencia de C.gástrico.

Ford et al, BMJ 2014

Study	Location	Method to confirm *H pylori* infection	Sample size (No receiving *H pylori* eradication therapy)	Characteristics of participants	% with pre-neoplastic lesions* at baseline	*H pylori* eradication therapy regimen	Eradication rate (%)†	Last point of follow-up	Method to detect gastric cancer cases	Methodology
Correa 2000 [22] and Correa 2001 [35]	2 communities in Narino Province, Colombia	Histological examination‡	852 (437)	Mean (range) age 51.1 (29-69) years, 46.1% men	100	Bismuth subsalicylate 262 mg, amoxicillin 500 mg, metronidazole 375 mg thrice daily for 2 weeks	58.0	6 years	Histological examination‡ at 6 years	Method of randomisation and concealment of allocation stated. Unblinded
Leung 2004 [28] and Zhou 2008 [27]	11 villages in Yantai County, Shandong Province, China	Histological examination and rapid urease testing‡	Leung: 587 (295) Zhou: 552 (276)	Mean (range) age 52.0 (35-75) years, 47.8% men	33.7	Omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg twice daily for 1 week	55.6	Leung: 5 years Zhou: 10 years	Histological examination‡ at 2, 5, 8, and 10 years	Method of randomisation and concealment of allocation stated. Double blind
Wong 2004 [24]	7 villages in Changle County, Fujian Province, China	Histological examination and rapid urease testing‡	1630 (817)	Mean (range) age 42.2 (35-65) years, 54.0% men	37.7	Omeprazole 20 mg, co-amoxiclav 750 mg, metronidazole 400 mg twice daily for 2 weeks	83.7	7.5 years	Histological examination‡ at 7.5 years or, if diagnosed before 7.5 years, review of clinical records and pathology specimens by three blinded clinicians	Method of randomisation and concealment of allocation stated. Double-blind
Saito 2005 [23]	145 centres in Japan	Not reported	692 (379)	Mean age not reported (range 20-59 years), proportion men not reported	Not reported	Lansoprazole 30 mg, amoxicillin 1.5 g, clarithromycin 400 mg once daily for 1 week	74.4	≥4 years	Histological examination‡ at ≥4 years	Method of randomisation, concealment of allocation, and blinding not stated
You 2006[32] and Ma 2012 [26]	13 villages in Linqu County, Shandong Province, China	Serological testing	2258 (1130)	Mean (range) age 46.8 (35-64) years, 50.0% men	64.0	Omeprazole 20 mg and amoxicillin 1 g twice daily for 2 weeks	73.2	14.7 years	Histological examination‡, clinical, laboratory, or pathological data	Method of randomisation and concealment of allocation stated. Double blind
Wong 2012 [25]	12 villages in Linqu County, Shandong Province,	^{13}Carbon-urea breath testing	513 (255)	Mean (range) age 53.0 (35-64) years, 46.4% men	100	Omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg twice	63.5	5 years	Histological examination‡ at 5 years	Method of randomisation and concealment of allocation

Resultados

Objetivo 1º: Efecto de la erradicación en la aparición de Cáncer gástrico

Country	Sex	Lifetime risk (%)	Number needed to treat (95% CI)
China	Men	19.5	15.1 (9.5 to 102.6)
	Women	12.4	23.7 (14.9 to 161.3)
Japan	Men	19.2	15.3 (9.6 to 104.2)
	Women	12.8	23.0 (14.5 to 156.3)
USA	Men	1.8	163.4 (102.9 to 1111.1)
	Women	1.2	245.1 (154.3 to 1666.7)
UK	Men	3.1	94.9 (59.7 to 645.2)
	Women	1.8	163.4 (102.9 to 1111.1)

Incidencia 1,6% en brazo de tratamiento vs 2,4% en no tratados.

Contextualizando….

BMC Med Inform Decis Mak. 2009 Apr 2;9:18. doi: 10.1186/1472-6947-9-18.

What is the point: will screening mammography save my life?

Keen JD[1], Keen JE.

Author information

Abstract

BACKGROUND: We analyzed the claim "mammography saves lives" by calculating the life-saving absolute benefit of screening mammography in reducing breast cancer mortality in women ages 40 to 65.

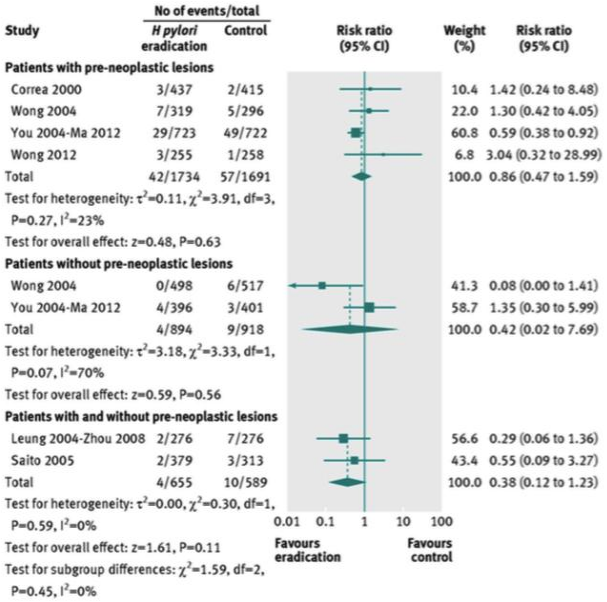
METHODS: To calculate the absolute benefit, we first estimated the screen-free absolute death risk from breast cancer by adjusting the Surveillance, Epidemiology and End Results Program 15-year cumulative breast cancer mortality to account for the separate effects of screening mammography and improved therapy. We calculated the absolute risk reduction (reduction in absolute death risk), the number needed to screen assuming repeated screening, and the survival percentages without and with screening. We varied the relative risk reduction from 10%-30% based on the randomized trials of screening mammography. We developed additional variations of the absolute risk reduction for a screening intervention, including the average benefit of a single screen, as well as the life-saving proportion among patients with earlier cancer detection.

RESULTS: Because the screen-free absolute death risk is approximately 1% overall but rises with age, the relative risk reduction from repeated screening mammography is about 100 times the absolute risk reduction between the starting ages of 50 and 60. Assuming a base case 20% relative risk reduction, repeated screening starting at age 50 saves about 1.8 (overall range, 0.9-2.7) lives over 15 years for every 1000 women screened. The number needed to screen repeatedly is 1000/1.8, or 570. The survival percentage is 99.12% without and 99.29% with screening. The average benefit of a single screening mammogram is 0.034%, or 2970 women must be screened once to save one life. Mammography saves 4.3% of screen-detectable cancer patients' lives starting at age 50. This means 23 cancers must be found starting at age 50, or 27 cancers at age 40 and 21 cancers at age 65, to save one life.

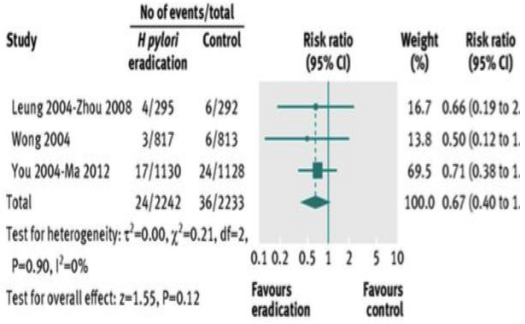
CONCLUSION: The life-saving absolute benefit of screening mammography increases with age as the absolute death risk increases. The number of events needed to save one life varies depending on the prospective screening subset or reference class. Less than 5% of women with screen-detectable cancers have their lives saved.

Resultados
(Objetivos secundarios)

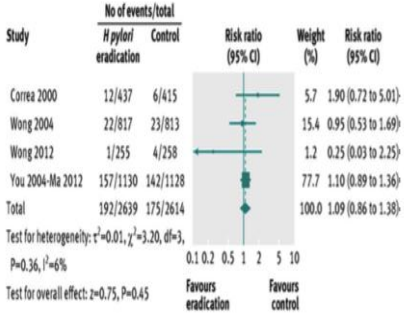
Lesiones premalignas



Mortalidad por C.gástrico



Mortalidad por todo tipo de causas



- ✓ **No efecto en la incidencia de Cáncer de esófago.**
- ✓ **Ef.2º: más rash (3,1%) vs 0,1% en rama de placebo.**
- ✓ **Más reducción Cáncer gástrico si uso con antioxidantes.**

Helicobacter pylori eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis

Hai-Ning Chen · Zhu Wang · Xiao Li ·

Table 1 Characteristics of studies included in the meta-analysis

Study	Country	Enrollment period	Follow-up (years)	Age range	Male–female ratio	Primary outcome	Total number of patients	Treatment group	Control group	Treatment complete	Control complete	Treatment cancer	control cancer
Correa et al. [1]	Colombia	1991	6	29–69	1:1	PL	852	437	415	320	311	3	2
Sung et al. [17][a]	China	1996	5	16–75	1:1	PL	587	295	292	219	214	NA	NA
Leung et al. [3][a]	China	1996	5	16–75	1:1	PL	587	295	292	220	215	4	6
Wong et al. [7]	China	1994	7.5	35–65	1:1	GC	1,630	817	813	735	703	7	11
You et al. [b][4]	China	1995	9	35–64	1:1	PL	2258	1130	1128	1,008	1,002	19	27
Ma et al. [18][b]	China	1995	15	35–64	1:1	GC	2,258	1,130	1,128	NA	NA	34	52
Fukase et al. [6]	Japan	2001	3	20–79	3:1	GC	542	271	271	255	250	9	24
Wong et al. [9]	China	2002	2	35–64	1:1	PL	1,024	510	514	453	466	4	3
Cho et al. [19]	Korean	2003	3	18–70	1:1	PL	169	87	82	80	71	3	1
Choi et al. [10]	Korean	2005	3	20–75	2:1	GC	891	444	447	439	441	10	17

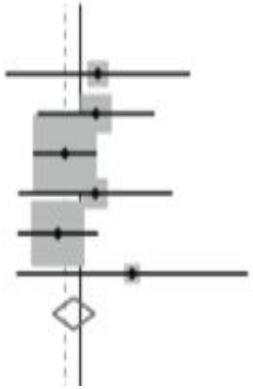
PL precancerous lesions, *GC* gastric cancer

[a] The study by Sung et al. which is from the same trail of Leung, was included to provide supplemental data of histological change

Chen et al, Gastric Cancer 2016

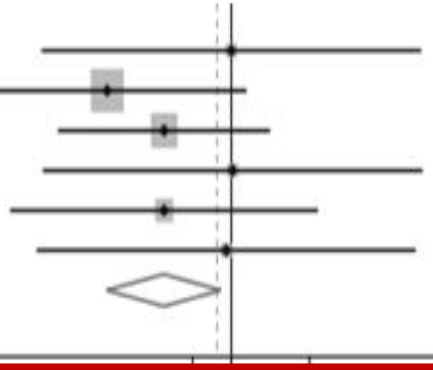
Metaplasia intestinal/Displasia

Source	Treatment Events,	Control Events,	Weight %	RR (95% CI)
≥IM †				
Correa et al, 2000 (1)	3/340	2/318	3.25	1.40 (0.24, 8.34)
Wong et al, 2004 (7)	7/247	5/239	7.99	1.35 (0.44, 4.21)
You et al, 2006 (4)	17/664	23/667	36.10	0.74 (0.40, 1.38)
Wong et al, 2012 (9)	4/398	3/399	4.71	1.34 (0.30, 5.93)
Choi et al, 2013 (10)	10/389	16/403	24.72	0.65 (0.30, 1.41)
Cho et al, 2013 (19)	3/77	1/70	1.65	2.73 (0.29, 25.62)
Subtotal	44/2115	50/2096	78.43	0.88 (0.59, 1.31)
(I-squared = 0.0%, p = 0.702 for Q statistic)				



Normal,gastritis atrófica,gastritis no atrófica

<IM †				
Correa et al, 2000 (1)	0/97‡	0/97	0.79	1.00 (0.02, 49.89)
Wong et al, 2004 (7)	0/557	6/560	10.20	0.08 (0.00, 1.37)
You et al, 2006 (4)	1/455	4/456	6.29	0.25 (0.03, 2.23)
Wong et al, 2012 (9)	0/112	0/115	0.78	1.03 (0.02, 51.29)
Choi et al, 2013 (10)	0/47	1/35	2.70	0.25 (0.01, 5.96)
Cho et al, 2013 (19)	0/69	0/62	0.83	0.90 (0.02, 44.69)
Subtotal	1/1337	11/1325	21.57	0.25 (0.08, 0.81)
(I-squared = 0.0%, p = 0.843 for Q statistic)				



Preneoplastic Conditions in the Stomach: Always a Point of No Return?

Marino Venerito Peter Malfertheiner

Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University, Magdeburg, Germany

- ✓ Parece que la erradicación no elimina todas las lesiones precancerosas, depende del grado y la extensión de las lesiones precancerosas.
- ✓ Debemos identificar cuál es el punto de no retorno.
- ✓ **Impresiona que es la metaplasia intestinal.**

Venerito et al.Dig Dis, 2015

Metanálisis que combine profilaxis Primaria y Prevención Terciaria

CLINICAL—ALIMENTARY TRACT

Association Between *Helicobacter pylori* Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis

Yi-Chia Lee,[1,2,*] **Tsung-Hsien Chiang,**[1,3,4,*] Chu-Kuang Chou,[1,5] Yu-Kang Tu,[2] Wei-Chih Liao,[1,2] Ming-Shiang Wu,[1,6] and David Y. Graham[7]

[1]Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [2]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [3]Department of Integrated Diagnostics and Therapeutics, National Taiwan University Hospital, Taipei, Taiwan; [4]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [5]Division of Gastroenterology and Hepatology, Chia-Yi Christian Hospital, Chia-Yi, Taiwan; [6]Department of Primary Care Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; and [7]Department of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine Houston, Texas

Ensayos randomizados o de cohortes que evaluaban la erradicación e incidencia de Cáncer gástrico o bien la aparición de un tumor metacrónico tras la resección de un cáncer gástrico.

Análisis

- ✓ Cohortes o randomizados.
- ✓ Según área: baja, intermedia y alta.
- ✓ Según profilaxis primaria o terciaria.

Ponderaron la diferencia de seguimiento en ellos.

Lee et al, Gastroenterology 2016.

First author, Year	Country	Mean age, *y*	Male, %	Mean follow-up, *mo*	Treatment group Total, n	Treatment group GC, n	Treatment group GC incidence, /100,000 PY	Comparison group Total, n	Comparison group GC, n	Comparison group GC incidence (baseline incidence), /100,000 PY
Studies on asymptomatic infected individuals (primary prevention)										
RCT										
Correa, 2000[25]	Colombia	51.1	46.0	72	491	3	101.8	485	2	68.7
Wong, 2004[11]	China	42.2	54.0	90	817	7	114.2	813	11	180.4
Saito, 2005[26]	Japan	NA	NA	48	379	2	131.9	313	3	239.6
You, 2006[27]	China	50.7	51.4	176	1130	34	205.1	1128	52	314.3
Zhou, 2008[28]	China	53.4	47.8	120	276	2	72.5	276	7	253.6
Wong, 2012[29]	China	52.9	46.1	60	255	3	235.3	258	1	77.5
Cohort study										
Saito, 2000[30]	Japan	79.2	54.7	24	32	0	0	32	4	6250.0
Take, 2007[31]	Japan	50	88.7	47	953	9	241.1	178	4	573.8
Takenaka, 2007[32]	Japan	53.6	71.3	38	1519	6	124.7	288	5	548.2
Ogura, 2008[33]	Japan	62.9	56.5	38	404	6	469.0	304	13	1350.4
Mabe, 2009[34]	Japan	52.9	71.7	67	3781	47	222.6	352	9	457.9
Yanaoka, 2009[35]	Japan	49.8	99.9	112	473	5	117.3	3656	55	156.7
Kosunen, 2011[36]	Finland	55.3	50.0	121	3650	11	29.0	11638	37	34.3
Lee, 2013[37]	Taiwan	49.2	45.8	60	4121	15	72.8	4121	16	77.7
Studies on individuals after endoscopic resection of early GC (tertiary prevention)										
RCT										
Fukase, 2008[13]	Japan	68	76.5	36	272	9	1102.9	272	24	2941.2
Choi, 2014[38]	Korea	60	67.7	36	444	10	750.8	457	17	1240.0
Cohort study										
Uemura, 1997[39]	Japan	69	72	36	65	0	0	67	6	2985.1
Nakagawa, 2006[40]	Japan	NA	NA	24	356	8	1123.6	2469	129	2612.4
Shiotani, 2008[41]	Japan	66	84	33	80	9	4090.9	11	1	3305.8
Maehata, 2012[42]	Japan	69	72.3	36	177	15	2824.9	91	13	4761.9
Seo, 2013[43]	Korea	62	67.6	27	61	6	4371.6	13	3	10,256.4
Kwon, 2014[44]	Korea	61	67.1	40	214	10	1401.9	69	10	4347.8
Bae, 2014[45]	Korea	63	78.5	56	485	34	1470.0	182	24	2970.0
Kim, 2014[46]	Korea	64	74.3	58	49	2	844.5	107	16	3093.8

GC, gastric cancer; NA, not available; PY, person year.

Resultados

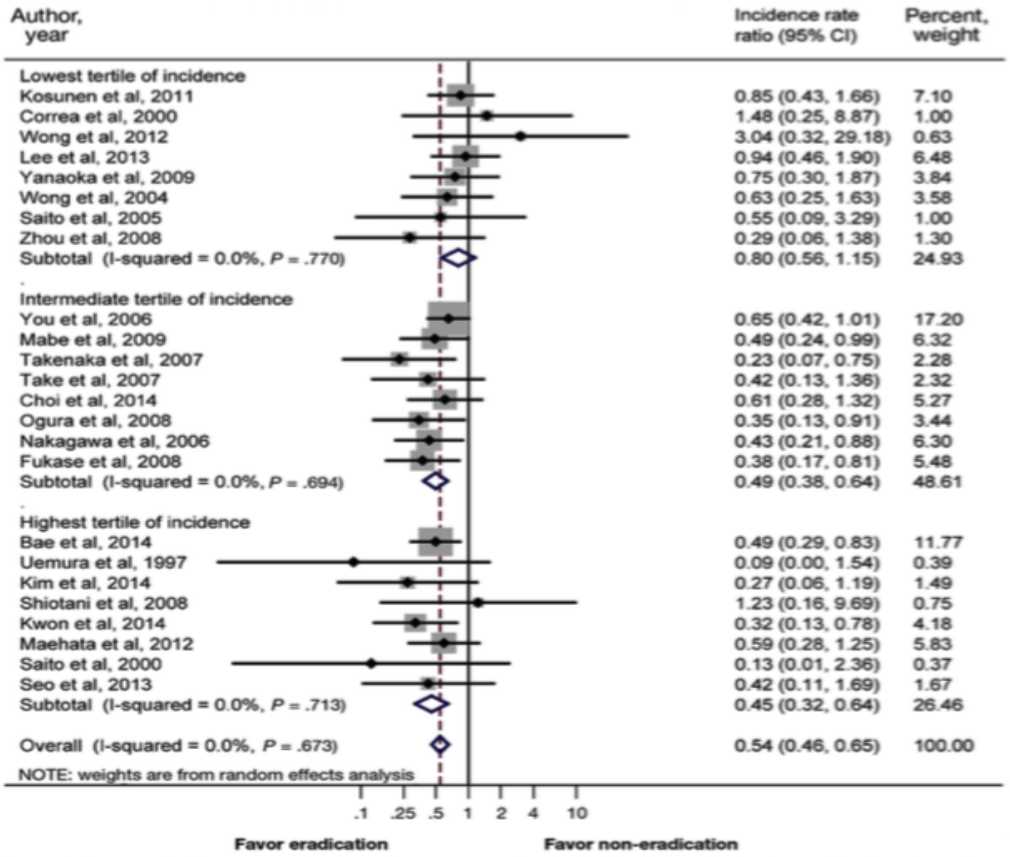
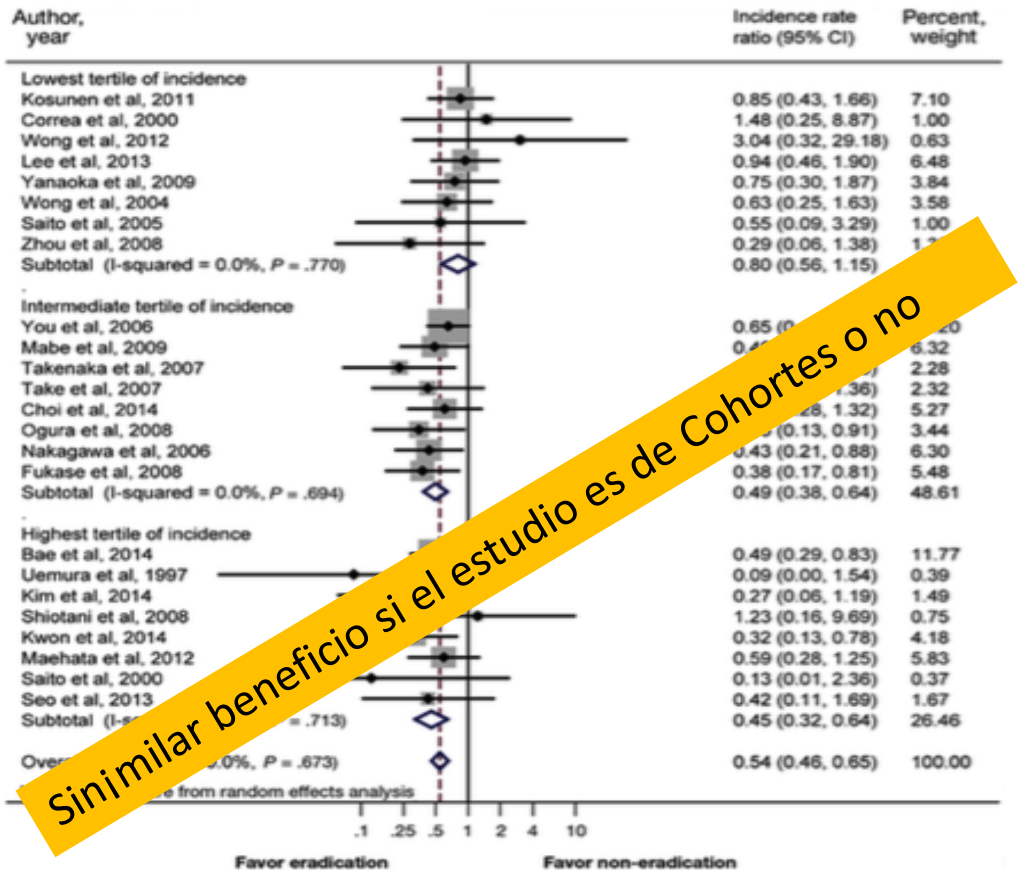


Figure 2. Summary incidence rate ratio of gastric cancer associated with *H pylori* eradication by traditional random-effects meta-analysis, stratified by baseline incidence of gastric cancer.

HR:0,54 (IC 95%_0,46-0,65)

Heterogeneidad I=0%,p:0,067

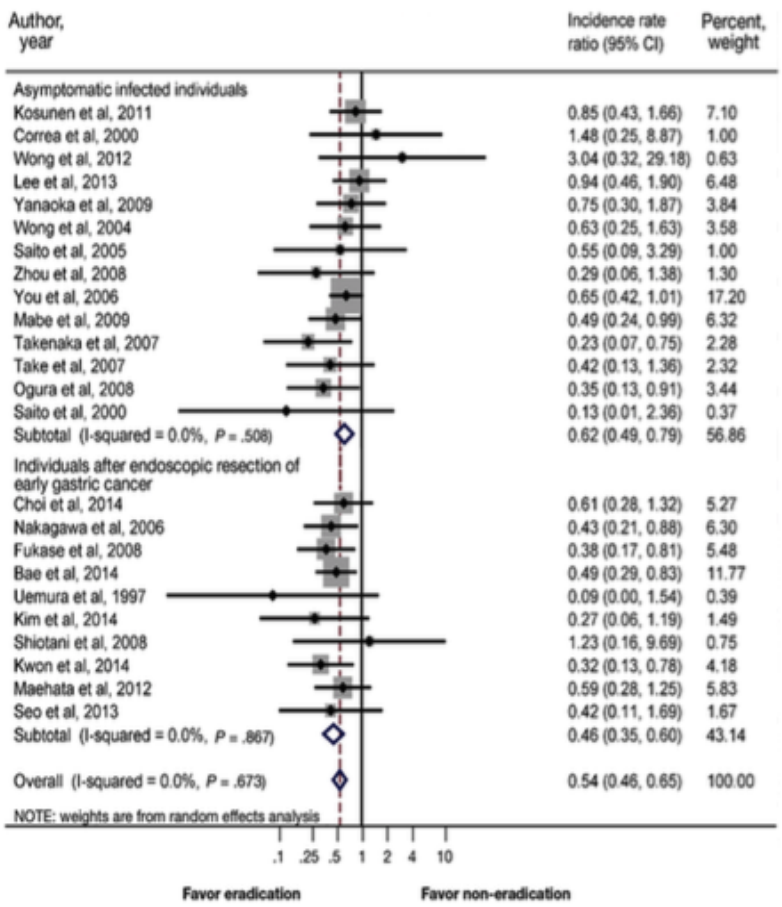
Alta vs Baja Incidencia



Sinimilar beneficio si el estudio es de Cohortes o no

Figure 2. Summary incidence rate ratio of gastric cancer associated with *H pylori* eradication by traditional random-effects meta-analysis, stratified by baseline incidence of gastric cancer.

Asintomáticos /C.gástrico EDA



La erradicación reduce el riesgo y la aparición de un tumor de gástrico metacrónico

…en áreas de alta incidencia

5 Cuestiones objeto de debate

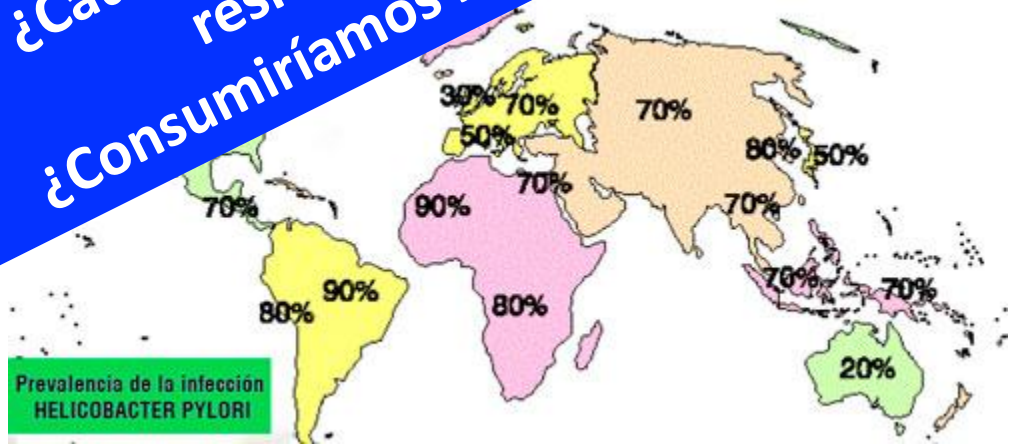
¿Debemos erradicar H.pylori a toda la población? ¿Es una medida coste efectiva?

Afecta a la mitad de la población mundial

- 80% países en vías de desarrollo.
- 20-50% de países desarrollados.

Suerbaum S(1) ngl J Med. 2002 Oct 10;347(15):1175-86.

¿Causaríamos bacterias resitentes?
¿Consumiríamos recursos?



Screening for Gastric Cancer and Surveillance of Premalignant Lesions: a Systematic Review of Cost-Effectiveness Studies

Miguel Areia,*,† Rita Carvalho,† Ana Teresa Cadime,† Francisco Rocha Gonçalves*,‡ and Mário Dinis-Ribeiro*,‡

*CINTESIS – Center for Research in Health Technologies and Information Systems, Faculty of Medicine, Porto University, Porto, Portugal, †Gastroenterology Department, Portuguese Oncology Institute – Coimbra, Coimbra, Portugal, ‡Portuguese Oncology Institute – Porto, Porto, Portugal

Obtener el estado del arte en coste-efectividad en el screening del cáncer gástrico y el seguimiento de lesiones premalignas.

Evaluaron 23 artículos: 19 de screening y 4 de seguimiento.

- ✓ La serología para detectar *H.pylori* es coste efectiva y la erradicación es coste/efectiva.
- ✓ La EDA como screening es coste efectiva.
- ✓ La EDA como seguimiento tiene resultados discordantes.

Areia et al, Helicobacter 2013.

¿Resistencias antibióticas?

Problemas

- Matar cepas sensibles hace que crezcan cepas resistentes de *H.pylori.*
- Crear resistencias en otra flora del tracto gastrointestinal.

Se investigó el patrón de resistencias de H.pylori desde 2012 a 2014:

✓ Resistencia a claritromicina 7,6%
✓ Resistencia a metronidazol 22,7%
✓ Resistencia a amoxicilina [illegible]
✓ Resistencia a [illegible] 3,9%

***Cat[illegible] como bajo en comparación con registros hospitalarios.

Necesitamos mayor número de estudios

Lee et al,J gastroenterol Hepatol 2017.

Dos estudios indican la aparición de enterococos resistentes y de resistencia a macrólidos en microbiota normal tras tratar *H.pylori.*

Sjölund et al, Am Intern Med 2003.
Jakobsson et al. Scand Infect Dis 2007.

¿Cuál es la duración de tratamiento óptima en población asintomática? ¿Qué hay de la enfermedad extragastrointestinal?

La mayoría de estudios son en población con síntomas que acuden a servicios digestivo /primaria.

La población asintomática tolerará peor los antibióticos y tendrá menor adherencia terapéutica.

En población de Taiwan se erradicó menos *H.pylori e*n asintomáticos (población general) que en registros hospitalarios….traduce menor adherencia.

Liou et al. Gut 2015

Infección por *H.pylori* se asocia a atopia, enfermedades cardiovasculares y ERGE.

En Taiwan tras la erradicación aumentaron el número de esofagitis (se restaura la producción de ácido tras revertir la gastritis atrófica)

¿Podríamos incrementar los cánceres de esófago?

Lee et al, Gut 2013.

6

¿A quién erradicar/tratar?

ELSEVIER DOYMA

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ARTÍCULO ESPECIAL

III Conferencia Española de Consenso sobre la infección por *Helicobacter pylori*

III Spanish Consensus Conference on *Helicobacter pylori* infection

Javier P. Gisbert[a,*,1], Xavier Calvet[b,1], Fernando Bermejo[c], Daniel Boixeda[d], Felipe Bory[e], Luis Bujanda[f], Manuel Castro-Fernández[g], Enrique Dominguez-Muñoz[h], Juan Ignasi Elizalde[i], Montserrat Forné[j], Emili Gené[k], Fernando Gomollón[l], Ángel Lanas[m], Carlos Martín de Argila[d], Adrián G. McNicholl[a], Fermín Mearin[m], Javier Molina-Infante[n], Miguel Montoro[o], José María Pajares[a], Angeles Pérez-Aisa[p], Emilio Pérez-Trallero[q] y Jordi Sánchez-Delgado[b]

Recomendación A6: En pacientes con resección quirúrgica o endoscópica de un cáncer gástrico se recomienda investigar y tratar la infección por *H. pylori* como prevención de la recidiva neoplásica

Recomendación A7: En los familiares de primer grado de los pacientes con cáncer gástrico se recomienda investigar y tratar la infección por *H. pylori*

Recomendación A8: En pacientes con atrofia mucosa gástrica o metaplasia intestinal asociada a infección por *H. pylori* se recomienda tratamiento erradicador

Gisbert et al, Gastroenterología y Hepatología 2013

¿En qué basan su evidencia?

Tratar afectos de Cáncer gástrico para prevenir un tumor metacrónico
Artículo Fukase et al, Lancet 2008 (RR:0,35)
Evidencia epidemiológica que relaciona H.pylori y cáncer
La erradicación previene a nivel poblacional la incidencia de C.gástrico
Los afectos de C.gástrico presentan cepas más resistentes de H.pylori (Cag A y vac A)

Tratar familiares de primer grado de afectos de cáncer gástrico
No hay estudios
La basan en datos fisiopatológicos y en datos epidemiológicos (tienen 2-3 veces más riesgo que los controles y más alteraciones histopatológicas consideradas preneoplásicas) y en la opinión de expertos .

Tratar pacientes con atrofica gástrica o metaplasia intestinal.
Son lesiones preneoplásicas con aumento significativo de C.gástrico.
A pesar de que la metaplasia se considera un punto de no retorno el hecho de que tratar C.gástricos reduzcan la aparición de tumores metacrónico hace que recomienden el tratarla (se asume al tratarlo que se reducen los fenómenos inflamatorios y la proliferación celular secundaria a H.pylori)

Gisbert et al, Gastroenterología y Hepatología 2013

Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report

Peter Malfertheiner,[1] Francis Megraud,[2] Colm A O'Morain,[3] John Atherton,[4] Anthony T R Axon,[5] Franco Bazzoli,[6] Gian Franco Gensini,[8] Javier P Gisbert,[9] David Y Graham,[10] Theodore Rokkas,[11] Emad M El-Omar,[7] Ernst J Kuipers,[12] The European Helicobacter Study Group (EHSG)

Statement 16: H pylori eradication to prevent gastric cancer should be considered in the following:

first-degree relatives of family members with a diagnosis of gastric cancer;

patients with previous gastric neoplasia already treated by endoscopic or subtotal gastric resection;

patients with a risk of gastritis: severe pan-gastritis, corpus-predominant gastritis, severe atrophy;

patients with chronic gastric acid inhibition for more than 1 year;

patients with strong environmental risk factors for gastric cancer (heavy smoking, high exposure to dust, coal, quartz, cement and/or work in quarries);

H pylori-positive patients with a fear of gastric cancer.

Evidence level: 1a to 4 **Grade of recommendation: A**

H pylori eradication to prevent gastric cancer should be undertaken in patients at high risk. A first-degree relative of a family member with a diagnosis of gastric cancer is at high risk.[294] First- degree relatives have a two to three times increased risk of developing gastric cancer.[295–300] If more than one first-degree relative has contracted gastric cancer the risk for others is increased by a factor of 10. Patients with the CDH-1 mutation should be offered genetic consultation and prophylactic gastrectomy.[301–307]

Malfertheiner et al,Gut 2013

Gut 2017;**66**:6–30 doi:10.1136/gutjnl-2016-312288

Guidelines

Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report

Editor's choice

Statement 1: *H. pylori* infection is accepted as the major aetiological factor for gastric cancer.

Level of evidence: 1a **Grade of recommendation: A**

Statement 4: The influence of environmental factors is subordinate to the effect of *H. pylori* infection.

Level of evidence: 2a **Grade of recommendation: A**

Statement 5: *H. pylori* eradication abolishes the inflammatory response and early treatment prevents progression to preneoplastic lesions.

Level of evidence: 1b **Grade of recommendation: B**

Statement 7: The risk of developing gastric cancer can be reduced more effectively by employing eradication treatment before the development of atrophy and intestinal metaplasia.

Level of evidence: 2b **Grade of recommendation: B**

Statement 8: *H. pylori* eradication for gastric cancer prevention is cost-effective in communities with a high risk for gastric cancer.

Level of evidence: moderate **Grade of recommendation: strong**

Statement 10: *H. pylori* 'screen-and-treat' strategies are recommended in communities at high risk of gastric cancer.

Level of evidence: moderate **Grade of recommendation: strong**

So far such strategies have been conducted in few countries (Taiwan, China).[301 321] Screen-and-treat strategies are recommended in high-risk populations and are considered to be cost-effective as to the expected level of adverse events and compliance;[331] a large population-based Chinese screen-and-treat trial undertaken in a rural area at high risk of gastric cancer reported excellent compliance, minor adverse effects and low cost, altogether indicating good feasibility. Long-term follow-up in gastric cancer prevention trials will provide a final answer.[310]

Statement 11: A screen-and-treat strategy of *H. pylori* gastritis should be considered in communities with intermediate to low risk for gastric cancer

Level of evidence: low **Grade of recommendation: weak**

Statement 12: Screen-and-treat for *H. pylori* is recommended in individuals at increased risk for gastric cancer.

Level of evidence: moderate **Grade of recommendation: strong**

Individuals with the 'gastric cancer phenotype' are at increased risk of cancer. This is characterised by corpus predominant gastritis, gastric atrophy/intestinal metaplasia, hypochlorhydria, and evidence of current or past *H. pylori* infection. Screening on a population-wide basis by invasive approaches is not feasible but the gastric cancer phenotype can be detected by a combination of non-invasive markers including *H. pylori* serology and pepsinogen levels (Pgl or Pgl/II ratio).[333 334] Genomic approaches are also promising but require validation in prospective studies.[335] Some indigenous sub-populations and immigrants from high incidence countries may also be at increased risk and could be targeted for screening and prevention.[336 337] Those with a positive family history have a modestly increased risk and in the presence of *H. pylori* infection have an increased prevalence of preneoplastic abnormalities including atrophy and hypochlorhydria.[338 339] They should also be screened and treated.

SPECIAL ARTICLE

Asia–Pacific consensus guidelines on gastric cancer prevention

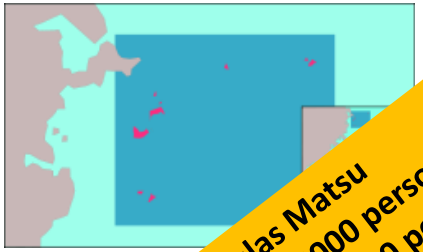
Kwong Ming Fock,* Nick Talley,† Paul Moayyedi,‡ Richard Hunt,‡ Takeshi Azuma,§ Kentaro Sugano,¶ Shu Dong Xiao,** Shiu Kum Lam,†† Khean Lee Goh,‡‡ Tsutomu Chiba,§§ Naomi Uemura,¶¶ Jae G Kim,*** Nayoung Kim,††† Tiing Leong Ang,* Varocha Mahachai,‡‡‡ Hazel Mitchell,§§§ Abdul Aziz Rani,¶¶¶ Jyh Ming Liou,**** Ratha-korn Vilaichone†††† and Jose Sollano‡‡‡‡

Statement 28: In high gastric cancer-risk populations in the Asia–Pacific region, population screening and treatment of *H. pylori* infection is the strategy of choice

Level of agreement: a, 10%; b, 90%; c, 0%; d, 0%.
Level of evidence: I.
Grade of recommendation: A.

To date, all randomized controlled trials on *H. pylori* eradication to prevent precancerous gastric lesions and gastric cancer have been conducted in high-risk populations. In the long term, if *H. pylori* infection were to be eradicated, it may even mean that endoscopic surveillance for gastric cancer may no longer be necessary, if this eradication occurred before the development of advanced precancerous gastric lesions. For developing countries in the Asia–Pacific region, affordability would be a major concern and, on a national level, individual strategies need to be developed.

Fock et al.Journal of Gastroenterology and Hepatology, 2008



Islas Matsu
Archipiélago vivían 5000 personas en 1995.
Hoy residen 12000 personas.

¿Se ha implantado en algún país?

Año 1995-1998
Incidencia 100 casos/100.000 personas año (año 1995)
Mortalidad 52/100.000 del 1985-1989 y 61/100.000 del 1995-1999

Año 2004 implantan un programa de screening de *H.pylori*
Objetivos: Cambios en histología gástrica, incidencia de lesiones premalignas, incidencia de cáncer gástrico

Año 2008 (reevalúan)
Caen 78,7% la infección , 77,2% gastritis atrófica, úlcera péptica 67,4%.

Campañas de screening en 2004,2008,2012,2014 y 2016
La infección pasa del 63% en 2004 a 10% en 2016.
Reducción C.gástrico 25% en 2008 y 47 % en 2015 (estimaciones). Se verificará en 2018.

Lee et al, Gut 2013.
Lee et al. J Gastroenterol Hepatol. 2017.

¿Se ha implantado en algún país?

Implantaron detección en heces *H.pylori* asociado a FOBT en 2012 estudio de fesibility .

En marcha desde 2014 un randomizado a FOBT y FOBT con test de H.pylori

Estimaciones…reducción de riesgo de C.gástrico del 50%

1.300.000 habitantes
Incidencia 29/100.000
Mortalidad 15/100.000 año 2013

Lee et al.BMJ 2013.

7 ¿Qué futuro cercano nos espera?

¿Qué futuro nos espera?
Vacunación

Fase III (China). Niños 6-15 años.

N:4464 participantes randomizados a vacunación (n:2232) o placebo (2232).

Vacuna oral.

Seguimiento 3 años.

64 infecciones por H.pylori en el primer año (14 en vacunados y 54 en grupo placebo).

Eficacia del 71,8% en el grupo vacunado.

Efectos 2º en 7% de los casos.

***Es preciso un seguimiento a mayor largo plazo .

Zeng et al, Lancet 2015

¿Qué futuro nos espera?
Empleo de Biomarcadores

Se ha erradicado *H.pylori* pero en alto porcentaje de remanente tenemos gastritis atrófica/metaplasia intestinal

Niveles de Pepsinógeno I/II

- Los niveles de pepsinógeno I caen durante la gastritis atrófica
- Los de pepsinógeno II se mantiene constantes
- Se combinan estos niveles con anti IgG antihelicobacter

Kato et al.JpnJ Clin Oncol 2012

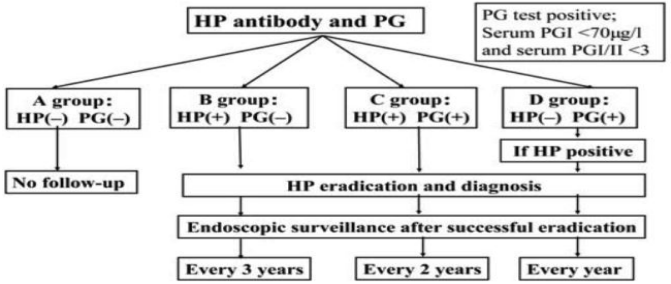


Figure 1. The strategy for elimination of gastric cancer.

Otros factores futuros: niveles bajos de grelina, gastrina-17 ,factor 3 trefoil, anticuerpos anticélulas parietales gástricas…

Cheng et al.Gasrtointest Tumors 2016.

Conclusiones

¿Es la erradicación de *H. pylori* un modo de prevenir el Cáncer gástrico?

Sí…en zonas de alta incidencia

¿Deberíamos erradicar todos los *H.pylori*?

Causaríamos bacterias resistentes

Consumiríamos recursos

Tenemos obviamente que identificar cuáles son las personas de alto riesgo claramente:

- qué factores genéticos están implicados.

- qué factores ambientales para ver quienes se benefician del tratamiento erradicador.

- De momento seguiremos las **Guías Clínicas**

Conclusiones

- ✓ ¿Qué hacer? Seguir guías clínicas e investigar quién es nuestra población de riesgo.
- ✓ ¿Cuál es nuestro futuro? Vacunación
- ✓ En España: necesitamos saber la positividad para *H.pylori* de nuestra serie

THANK
YOU
GRACIAS
ARIGATO
SHUKURIA
BÏYAN
SHUKRIA
DANKSCHEEN
TASHAKKUR ATU
YAQHANYELAY
SUKSAMA
EKHMET
GRAZIE
MEHRBANI
MAAKE
KOMAPSUMNIDA
PALDIES
BOLZÏN
MERCI
JUSPAXAR
GOZAIMASHITA
EFCHARISTO
TINGKI
SPASIBO
DENKAUJA
NENACHALHYA
MERASTAWHY
GAEJTHO
TAVTAPUCH
MEDAWAGSE
AGUYJE
FAKAAUE
LAH
SAINCO
BAIIKA
SPASSIBO
SNACHALHUYA
NUHUN
CHALTU
WABEEJA
MAITEKA
YUSPAGARATAM
HUI
ATTO
AMHA
DHANYABAAD
MERSI
UNALCHÉESH
HATUR
GUI
EKOJU
SIKOMO
MAKETAI
MINMONCHAR