H. pylori and gastric cancer

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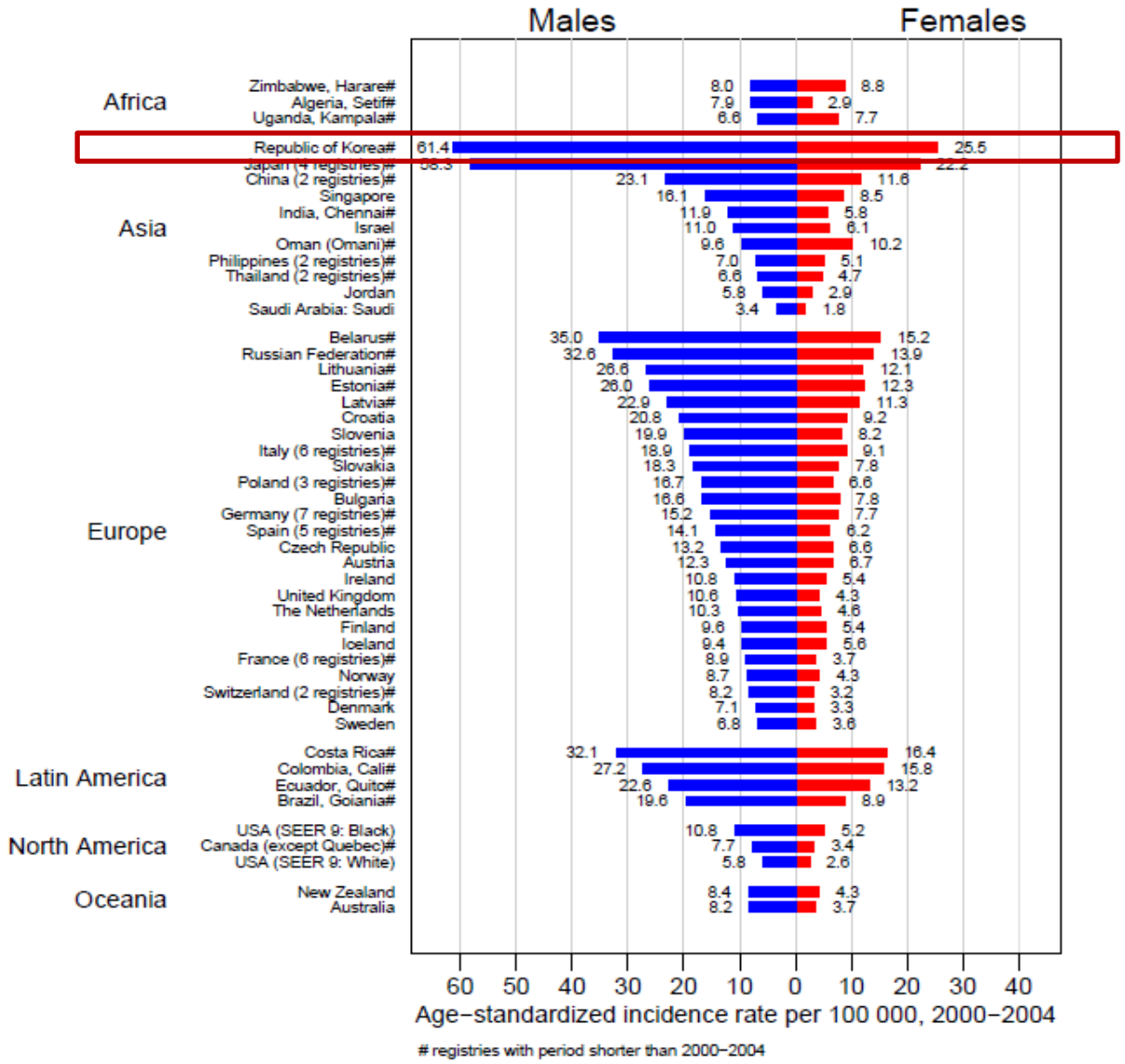
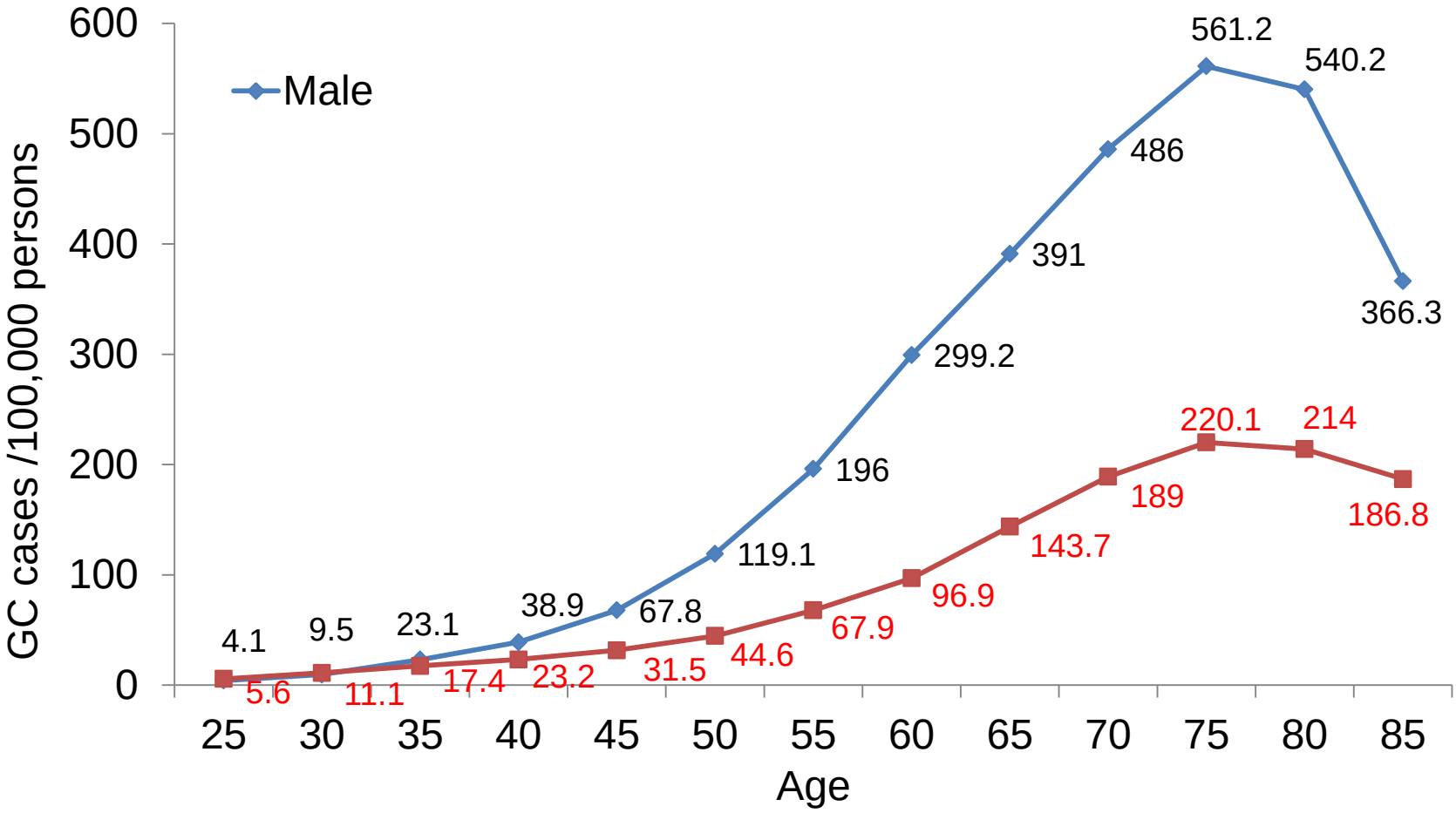
April 2017

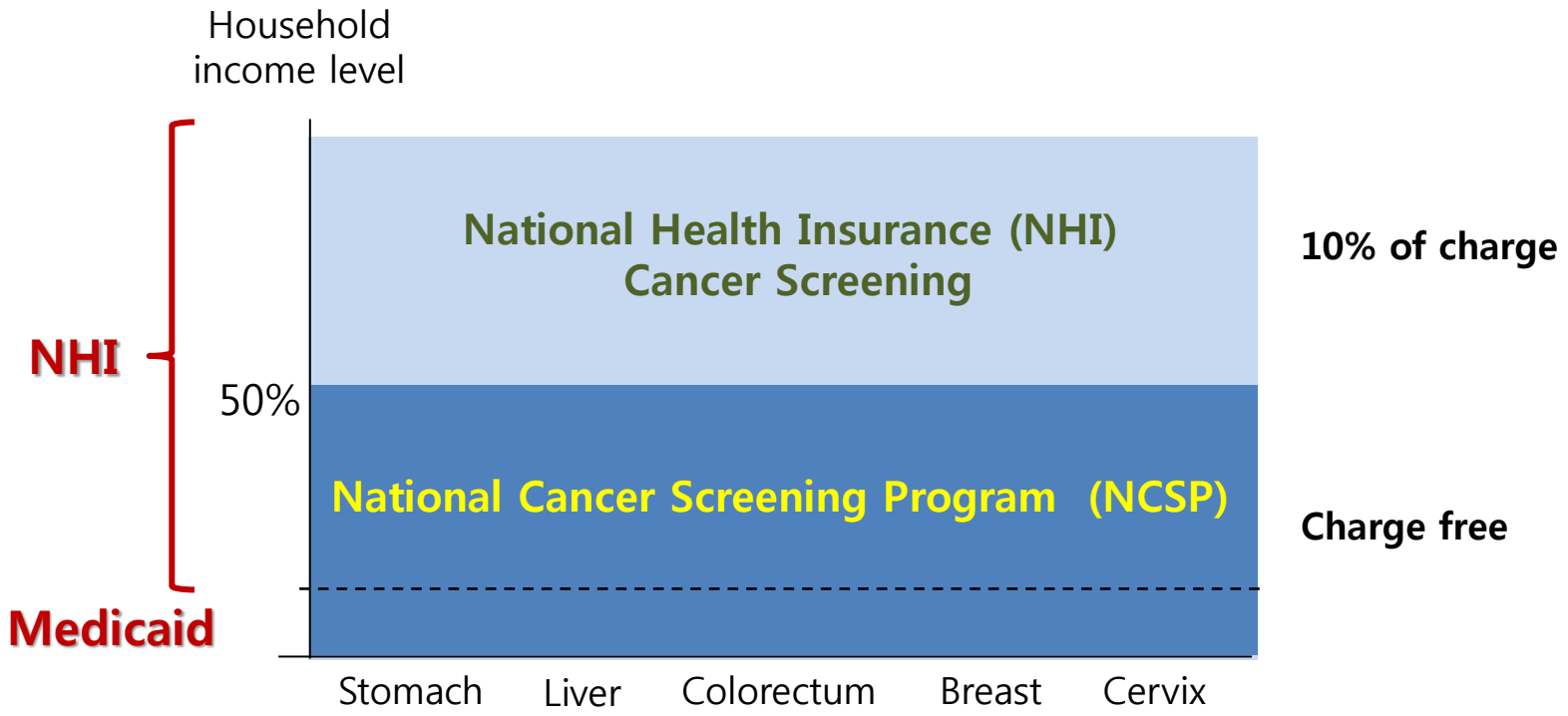
Gastric cancer in Korea



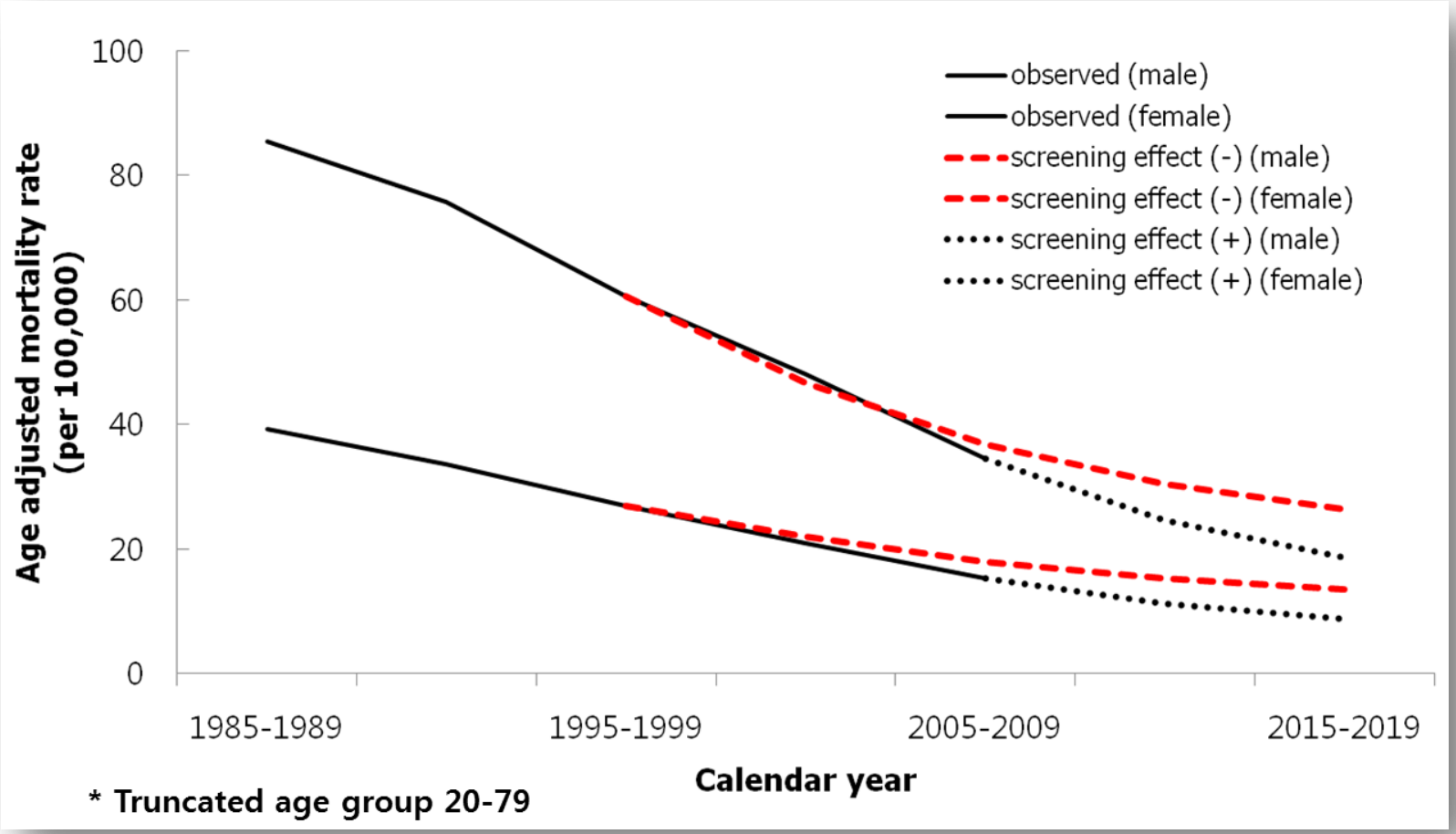
Gastric cancer is common in the elderly



National cancer screening program



Screening effect



Jun, et al. 9th International Gastric Cancer Congress 2011

A very famous lie. Is it white?

Screening is not a prevention.

Screening is just early detection and prevention of gastric cancer-related death.

In order to prevent gastric cancer, *H. pylori* eradication may be the best option.

Why *Helicobacter pylori* ?

Hp negastive gastric cancer is rare.

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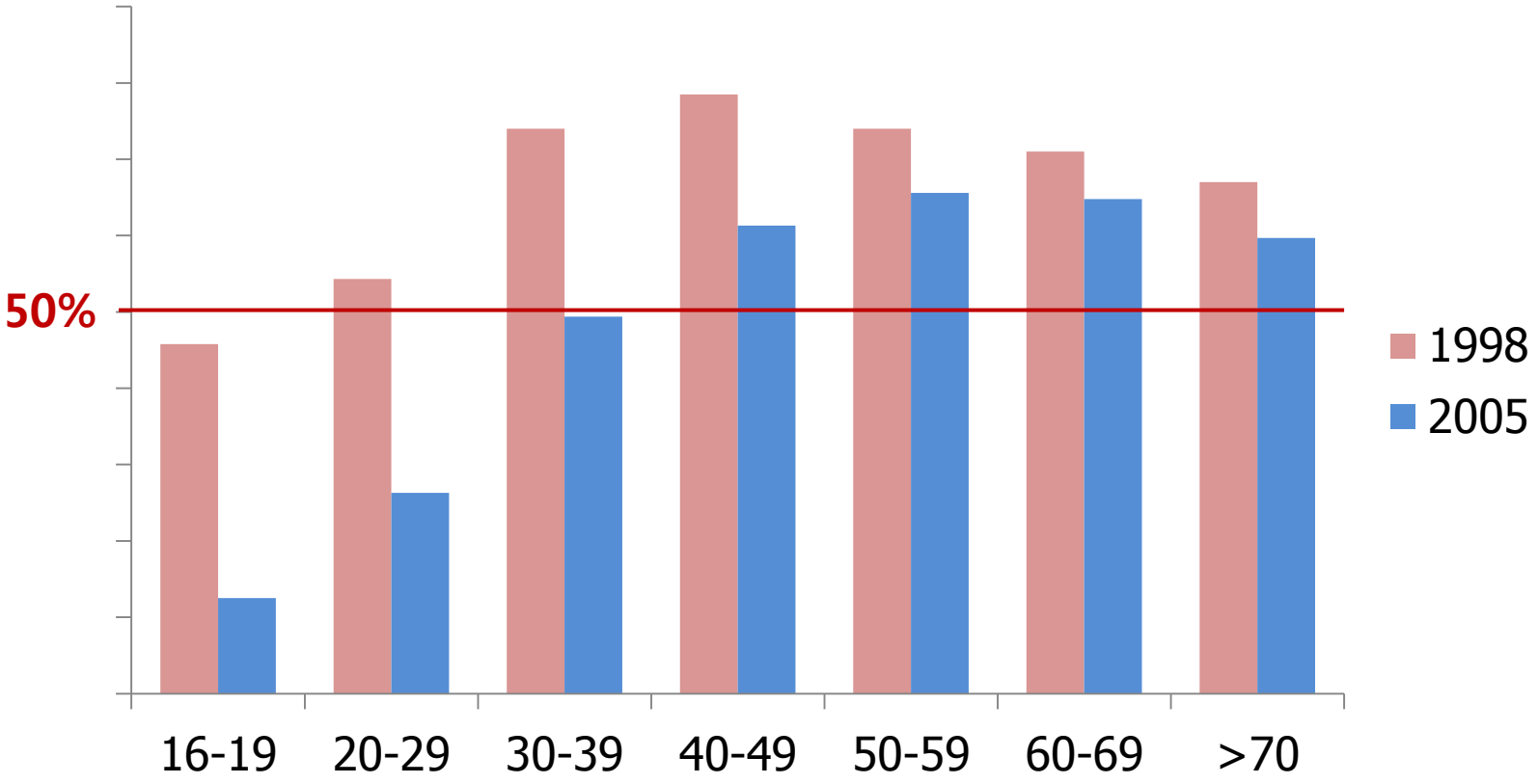
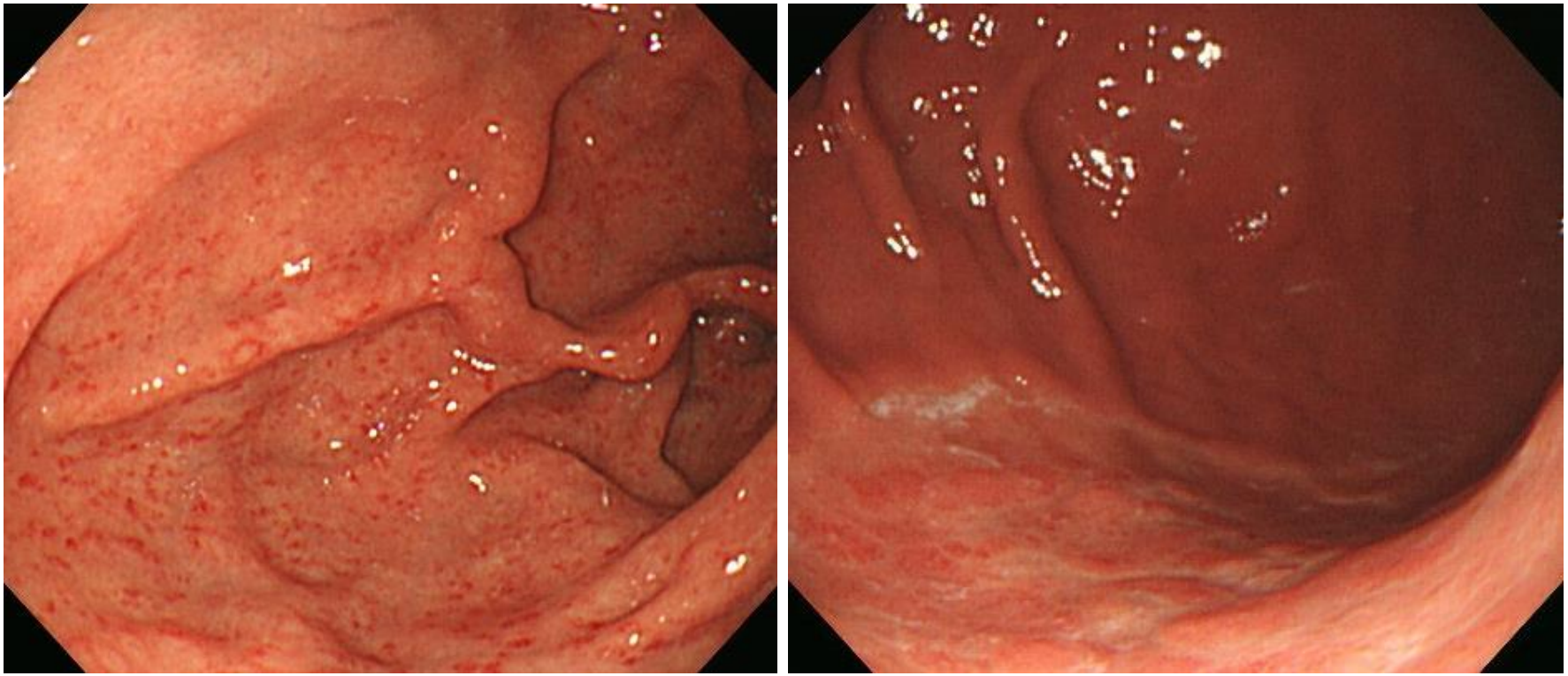
Helicobacter pylori in Korea



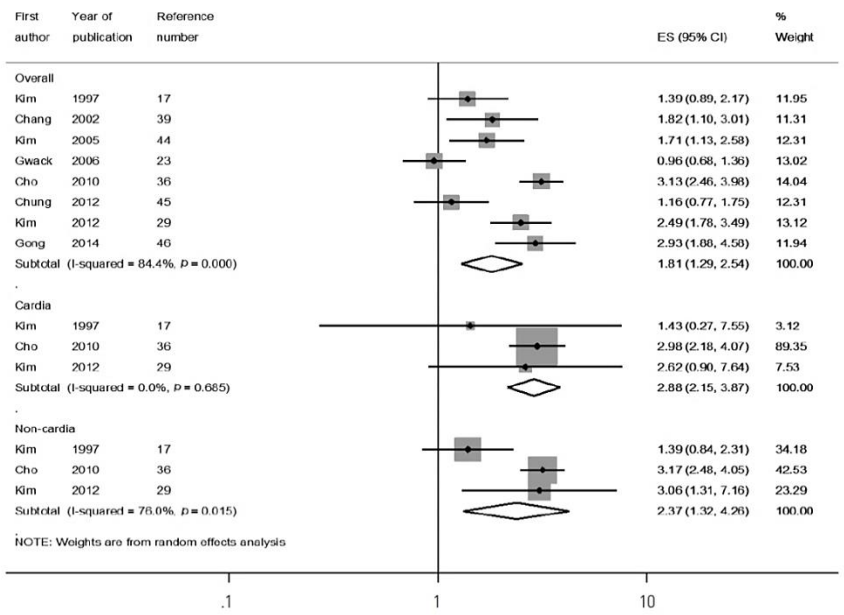
Yim. Helicobacter 2007

Gastric cancer in Hp (+) male/44

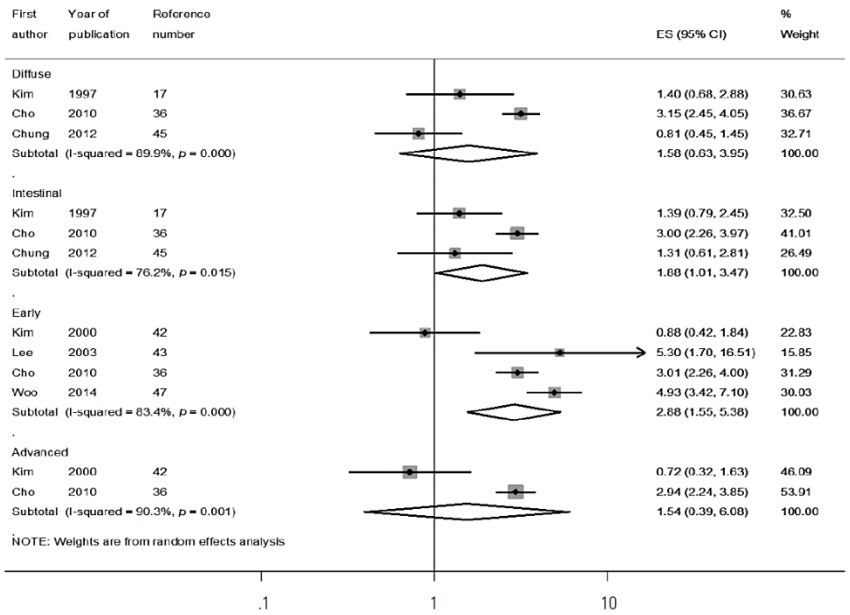


A few years ago: *H. pylori* gastritis

Helicobacter pylori in Korean gastric cancer patients



Effect size of *H. pylori* infection on overall, cardia, and non-cardia gastric cancer in Korean.

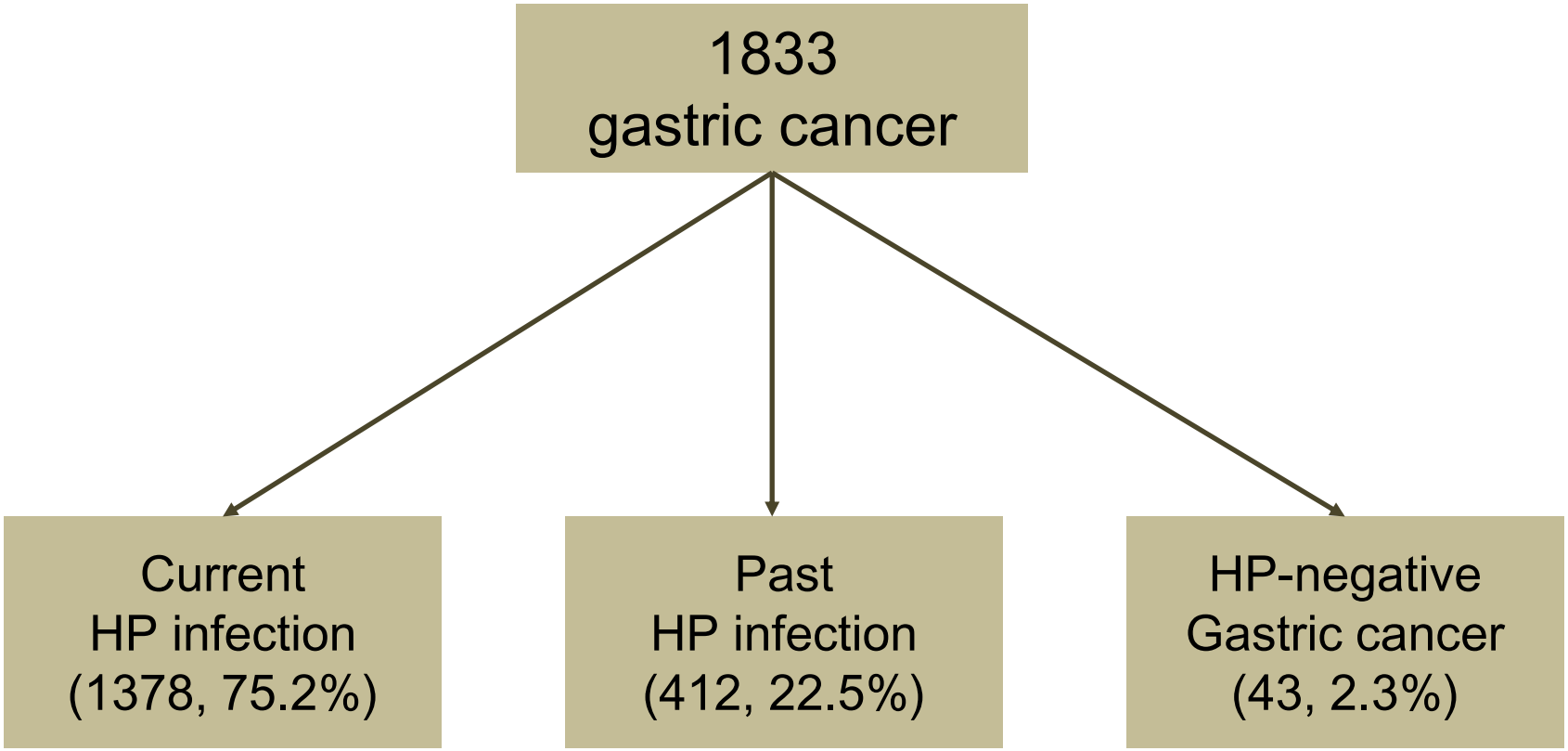


Effect size of *H. pylori* infection on diffuse type, intestinal type, early, and advanced gastric cancer in Korean

Bae. J Prev Med Public Health 2016

True Helicobacter (-) cancer is rare.

- Rapid urease tests, serology examinations, and histological evaluations.



Kwak. J Gastroenterol Hepatol 2014

Current vs past Hp infection

	Current HP infection	Past HP infection	p
Mean age (mean age ± SD years)	57.1 ± 11.4	60.6 ± 11.0	<0.001
Age groups, n (%)			<0.001
–39	96 (7.0%)	22 (5.3%)	
40–49	252 (18.3%)	43 (10.4%)	
50–59	414 (30.0%)	103 (25.0%)	
60–69	409 (29.7%)	143 (34.7%)	
70–	207 (15.0%)	101 (24.3%)	
Sex (male), n (%)	898 (65.2%)	306 (74.3%)	0.001
Lauren's classification			<0.001
Intestinal	685 (49.7%)	263 (63.8%)	
Diffuse	529 (38.4%)	122 (29.6%)	
Mixed	164 (11.9%)	27 (6.6%)	

Kwak. J Gastroenterol Hepatol 2014

More examination, less Hp (-) cancer

- METHODS: A total of 240 early gastric cancers were included in this study. The status of H. pylori infection was determined from the rapid

H. pylori-Negative

Status of *H. pylori*-negative was determined when results of all *H. pylori* tests (RUT, ^{13}C-UBT, culture, histopathology, and IgG antibody) were negative without a history of eradication.

- RESULTS: The rate of H. pylori infection was 77.9% and 19 patients (7.9%) had a history of eradication. 34 patients (14.2%) were diagnosed with H. pylori-negative gastric cancer using diagnostic tools of H. pylori. However, most of the patients with H. pylori-negative gastric cancer had histological atrophy and intestinal metaplasia. **Only 1 gastric cancer (0.42%)** occurred in the mucosa without histological atrophy, endoscopic atrophy or serological atrophy.

Ono S. Digestion 2012

It's not a yes or no phenomenon.

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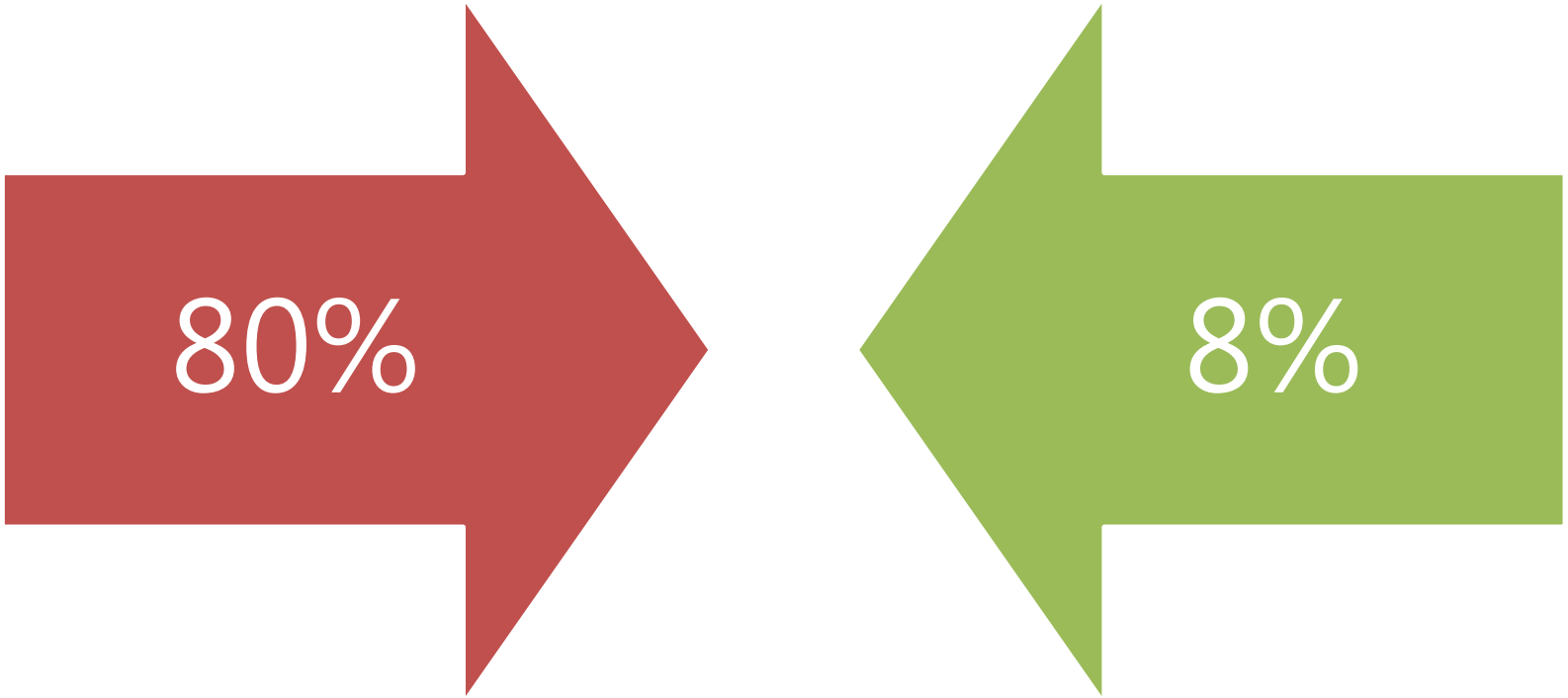
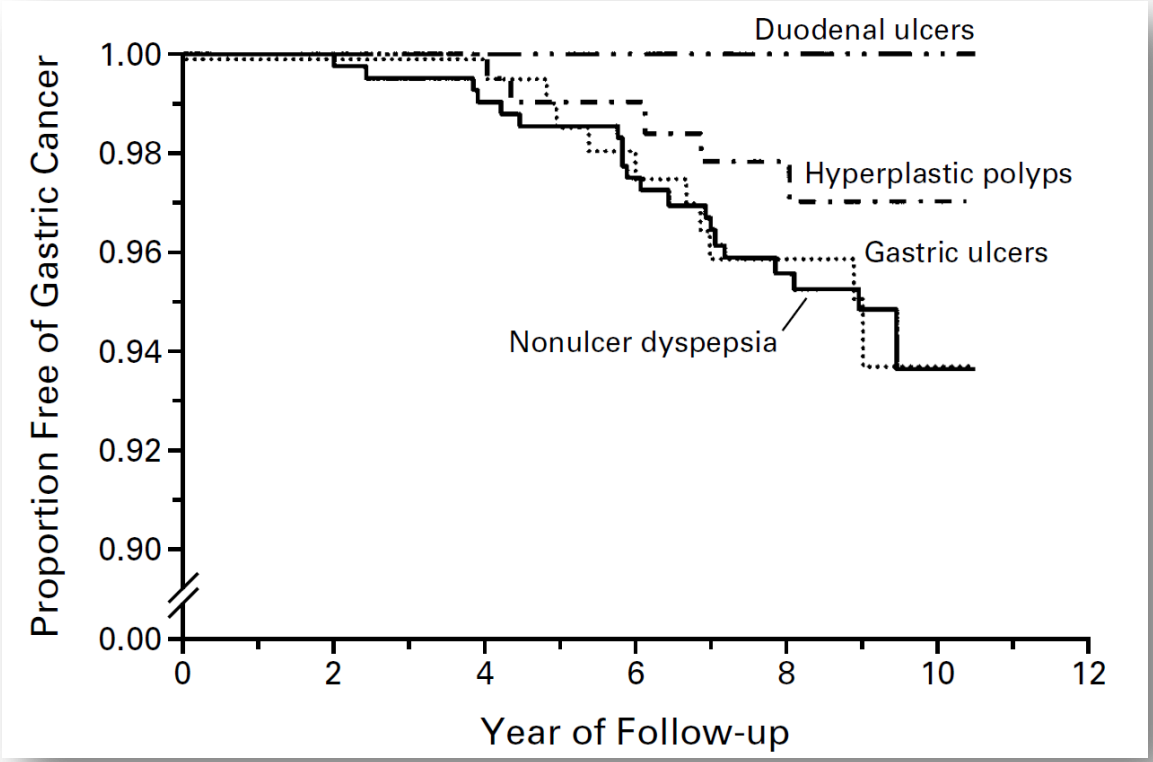

80%
8%

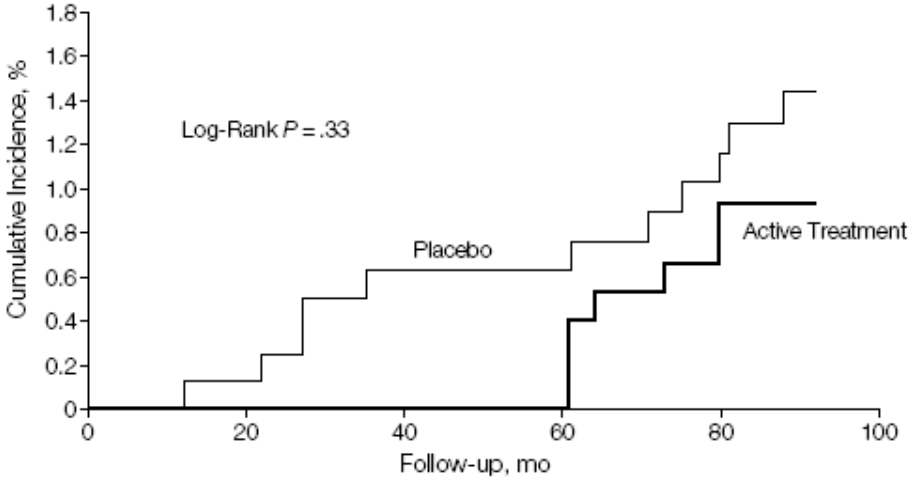
Gastric cancer in Hp–positive patients according to initial diagnosis



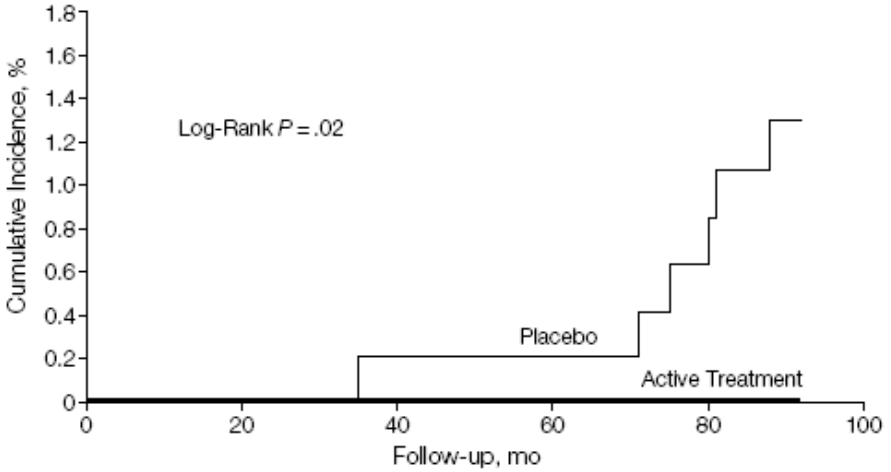
Uemura N. NEJM 2001;345:784-789

Prospective intervention study

- Failure in general, but there is some hope



Overall outcome

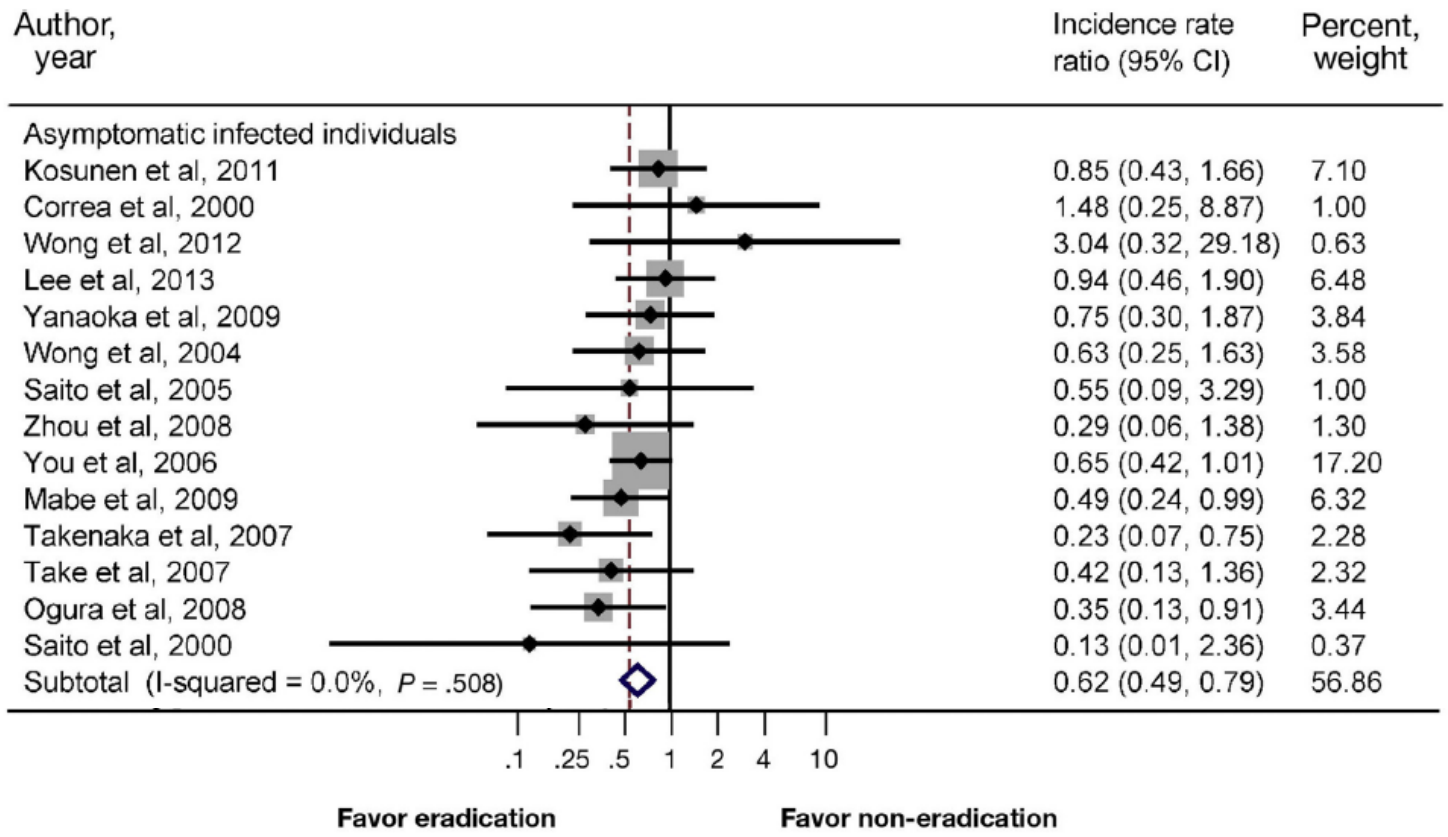


No atrophy, no metaplasia, no dysplasia

Wong BC. JAMA 2004;291:187-94

Meta-analysis

- Asymptomatic general population



Lee. Gastroenterology 2016;150:1113-1124

Even atrophic stomach, Hp eradication is not nothing.

	Hp− (n = 39)		Eradication success (n = 54)		Eradication failure (n = 16)	
	Baseline	3 years	Baseline	3 years	Baseline	3 years
Antrum						
Activity	0.40 ± 0.10	0.37 ± 0.12	**1.47 ± 0.13**	**0.49 ± 0.09**[a]	1.55 ± 0.25	1.91 ± 0.29
Chronic inflammation	1.17 ± 0.08	1.37 ± 0.09	**1.94 ± 0.09**	**1.50 ± 0.08**[a]	2.00 ± 0.00	2.18 ± 0.18
Atrophy	0.75 ± 0.21	0.50 ± 0.20	0.96 ± 0.14	1.32 ± 0.20	1.00 ± 0.58	0.00 ± 0.00
Intestinal metaplasia	0.91 ± 0.20	0.82 ± 0.16	1.02 ± 0.14	1.29 ± 0.14	1.11 ± 0.31	1.11 ± 0.31
Corpus						
Activity	0.41 ± 0.08	0.24 ± 0.11	**1.74 ± 0.10**	**0.43 ± 0.09**[a]	1.88 ± 0.18	1.63 ± 0.27
Chronic inflammation	1.51 ± 0.08	1.43 ± 0.10	**1.94 ± 0.08**	**1.46 ± 0.08**[a]	1.94 ± 0.14	2.06 ± 0.14
Atrophy	0.75 ± 0.21	0.38 ± 0.18	**0.91 ± 0.20**	**0.45 ± 0.15**[b]	1.00 ± 0.52	0.83 ± 0.40
Intestinal metaplasia	0.78 ± 0.17	0.69 ± 0.16	0.68 ± 0.15	0.83 ± 0.14	0.80 ± 0.26	0.67 ± 0.21
Pepsinogen I/II ratio	4.8 ± 0.4	4.4 ± 0.3	3.2 ± 0.2	**4.7 ± 0.3**[a]	3.6 ± 0.5	4.0 ± 0.4

- In patients with successful eradication
  - Grades of activity and chronic inflammation of gastritis significantly decreased.
  - Scores for atrophic gastritis in the corpus significantly decreased.

Kang. Helicobacter 2012

Ongoing trials in Korea (1)

Effect of *Helicobacter pylori* eradication on gastric cancer prevention **in general population**: a randomized controlled clinical trial

ClinicalTrials.gov

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Helicobacter Pylori Eradication for Gastric Cancer Prevention in the General Population (HELPER)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2014 by National Cancer Center, Korea

Sponsor:
National Cancer Center, Korea

Collaborators:
International Agency for Research on Cancer
Chonnam National University Hospital
Chung-Ang University Hosptial, Chung-Ang University College of Medicine
Pusan National University Hospital
Kyungpook National University
The Catholic University of Korea

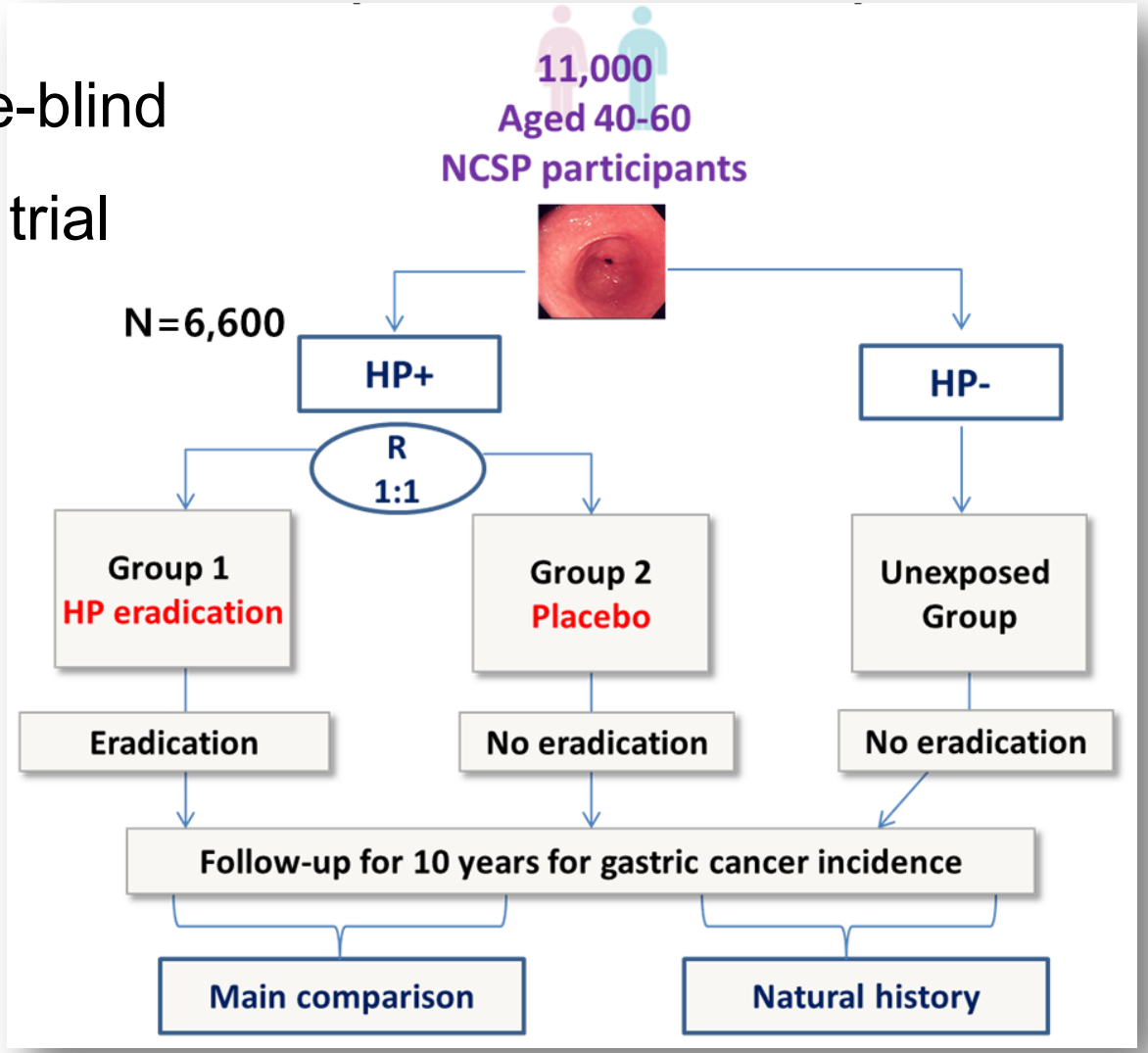
Information provided by (Responsible Party):
Il Ju Choi, National Cancer Center, Korea

ClinicalTrials.gov Identifier:
NCT02112214

First received: April 3, 2014
Last updated: November 12, 2014
Last verified: November 2014
History of Changes

Prospective double-blind

placebo controlled trial



Ongoing trials in Korea (2)

Helicobacter pylori eradication to prevent gastric cancer **in subjects with family history** of gastric cancer: A randomized controlled study

ClinicalTrials.gov

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Prev

Gastric Cancer Prevention in the Family Members by Helicobacter Pylori Eradication

This study is ongoing, but not recruiting participants.

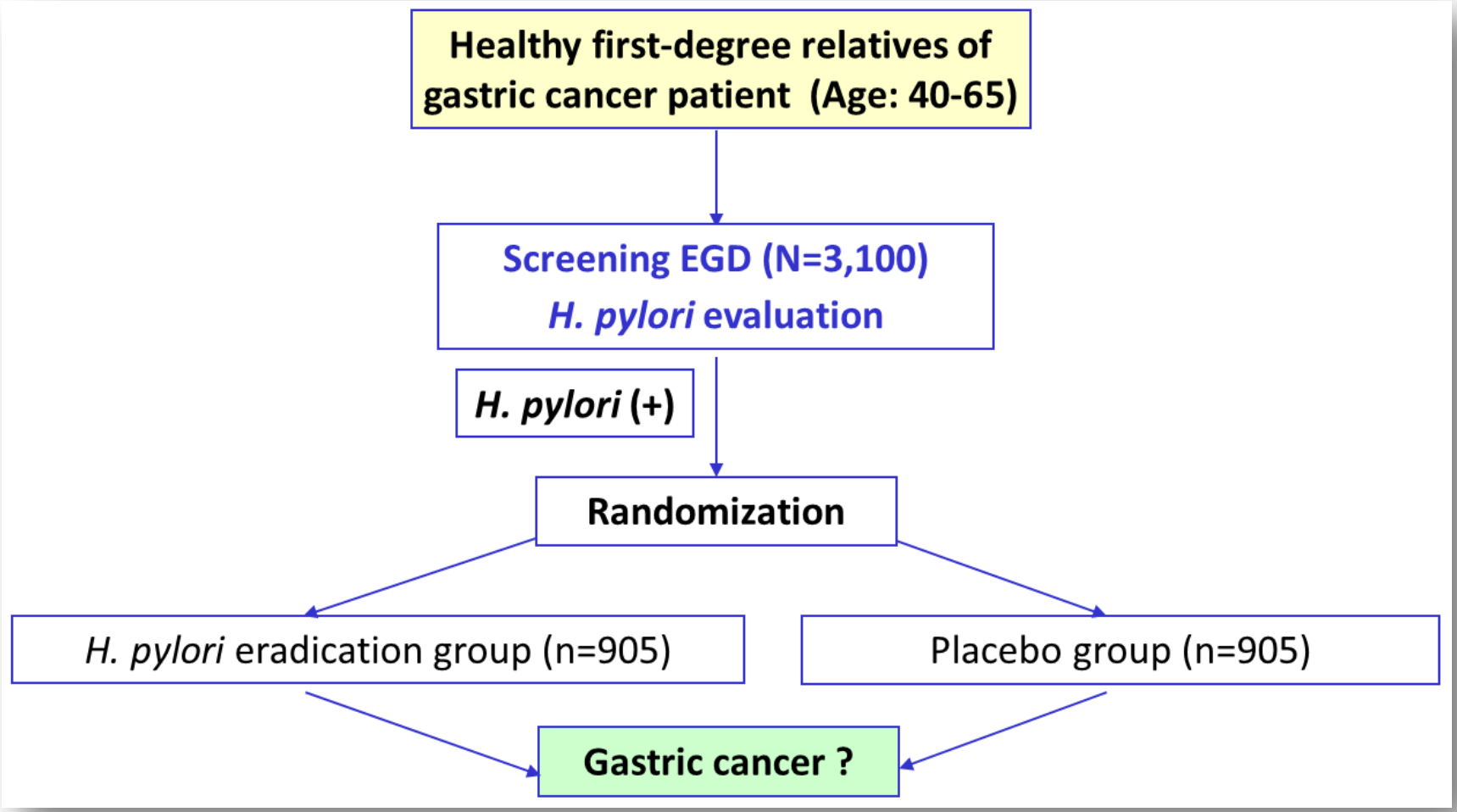
Sponsor:
National Cancer Center, Korea

Information provided by (Responsible Party):
Il Ju Choi, National Cancer Center, Korea

ClinicalTrials.gov Identifier:
NCT01678027

First received: August 17, 2012
Last updated: April 28, 2016
Last verified: April 2016
History of Changes

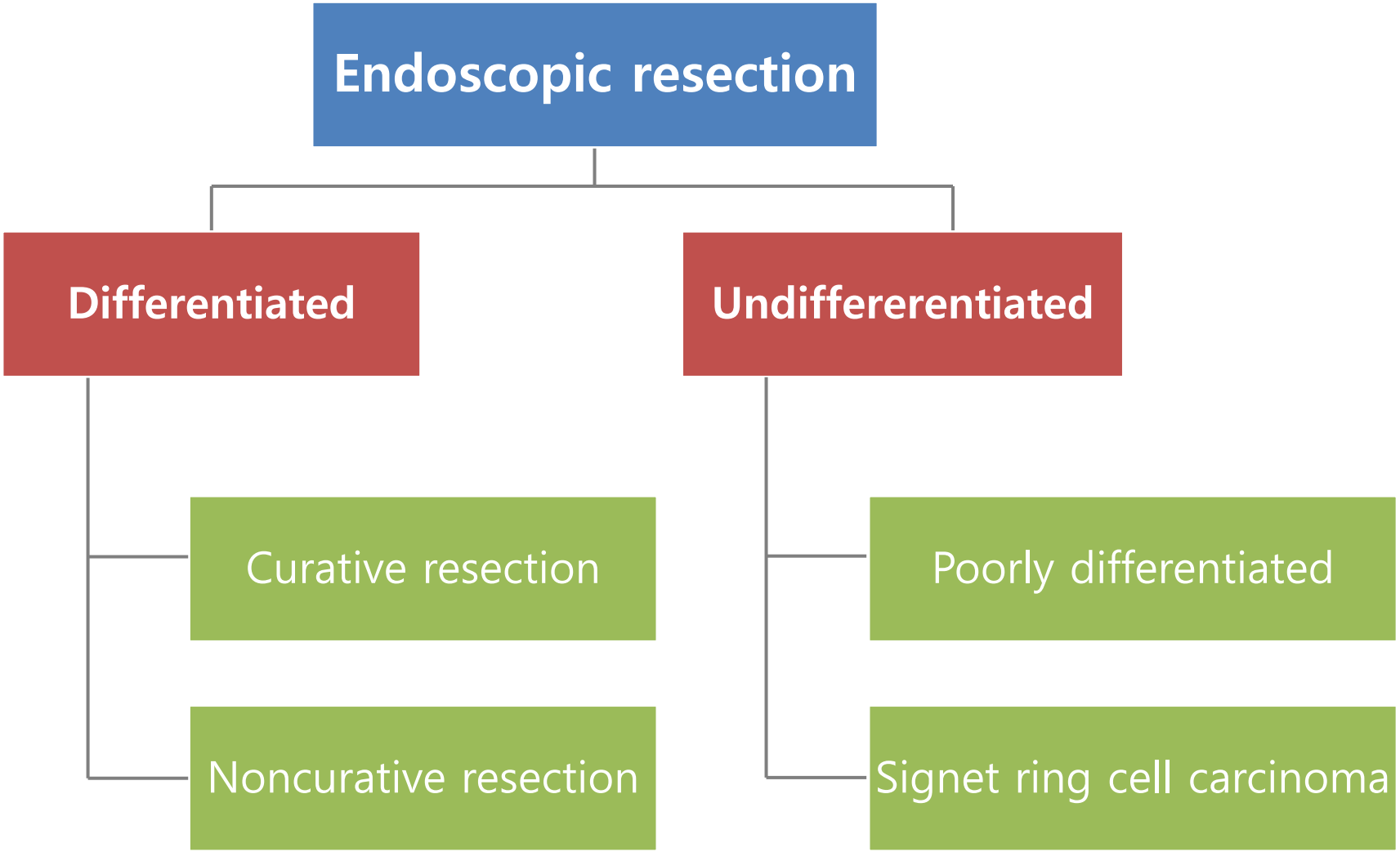
Prospective double-blind placebo controlled trial

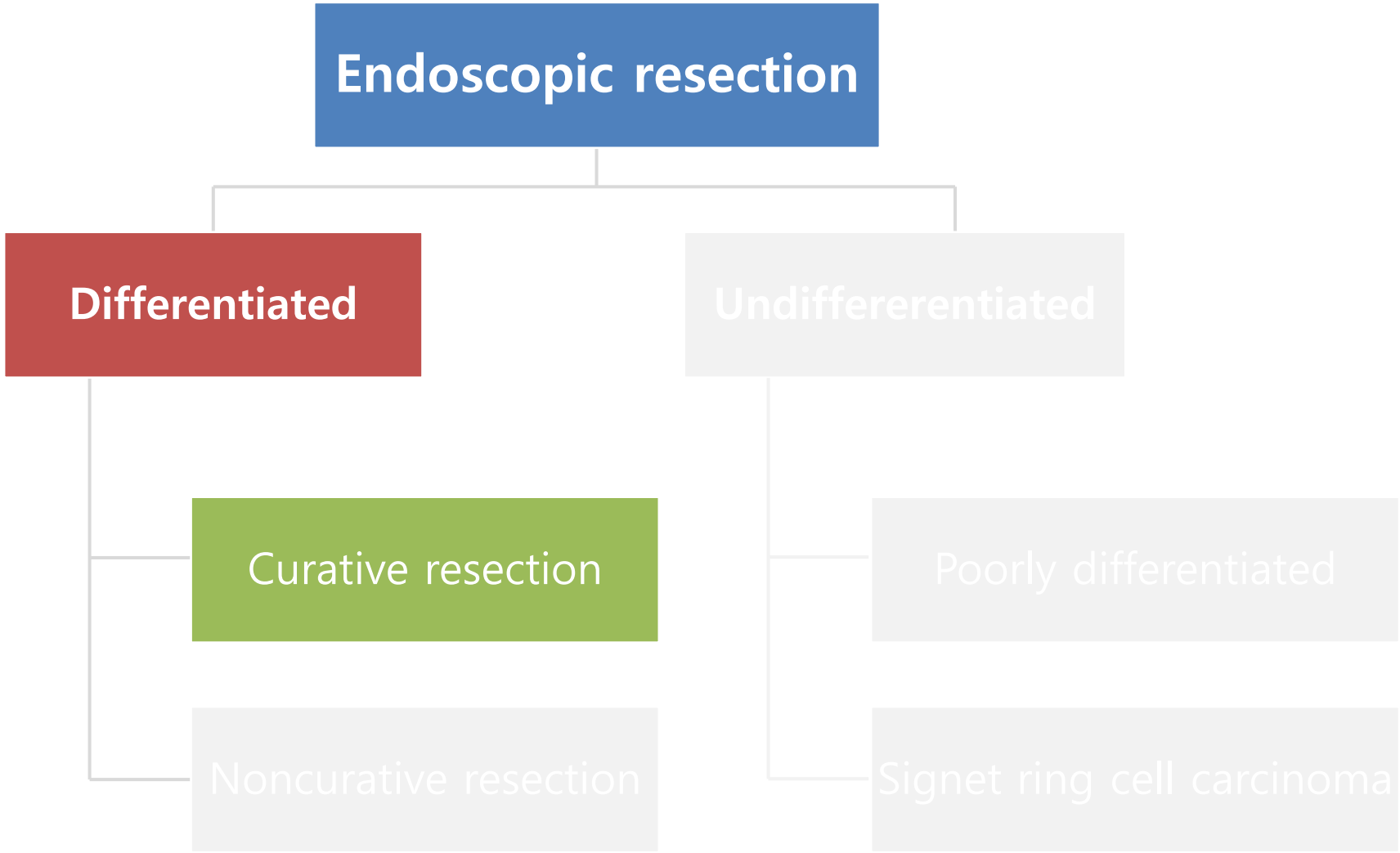


Hp eradicaton after ESD

성균관대학교 의과대학 내과 이준행

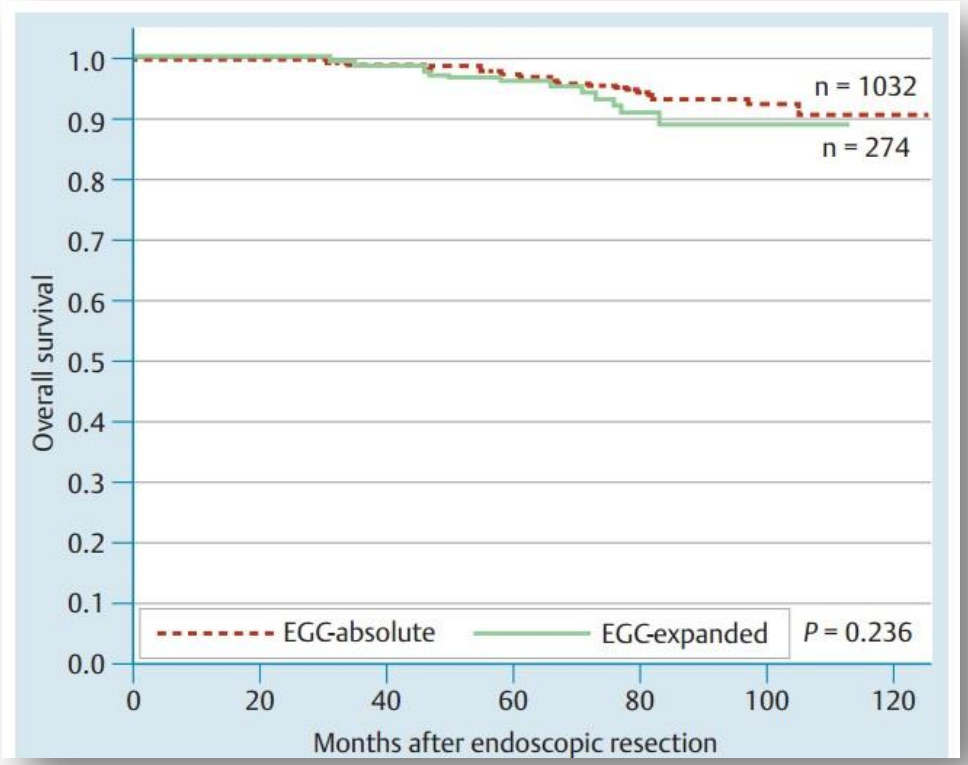
EMR/ESD data analysis at SMC




Endoscopic resection
Differentiated
Undiffererentiated
Curative resection
Noncurative resection
Poorly differentiated
Signet ring cell carcinoma

Overall-survival

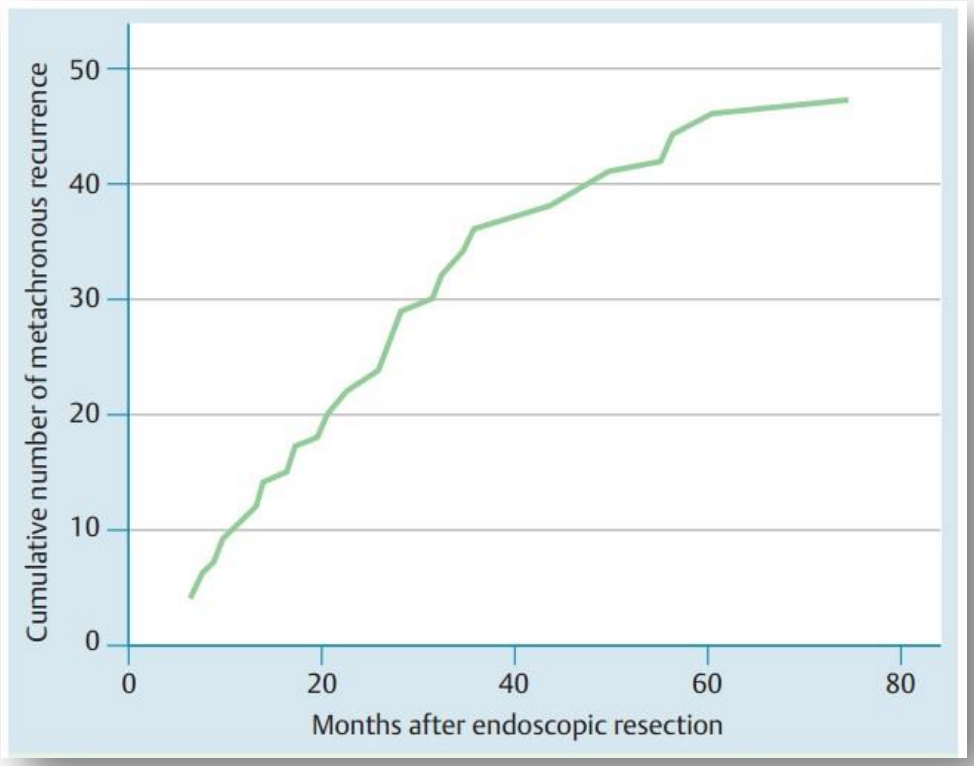
- 1,306 curative ESDs from December 2003 to May 2011



Min BH (SMC). Endoscopy 2015

Metachronous recurrence (n=47, 3.6%)

- Among 1,306 curative ESDs from December 2003 to May 2011



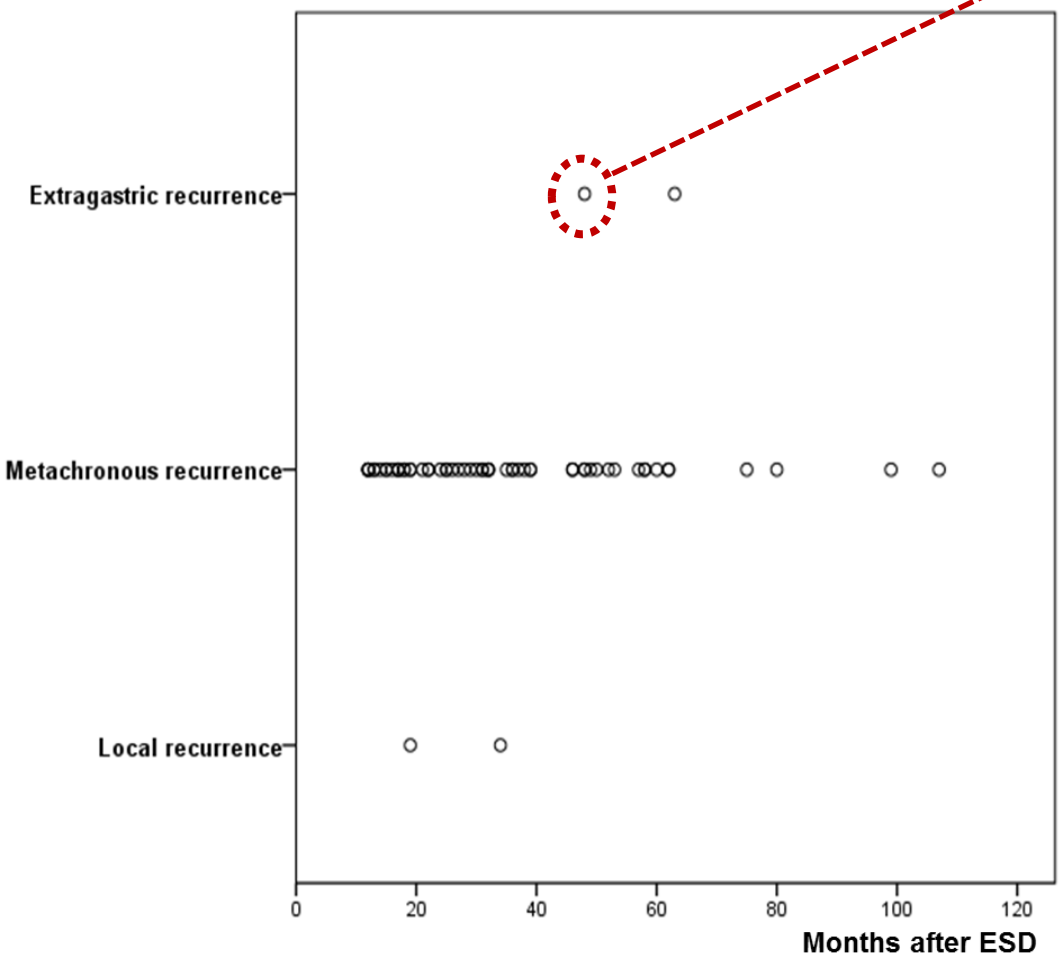
♠ EGC: 44 cases
- LN (-): 44

♠ AGC: 3 cases
- pT2, LN (-): 1
- pT2, LN (+): 2

Min BH (SMC). Endoscopy 2015

Pattern of recurrences (n=1,460)

- Complete resection, absolute + expanded
- Differentiated type histology
- EMR or ESD from April 2000 - May 2011



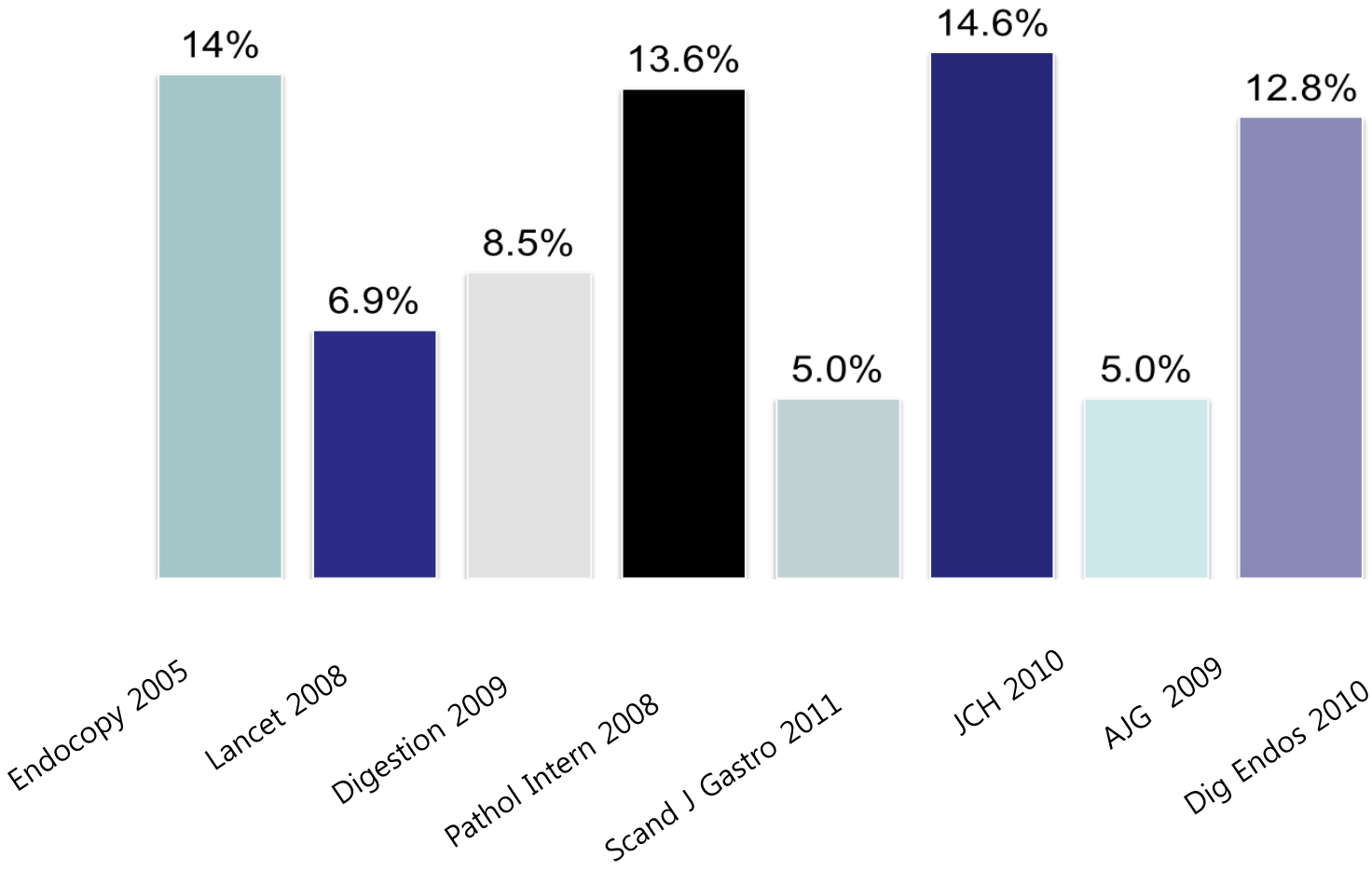
The only one unhappy outcome (lymph nodes and peritoneal recurrence).

Table 2 Univariate and multivariate analysis of factors associated with metachronous recurrence after curative endoscopic submucosal dissection (ESD) for differentiated-type early gastric cancer.

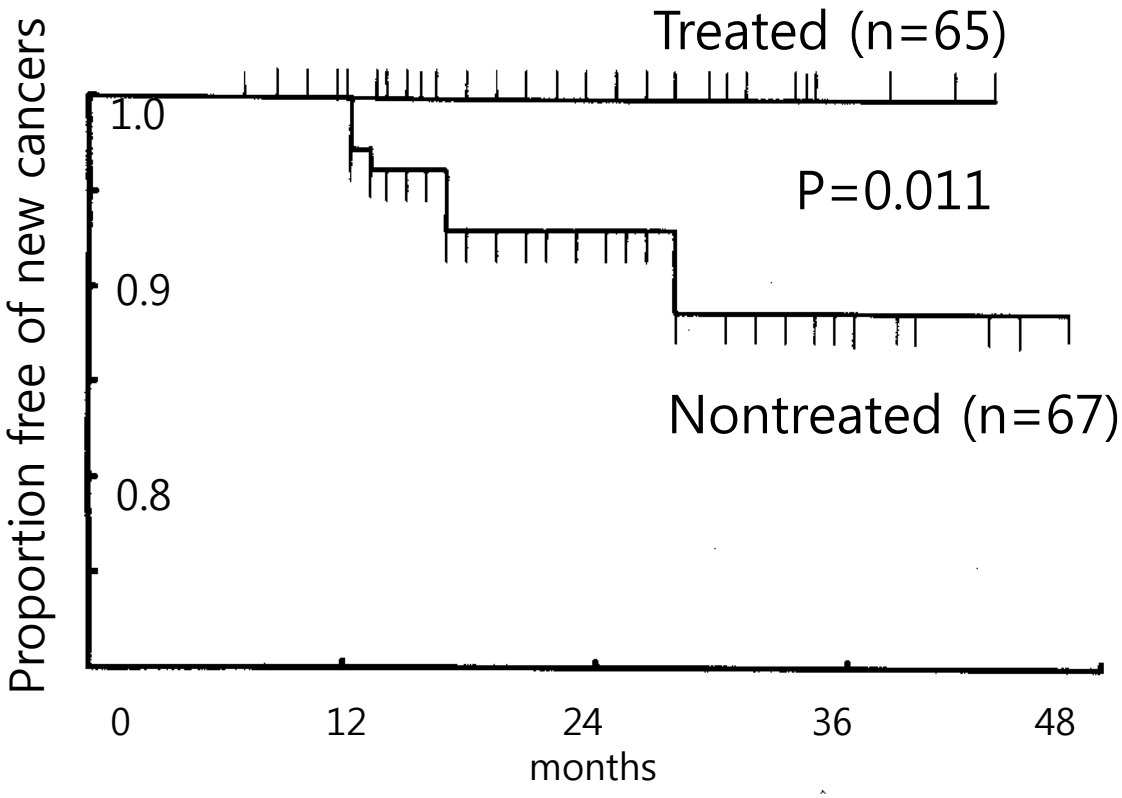
	Metachronous recurrence[1]		Odds ratio	95%CI	*P* value
	None (n=1259)	Present (n=47)			
Age, mean ± SD, y	61.5 ± 9.7	63.1 ± 8.8	1.015	0.983 – 1.047	0.364
Gender, n (%)					0.427
Male	1004 (79.7)	40 (85.1)			
Female	255 (20.3)	7 (14.9)	0.714	0.311 – 1.640	
Number of lesions, n (%)					0.025
Single	1229 (97.6)	43 (91.5)			
Multiple	30 (2.4)	4 (8.5)	3.691	1.177 – 11.574	
Tumor site, n (%)					0.238
Antrum/angle	994 (79.0)	34 (72.3)			
Body/fundus/cardia	265 (21.0)	13 (27.7)	1.491	0.768 – 2.896	
Tumor shape, n (%)					0.683
Elevated	715 (56.8)	28 (59.6)			
Flat or depressed	544 (43.2)	19 (40.4)	0.882	0.482 – 1.613	
Tumor size, mean ± SD, cm	1.4 ± 0.8	1.3 ± 0.8	0.724	0.409 – 1.280	0.267
Tumor depth (%)					0.516
Mucosa	1194 (94.8)	45 (95.7)			
sm1[2]	65 (5.2)	2 (4.3)	0.556	0.094 – 3.274	
Differentiation, n (%)					0.016
Well differentiated	506 (40.2)	28 (59.6)			
Moderately differentiated	753 (59.8)	19 (40.4)	0.477	0.262 – 0.869	
Indication, n (%)					0.595
Absolute	994 (79.0)	38 (80.9)			
Expanded	265 (21.0)	9 (19.1)	1.406	0.400 – 4.937	

Min BH (SMC). Endoscopy 2015

Incidence of metachronous gastric cancers after ER for EGC – early studies



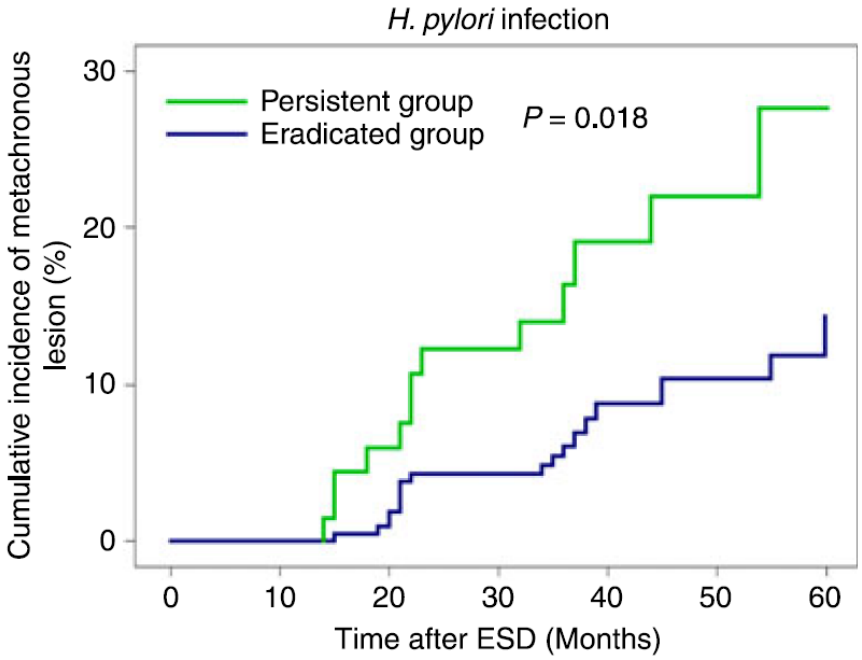
Early retrospective data

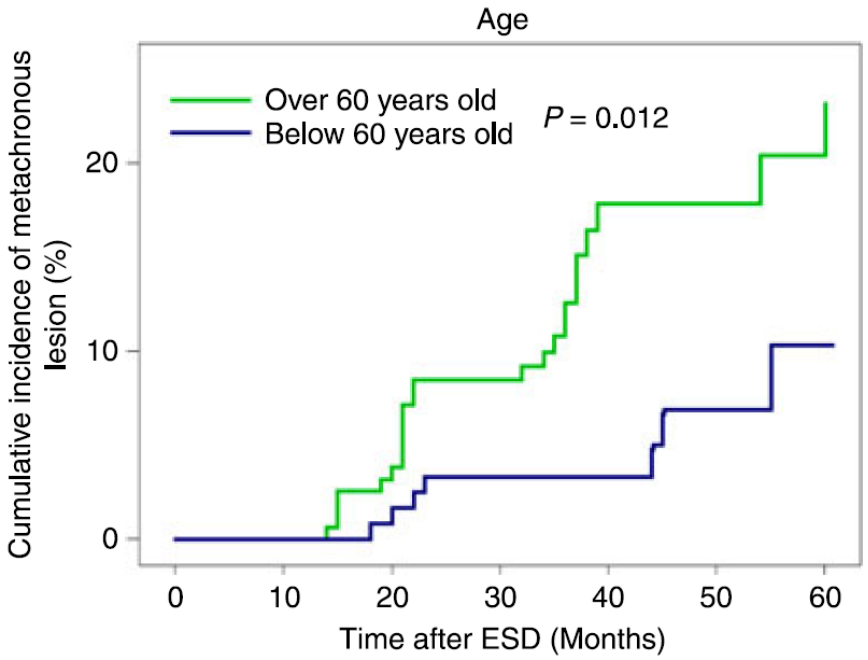


Uemura N. CEBP 1997

Korean retrospective study (1)

- Positive result

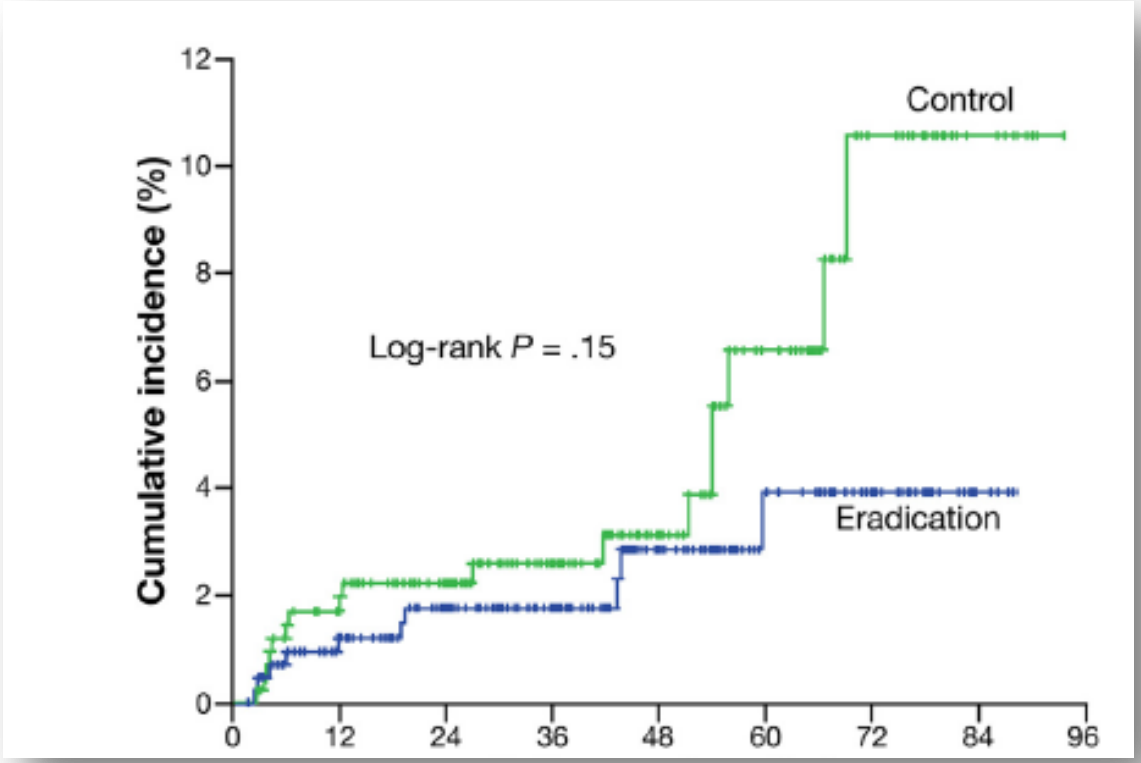




Kwon. Aliment Pharmacol Ther 2014;39:609-18

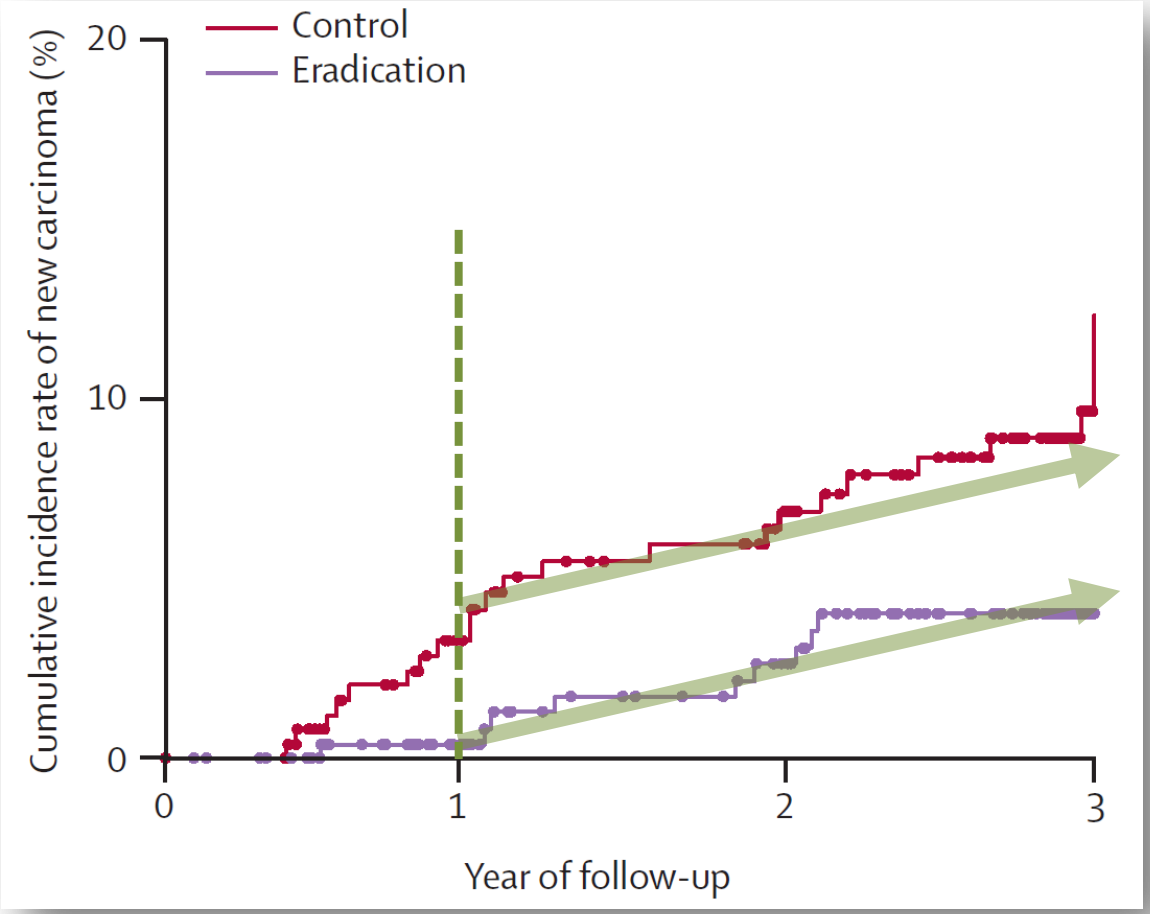
Korean retrospective study (2)

- Negastive result



Choi. Clin Gastroenterol Hepatol 2014;38:118-125

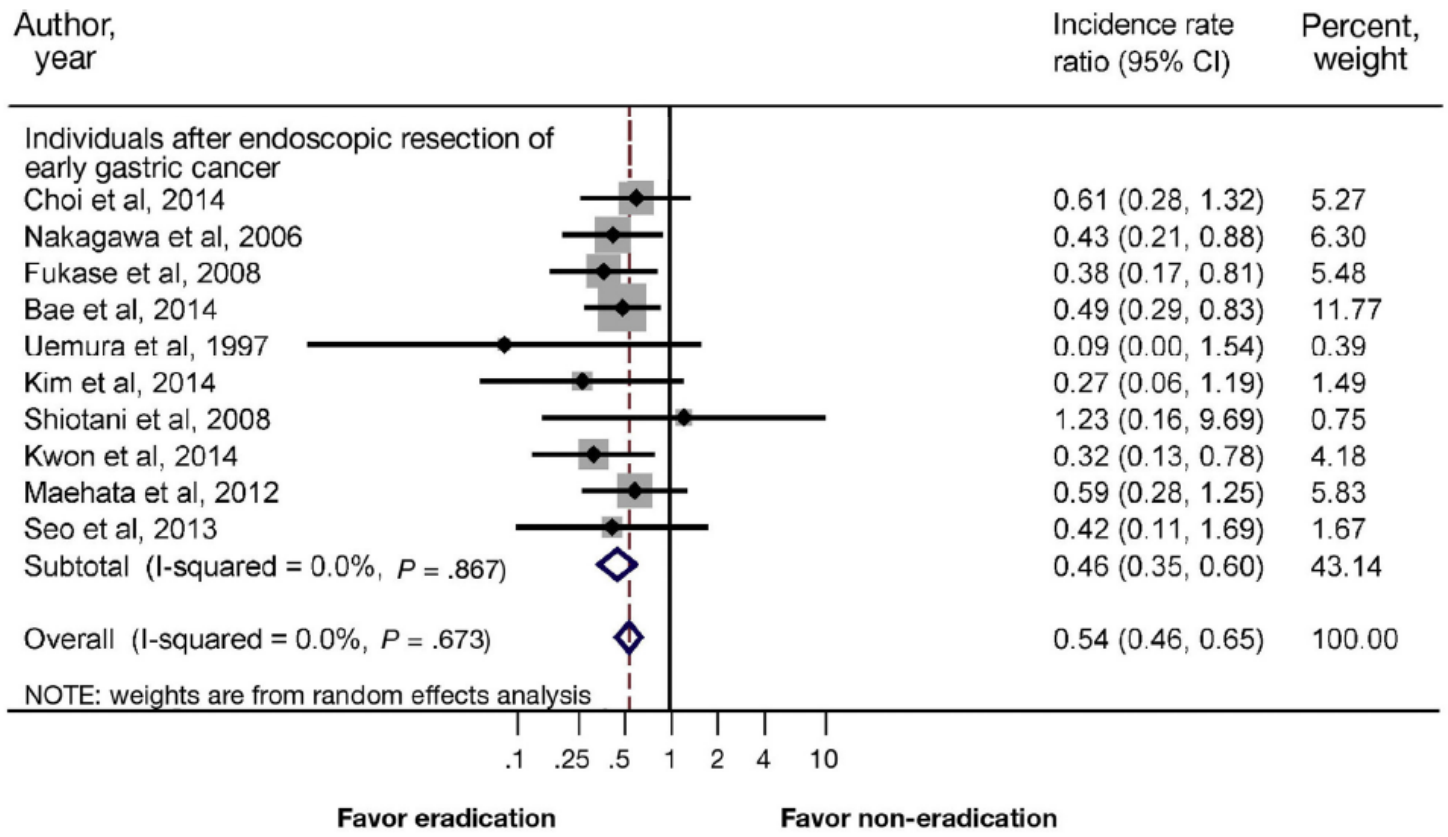
Japanese multi-center, open-label, randomized trial



Fukase K. Lancet 2008;372:392-7

Meta-analysis

- After endoscopic resection of EGC

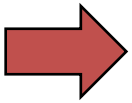


Lee. Gastroenterology 2016;150:1113-1124

Guideline by experts' group

- 2009 & 2013

Therapeutic target – indication of 2009
Definite indication
Peptic ulcer including scar
Marginal zone B cell lymphoma
Early gastric cancer
Recommended indication
First relatives of gastric cancer
Unexplained IDA
Chronic ITP
Possible indication
Atrophic gastritis
Non-ulcer dyspepsia
Long-term use of NSAID



Therapeutic target – indication of 2013
Peptic ulcer (1A)
Marginal zone B cell lymphoma (1A)
EGC after endoscopic resection (1A)
ITP (1A)
Long-term aspirin use with peptic ulcer history (1C)
Atrophic gastritis / intestinal metaplasia (2C)
Family history of gastric cancer (2B)
Functional dyspepsia (in some patients) (2A)

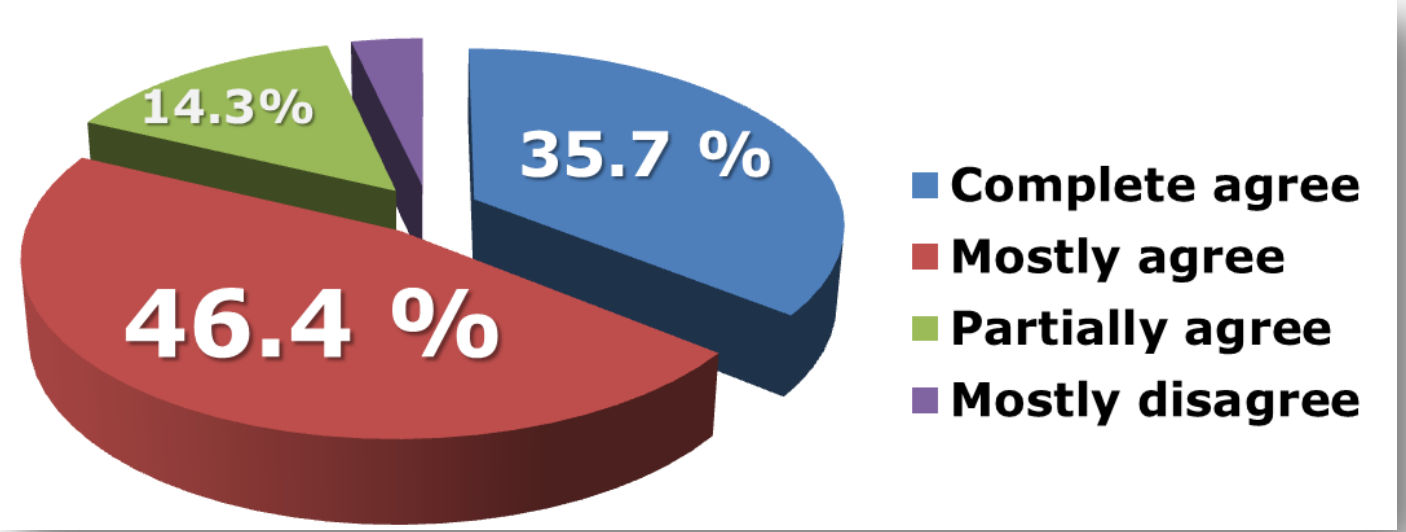
Kim SG. J Gastroenterol Hepatol 2014;29:1371-1386

- In some studies, the incidence rate of metachronous gastric cancer decreased with H. pylori eradication after endoscopic resection of EGC. In a multicenter study of 544 patients with endoscopic resection of EGC, the incidence rate of metachronous gastric cancer was significantly reduced in the H. pylori eradication group compared with the non-eradication group. However, another retrospective study of 268 patients with endoscopic resection of EGC showed **contradictory results**, in that there was no significant difference in metachronous gastric cancer between the eradication group and the non-eradication group.
- Considering the high incidence of gastric cancer in Korea, H. pylori eradication is necessary to prevent metachronous gastric cancer after endoscopic resection of EGC.

Kim SG. J Gastroenterol Hepatol 2014;29:1371-1386

Expert voting

- Eradication is indicated after ER for EGC (1A)



Kim SG. J Gastroenterol Hepatol 2014;29:1371-1386

Is it time to eradicate Hp for cancer prevention?

성균관대학교 의과대학 내과 이준행

Hill's epidemiologic criteria for causal association.

Causal criterion	Causal association
Strength of association	What is the relative risk?
Consistency of association	Is there agreement among repeated observations in different places, at different times, different methodology, by different researchers, under different circumstances?
Specificity of association	Is the outcome unique to the exposure?
Temporality	Does exposure precede the outcome variable?
Biological gradient	Is there evidence of a dose-response relationship?
Plausibility	Does the causal relationship make biological sense?
Coherence	Is the causal association compatible with present knowledge of the disease?
Experimentation	Does controlled manipulation of the exposure variable change the outcome?
Analogy	Does the causal relationship conform to a previously described relationship?

We can make a decision
based on variable level of evidence.

Fredricks. Clin Microbiol Rev 1996;9:18-33

Policy change in Japan

- Not based on newly available data

- February 21, 2013
- ***Helicobacter pylori* gastritis** has been approved by Japan's Ministry of Health, Labour and Welfare as an additional indication for H. pylori eradication by triple therapy with proton pump inhibitors.

Conclusion

- *H. pylori* is the most important factor for the development of gastric cancer.
- Considering the high incidence of gastric cancer and high prevalence of gastric cancer, it's time to make a reasonable decision based on best available data.
- Indications for Hp eradication should be expanded immediately in Korea.

Thank you for your attention.