Mide Kanseri Taramasında Pepsinojen I ve II ‘nin Önemi

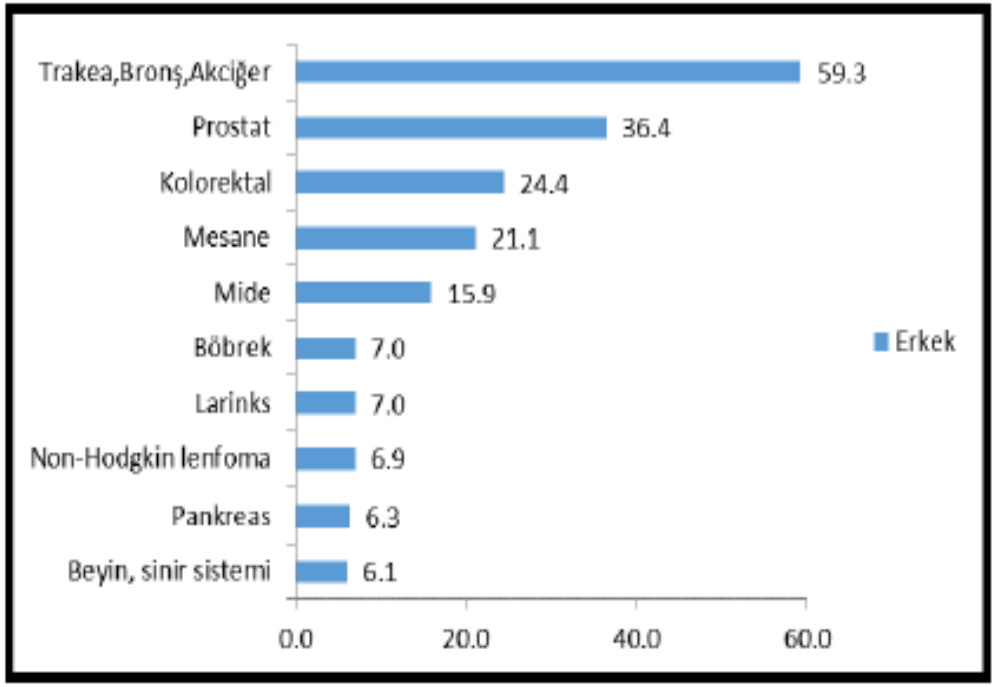
Prof Dr Necati Örmeci.

Ankara Üniversitesi Tıp Fakültesi

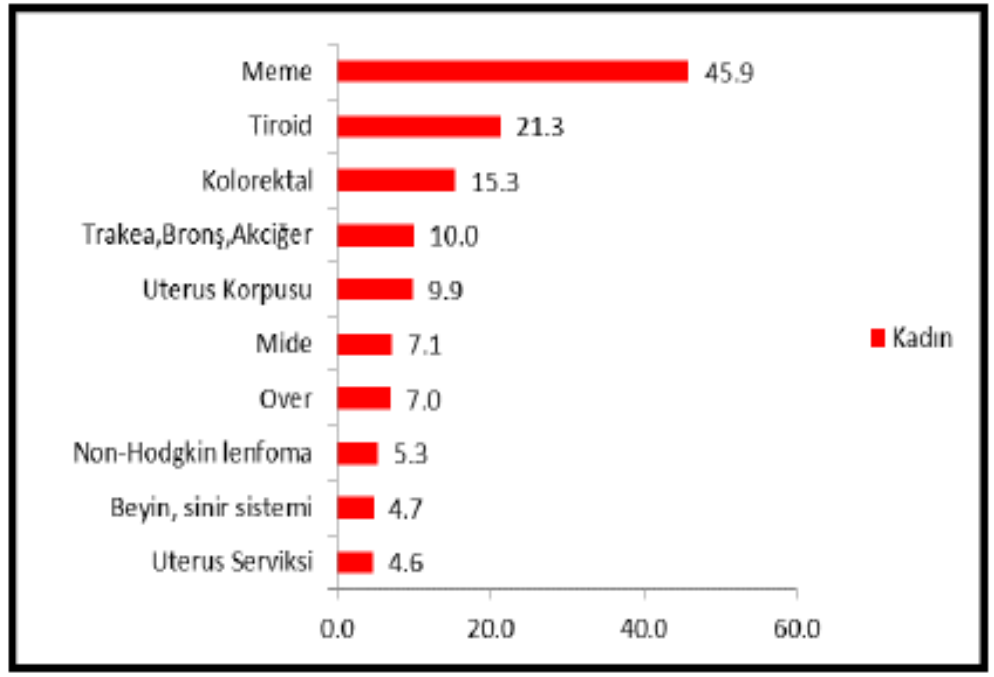
Gastroenteroloji Bilim Dalı

Öğretim Üyesi

Statistical Data for All Cancers from Turkish Ministry of Health



Şekil 7. Erkeklerde En Sık Görülen 10 Kanserin Yaşa Göre Standardize Edilmiş Hı
Birleşik Veri Tabanı, 2013) (Dünya Standart Nüfusu, 100.000 Kişide)



Şekil 8. Kadınlarda En Sık Görülen 10 Kanserin Yaşa Göre Standardize Edilmiş Hızları (Türkiye
Birleşik Veri Tabanı, 2013) (Dünya Standart Nüfusu, 100.000 Kişide)

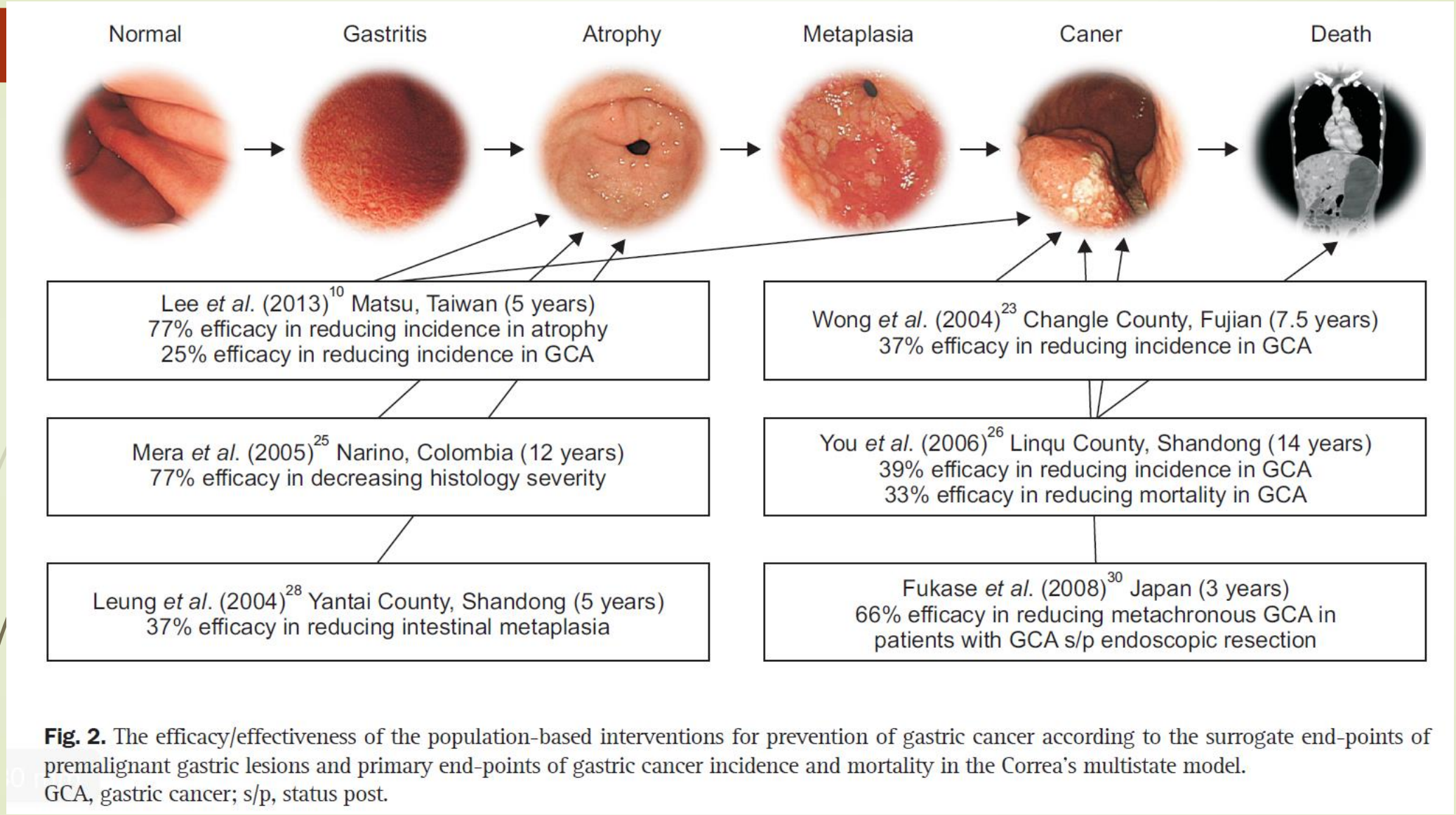


Fig. 2. The efficacy/effectiveness of the population-based interventions for prevention of gastric cancer according to the surrogate end-points of premalignant gastric lesions and primary end-points of gastric cancer incidence and mortality in the Correa's multistate model.
GCA, gastric cancer; s/p, status post.

Lee C-Y et al, Gut and Liver, Vol. 10, No. 1, January 2016, pp. 12-26

Premalign Gastrik Lezyonlu Hastalarda Mide Kanser Gelişme Riski Araştırması(1)

Araştırma Popülasyonunun Temel Karakteristikleri

	Total	Atrofik gastrit	İntestinal metaplazi	Hafif-Orta displazi	Ciddi displazi
Hasta sayısı (n) (%)	92,250	22,365 (%24)	61,707 (%67)	7616 (%8,3)	562 (%0,6)
Erkek/Kadın	46,985/45,265	10,110/12,255	32,415/29,292	4153/3463	307/255
Yaş ortalaması	65,7	60,7	66,5	68,7	75,3
Barret özofagus	1,934 (%2,1)	460 (%2,1)	1219 (%2,0)	244 (%3.2)	11(%2,0)

Annemarie C. De Vries et al. Gastroenterology 134:945-952, 2008.

Screening for and Surveillance of Gastric Cancer

		Annual Incidence of Gastric Ca in 5 years
Atrophyc Gastritis	N= 22,365 (24 %)	0,1 %
İ. Metaplasia	N= 61,707 (67%)	0,25 %
Mild-Mod. Dysplasia	N= 7,616 (8%)	0,6 %
Severe Dysplasia	N=562 (0,6 %)	6 %

Risk factors for gastric cancer

Severe dysplasia Hazard Ratio : 40,14 (95% CI 32,2-50,1)

Increased age (7584 years) Hazard Ratio 3,75 (95 % CI 2,8-5,1)

Male Gender Hazard Ratio 1,50 (95 % CI 1,3-1,7)

Annemarie C de Vries et al. Gastroenterology 134:945-952,2008.

Risk of Developing Stomach Cancer (2)

	1. Yıl	5. Yıl	10. Yıl	Total
Chronic atrophyc gastritis	**% 0,3**	**% 0,6**	**% 0,8**	**161**
Intestinal metaplasia	**% 0,7**	**% 1,2**	**% 1,8**	**874**
Mild-Moderate dysplasia	**% 2,1**	**% 3,1**	**% 3,9**	**270**
Severe dysplasia	**% 24,9**	**% 29,5**	**% 32,7**	**165**

Annemarie C. De Vries et al. Gastroenterology 134:945-952, 2008

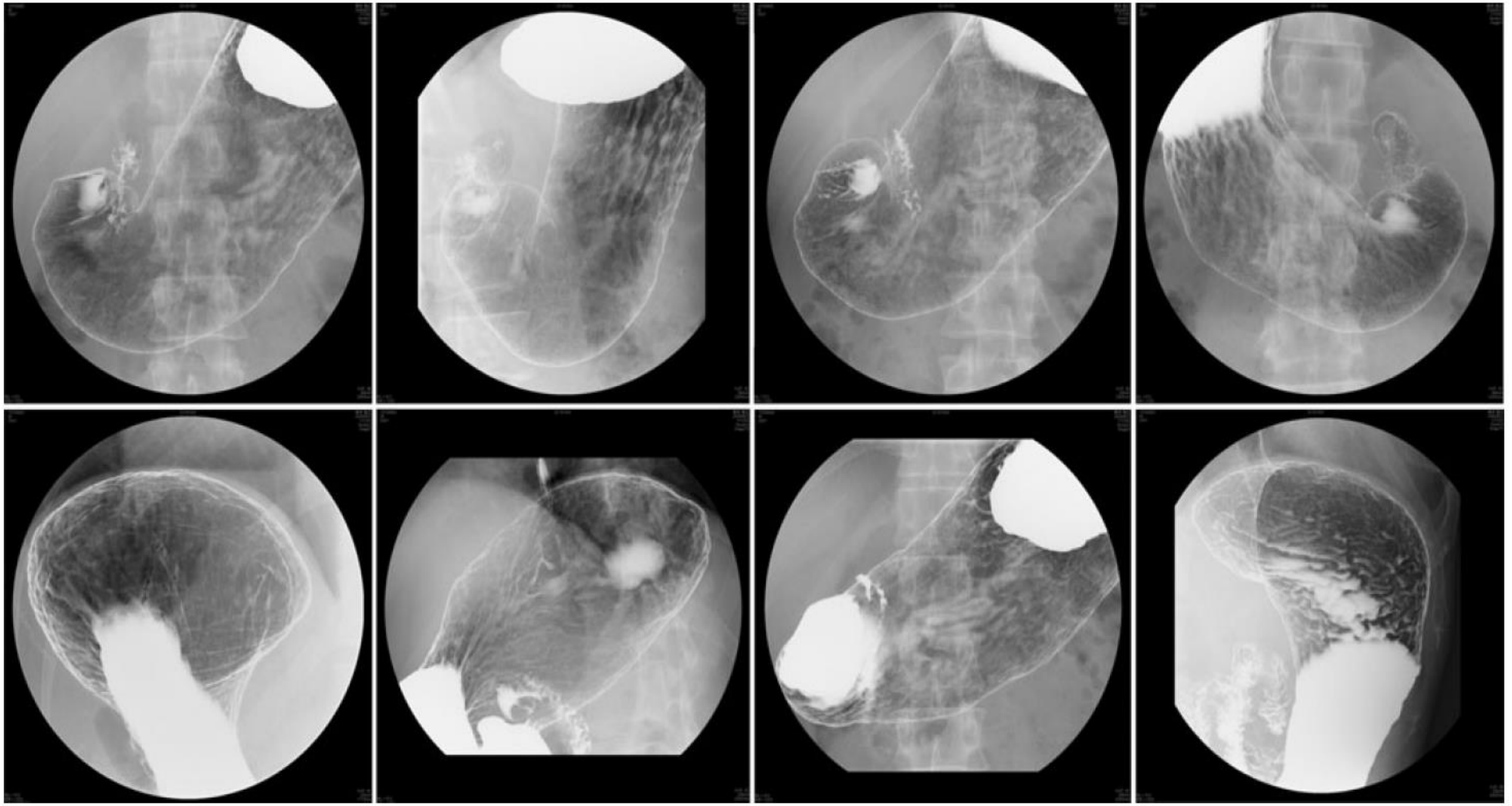
Histopatolojik tanım	Hasta Sayısı	Kanser Gelişimi n (%)	P. Değeri
Low grade displazi	90	8	
High grade displazi	16	11	P<0.001
Şüpheli invaziv kanser	3	1	
Tanımlanamayan	9		
Toplam	118	20 (%17)	

Takip süresi : 52 (12-206) ay

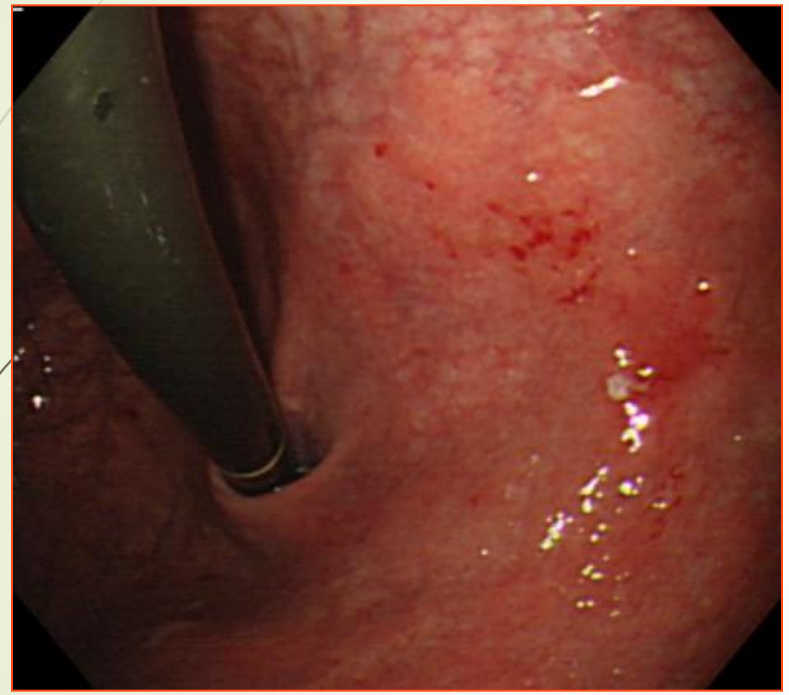
M. Rugge et al. Gut. 2003;52:1111-1116

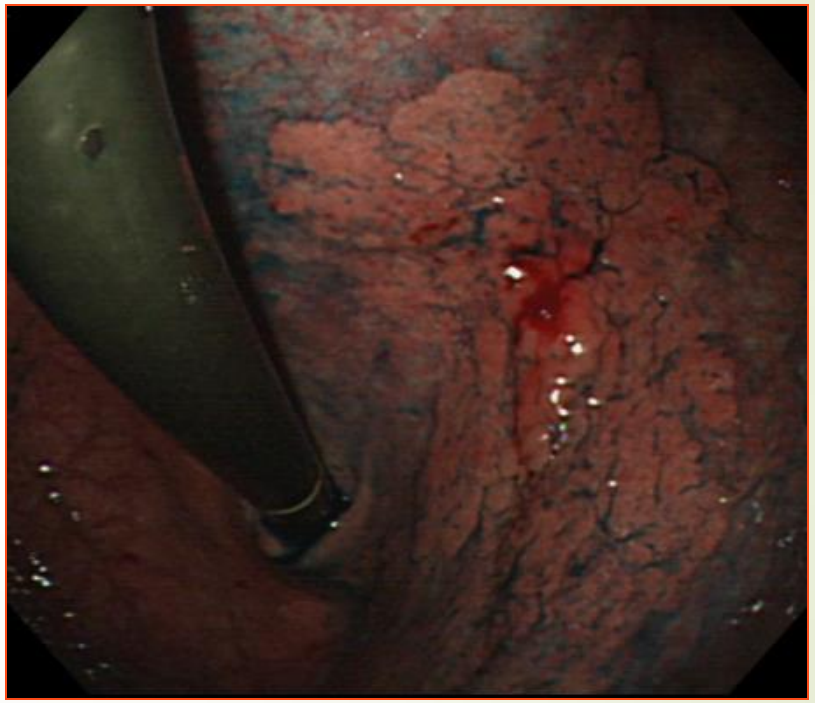
Mide kanserinde tarama neden önemli ?

Mass screening for gastric cancer: how to select patients for endoscopic examination

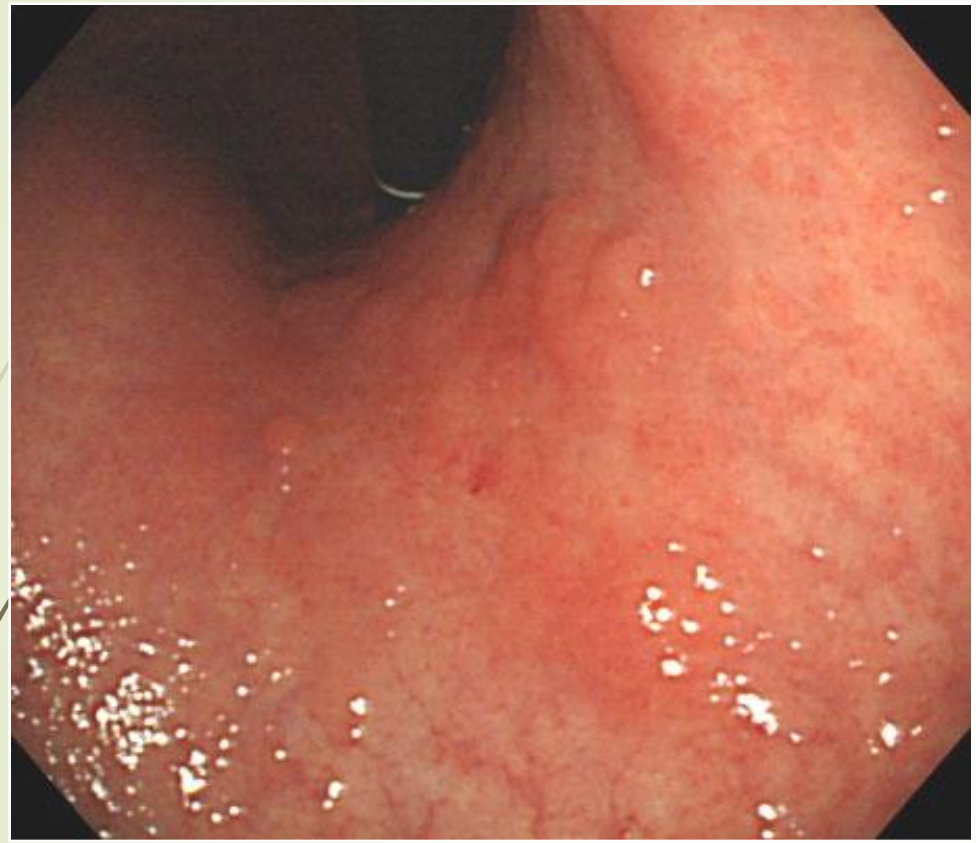


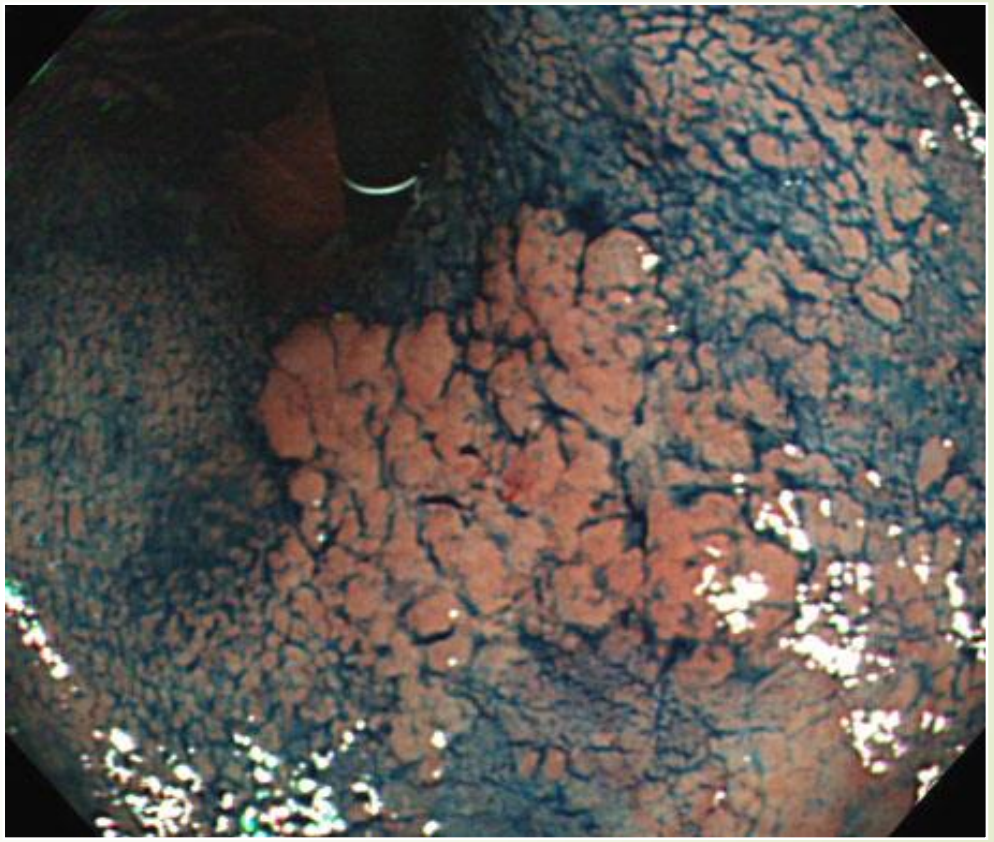
Nakashima H et al, Gastric Cancer (2010) 13: 78–83. DOI 10.1007/s10120-009-0538-3

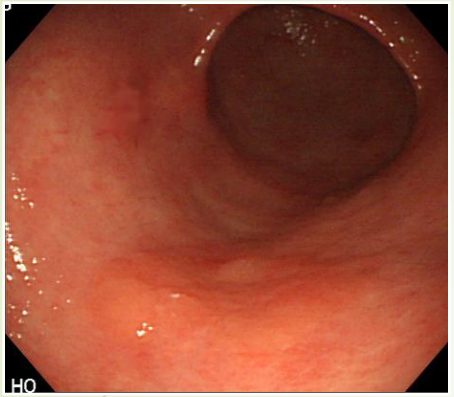
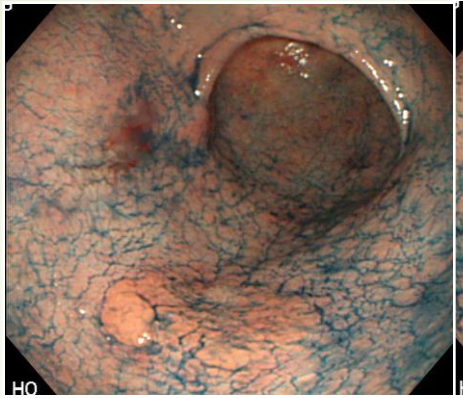
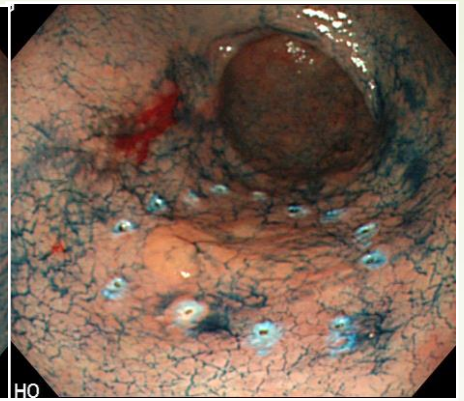
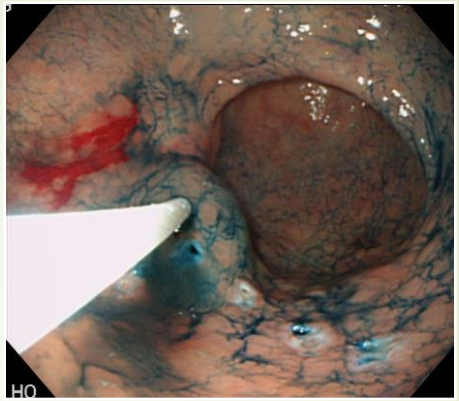
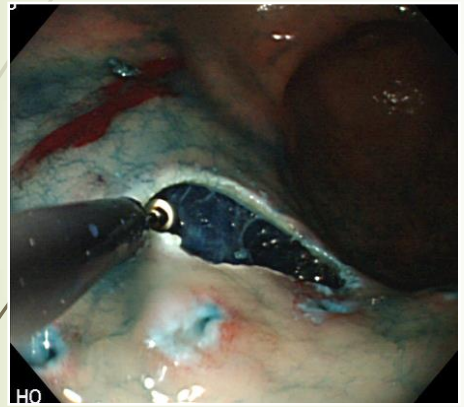
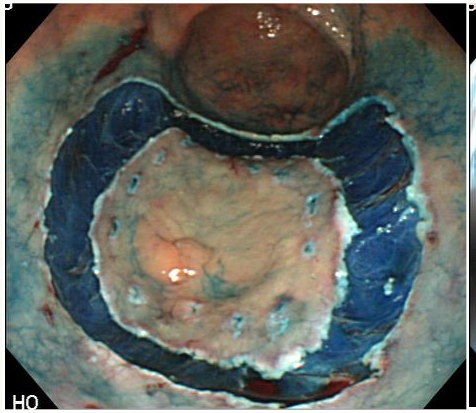
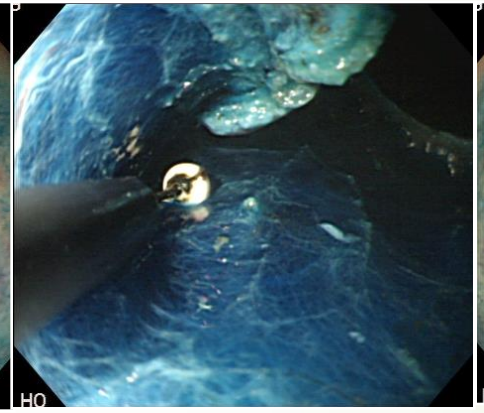
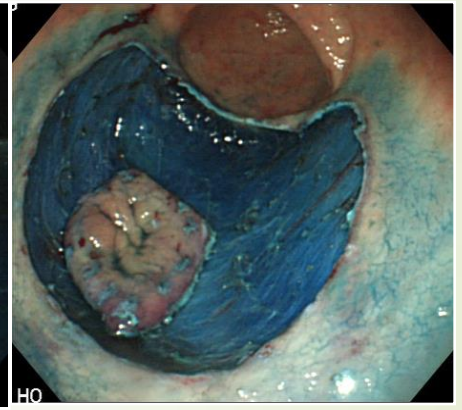
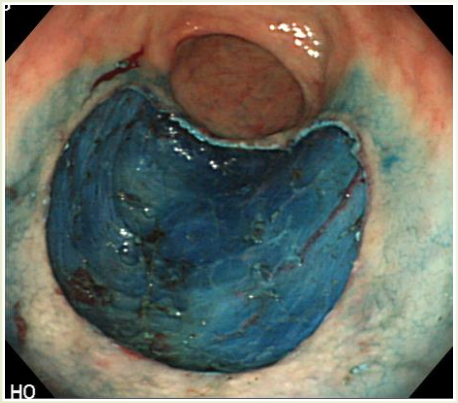
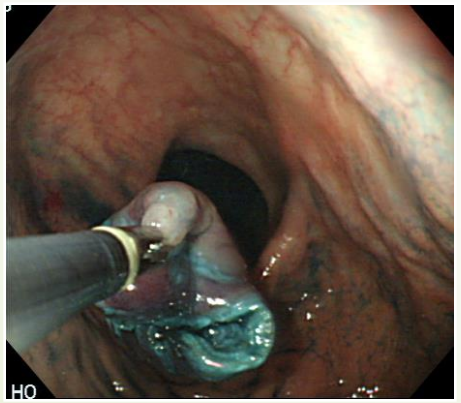
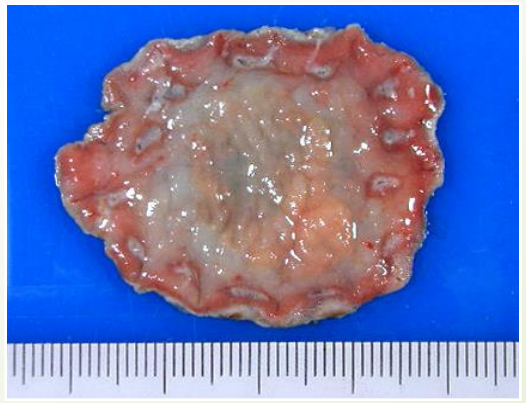




From Dr ONO.





Comparison of population-based gastric cancer screenings in Japan and Korea.

	Japanese guideline (2008)	Japanese guideline (2015)	Korean guideline
Radiology	○	○	○
Endoscopy	X	○	○
Serology	X	X	X
Starting Age	40	50	40
Interval (Y)	1	2–3	2

Sugano K et al, Best Practice & Research Clinical Gastroenterology 29 (2015) 895e905

Tanımlar

- **Pepsinojen , pepsin'in proenzimi olup Pepsinojen I ve Pepsinojen II olmak üzere 2 tipi mevcuttur.Gastrik lümene salınırlar. % 1 i serumda bulunur.**
- **Serum pepsinojen I**, korpusta, parietal hücrelere komşu **esas hücrelerden ve fundik glandlardaki mukus boyun hücrelerinden** sekrete olur.
- **Serum pepsinogen II**, **duodenal bulbus dahil mide mukozasının her yerinden pilorik ve Brunner bezi hücrelerinden salgılanır.**
- Pepsinogen I, mide tümörlerinde nadiren salgılanırken, Pepsinojen II undiferansiye tümörlerden ziyade **diferansiye mide tümörlerinde salgılanabilir**.
- Pepsinojen II nin tümör dokusunda expressionu, tümör prognozu açısından önemli bir belirteçtir.
- **Gastrin 17:** Mide **antrumundaki G hücreleri** tarafından salgılanır.
- Antrum ve korpusda süperfisyel gastrit gelişmesi durumunda her iki enzim serumda yükselir.
- Korpusda süperfisyel gastritin atrofik gastrite ilerlemesi durumunda Pepsinojen I azalırken , Pepsinojen II artar.

Pepsinogen I and II expressions in situ and their correlations with serum pesignogen levels in gastric cancer and its precancerous disease

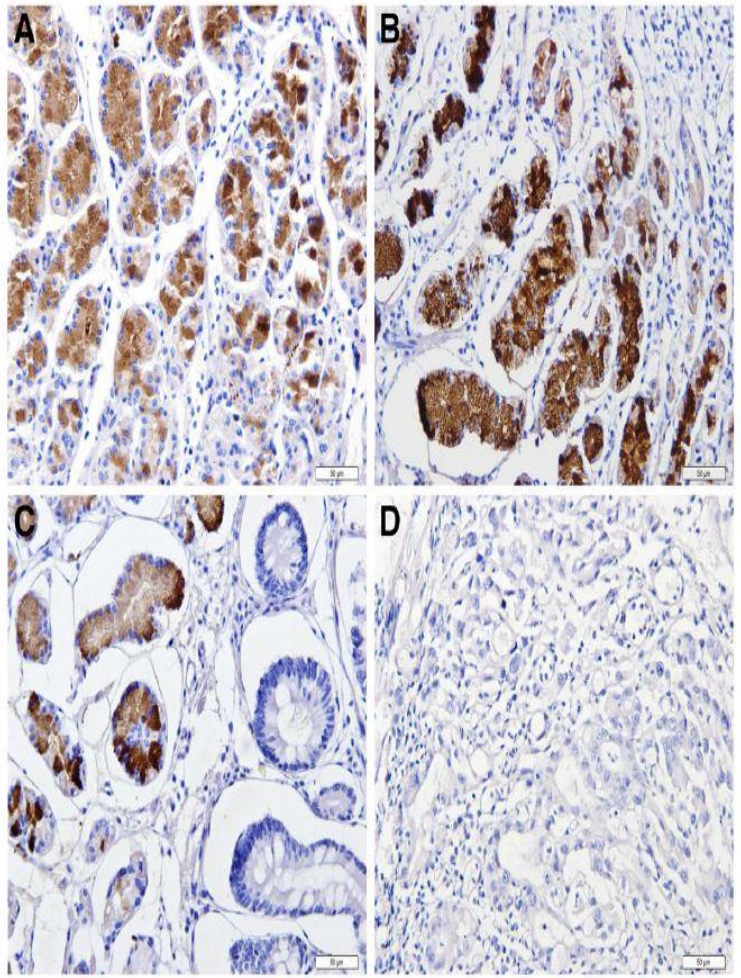


Figure 1 Expression of PGI in corpus glands in different gastric tissues (immunohistochemical staining × 200). **(A)** NOR r mucosa; **(C)** GA mucosa; **(D)** GC mucosa.

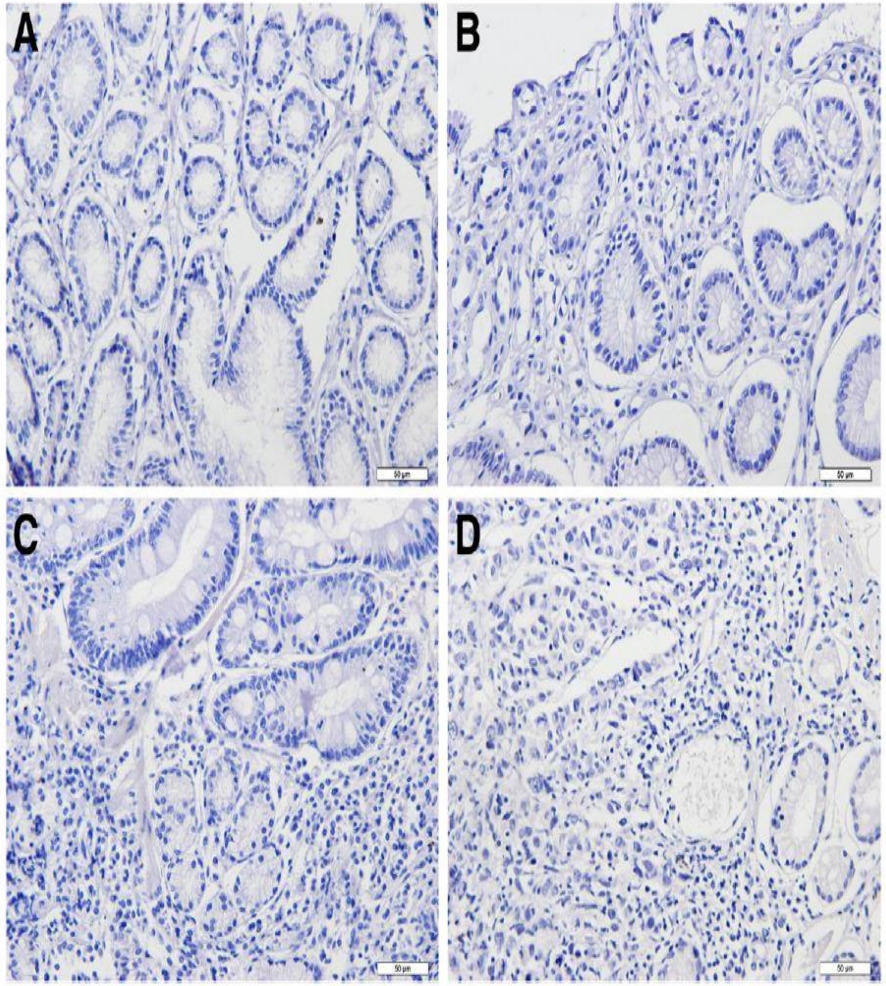


Figure 2 Negative expression of PGI in all antral glands in different gastric tissues (immunohistochemical staining × 200). **(A)** NOR mucosa; **(B)** GS mucosa; **(C)** GA mucosa; **(D)** GC mucosa.

Li et al. BMC Clinical Pathology 2013, 13:22

Pepsinogen I and II expressions in situ and their correlations with serum pesignogen levels in gastric cancer and its precancerous disease

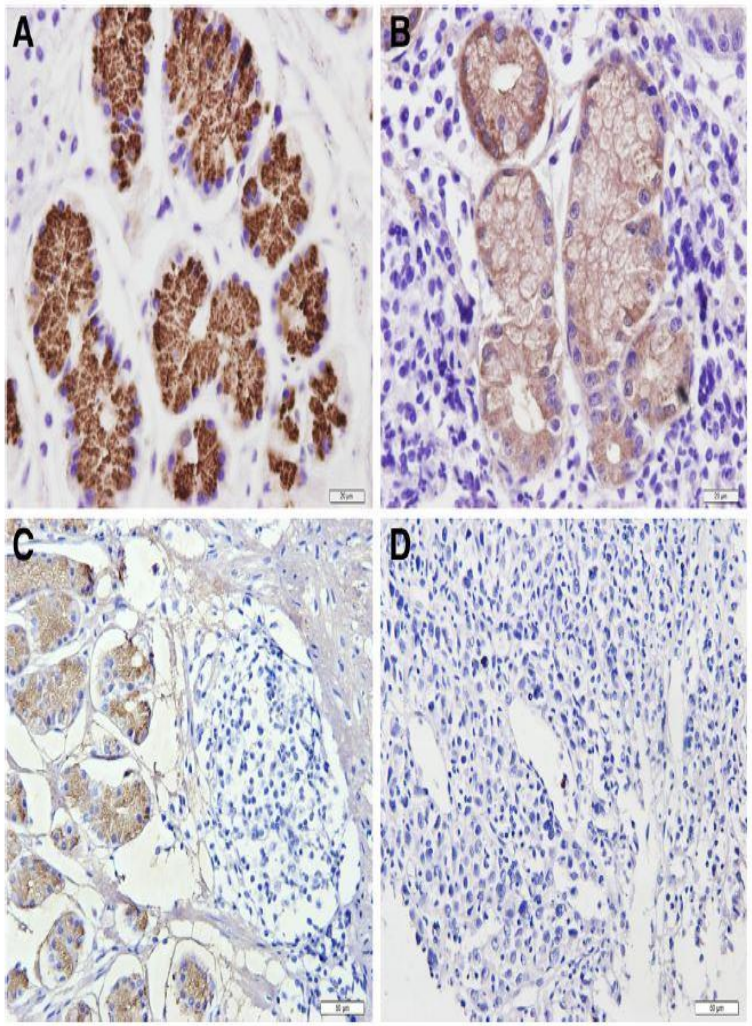


Figure 3 Expression of PGII in corpus glands in different gastric tissues (immunohistochemical staining × 200). **(A)** NOR mucosa; **(B)** GS mucosa; **(C)** GA mucosa; **(D)** GC mucosa.

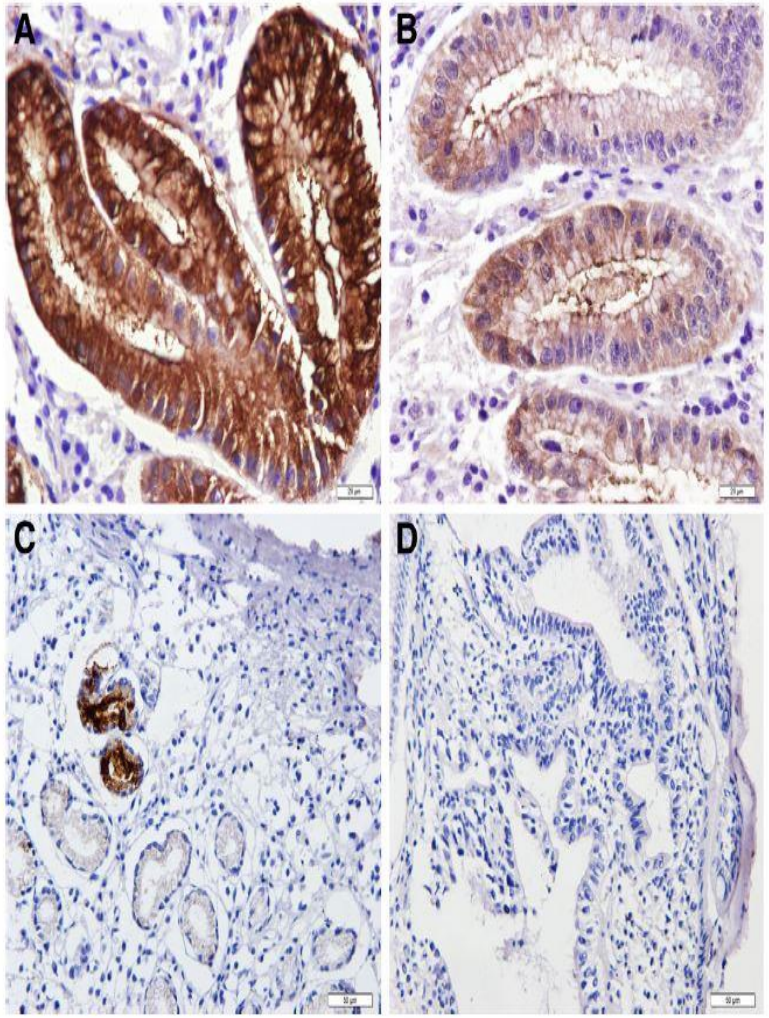


Figure 4 Expression of PGII in antral glands in different gastric tissues. **(A)** NOR mucosa (immunohistochemical staining × 400); **(B)** mucosa (immunohistochemical staining × 400); **(C)** GA mucosa (immunohistochemical staining × 200); **(D)** GC mucosa (immunohistochemical staining × 200).

Meta Analysis for Pepsinogen levels n=300,000

PGI < 70 mg / L

PGI / PG II < 3,0 are common cut off used for identification of patients with atrophyc gastritis.

Sencitivity : 77 %

Specificity : 73 %

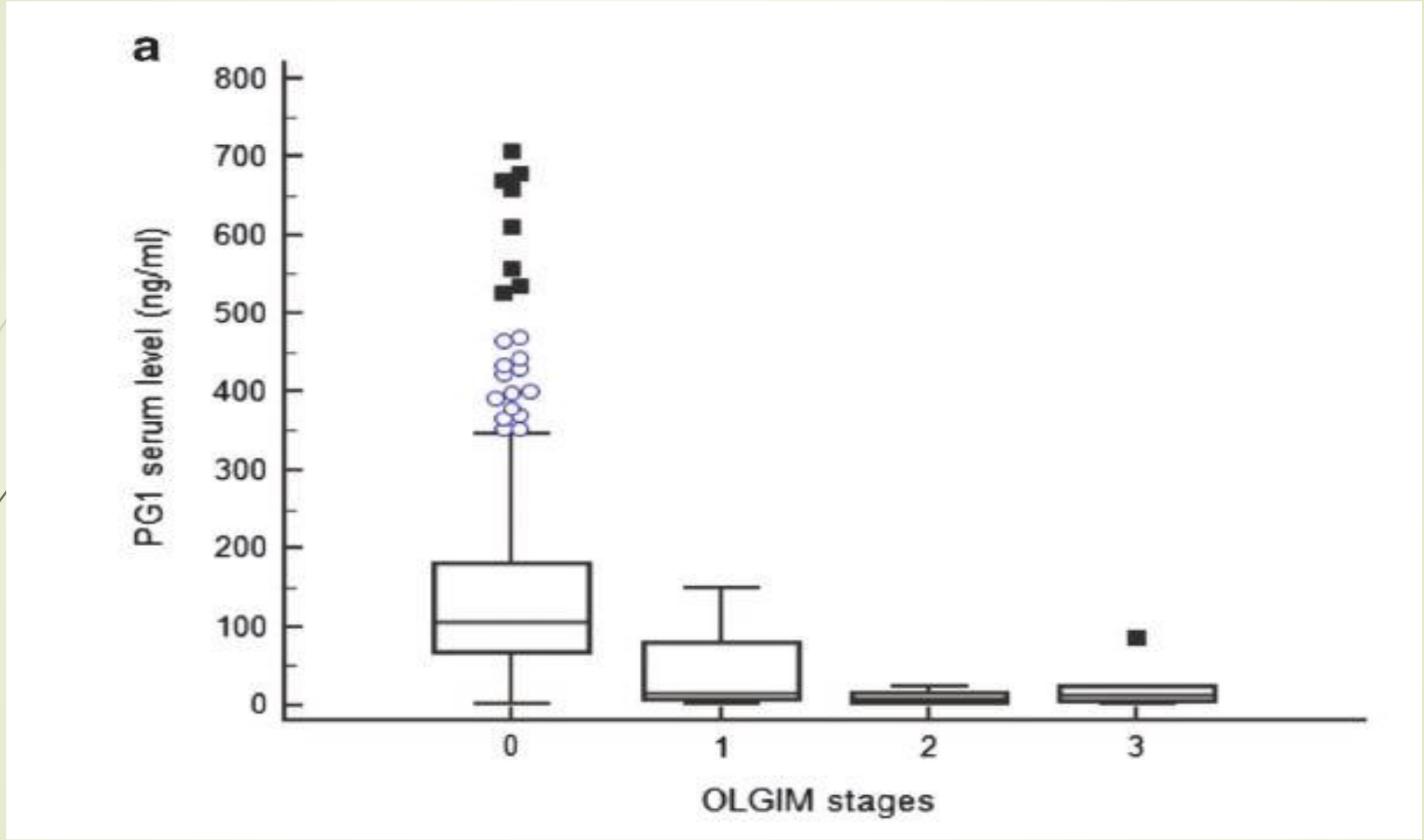
Leung WK et al, The Lancet Oncol 9:279-287,2008

Table 1 Serum PG I and II levels in various gastric disorders (n = 282)

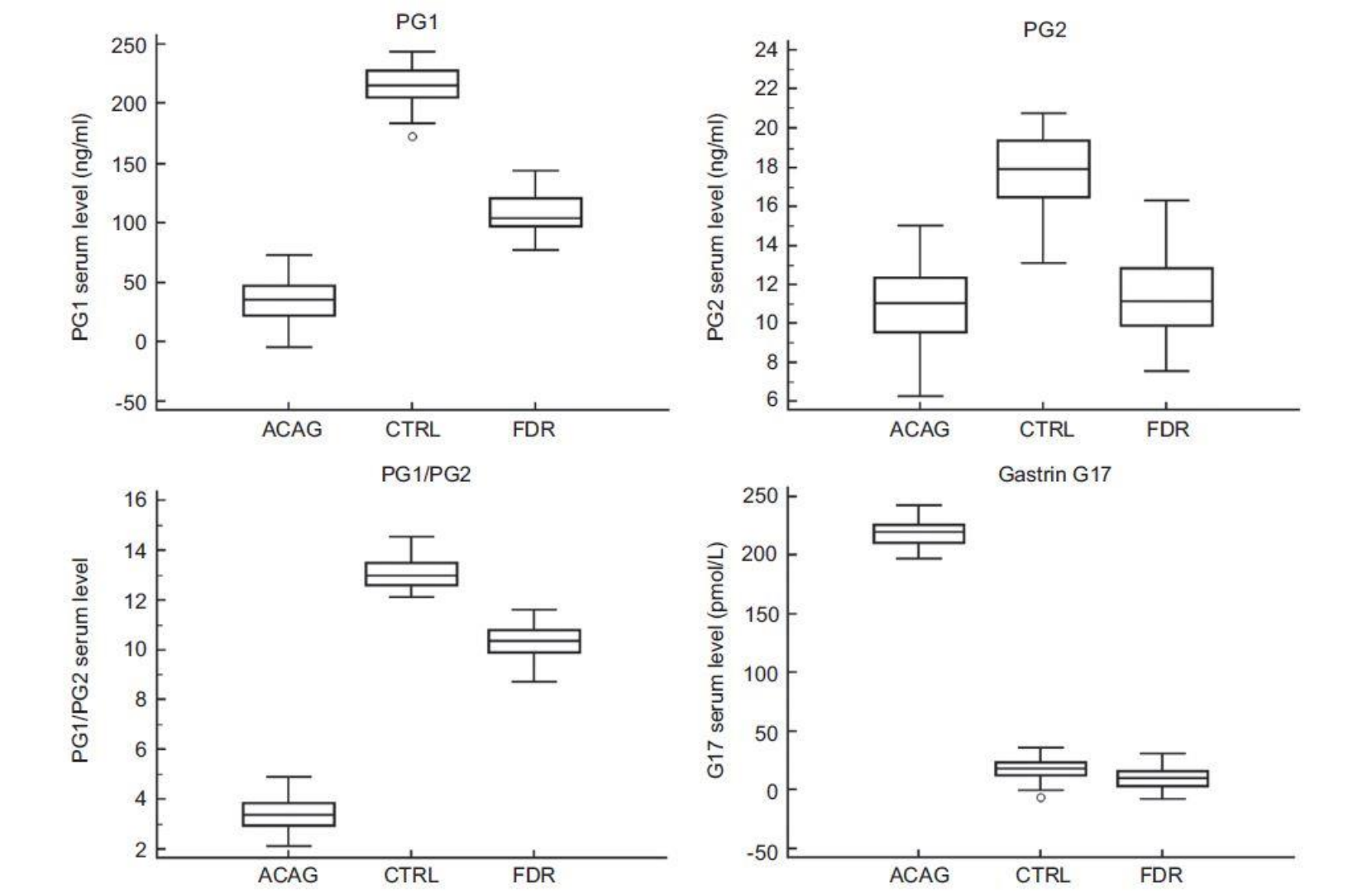
Group	N	PG I (μg/L)	PG II (μg/L)	PG I/PG II
Healthy controls	34	118.39 ± 47.80	12.39 ± 5.90	11.74 ± 6.23
Non-atrophic gastritis	55	112.46 ± 51.71	12.57 ± 5.98	10.63 ± 5.74
Atrophic gastritis	20	93.63 ± 49.34	10.85 ± 4.58	11.07 ± 5.78
Early gastric cancer	13	71.48 ± 28.78$^{‡▼}$	14.22 ± 4.90	5.19 ± 1.70‡†
Advanced gastric cancer	69	53.39 ± 34.03‡†	12.29 ± 5.63	4.88 ± 3.76‡†
Gastric ulcer	36	147.58 ± 57.81$^{▲†}$	15.60 ± 13.42	14.47 ± 13.02
Duodenal ulcer	31	217.43 ± 51.12‡†	21.90 ± 19.45$^{▲†}$	18.57 ± 16.63$^{▲†}$
Gastrectomy	23	40.70 ± 15.38‡*	8.52 ± 4.52	4.43 ± 2.38‡
Recurrence after gastrectomy	1	289.32	65.89	4.39

Data were shown as mean ± SD.
$^{‡}p < 0.005$, $^{▲}p < 0.05$ vs. Healthy controls; $^{†}p < 0.005$, $^{▼}p < 0.05$ vs. NAG; $^{*}p < 0.05$ vs. CAG.

Zhang et al. BMC Gastroenterology 2014, 14:3



Re VD et al, Clinical and Translational Gastroenterology (2016) 7, e183; doi:10.1038/ctg.2016.42



Re VD et al, Clinical and Translational Gastroenterology (2016) 7, e183; doi:10.1038/ctg.2016.42

Variable	n	PG1 Mean ng/ ml (Std)	PG2 Mean ng/ ml (Std)	PG1/PG2 ratio	G17 Mean pmol/L (Std)
CTRL	53	215.7 (15)	18.3 (2)	13.2 (0.6)	19.3 (16)
FDR-GC	82	110.2 (13)	11.2 (2)	10.0 (0.5)	14.1 (14)
ACAG	67	40.7 (13)	10.8 (2)	3.5 (0.5)	221 (15)
p^c		*<0.001*	*0.001*	*<0.001*	*<0.001*

Figure 1 Box-and-whisker plots of age- and gender-adjusted means of pepsinogens 1 and 2 (PG1 and PG2), PG1/PG2 ratio, and gastrin G17 for comparison of patients and control groups. Mean and s.e. are reported in more detail in the graph below. Median PG1 level and PG1/PG2 ratio were found significantly decreased in individuals at risk for GC (i.e., ACAG and FDR-GC) compared with controls. Gastrin G17 showed the highest mean level associated with ACAG status. ACAG, autoimmune chronic atrophic gastritis; CTRL, general population; FDR-GC, first-degree relatives of patient with gastric cancer. *Pc*: Bonferroni corrected value of analysis of variance (ANOVA) for age and gender.

Re VD et al, Clinical and Translational Gastroenterology (2016) 7, e183; doi:10.1038/ctg.2016.42

Combination of Helicobacter pylori Antibody and Serum Pepsinogen as a Good Predictive Tool of Gastric Cancer Incidence: 20-Year Prospective Data From the Hisayama Study. N: 2446/123 stomach Ca.

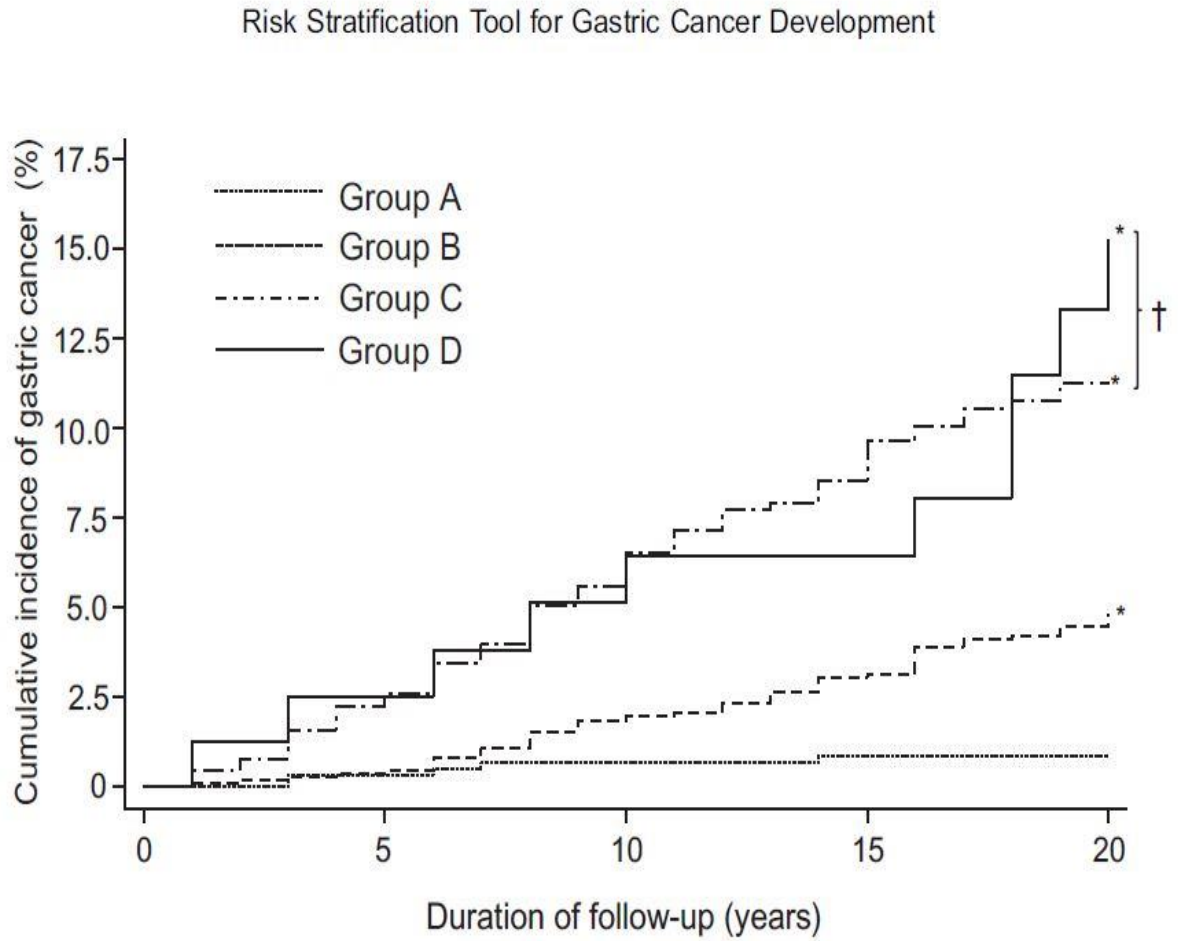


Figure. 20-year cumulative incidence of gastric cancer according to the combination of *H. pylori* antibody and serum pepsinogen at baseline. Groups A to D, see text for details.
*$P < 0.01$ vs Group A, †$P = 0.53$ by log rank test.

Group D (H. pylori[−], sPG[+]),

Group C (H. pylori[+], sPG[+]),

Group B (H. pylori[+], sPG[−])

Group A (H. pylori[−], sPG[−]),

Ikeda F et al, J Epidemiol 2016, doi:10.2188/jea.JE20150258

N=9293

Risk of Cancer development

Group A	N= 3324	Normal pepsinogen	H. Pylori (-)	0,04 % (95% CI : 0,02-0,09)
Group B	N= 2134	Normal pepsinogen	H. Pylori (+)	0,06% (95%CI : 0,03-0,13)
Group C	N= 1082	Atrophic pepsinogen	H. Pylori (+)	0,35% (95% CI : 0,23-0,57)
Group D	N=443	Atrophic pepsinogen	H. Pylori (-)	0,60% (95% CI : 0,34-1,05)

Every year endoscopıc examination was performed

Mean endoscopy : 5,1 year

Mean follow up : 4,7 year

The annual incidence of gastric cancer was determined of anually endoscopic examinations.

Watabe H. Et al. Gut 54:764-768,2005.

The Impact of Pepsinogen I/II ve gastrin 17 levels for the diagnosing of stomach cancer in early stage. n=11707

- Pepsinogen I ≤ 70 mg/l
- Pepsinogen I/II ≤ 3.0 ise

- Predictivity rate : % 0.55
- False negativity : % 20
- False positivity : % 1.5

Yoshida S. Et al. Best Practice and Research Clinical Gastroenterology 20(4):745-765, 2006

Significance of Serum Pepsinogens as a Biomarker for Gastric Cancer and Atrophic Gastritis Screening: A Systematic Review and Meta-Analysis: 31 Çalışma (n:1520 GC, 2265 AG)

Table 5. Sensitivity analyses for the diagnostic accuracy of SPG for AG.

Study omitted	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC (95% CI)
Manami Inoue,1998	0.68 (0.53–0.80)	0.90 (0.77–0.95)	17.00 (7.88–36.70)	0.85 (0.82–0.88)
F. Sitas, 1993	0.72 (0.59–0.82)	0.88 (0.75–0.95)	17.89 (8.47–37.79)	0.86 (0.82–0.88)
A. Oksanen, 2000	0.73 (0.61–0.82)	0.86 (0.74–0.92)	15.94 (7.70–31.37)	0.85 (0.82–0.88)
Cai-yun He, 2011	0.69 (0.54–0.81)	0.89 (0.77–0.95)	18.27 (8.61–38.76)	0.86 (0.83–0.89)
Diana Aulia, 2009	0.69 (0.54–0.81)	0.89 (0.79–0.95)	18.68 (9.26–37.69)	0.87 (0.83–0.89)
Metin Agkoc, 2010	0.67 (0.53–0.79)	0.87 (0.75–0.94)	13.56 (7.33–25.08)	0.84 (0.80–0.87)
Katsunori Iijima, 2009	0.71 (0.56–0.82)	0.87 (0.74–0.94)	16.42 (7.70–35.03)	0.86 (0.82–0.88)
Hyojin Chae, 2008	0.68 (0.53–0.80)	0.88 (0.75–0.95)	15.25 (7.36–31.61)	0.85 (0.81–0.87)
R. Sierra, 2006	0.67 (0.53–0.78)	0.90 (0.80–0.95)	17.32 (8.31–36.12)	0.86 (0.83–0.89)
Ma ´rio Dinis-Ribeiro, 2004	0.69 (0.55–0.81)	0.89 (0.77–0.95)	18.00 (8.42–38.47)	0.86 (0.83–0.89)
Kai Chun WU, 2004	0.67 (0.53–0.79)	0.89 (0.76–0.95)	15.88 (7.32–33.52)	0.84 (0.81–0.87)
N Broutet, 2003	0.70 (0.55–0.81)	0.89 (0.77–0.95)	18.17 (8.52–38.76)	0.86 (0.83–0.89)
Abbas Zoalfaghari, 2013	0.69 (0.54–0.81)	0.89 (0.77–0.95)	18.07 (8.51–38.34)	0.86 (0.83–0.89)
David Y Graham, 2006	0.68 (0.54–0.80)	0.89 (0.77–0.95)	17.43 (8.24–36.86)	0.86 (0.82–0.88)
M. Kekki, 1991	0.67 (0.53–0.79)	0.87 (0.74–0.94)	13.55 (7.14–25.74)	0.84 (0.80–0.86)
G. Nardone, 2005	0.71 (0.58–0.82)	0.86 (0.74–0.92)	14.75 (7.39–29.46)	0.85 (0.82–0.88)

Note: AUC, area under the summary receiver operating characteristic curve; DOR, diagnostic odds ratio; CI, confidence interval.

doi:10.1371/journal.pone.0142080.t005

Significance of Serum Pepsinogens as a Biomarker for Gastric Cancer and Atrophic Gastritis Screening: A Systematic Review and Meta-Analysis: 31 Çalışma (n:1520 GC, 2265 AG)

Table 4. Sensitivity analyses for the diagnostic accuracy of SPG for GC.

Study omitted	Sensitivity (95% CI)	Specificity(95% CI)	DOR(95% CI)	AUC (95% CI)
F Kitahara, 1999	0.68 (0.59–0.76)	0.73 (0.61–0.83)	5.80 (3.48–9.68)	0.75 (0.71–0.79)
Abraham M. Y. Nomura, 2005	0.71 (0.63–0.78)	0.71 (0.58–0.82)	6.16 (3.61–10.49)	0.77 (0.73–0.80)
Masahira Haneda, 2012	0.70 (0.61–0.77)	0.74 (0.61–0.83)	6.37 (3.79–10.69)	0.77 (0.73–0.80)
Ryousuke kikuchi, 2011	0.68 (0.59–0.76)	0.74 (0.60–0.83)	6.05 (3.55–10.30)	0.76 (0.72–0.79)
KENTARO SHIKATA, 2012	0.69 (0.60–0.77)	0.74 (0.62–0.83)	6.11 (3.59–10.38)	0.76 (0.72–0.80)
Rafael Lomba-Viana, 2012	0.69 (0.60–0.76)	0.75 (0.64–0.84)	6.48 (3.95–10.62)	0.77 (0.73–0.80)
Jung Mook Kang, 2008	0.70 (0.61–0.78)	0.74 (0.62–0.83)	6.59 (4.01–10.83)	0.77 (0.73–0.81)
Xiao-mei Zhang, 2014	0.69 (0.60–0.77)	0.71 (0.60–0.80)	5.39 (3.41–8.52)	0.75 (0.71–0.79)
SHIGETO MIZUNO, 2009	0.69 (0.60–0.77)	072 (0.60–0.82)	5.71 (3.45–9.47)	0.76 (0.72–0.79)
Yu-Yan Huang, 2013	0.66 (0.58–0.73)	0.76 (0.66–0.84)	6.12 (3.62–10.33)	0.75 (0.71–0.79)
Zhong-Lin Yu, 2008	0.70 (0.61–0.77)	0.73 (0.60–0.82)	6.16 (3.63–10.56)	0.77 (0.73–0.80)
Masaharu Yoshihara, 1998	0.67 (0.59–0.75)	0.76 (0.65–0.84)	6.38 (3.85–10.58)	0.76 (0.73–0.80)
F.-Y. CHANG, 1992	0.69 (0.60–0.77)	0.73 (0.60–0.82)	5.91 (3.50–9.96)	0.76 (0.72–0.80)
Metin Agkoc, 2010	0.68 (0.58–0.75)	0.71 (0.60–0.80)	5.15 (3.40–7.79)	0.74 (0.70–0.78)
Kazuo Aoki,1997	0.69 (0.60–0.77)	0.72 (0.60–0.82)	5.77 (3.46–9.62)	0.76 (0.72–0.79)

Note: AUC, area under the summary receiver operating characteristic curve; DOR, diagnostic odds ratio; CI, confidence interval

doi:10.1371/journal.pone.0142080.t004

Accuracy of GastroPanel for the diagnosis of atrophic gastritis

Prospektif, randomize, çift kör mültisentrik çalışma. N:91

Table 2 GastroPanel versus histology contingency table

	Histology		
	No atrophy	Atrophy	Total
GastroPanel			
No atrophy	60	5	65
Atrophy	15	5	20
Total	75	10	85

CAG için sensitivite: 50% (95% CI= 39–61%),
CAG için specificite 80% (95% CI= 71–88%),
Pozitif Prediktivite 25% (95% CI =16–34%)
Negative Prediktivite 92% (95% CI= 86–98%)
Positive likelihood 2.4 (95% CI =1.1–5.2)
Negative likelihood 0.6 (95% CI= 0.3–1.18%)

GastroPanel kronik atrofik Gastrit tanısı için yeterince kesin olmadığı için klinik pratikte sistematik olarak kullanılması tavsiye edilmez.
İspanyol Gastroenteroloji H.Pylori Çalışma Grubu.

McNichol AG et al,European Journal of Gastroenterology & Hepatology 2014, 26:941–948

RİSK FACTORS (2)

- **Gastric Polyps**
- **Pernisiyous Anemia**
- **Conjenital Cystic Stomach Diseases**
- **Menetrier Disease**
- **Ectopic Pancreas**
- **Gastric Resections**

Kapadia C.R. J Clin Gastroenterol 2003;36 (suppl 1):S29-S36

RİSK FACTORS (3)

- Chronic Atrophyc Gastritis
- Intestinal Metaplasia
- Dysplasia
- Helicobakter Pylori

The Cost Effectiveness

* The screening of high risk populations rather than population screening might be more cost effective in most Asian countries.

Parsonnet J et al, Lancet 1996; 348: 150–54.

Sonuçlar

- Mide kanserinin endemik görüldüğü ülkelerde **(>70/100 000), 50 yaş** üzerindeki bireylerde **mide kanseri açısından tarama yapılabilir.**
- **Türkiye gibi orta derecede veya düşük riskli ülkelerde mide kanseri açısından tarama yapılması maliyet etkin değildir.**
- Mide kanserinin orta derecede veya düşük riskli olduğu ülkelerde, **yüksek risk grubundaki bireylerin taranması maliyet etkindir.**
- **Türkiye için H.Pylori eradikasyonu, yalnızca yüksek risk grubuna giren bireylerde yapılmalıdır. Her H.Pylori pozitif bireyde eradikasyon yapılması maliyet etkin değildir.**
- Mide kanseri için yüksek risk grubuna giren hastalar, **Pepsinojen I/II tetkiki ile yılda bir, veya Endoskopik muayene ile her iki yılda bir taranmalıdır**