On Equality in Beating Cancer

Recent progress in gastric cancer prevention and GISTAR study

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Conflict of interest

- None declared

OUTLINE

PART 1

- **Gastric cancer – a disease of high importance for global health**
- ***H. pylori* – major cause of gastric cancer**

PART 2

- **Gastric cancer prevention:**
  - Population-based *H. pylori* test- and treat programs
  - Gastric cancer screening programs

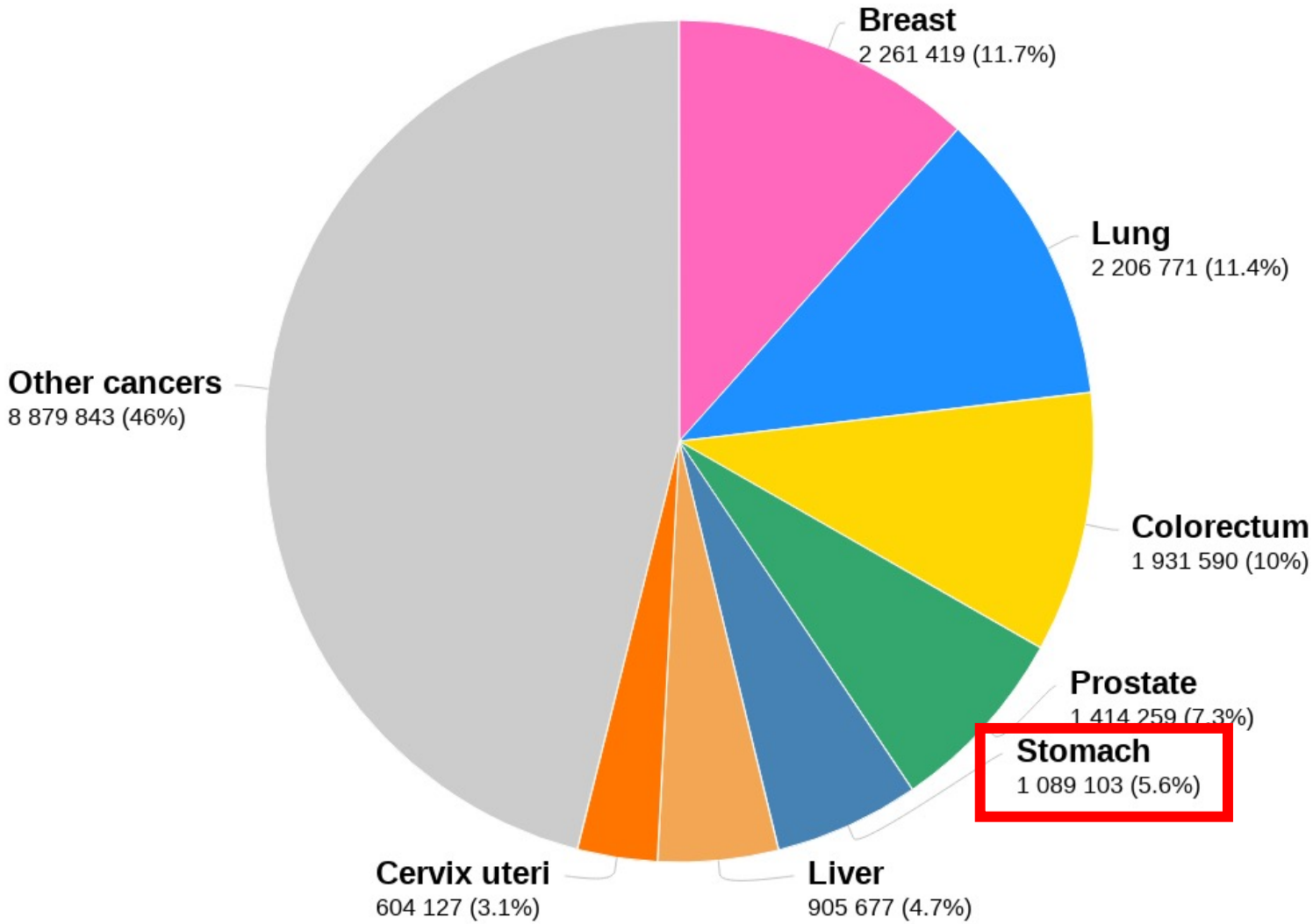
PART 3

- **GISTAR study**
  - Design
  - Progress
  - Implications

Gastric cancer remains an enormous public health problem globally

PART 1

Estimated number of new cases in 2020, worldwide, both sexes, all ages

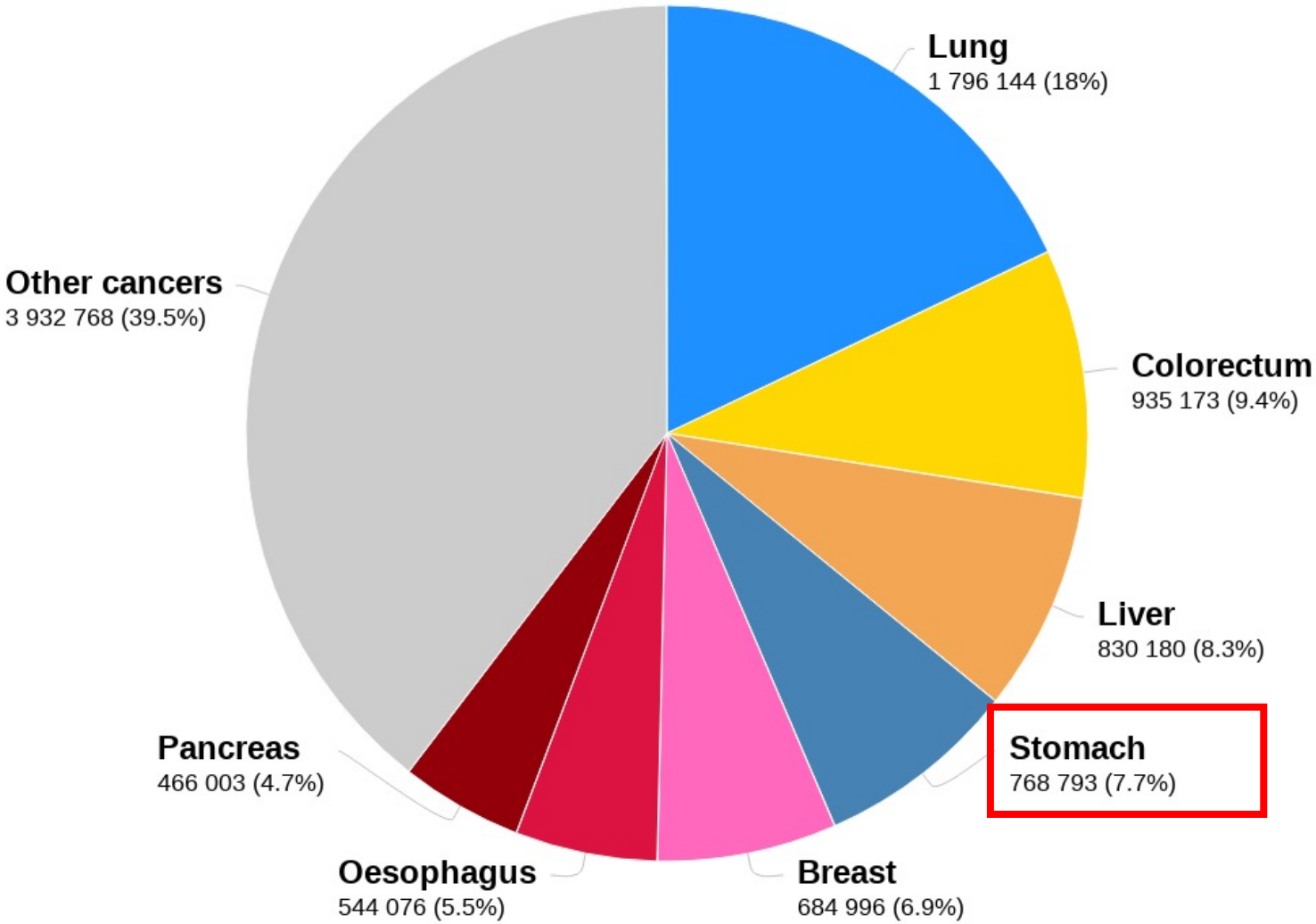


Total : 19 292 789

Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

Estimated number of deaths in 2020, worldwide, both sexes, all ages

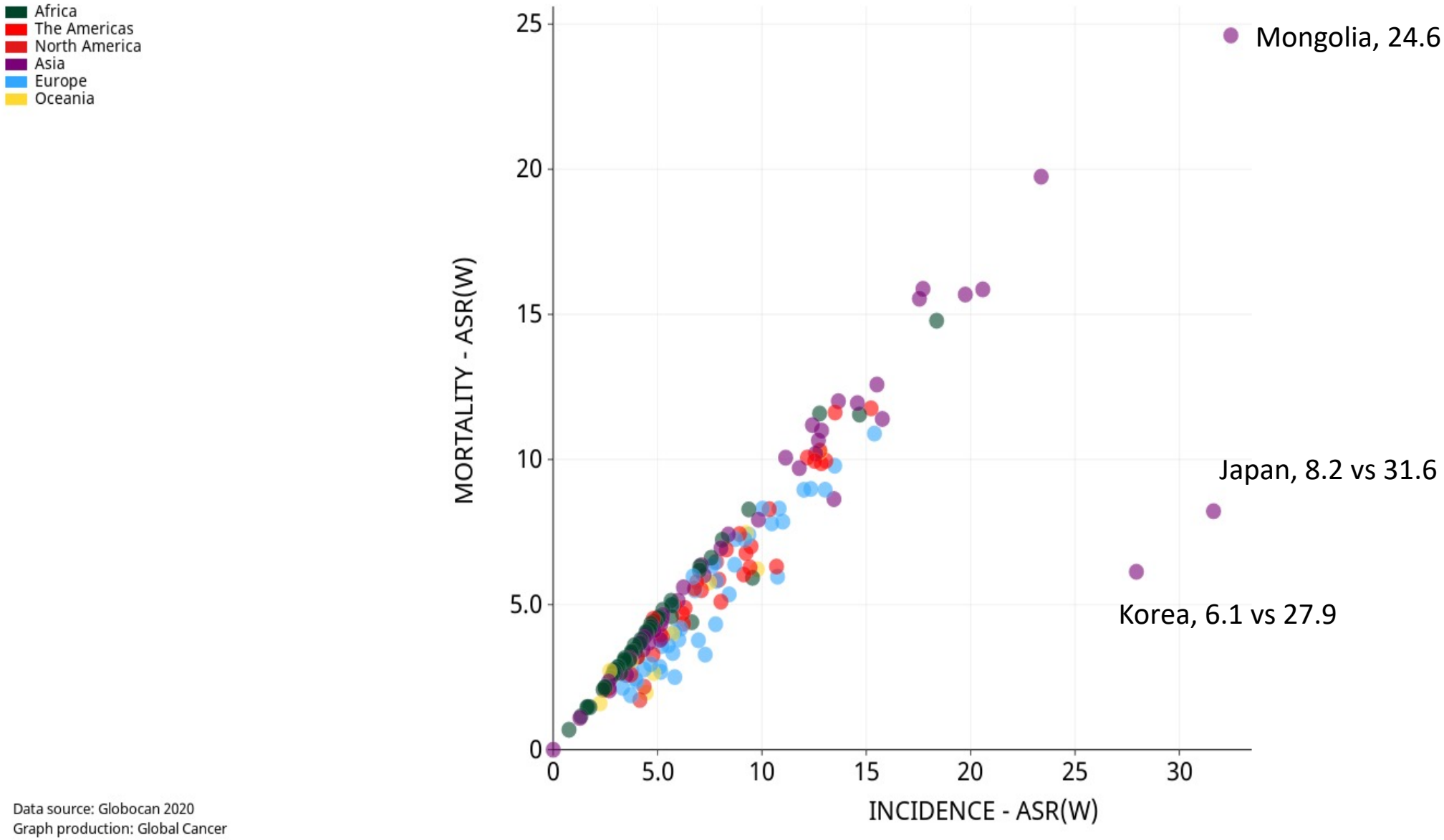


Total : 9 958 133

Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

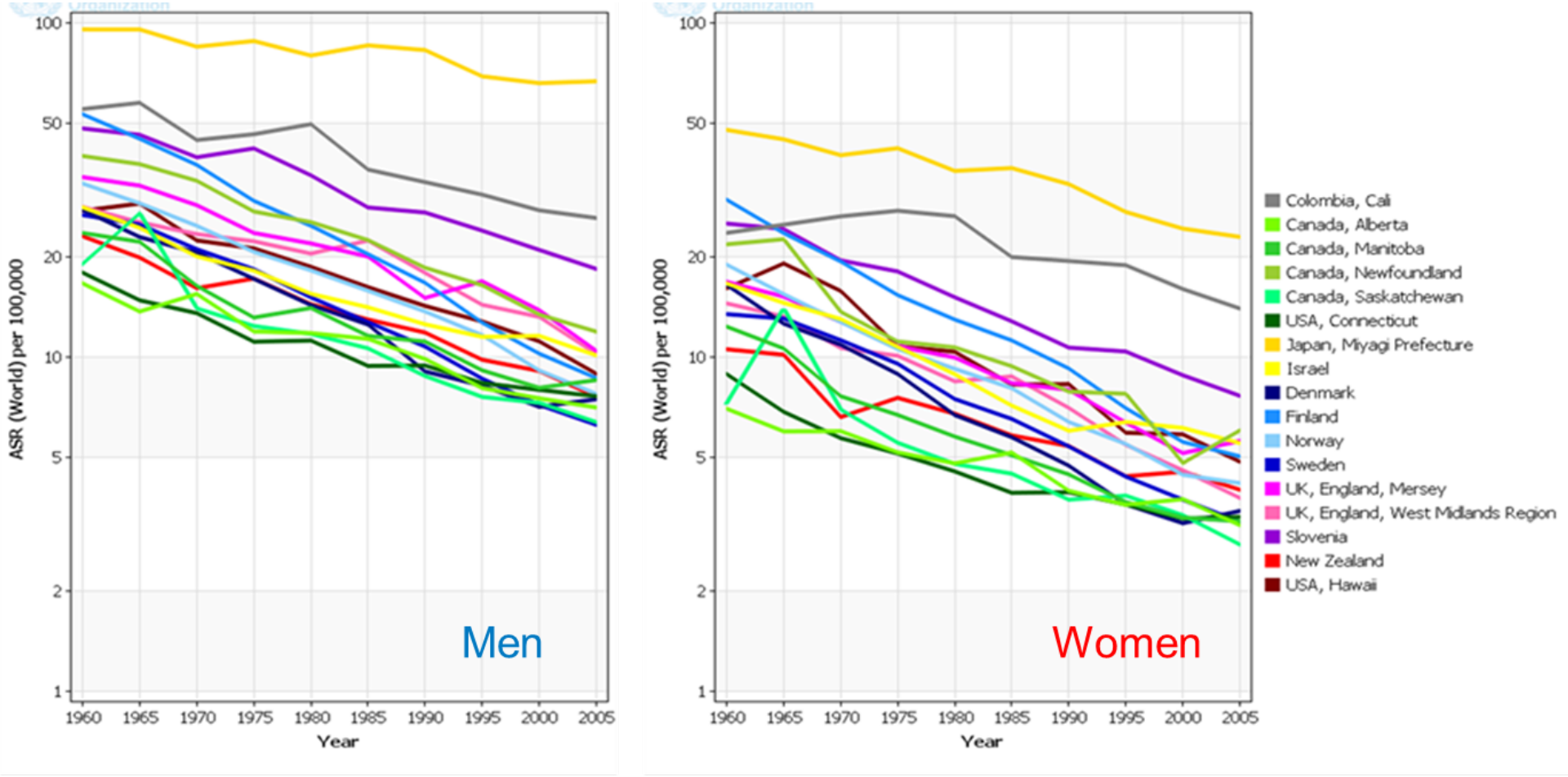
Mortality - ASR(W) vs Incidence - ASR(W), stomach, in 2020, both sexes, all ages



Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

Gastric cancer: age-standardised (world) incidence rates by year for cancer registries in CI5 I-X



Source: Cancer Incidence in Five Continents, CI5plus, 2014, International Agency for Research on Cancer

Estimated number of new cases from 2020 to 2040, Both sexes, age [0-85+]
Stomach
World

International Agency for Research on Cancer
World Health Organization

Estimated number of deaths from 2020 to 2040, Both sexes, age [0-85+]
Stomach
World

International Agency for Research on Cancer
World Health Organization

90% of non- cardia gastric cancer is attributable to *H. pylori* infection

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

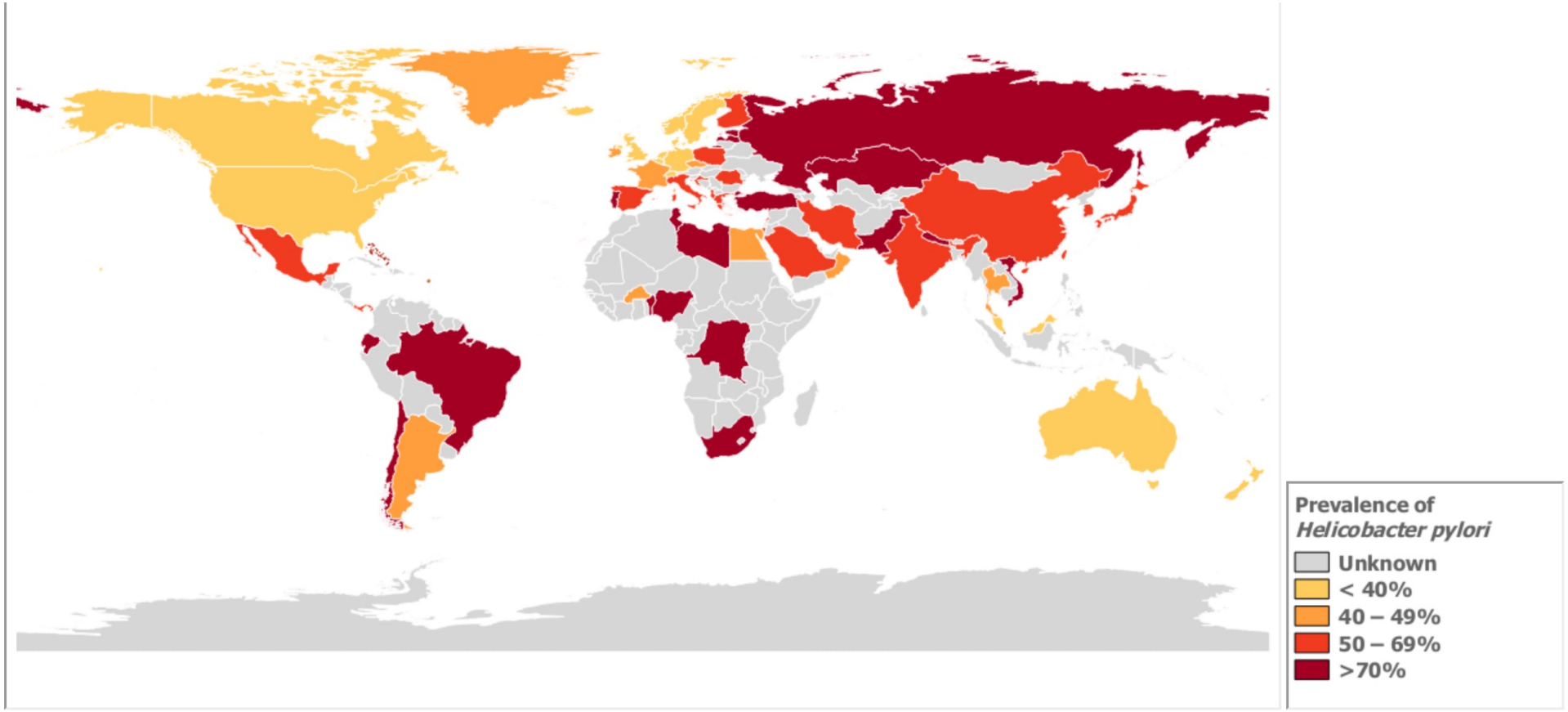
Catherine de Martel, Damien Georges, Freddie Bray, Jacques Ferlay, Gary M Clifford

	New cases	New cases attributable to infectious pathogens	New cases	New cases attributable to infectious pathogens	New cases	New cases attributable to infectious pathogens
Helicobacter pylori						
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

De Martel et al, Lancet, 2020

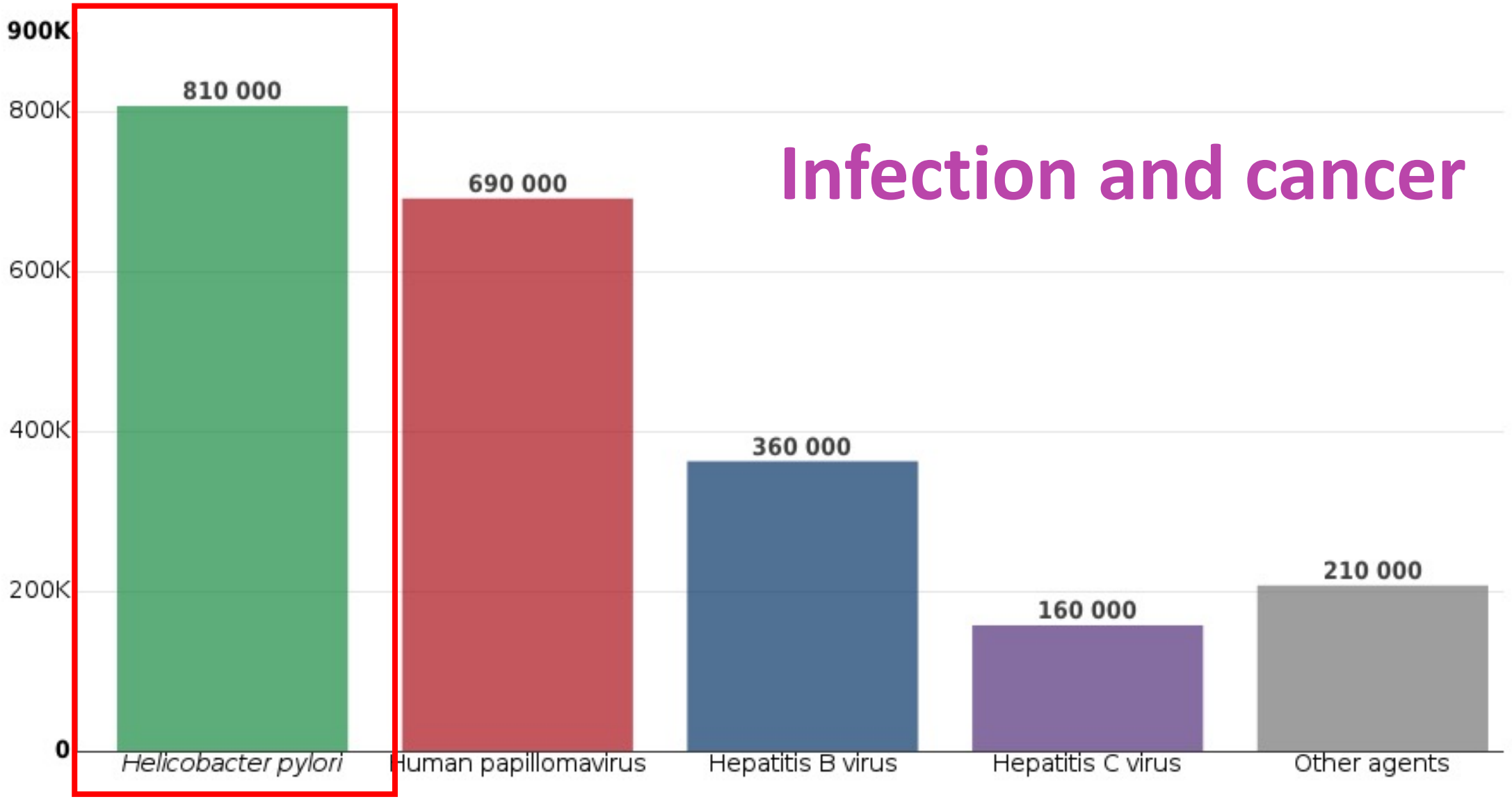
H. pylori infects >50% world population

- 4.4 billion individuals infected in 2015
- Persisting infection in LMICs



Hooi et al, Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. *Gastroenterology.* 2017

Infection and cancer



Data source: de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020)
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)

International Agency for World Health Organization

Ongoing gastric cancer prevention efforts

Population-based *H. pylori* test-and-treat programmes

PART 2-1

***H. pylori* eradication can prevent 30-40% of gastric cancer development**

IARC Working Group Meeting

ORIGINAL RESEARCH

Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis

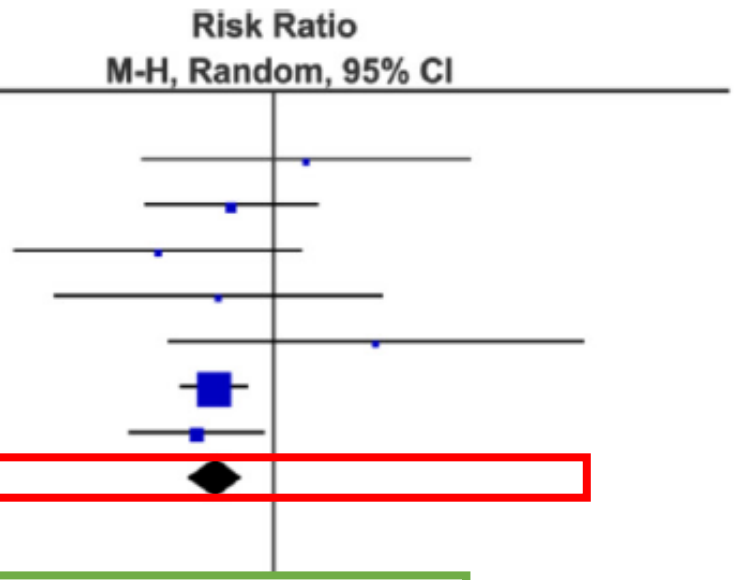
Alexander Charles Ford ,[1,2] Yuhong Yuan,[3] Paul Moayyedi[3]

Gut: first published as 10.11

Study or Subgroup	Hp eradication Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Healthy individuals							
Correa 2000-Correa 2001	3	437	2	415	2.7%	1.42 [0.24, 8.48]	2000
Wong 2004	7	817	11	813	9.7%	0.63 [0.25, 1.63]	2004
Leung 2004-Zhou 2014	2	276	7	276	3.5%	0.29 [0.06, 1.36]	2004
Saito 2005	2	379	3	313	2.7%	0.55 [0.09, 3.27]	2005
Wong 2012	3	255	1	258	1.7%	3.04 [0.32, 28.99]	2012
Ma 2012-Li 2019	41	1130	78	1128	63.6%	0.52 [0.36, 0.76]	2019
Choi 2020	10	912	23	914	16.0%	0.44 [0.21, 0.91]	2020
Subtotal (95% CI)		**4206**		**4117**	**100.0%**	**0.54 [0.40, 0.72]**	
Total events	68		125				

Heterogeneity: Tau² = 0.00; Chi² = 4.48, df = 6 (P = 0.61); I² = 0%

Test for overall effect: Z = 4.13 (P < 0.0001)



Gut. 2020 Dec;69(12):2113-2121

Areas of uncertainty

- **Generalizability of results**
- **Magnitude of the effect**
- **Age groups for the intervention**
- **Impact on cancer reduction in the presence of lesions**
- **Acceptability/Feasibility**
- **Recurrence/reinfection in different areas**
- **Potential adverse consequences**
  - Antibiotic resistance
  - GERD/Barrett/Esophageal adenocarcinoma
  - Asthma and other immune conditions
  - Weight gain
  - Alteration in microbiota

IARC Working Group Recommendations

- There is an acute need for countries with high rates
  - To focus more public health resources on gastric cancer
  - To include it within their national cancer control programs
  - To assess its human and economic impact of preventive strategies
- Countries explore the possibility of introducing *H. pylori* test and treat programs, considering disease burden, health priorities and cost-effectiveness
- The programs need to be implemented in conjunction with a scientific assessment of program processes, feasibility, effectiveness and possible adverse consequences


Best Practice & Research Clinical Gastroenterology 28 (2014) 1107–1114

Contents lists available at ScienceDirect

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ELSEVIER

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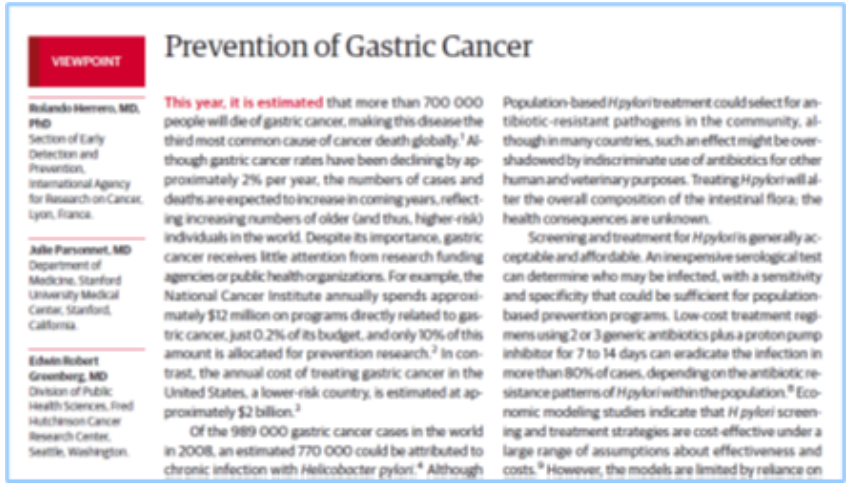
The fight against gastric cancer – the IARC Working Group report

Rolando Herrero, MD, PhD, Group Head *,
Jin Young Park, PhD, Scientist,
David Forman, PhD, Senior Visiting Scientist


VIEWPOINT

Prevention of Gastric Cancer

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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.[1] 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.[2] In contrast, the annual cost of treating gastric cancer in the United States, a lower-risk country, is estimated at approximately $2 billion.[3]

Of the 989 000 gastric cancer cases in the world in 2008, an estimated 770 000 could be attributed to chronic infection with *Helicobacter pylori*.[4] Although 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.[5] Economic modeling studies indicate that *H pylori* screening and treatment strategies are cost-effective under a large range of assumptions about effectiveness and costs.[6] However, the models are limited by reliance on

Ongoing gastric cancer prevention efforts

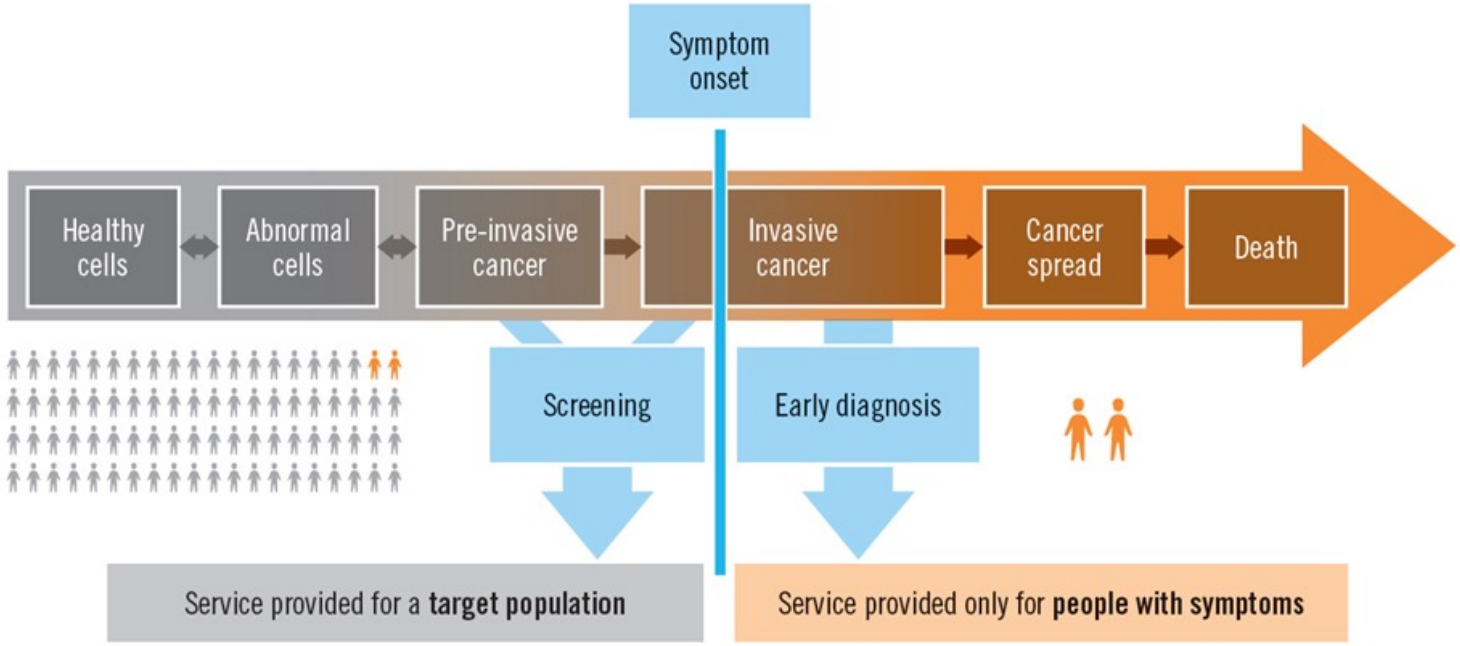
Gastric cancer screening programs

PART 2-2

Screening as part of early detection efforts

- **Early diagnosis**: early identification of cancer in patients who have symptoms of the disease

- **Screening**: seeks to identify unrecognized cancer or pre-cancerous lesions in an apparently healthy target population



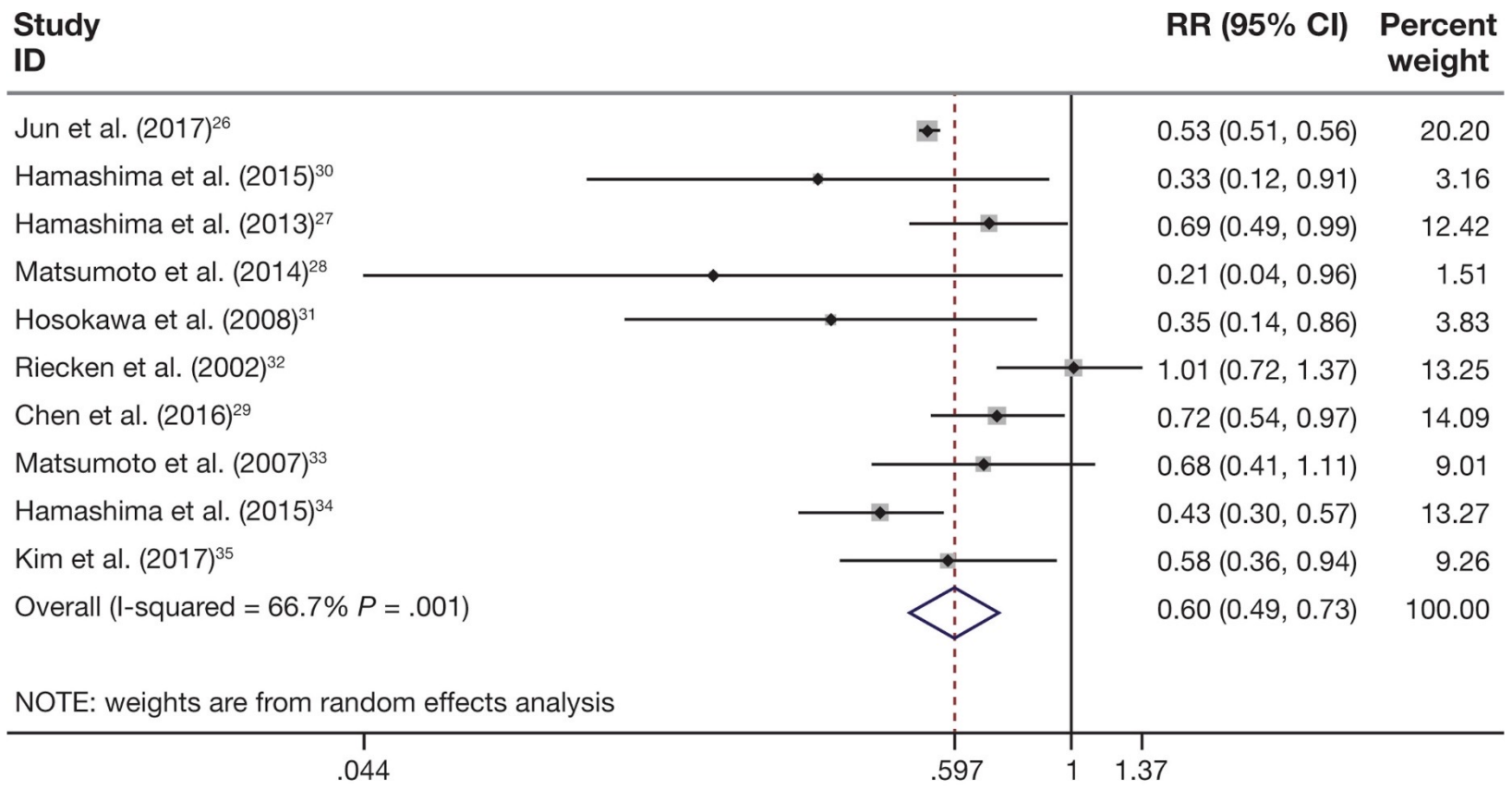
https://www.who.int/cancer/prevention/diagnosis-screening/screening/en/

Population-based screening of gastric cancer

- **Upper gastrointestinal series**
  - A procedure that uses x-rays to take a series of pictures of the esophagus, stomach, and duodenum
- **Esophagogastroduodenoscopy**
  - A procedure that includes visualization of the oropharynx, oesophagus, stomach, and proximal duodenum

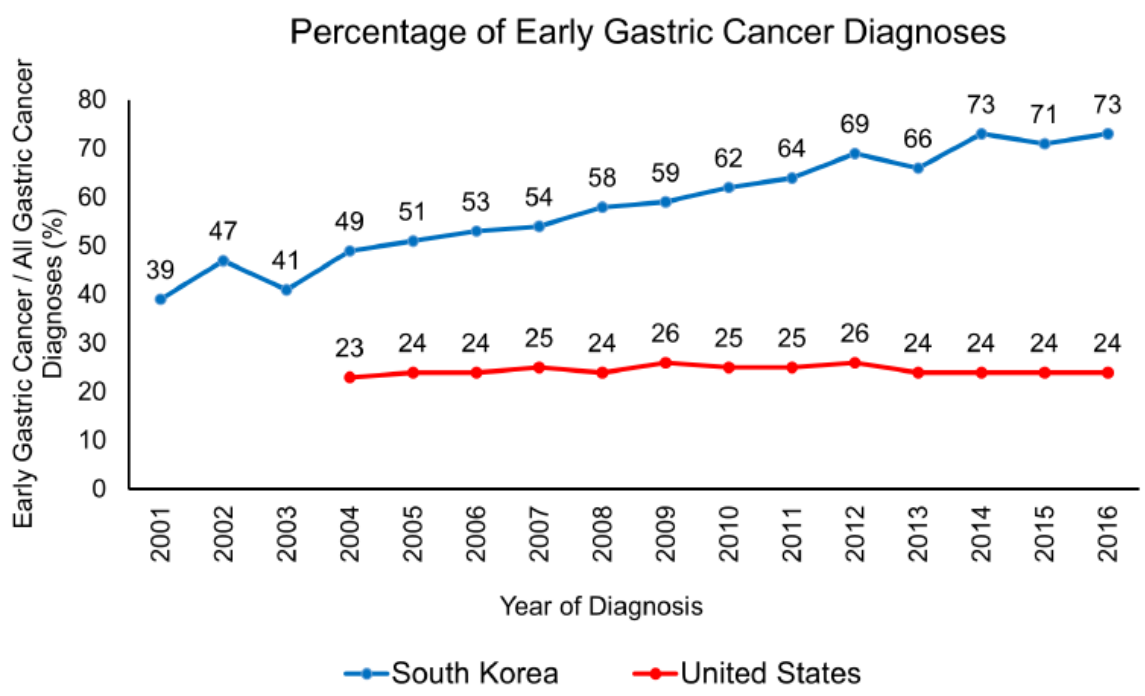
- **Current use**
  - In Japan, UGI with barium meal (photofluorography) was used in early 1960 and subsequently implemented in the nationwide cancer screening program in 1983
  - In 2016, the Japanese government approved biennial endoscopic screening for gastric cancer
  - In Korea, the National Gastric Cancer Screening Program was launched in 1999 with UGI and upper endoscopy being the two modalities
  - In 2015, the Korean Gastric Cancer Screening Guidelines Revision Committee recommended UGI not be the first choice of modality and biennial screening of asymptomatic participants aged 40-74 years old with upper endoscopy

Gastric cancer morality after endoscopic screening in Asia



Zhang et al (2018), *Gastroenterology* 155(2):347-354.e9

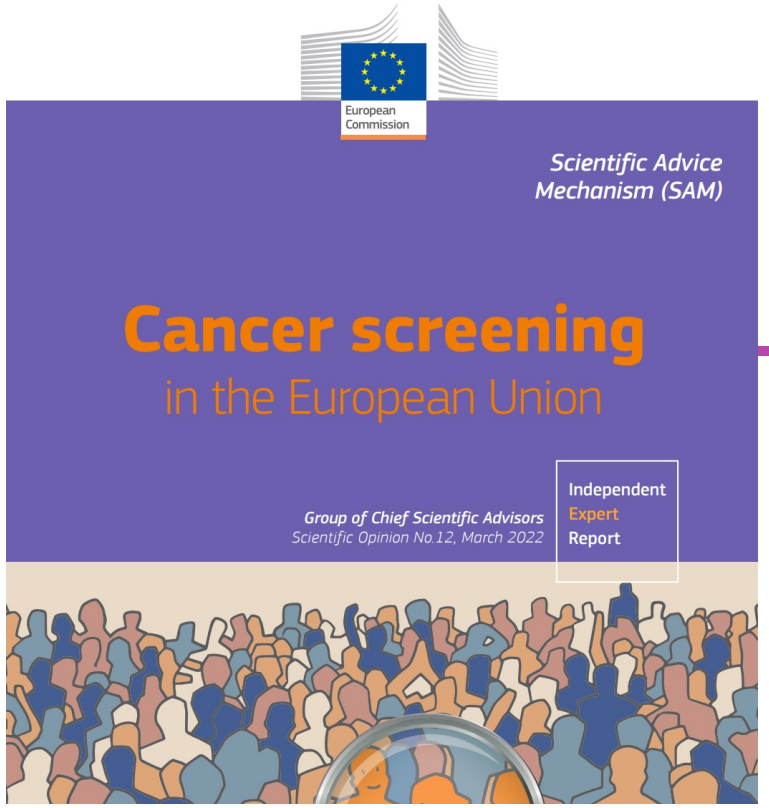
Table 1: Comparison of Gastric Cancer Stage of Diagnosis and Survival						
Country	**South Korea**		**Japan**		**United States**	
Years	2006-2010		2006-2008		2010-2014	
Screening	Biennial Radiography or Endoscopy		Biennial Radiography or Endoscopy		No screening program	
Stage at diagnosis	Distribution (%)	5-year Survival (%)	Distribution (%)	5-year Survival (%)	Distribution (%)	5-year Survival (%)
Localized	**51**	92.4	**48**	95.9	**28**	70.3
Regional	26	55.7	22	50.0	26	32.0
Distant	12	5.5	16	5.7	37	5.8
Unknown	11	49.2	14	-	9	21.8
All Stages	100	**67.0**	100	**64.6**	100	**32.1**



Huang et al (2020), *Gastroenterology.* S0016-5085(20)34993-3

GISTAR study- a European model for gastric cancer prevention

PART 3



Scientific Opinion on cancer screening in the European Union

There is insufficient evidence on the benefits of introducing screening for gastric cancer. However, the introduction of well-designed screen and treat strategies for reducing H. pylori infection could be considered for countries with high rates of the disease.

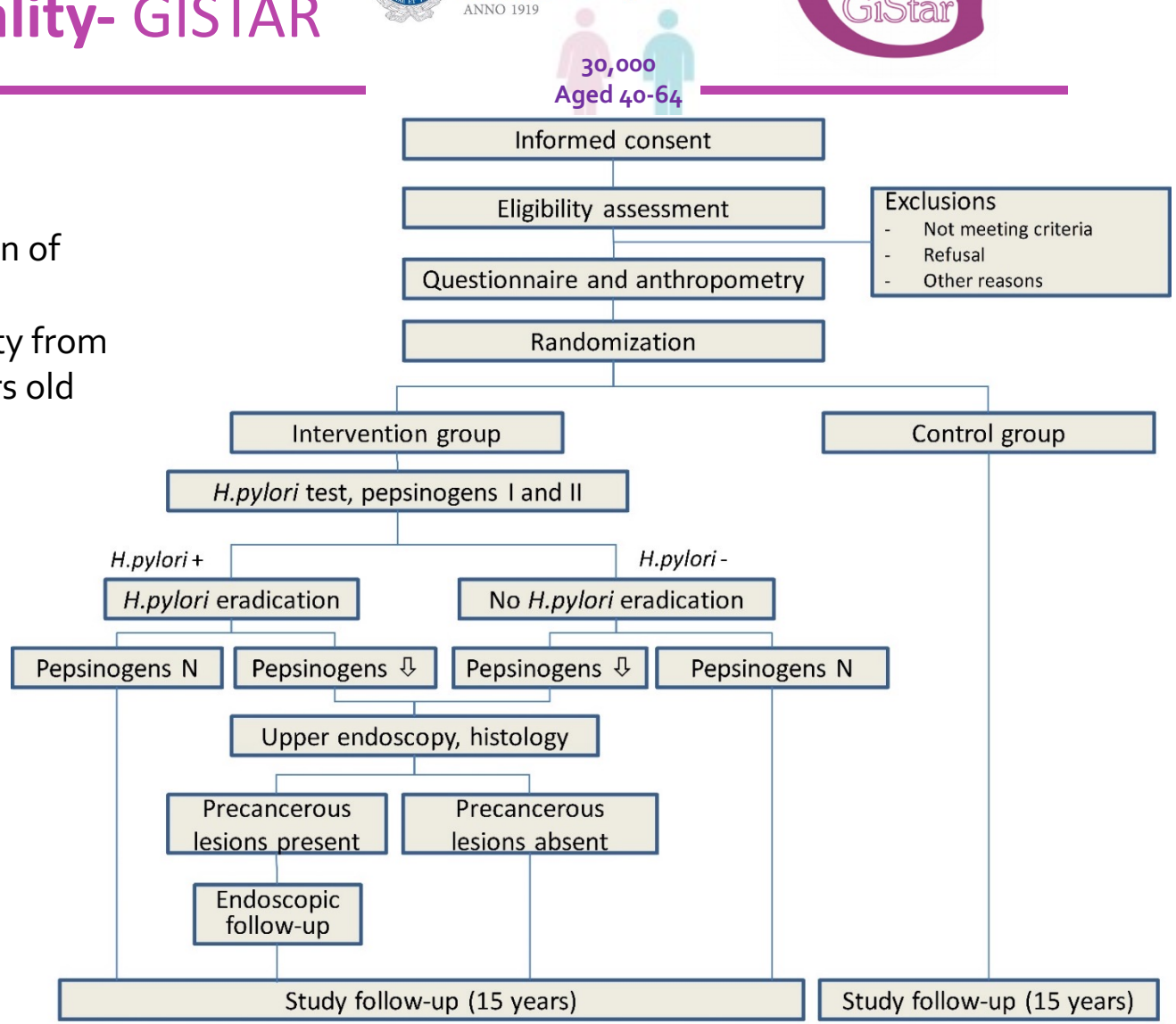
2.3 For gastric cancer, population-based screen and treat programmes for *Helicobacter pylori* are only recommended in regions with intermediate to high gastric cancer incidence, there is only a strong rationale for H. pylori test-and-treat strategies in countries with high rates of gastric cancer.

Gastric cancers are strongly linked with infection with *Helicobacter pylori*. Estimates, suggest that around 35-40% of gastric cancer deaths could be prevented through the identification and treatment of *H. pylori* infection. The incidence of gastric cancers in EU members differs significantly (three to four-fold differences), and the countries with the highest gastric cancer incidence and death rates should consider screening for *H. pylori*. Furthermore, it should be ensured that guidelines for endoscopy referral in at risk groups are followed to maximise opportunities for earlier diagnosis.

Multicentric randomized study of *H. pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality- GISTAR

Aim

To determine if *H. pylori* screening followed by eradication of positive subjects and endoscopic follow-up of those with serological evidence of atrophic gastritis reduces mortality from gastric cancer in a high risk population among 40-64 years old subjects.



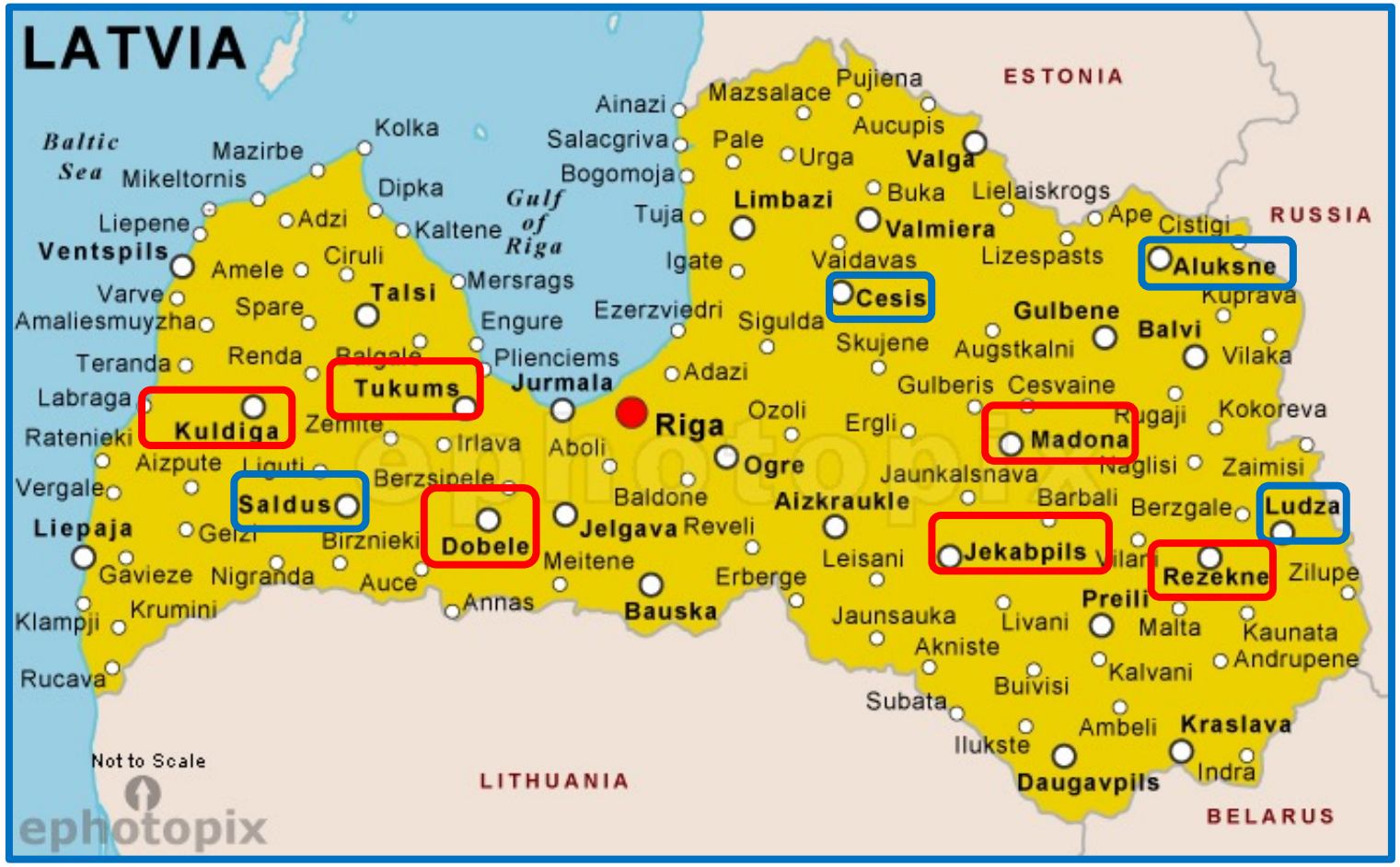
BMJ Open

Multicentric randomised study of *Helicobacter pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality: the GISTAR study

Marcis Leja,[1,2,3] Jin Young Park,[4] Raul Murillo,[4] Inta Liepniece-Karele,[1,2,5] Sergejs Isajevs,[1,2,5] Ilze Kikuste,[1,3] Dace Rudzite,[1,2] Petra Krike,[1] Sergei Parshutin,[1,6] Inese Polaka,[1,6] Arnis Kirsners,[1,6] Daiga Santare,[1,2] Valdis Folkmanis,[1] Ilva Daugule,[1] Martyn Plummer,[7] Rolando Herrero[4]

https://www.gistar.eu/

Current progress of GISTAR



- Pilot study completed in 2015 in **4 study centers** in Latvia
  - 3,455 subjects recruited (1613 men 1842women)
  - *H. pylori* seroprevalence 67.9%
  - Eradication success * tested by UBT 87%
  - 1,034 endoscopies with full histologic assessment
  - FIT positivity 5.6%

*The regimen consists of clarithromycin 500 mg (2 times a day), amoxicillin 1000 mg (2 times a day) and a proton pump inhibitor (Esomeprazole 40mg, twice a day) for 10 days

- Main study has been continued in **6 additional centers**
  - **n=10,338**
- To be expanded to other countries

Group	Women	Men	40-44	45-49	50-54	55-59	60-64	Total
1 - Main group	3089	2104	832	1068	1149	1186	940	5193
2 - Control group	3098	2097	820	1101	1141	1183	930	5195
Total	6187	4201	1652	2169	2290	2369	1870	10388

To accelerate reduction of global gastric cancer burden

- Population-based *H. pylori* test-and-treat programs should be integrated into healthcare priorities, especially in regions with high gastric cancer incidence
- For successful implementation of the programs require cautions:
  - That they should incorporate regional specific requirements in planning, e.g. accurate and affordable diagnostic tests, choice of treatment regimens, feasibility and cost-effectiveness at the regional level
  - That the selection of the optimal first-line eradication regimen should consider country/region-specific antibiotic resistance patterns
- Urgent need for more community-based demonstration studies with a long-term follow-up in various settings
- No data from randomised trials evaluating the impact of various screening strategies on gastric cancer mortality reduction have been reported. Potential harms less well quantitated outside Japan and Korea
- Risk stratification strategies need to be further developed to increase benefits, participation and to reduce costs
- Europe's Beating Cancer Plan and related projects should help accelerate reduction of gastric cancer burden in Europe