
2021
NCSCG
18TH ANNUAL HYBRID
GI SYMPOSIUM
June 26-27, 2021

Precancerous Lesions of the Upper Digestive Tract

Presented at the 18th Annual Northern California Society for Clinical Gastroenterology Symposium in Monterey, CA

Robert Huang, MD
Instructor
School of Medicine

STANFORD
UNIVERSITY

26 June, 2021

Learning Objectives

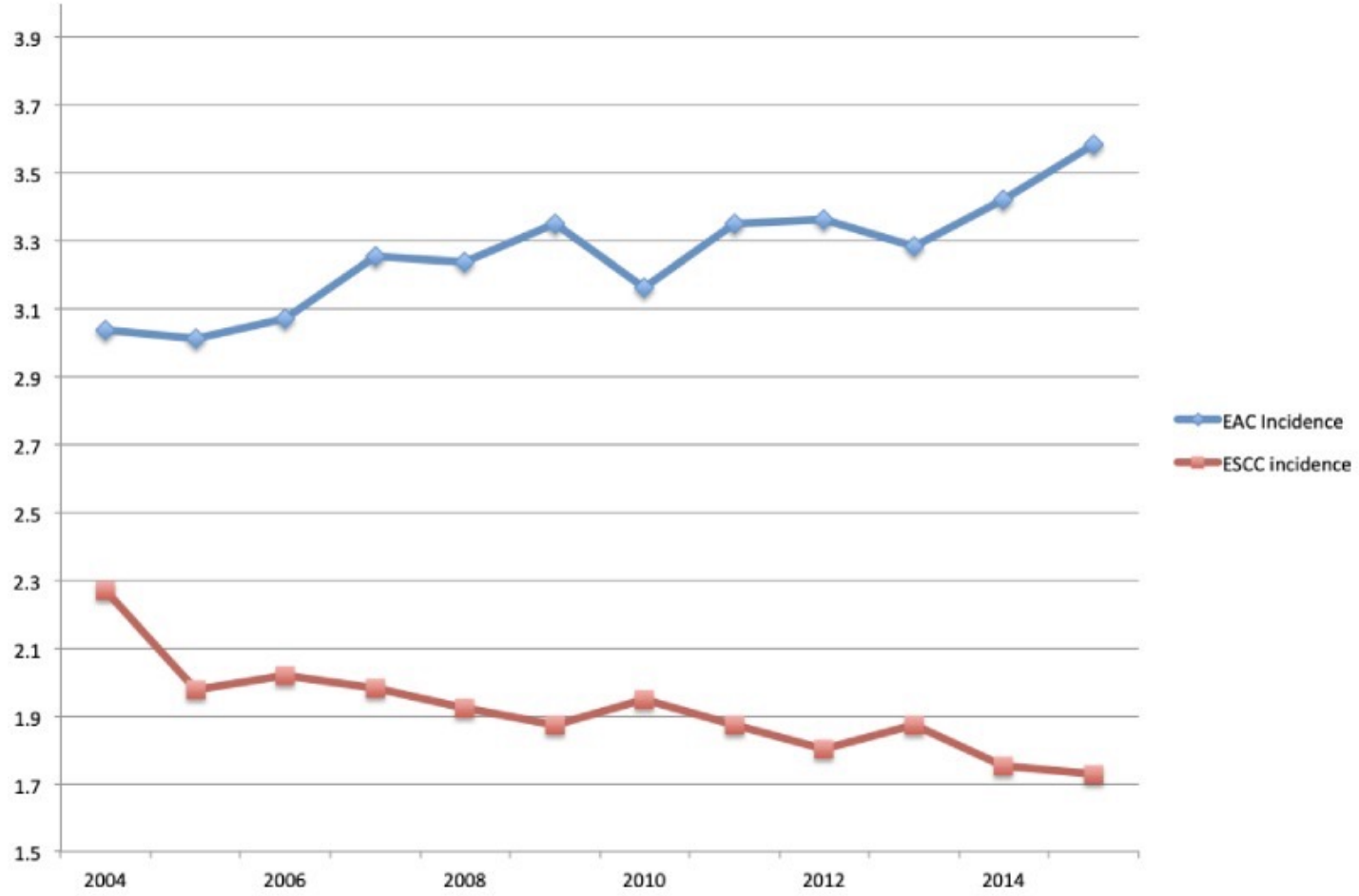
- Review current Professional Society recommendations for esophageal cancer screening and surveillance
- Review current Professional Society recommendations for gastric cancer screening and surveillance
- Interpret screening in a framework of high-value care

Disclosures

- I am supported by the National Cancer Institute of the National Institutes of Health under Award Number K08CA252635. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

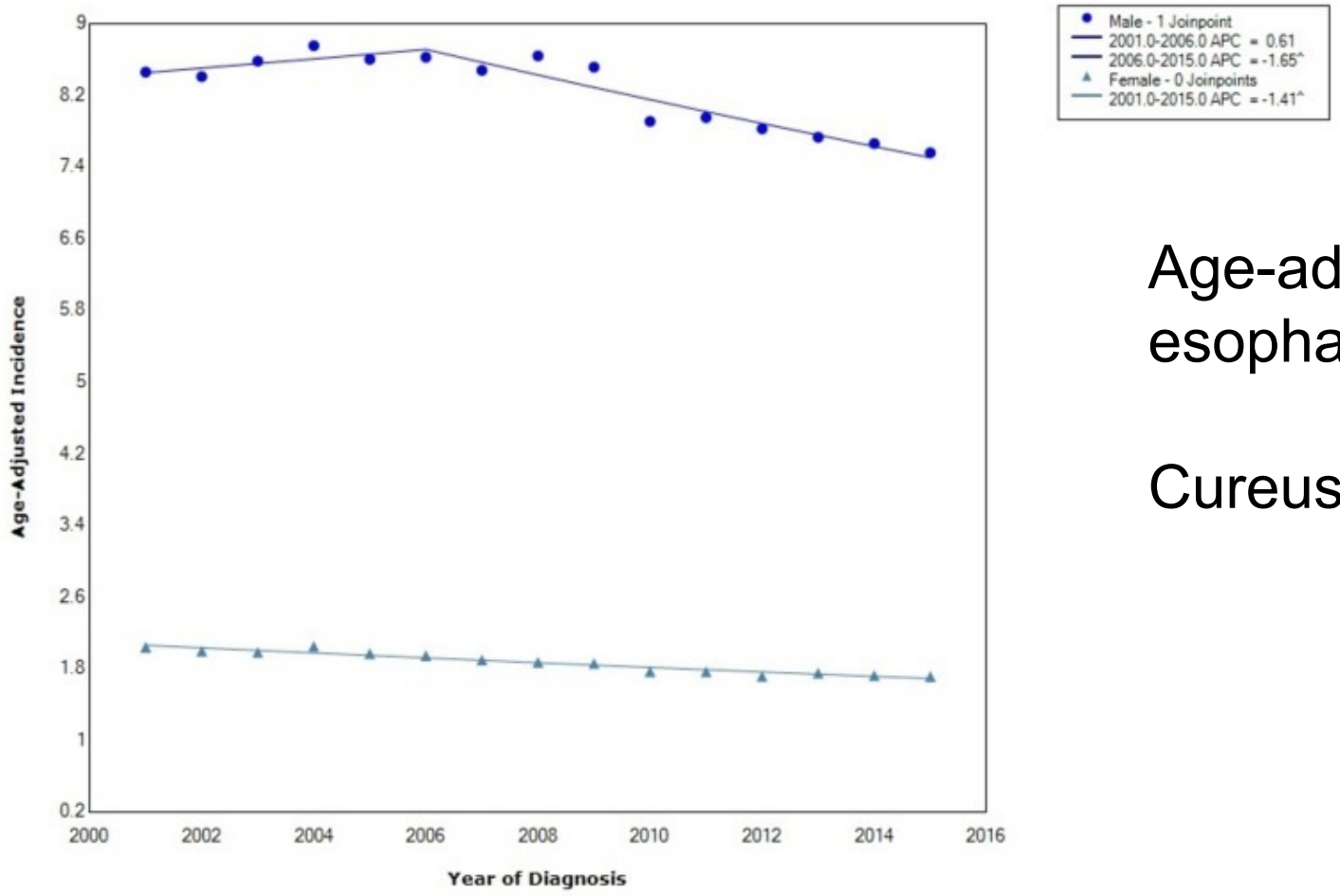
Esophageal Cancer Screening and Surveillance

Secular Trends in Esophageal Cancer



Annual incidence rate of esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). World J Oncol. 2020 Apr; 11(2): 55–64.

Trends by Sex



Age-adjusted incidence by sex of esophagus cancer (all histologic types).

Cureus. 2018 Dec; 10(12): e3709.

Barrett's Esophagus

- Barrett's Esophagus (BE) represents a a change of the normal squamous epithelium of the distal esophagus to a columnar-lined intestinal metaplasia. An established risk factor for esophageal adenocarcinoma (EAC) and GE junction adenocarcinoma (GEJAC).
- Risk factors for BE include
  - long-standing gastroesophageal reflux disease (GERD)
  - Male sex
  - Central obesity (Clin Gastroenterol Hepatol 2013 ; 11 : 1399 – 412)
  - Age over 50 years (Am J Gastroenterol 2013 ; 108 : 353 – 62)
  - Tobacco use, any lifetime (J. Gastroenterol Hepatol 2013 ; 28 : 1258 – 73
  - White race (vs Hispanics or Asians)
  - Family history of BE, EAC, or GEJAC
  - Alcohol consumption has not been demonstrated to be a significant risk factor for BE (potentially protective effect) (Gastroenterology 2009 ; 136 : 799 – 805).
  - *H. pylori* infection may be protective against BE (Clin Gastroenterol Hepatol 2014 ; 12 :239 – 45. Am J Gastroenterol 2014 ; 109 : 357 – 68.)
- Annual risk of progression estimated to be 0.25% per year for general BE population, 0.2-1.2% per year for BE with low-grade dysplasia (LGD), and 4-8% for BE with high-grade dysplasia (HGD) (Clin Gastroenterol Hepatol. 2006;4(5):566, Am J Gastroenterol. 2011;106(7):1231.)

Societal Guidance for BE Management

Society	Guidance					
	Screening for BE	Diagnosis and Staging of BE	Surveillance of BE	Diagnosis of Dysplasia	Management of Dysplasia	Post-EET Surveillance
American College of Gastroenterology	X	X	X	X	X	X
American Gastroenterological Association		X		X	X	X
American Society for Gastrointestinal Endoscopy	X		X	X	X	X

Whom Should we Screen for BE?

- Screening of the General Population is not recommended
- American College of Gastroenterology 2016 recommendations:
  - Screening for BE may be considered in men with chronic (>5 years) or frequent (weekly or more) symptoms of GERD and two or more risk factors for BE (age > 50, Caucasian race, central obesity, current or past smoking, and 1st degree family hx of BE or EAC)
  - In females, screening can be considered in individual cases as determined by the presence of multiple risk factors for BE
- American Society of Gastrointestinal Endoscopy 2019 (Standards of Practice document):
  - There is insufficient evidence on the effectiveness of screening for BE. However, if screening endoscopy for BE is performed, we suggest a screening strategy that identifies an at-risk population. An at-risk population is defined as individuals with a family history of EAC or BE (high risk) or patients with GERD plus at least 1 other risk factor (moderate risk).

Am J Gastroenterol 2016; 111:30–50; *Gastrointest Endosc* 2019;90(3): 335-359.

Diagnosis and Staging of BE

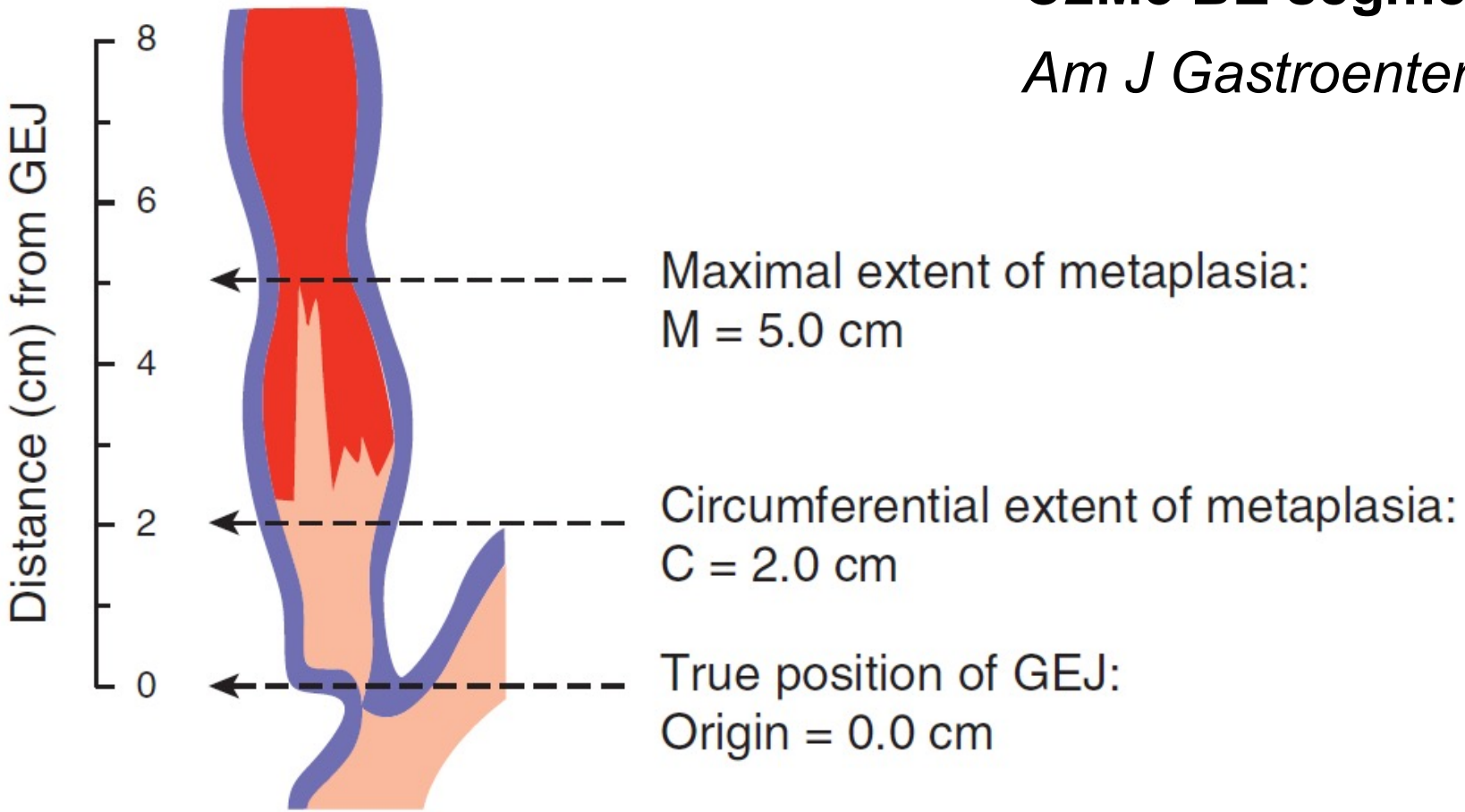
- In general, a normal Z line or Z line with <1 cm variability should not be biopsied.
- BE should be diagnosed when there is extension of salmon-colored mucosa extending >= 1 cm proximal to the GEJ.
- In presence of BE, endoscopist should describe the extent of metaplastic changes using the Prague classification
- The location of the diaphragmatic hiatus, GEJ, and squamocolumnar junction should be reported
- The location of all visible lesions (nodules, ulcers) should be clearly stated (including distance and laterality)

Am J Gastroenterol 2016; 111:30–50, Gastroenterology 2016;151:822–835

Prague Classification

C2M5 BE segment.

Am J Gastroenterol 2016; 111:30–50

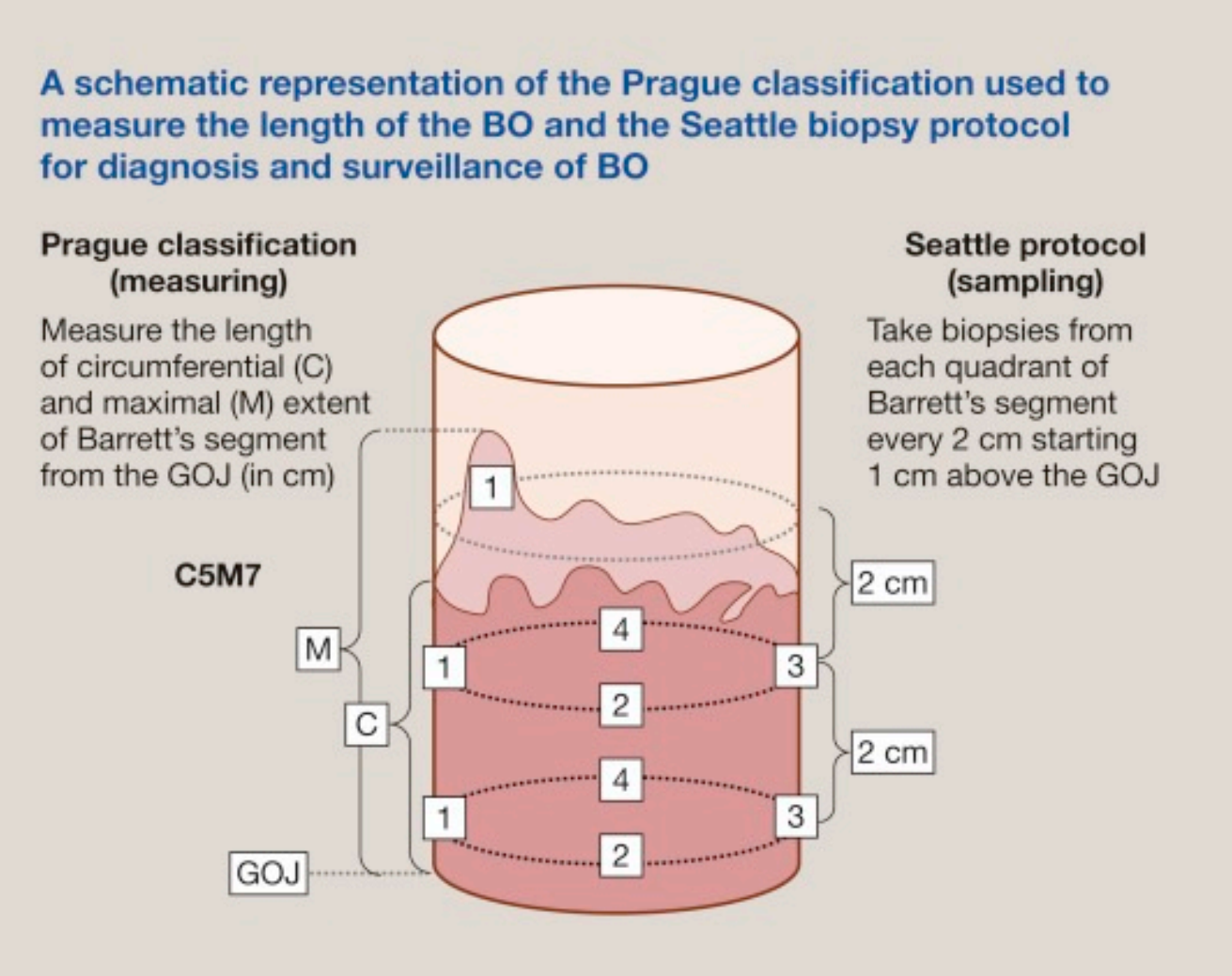


Surveillance of BE

- Patients should enter surveillance program only after counseling on risks and benefits (ACG) vs surveillance is recommended (ASGE)
- Routine use of advanced imaging (other than narrow band imaging) is not recommended (ACG and ASGE). Routine use of confocal laser endomicroscopy is not recommended
- Mucosal abnormalities should be sampled separately, preferably by EMR
- 4-quadrant biopsies every 2 cm (if no hx of dysplasia) and 1 cm (if hx of dysplasia) is recommended (Seattle protocol)
- Biopsies should not be performed in areas of active esophagitis until mucosal healing
- In non-dysplastic BE, 3-5 year interval is recommended (ACG and ASGE)

Am J Gastroenterol 2016; 111:30–50; *Gastrointest Endosc* 2019;90(3): 335-359.

Seattle Protocol



Medicine Volume 47, Issue 5, May 2019, Pages 275-285

Diagnosis of Dysplasia

- Dysplasia should be confirmed by a second pathologist with specialized expertise in GI pathology
- Patients indefinite for dysplasia should undergo optimization of acid suppression therapy and undergo repeat examination in 3-6 months
- Patients in whom the diagnosis of LGD is downgraded to non-dysplastic BE should be managed as nondysplastic BE (AGA recommendation)
- In BE patients with confirmed LGD, repeat upper endoscopy using HD white-light endoscopy should be performed 8-12 weeks after maximal acid suppression (AGA recommendation)

Gastroenterology 2016;151:822–835; *Am J Gastroenterol* 2016; 111:30–50;

Management of Dysplasia

- In patients with LGD, endoscopic eradication therapy (EET) is preferred over surveillance (however in patients who place high value on avoidance of adverse events surveillance may be preferred – ASGE). In patients with HGD, EET is preferred over surveillance.
- Patients with nodularity in BE segment should undergo EMR of all visible lesions (no matter how subtle) as initial diagnostic and therapeutic maneuver. In BE patients with nodules, routine use of EUS prior to EMR to differentiate mucosal from submucosal disease is discouraged.
- In patients with EMR specimens demonstrating neoplasia or cancer at deep margin or with evidence of lymphovascular invasion, surgical referral is recommended
- In BE patients with visible lesions who undergo endoscopic resection, we suggest ablation of the remaining Barrett's segment compared with no ablation. Radiofrequency ablation is currently the preferred endoscopic ablative therapy (ACG 2016 and AGA 2016).

Gastroenterology 2016;151:822–835; *Am J Gastroenterol* 2016; 111:30–50; *Gastrointest Endosc* 2018;87(4): 907-931.

Post-Ablation Surveillance

- Patients completing EET should be enrolled in an endoscopic surveillance program compared to no surveillance (ACG, AGA, ASGE)
  - AGA: patients who have achieved complete eradication of BE should undergo surveillance every year for 2 years, and then every 3 years thereafter. The Seattle protocol should be adopted throughout the length of the original segment of BE
  - ACG: HGD/cancer – every 3 months for 1st year, every 6 months for 2nd year, and annually thereafter. LGD – every 6 months for 1st year, and annually thereafter. Careful examination with white light and NBI should be performed.

Gastroenterology 2016;151:822–835; *Am J Gastroenterol* 2016; 111:30–50; *Gastrointest Endosc* 2018;87(4): 907-931.

Management of Reflux

- Patients with BE should receive once-daily PPI therapy. Routine use of twice-daily dosing is not recommended unless necessitated for poor symptom control (ACG, 2016)
- Aspirin and nonsteroidal anti-inflammatory drugs should not be prescribed as anti-neoplastic therapy (ACG, 2016).
- Anti-reflux surgery should not be pursued in patients with BE as an antineoplastic measure. However, this surgery should be considered in those with incomplete control of reflux on optimized medical therapy.

What about Squamous Cell Cancer?

- Currently, no recommendations for screening for esophageal squamous cell cancer (ESCC) in the United States
- Prevalence highest in Asian Esophageal Cancer Belt, which extends from the Caspian Sea to northern China
- Smoking, alcohol (especially in those with Asian flush reaction), achalasia, tylosis, infection with human papillomavirus, history of head and neck cancers are risk factors for SCC

Gastric Cancer Screening and Surveillance

Estimated age-standardized incidence rates (World) in 2020, stomach, both sexes, ages 40-74

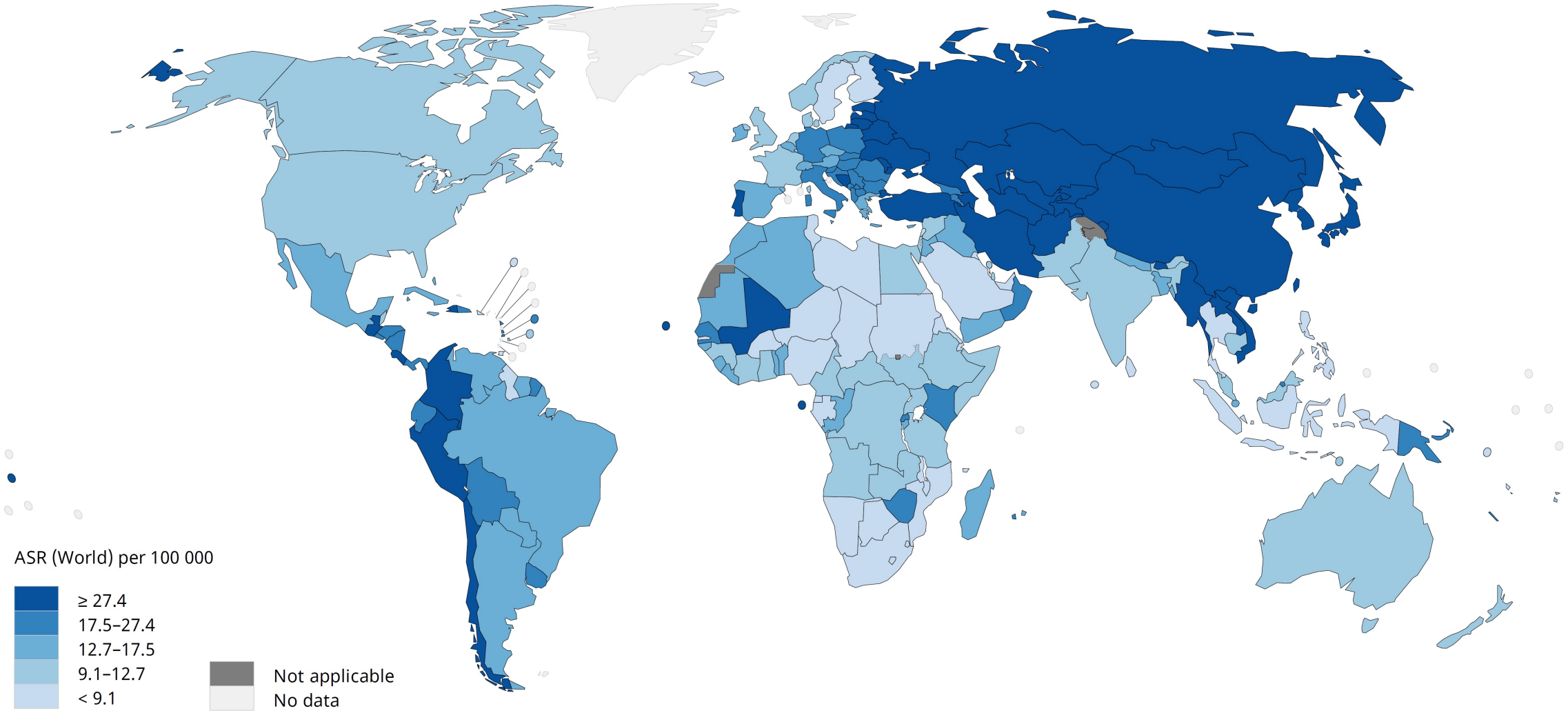


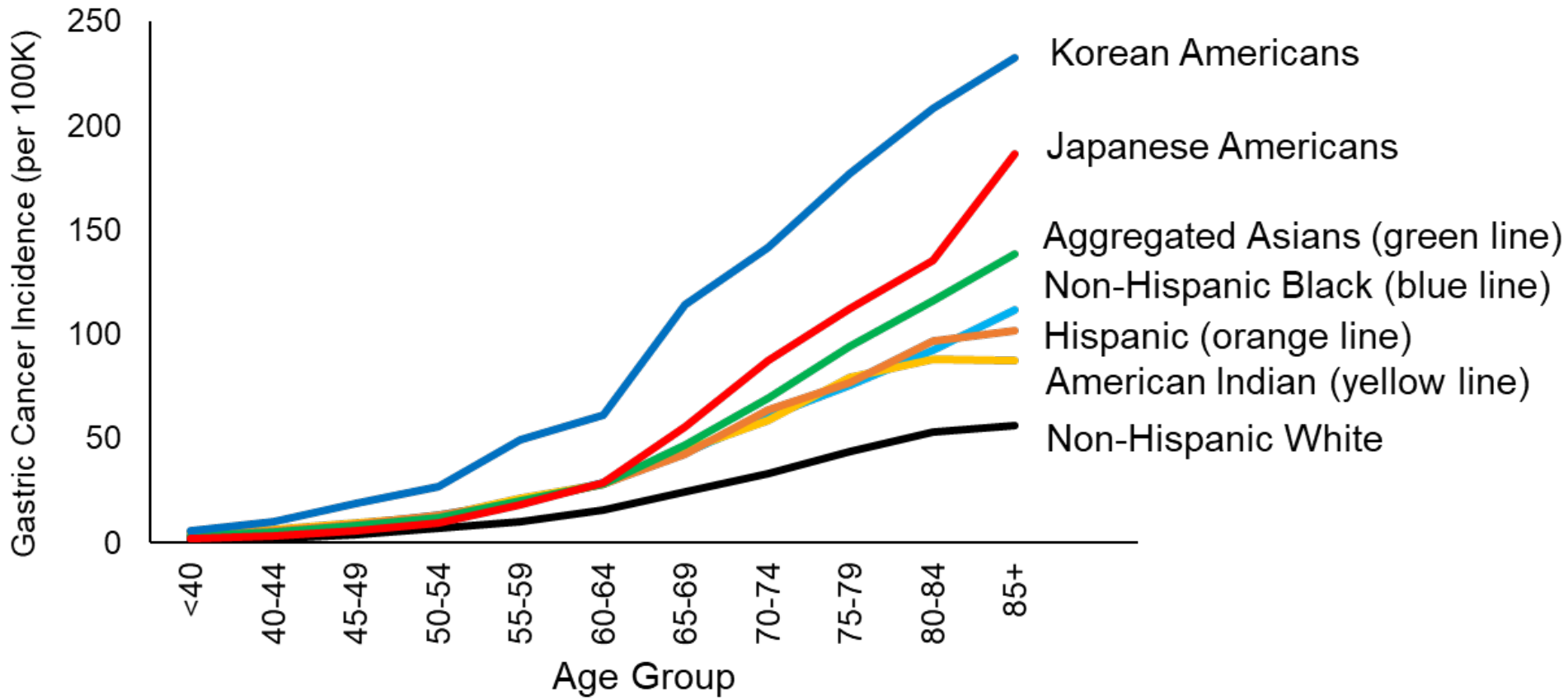
Figure 1: Worldwide incidence of gastric cancer (both cardia and non-cardia) in year 2020 among individuals aged 40-74, standardized to world population. Data source: GLOBOCAN 2020. Graph production: IARC (http://gco.iarc.fr/today), World Health Organization.

Upper Digestive Tract Cancers in the United States

	Esophageal		Gastric	
Stage at diagnosis	Stage distribution (%)	5-year RSR (%)	Stage distribution (%)	5-year RSR (%)
Localized	**20**	**42.9**	**27**	**67.2**
Regional	31	23.4	28	30.7
Distant	39	4.6	35	5.2
Unknown	10	12.4	10	22.1
# cases in 2017	**16,940**		**28,000**	

https://seer.cancer.gov/

Gastric Cancer, an Unequally Distributed Cancer



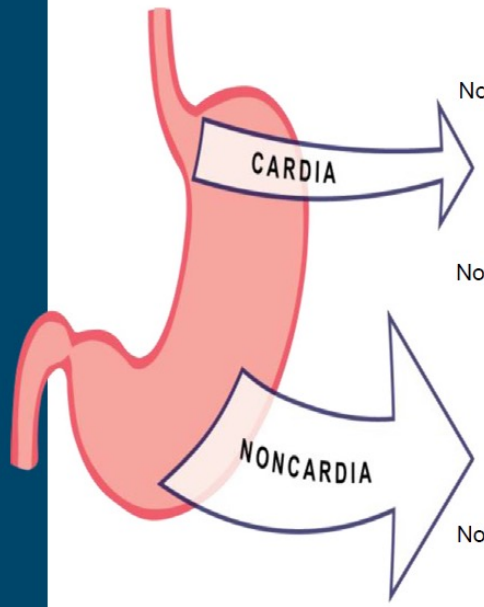
Gastrointestinal Endoscopy Clinics of North America. Volume 31, Issue 3, July 2021, Pages 503-517

Racial Differences predominantly due to non-cardia Gastric Cancers

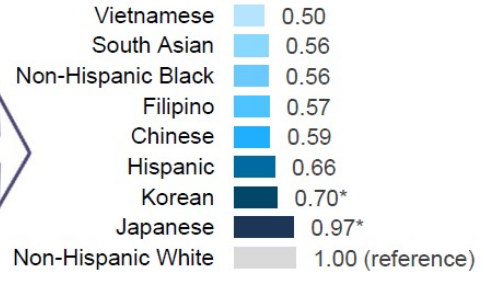
There are several-fold differences in the incidence of gastric adeno-carcinoma in specific anatomic sites among different race and ethnic groups in individuals age ≥50 years old.

These findings may inform risk reduction and early detection programs for gastric adenocarcinoma.

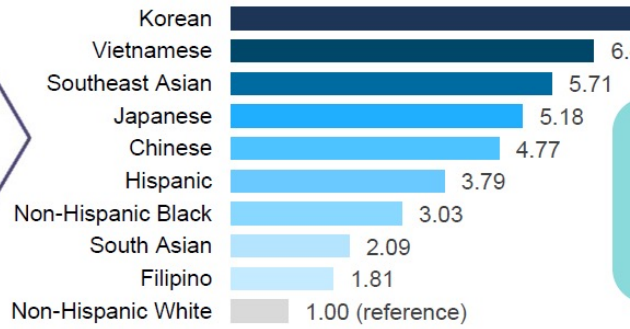
Shah SC, et al. 2020



Age- and sex-adjusted incidence rate ratios for individuals ≥50 years



All non-white race and ethnic groups, except Japanese and Korean Americans, had a *lower risk of* CARDIA gastric adenocarcinoma compared to non-Hispanic white individuals.



All non-white race and ethnic groups, especially Korean Americans, had a *higher risk of* NONCARDIA gastric adenocarcinoma compared to non-Hispanic white individuals

*Statistically non-significant
Data from California Cancer Registry (2011-2015)

Gastroenterology

Gastroenterology. 2020 Nov;159(5):1705-1714.e2.

GC in the United States – Opportunities for Improvement

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

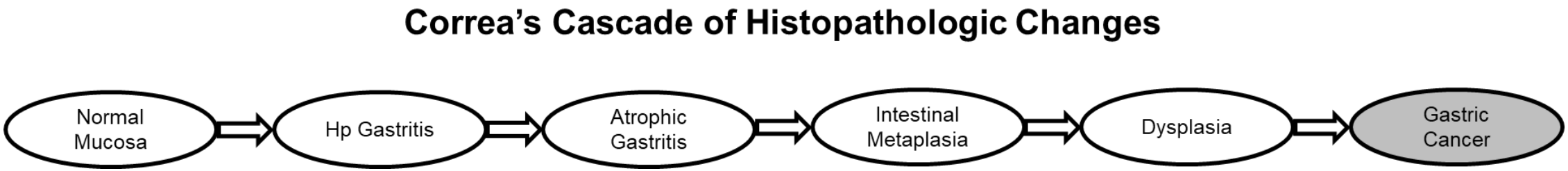
South Korean data adapted from the Korea National Cancer Incidence Database. Japanese data derived from the Center from the National Cancer Center of Japan. United States data derived from Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute. 5-year relative survival rates are presented. Summary stages defined by SEER criteria.

Gastroenterology. 2020 October;159(4):1221-1226.

Risk Factors for Gastric Cancer

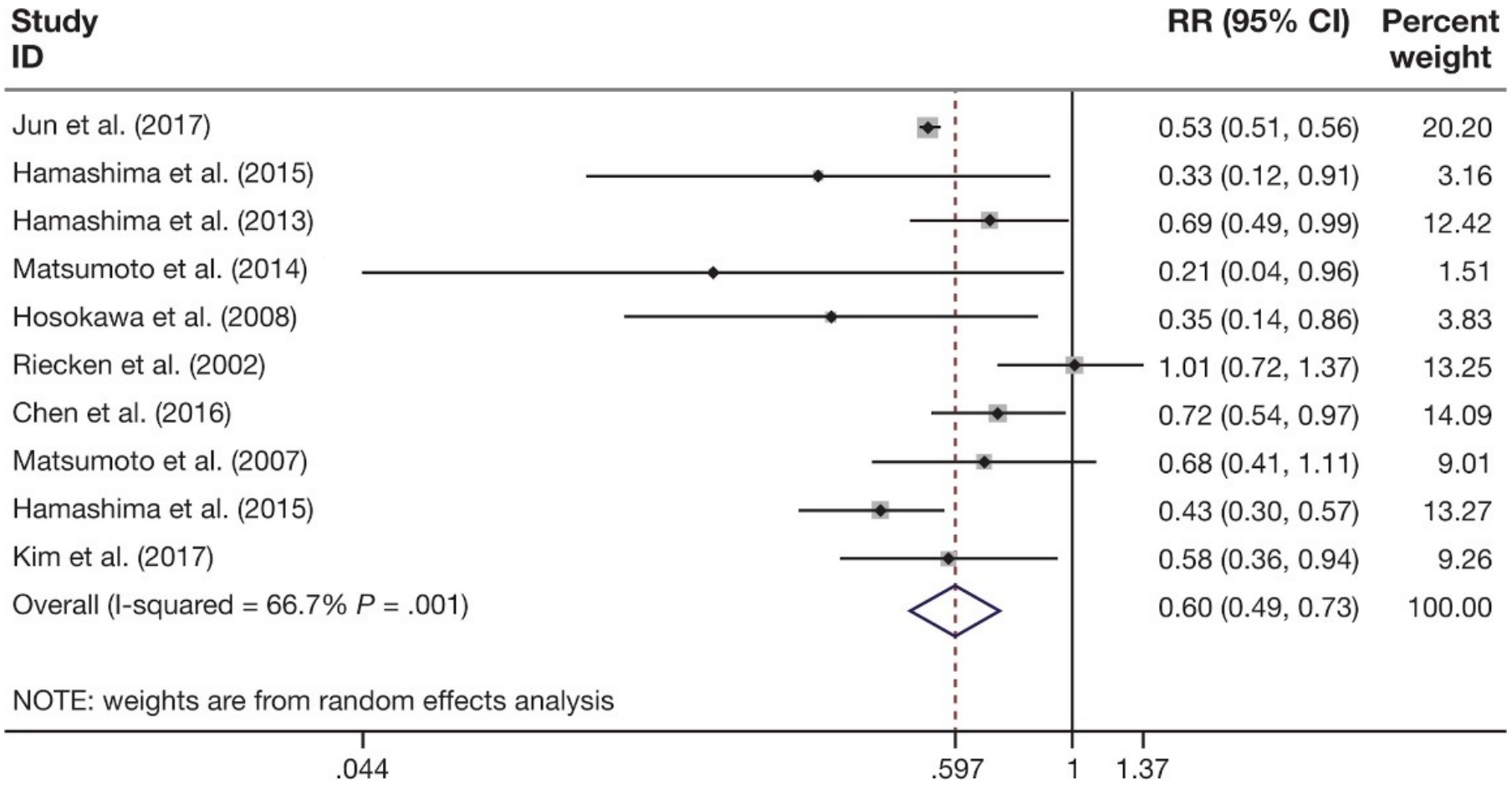
- Modifiable risk factors for gastric cancer include
  - Historical or current infection by *Helicobacter pylori* (Hp) (N Engl J Med 1991; 325:1127-1131)
  - Atrophic gastritis, intestinal metaplasia, and dysplastic lesions
  - Diet high in salt and salt-preserved foods
  - Smoking (Cancer Causes Control. 2008 Sep;19(7):689-701.)
  - Epstein-Barr virus infection (Am J Clin Pathol. 1996;105(2):174.
- Non-modifiable risk factors include
  - Asian, Black, American Indian, Alaskan Native race, Hispanic ethnicity
  - Family history (in first or second degree relative)
  - Hereditary cancer syndromes (Lynch, FAP, Li-Fraumeni)

Correa's Cascade



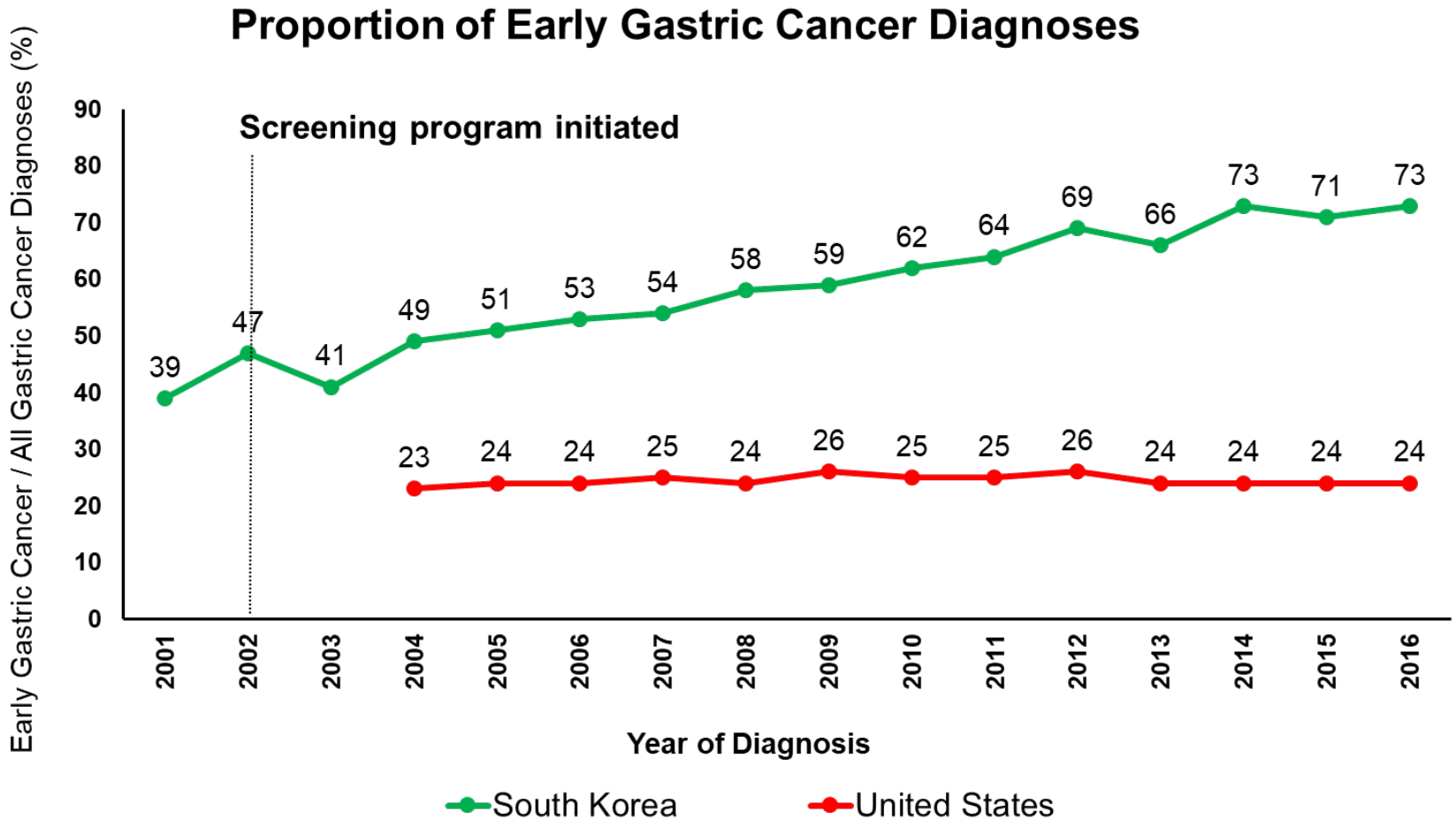
Gastrointestinal Endoscopy Clinics of North America.
Volume 31, Issue 3, July 2021, Pages 503-517

Evidence supporting endoscopic screening?



Zhang X, Li M, Chen S, et al. Endoscopic Screening in Asian Countries Is Associated With Reduced Gastric Cancer Mortality: A Meta-analysis and Systematic Review. Gastroenterology 2018;155:347-354 e9.

Ecological data from East Asia



Gastroenterology. 2020 October;159(4):1221-1226.

Existing Recommendations for endoscopic screening and surveillance

Society	Year	Recommendation
Gastric Cancer Screening		
American Society of Gastrointestinal Endoscopy[68]	2015	Endoscopic screening for gastric cancer in first-generation immigrants from high-risk regions (*e.g.* Japan, China, Russia, and South America) may be considered for those aged 40 years, particularly if there is a family history of gastric cancer in a first-degree relative

Surveillance of Intestinal Metaplasia (IM)		
American Society of Gastrointestinal Endoscopy[14,68]	2015	Endoscopic surveillance in patients with gastric atrophic gastritis or IM coupled with an increased risk of gastric cancer because of racial/ethnic background, extensive anatomic distribution, or family history
American Gastroenterological Association[69]	2019	Recommends against routine use of endoscopic surveillance in patients with IM. *Conditional recommendation, very low quality of evidence* Patients with IM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance. Patients with IM specifically at higher risk of gastric cancer include those with: • Incomplete vs complete IM • Extensive vs limited IM • Family history of gastric cancer • Patients at overall increased risk for gastric cancer include: • Racial/ethnic minorities • Immigrants from high incidence regions

Existing Recommendations for Hp testing and treatment

The American College of Gastroenterology (ACG) strongly recommends Hp testing for patients with:

- active peptic ulcer disease;
- past peptic ulcer disease (unless cure of Hp is documented);
- low-grade gastric mucosa associated lymphoid tissue lymphoma;
- history of endoscopic resection for early GC;
- and for patients <60 years old with uninvestigated dyspepsia and no alarm features

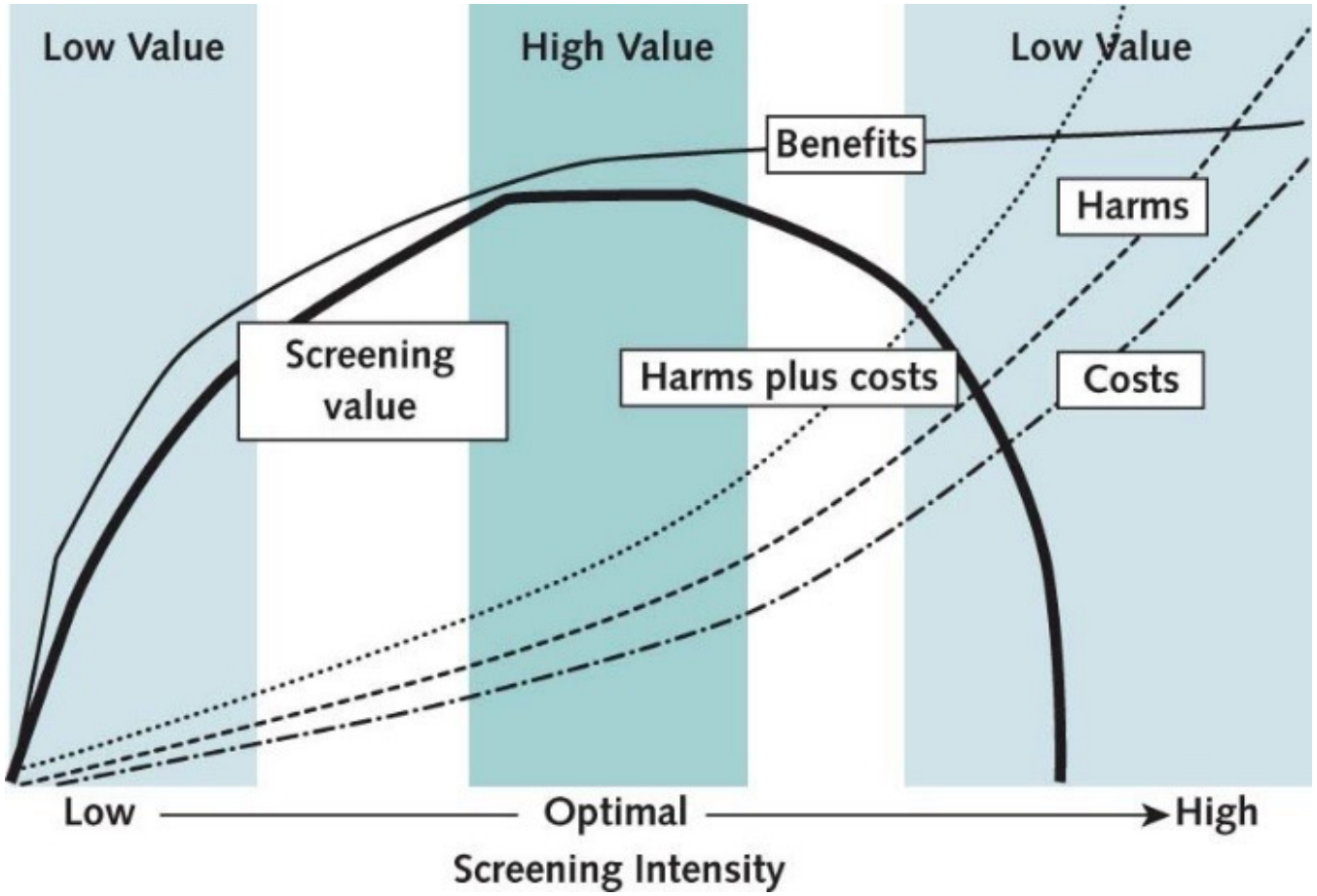
Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol 2017;112:212-239.

Houston Consensus Conference (2018) Expert Panel: in addition to ACG criteria, these additional groups should be tested:

- patients with a family history of gastric cancer;
- patients who are first-generation immigrants from high-Hp-prevalence areas;
- and patients of Asian, Hispanic, and African American racial or ethnic groups

El-Serag HB, Kao JY, Kanwal F, et al. Houston Consensus Conference on Testing for Helicobacter pylori Infection in the United States. Clin Gastroenterol Hepatol 2018;16:992-1002 e6.

Cancer Screening Framework and need for personalized decision making



Harris RP, Wilt TJ, Qaseem A, et al. A value framework for cancer screening: advice for high-value care from the American College of Physicians. Ann Intern Med 2015;162:712-7.


2021
NCSCG
18TH ANNUAL HYBRID
GI SYMPOSIUM
June 26-27, 2021