Gastric cancer: Exploring the differences between Asian and Western patients

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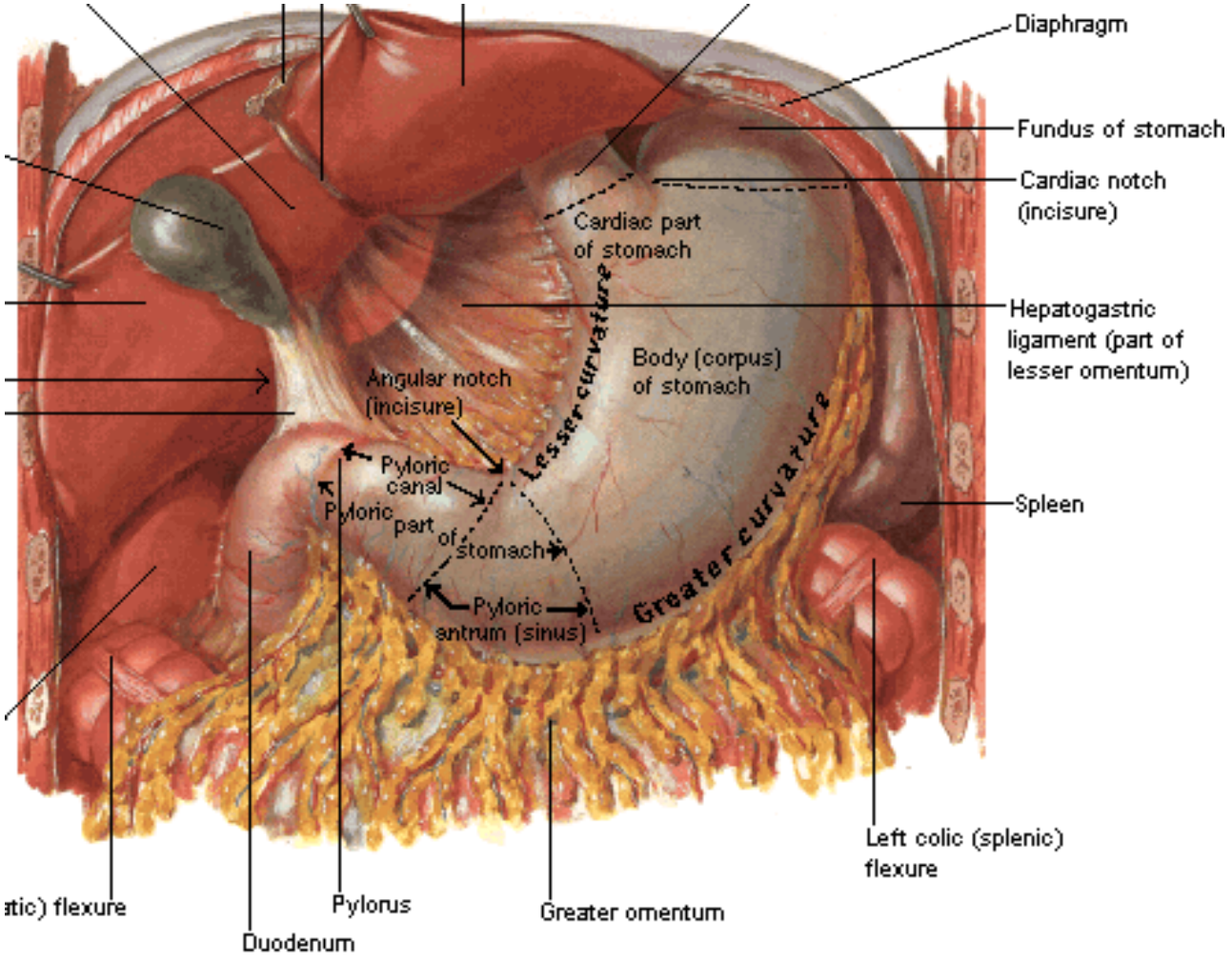
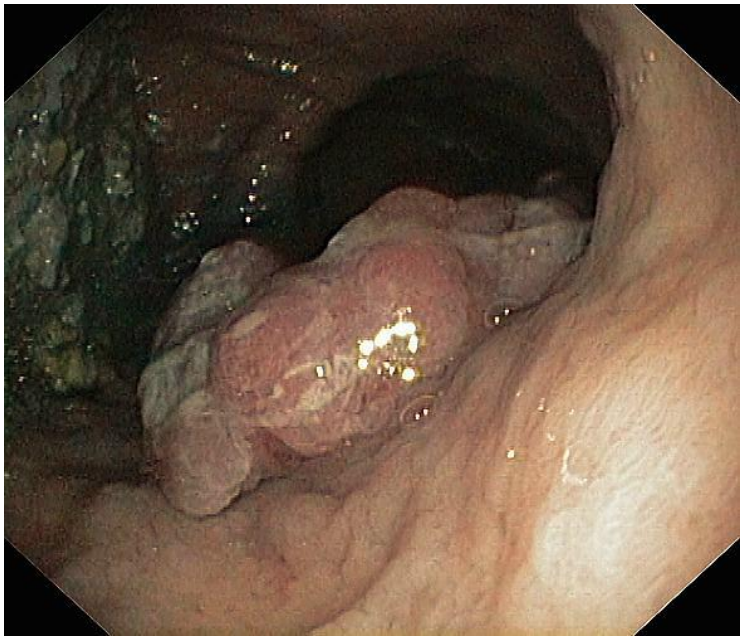
Refresher: Gastric anatomy



Lauren classification of gastric cancer



Intestinal type:
~50%; more common in distal stomach

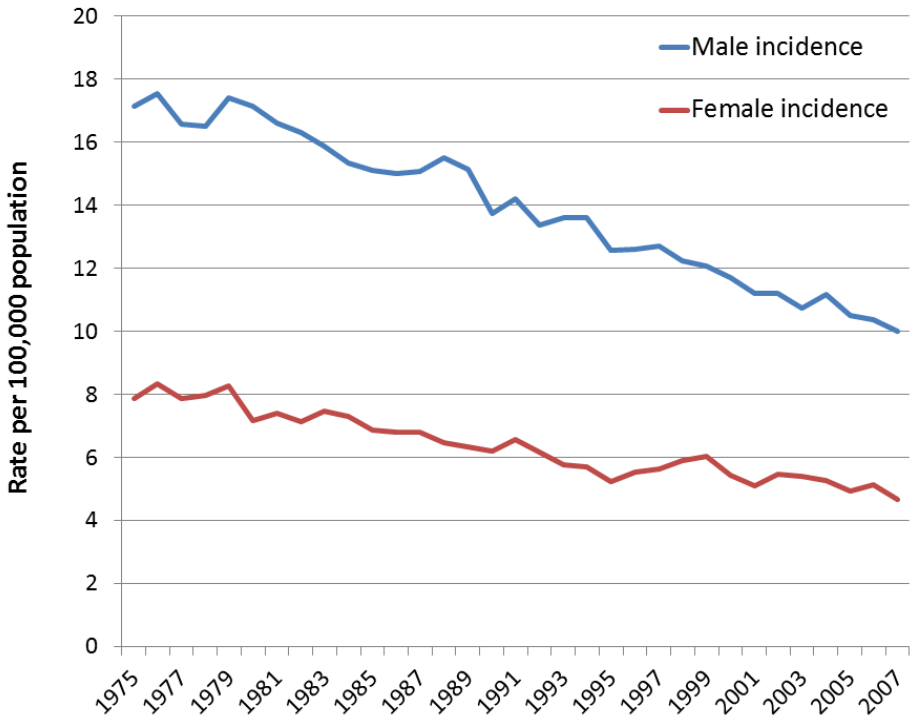
Diffuse type (infiltrative, linitus plastica):
~35%; more common in young patients, females, and a/w hereditary forms

Incidence and mortality associated with gastric cancer, 2016

	Estimated new cases			Estimated deaths		
	Male	Female	TOTAL	Male	Female	TOTAL
Gastric	16,480	9,890	**26,370**	6,540	4,190	**10,730**

American Cancer Society Facts and Figures, 2016.

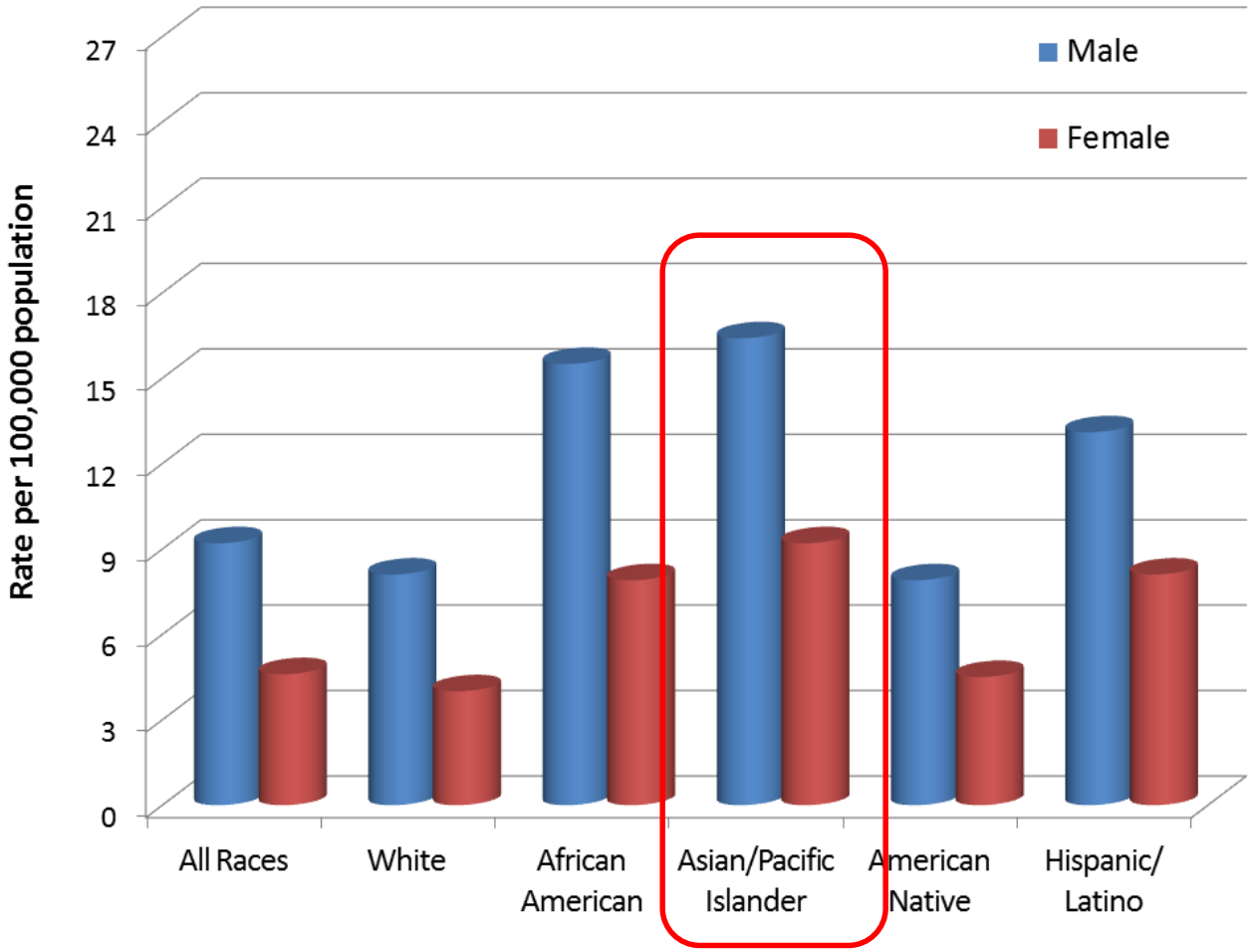
Temporal trends in the United states



- Leading cause of cancer deaths in the U.S. until late 1930s
- Decline in incidence and mortality related to improvements in diet, food storage, and effective treatment for *H. pylori*
- However, significant increase in one particular type/location: **GE junction cancers**

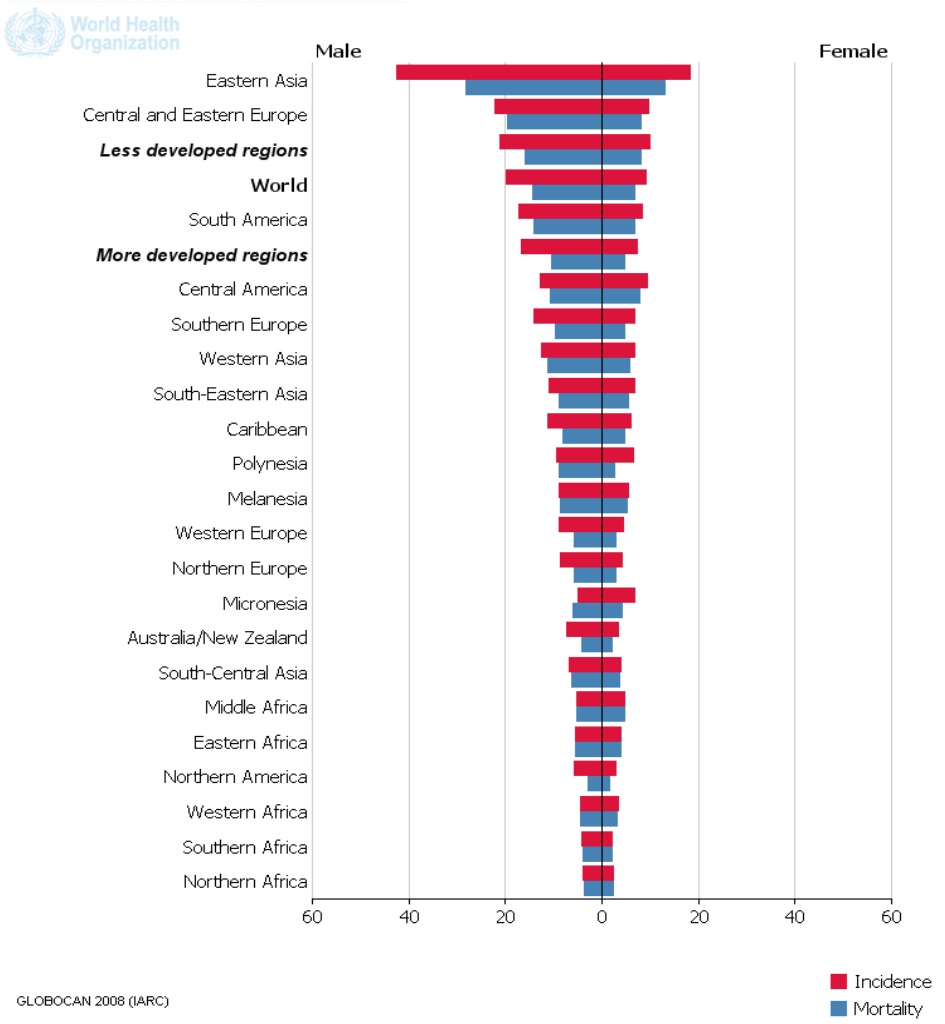
Medinfographics website

Gastric cancer is most common in the united states amongst **asian-americans**



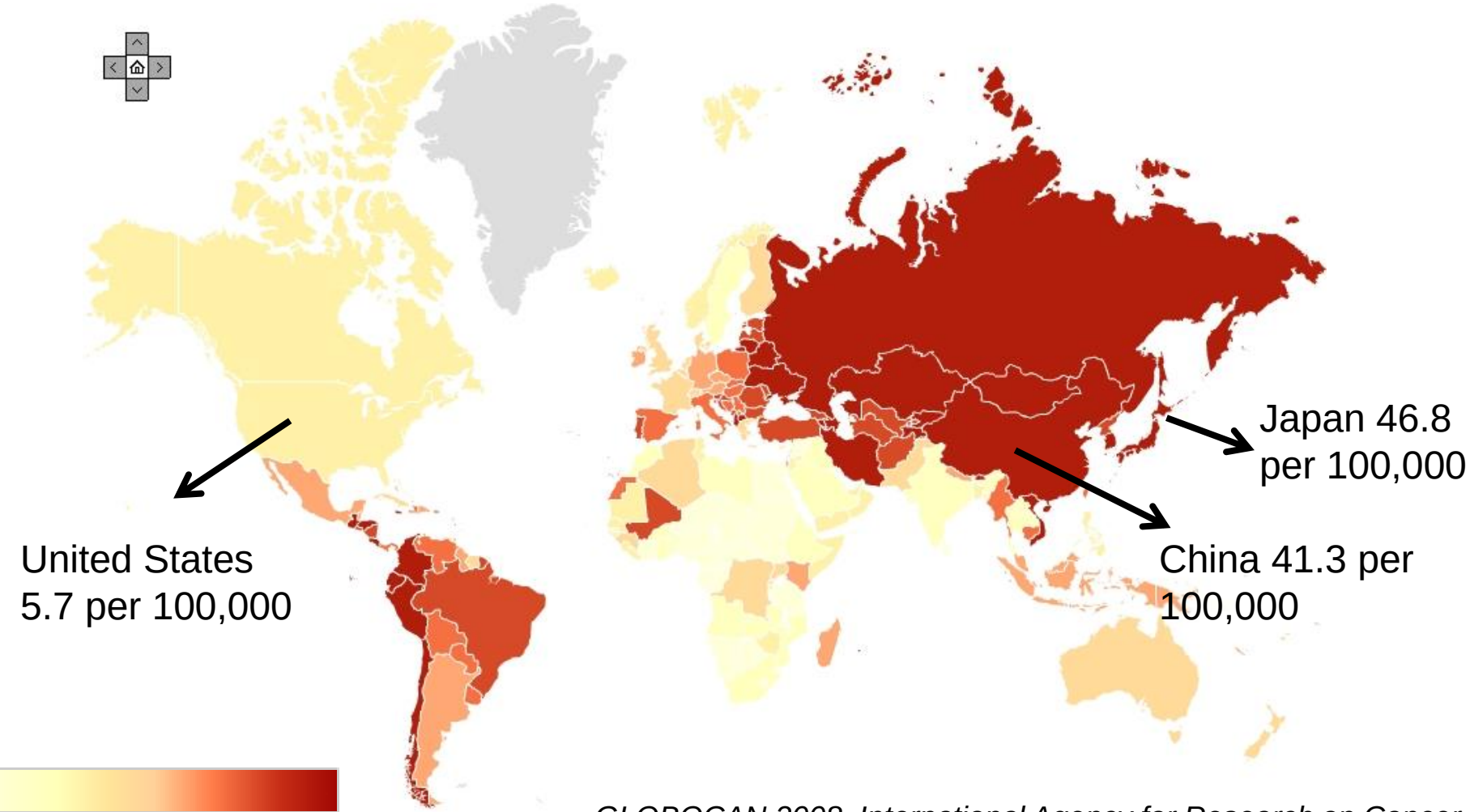
Gastric cancer: geographic trends

- Worldwide 2nd leading cause of cancer mortality (1 million/year)
- E. Asia > Europe/S America > United States/Australia/Africa
  - ½ of world total from Eastern Asia (esp China)
  - Mortality rates in E. Asia: 28.1 per 100,000 in men, 13.0 per 100,000 in women
  - Mortality rates in Northern America: 2.8 per 100,000 in men, 1.5 per 100,000 in women



Hohenberger and Gretchel, *Lancet* 2009; Hartgrink et al, *Lancet* 2003; Rastogi et al, *Nat Rev Cancer* 2004

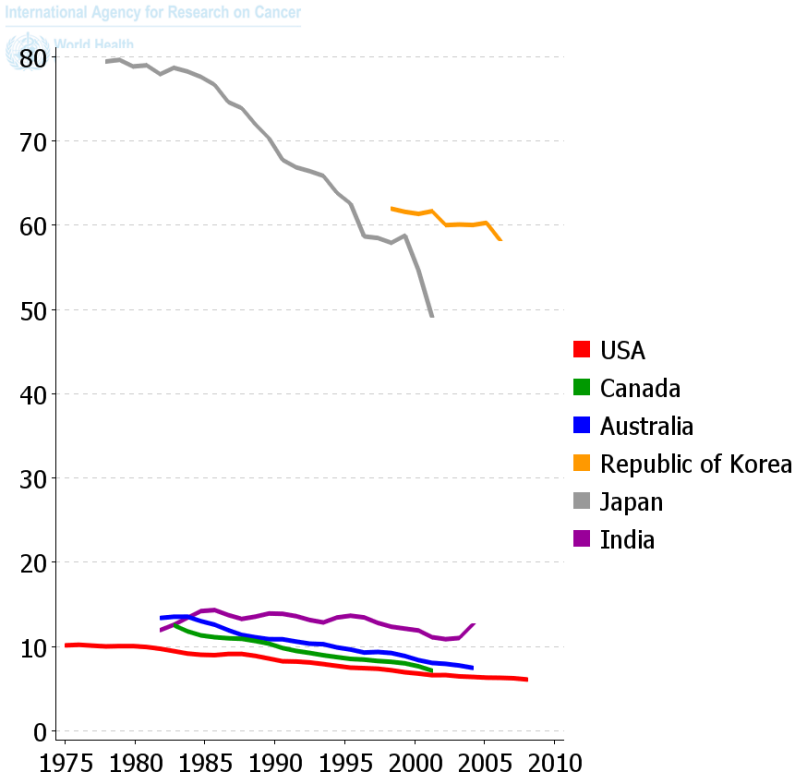
Estimated Gastric Cancer Incidence Worldwide in 2008*



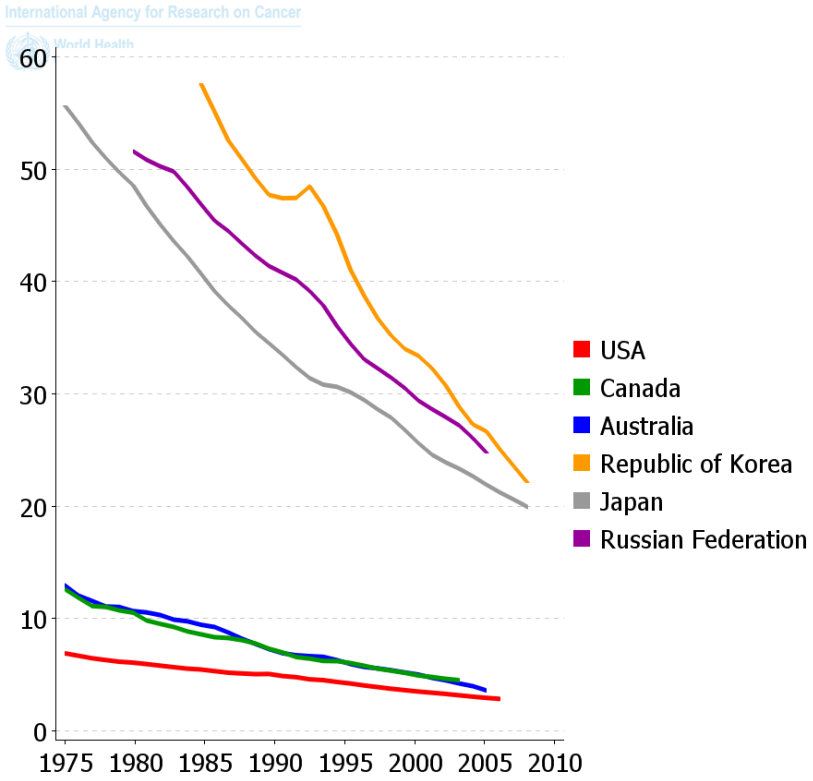
GLOBOCAN 2008, International Agency for Research on Cancer
**Data are for males only*

Temporal trends by geographic region

Age-standardized incidence rate per 100,000 men



Age-standardized mortality rate per 100,000 men



GLOBOCAN 2008, International Agency for Research on Cancer

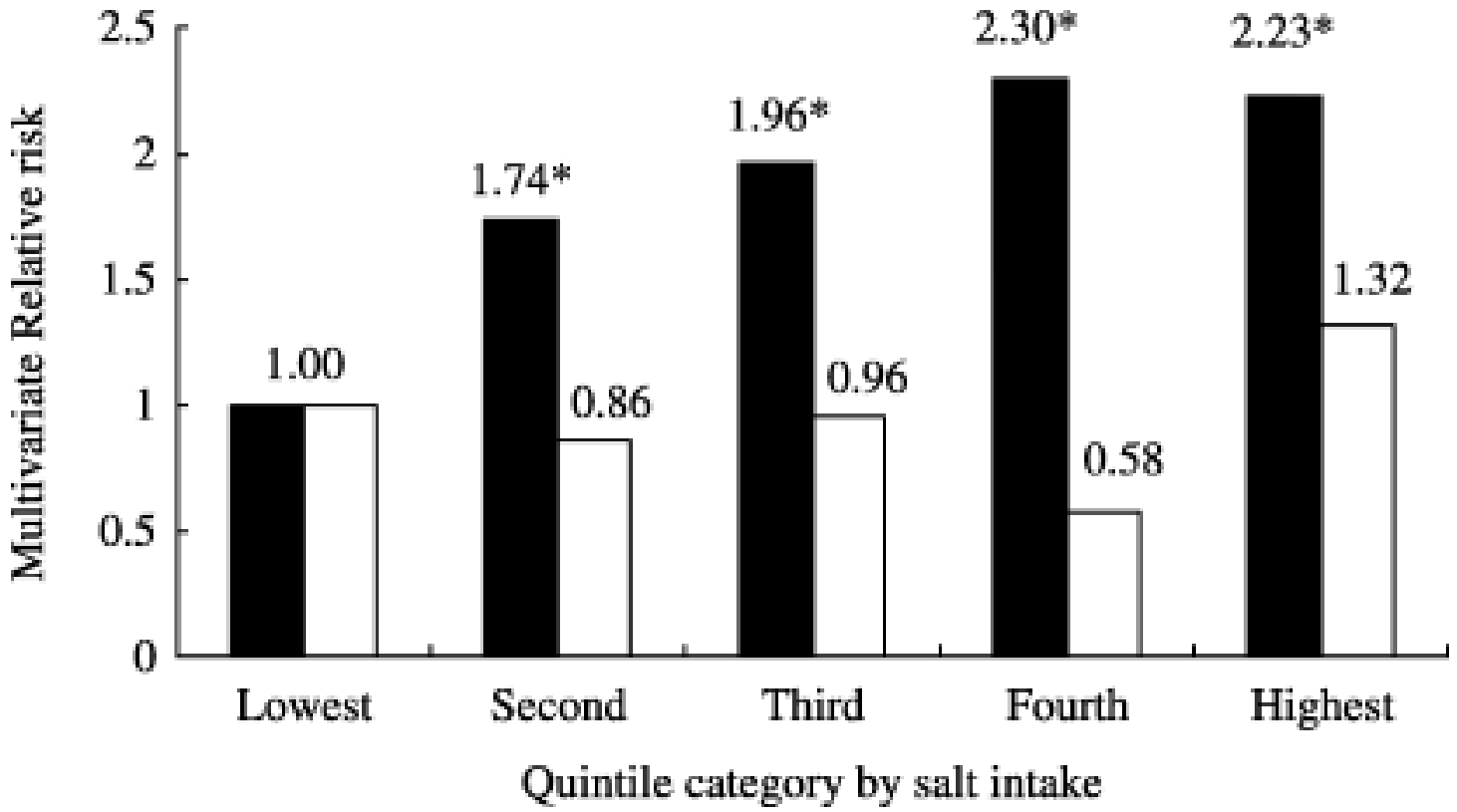
SO WHY IS GASTRIC CANCER MORE COMMON IN ASIANS?

- Genetic vs. environmental factors
- Evidence from migrant studies:
  - Subsequent generations of Japanese born in the United States show declining incidence and mortality rates from gastric cancer – however, still remain higher than U.S. whites
  - Groups with older immigration histories (Japanese, Filipinos) have cancer burdens more similar to those commonly observed in Westernized countries than groups with more recent immigration histories (Vietnamese, Korean)

why is gastric cancer more common in asians?: risk factors

- Consumption of salty foods, N-nitroso compounds; low fruit/vegetable consumption
- *H. pylori* infection (esp. cagA strain)
  - Increases risk for *distally* located, but NOT proximal, gastric cancers
- Tobacco
- Obesity/GERD/Barrett's
- Genetics: E-cadherin (**CDH1**) mutation
  - Associated with diffuse histology, autosomal dominant pattern, high penetrance rate (>70%), early-age onset
  - Also increased incidence of breast (lobular), colorectal, prostate ca
  - Appropriate candidates to consider prophylactic gastrectomy

JAPANESE PUBLIC HEALTH CENTER (STUDY COHORT I), 1990-2001: SALT INTAKE AND GASTRIC CANCER RISK ACCORDING TO GENDER



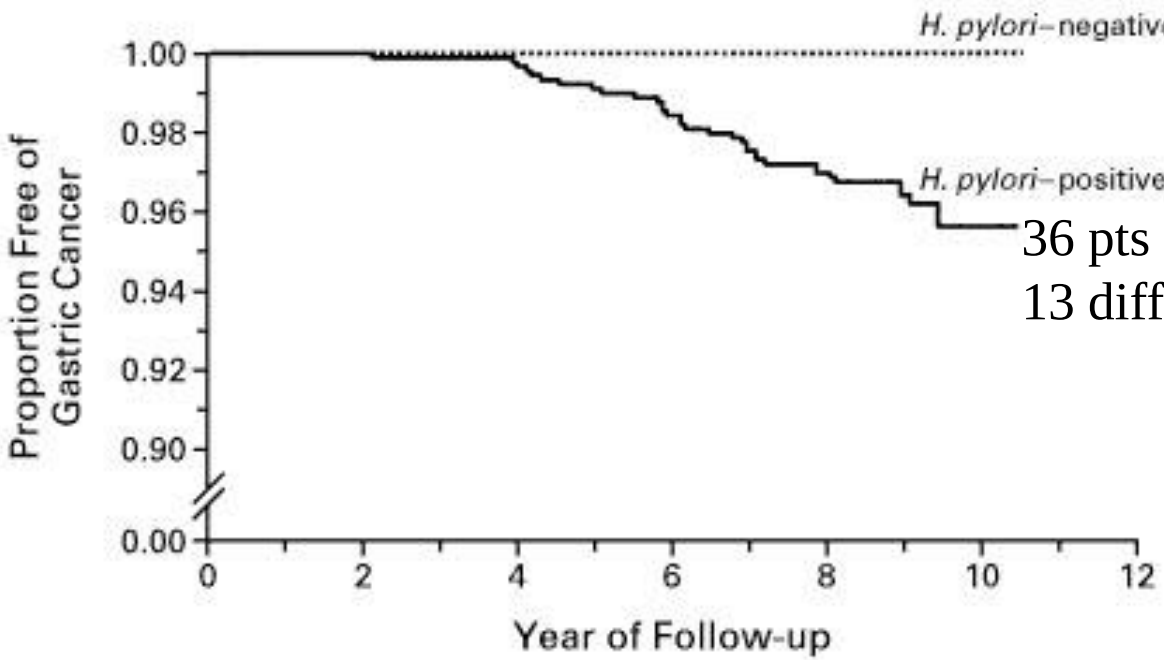
Tsugane, Cancer Science 2005, 96:1-6.

Habitual salt intake and risk of gastric cancer: A meta-analysis of prospective studies

(D'elia et al, *Clin Nutr ition* 2012, 31:489)

High vs. low intake of:	RELATIVE RISK
SALT	1.68 (95% CI, 1.17-2.41)

H. pylori and gastric cancer risk



(0)

36 pts (23 intestinal, 13 diffuse)

No. at Risk

H. pylori–negative	280	272	251	245	213	57
H. pylori–positive	1246	1219	1086	907	782	258

Uemura et al, N Engl J Med 345:784, 2001

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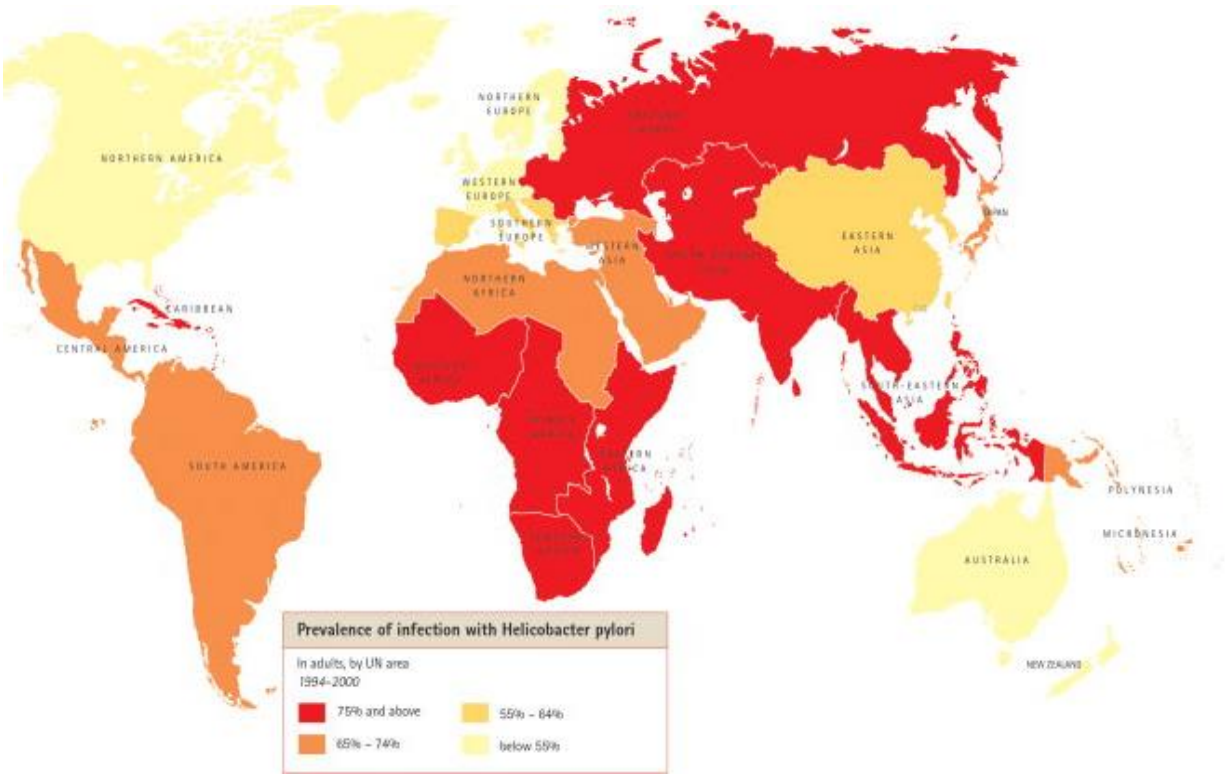
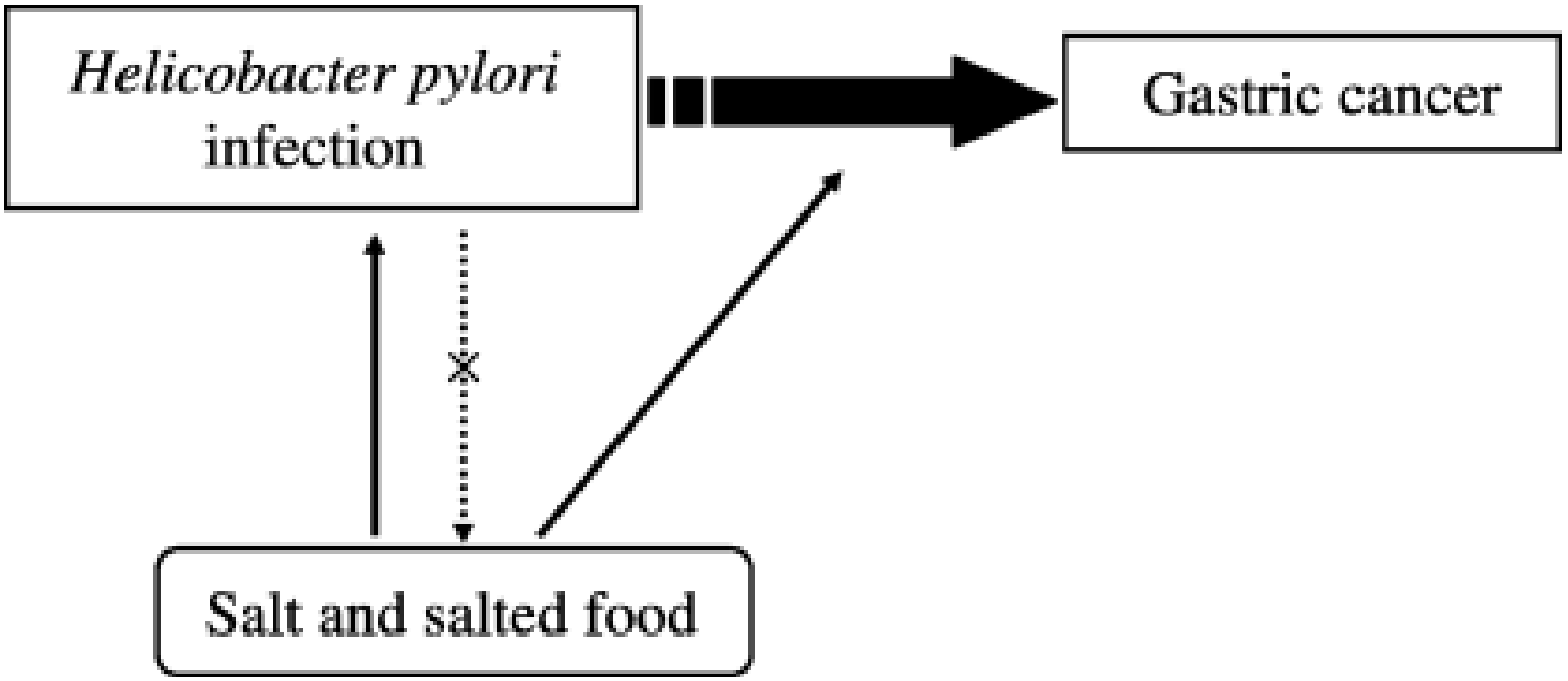
H. Pylori and gastric cancer: "The Asian Enigma"



Miwa et al, Am J Gastroent 2002; Parkin, Int J Cancer 2006.

- Large inter-country variation in incidence of gastric cancer and H. pylori seroprevalance among Asian countries
- Strong link between the two in some countries (Japan); weak link in others (India/ Bangaldesh)

Synergistic interaction between salt intake and H. Pylori infection to promote the development of gastric cancer?



Tsugane, Cancer Science 2005, 96:1-6.

Protective factors for development of gastric cancer

- Aspirin, NSAID use
  - Meta-analyses suggest possible lower risk associated with regular use (Yang, Dig Dis Sci 2010; 55:1533-9; Wang, J Natl Cancer Inst 2003;95:1784-91).
  - Effects may be more specific for non-cardia tumors and in Caucasians
- No clear association between circulating 25(OH)D concentrations and upper GI cancer risk (Abnet, Am J Epidem 2010;172:94-106).

SCREENING FOR GASTRIC CANCER

- Western countries: no population-wide screening approach
- Mass screening advocated in Asian countries (Japan, Korea)
  - May entail either double contrast barium x-ray/upper GI series *or* upper endoscopy
  - Screening intervals? (Every 2-5 years)
  - Age to begin screening? (40 or 50 y.o.)

HOW DOES GASTRIC CANCER DIFFER IN ASIANS VS NON-ASIANS?

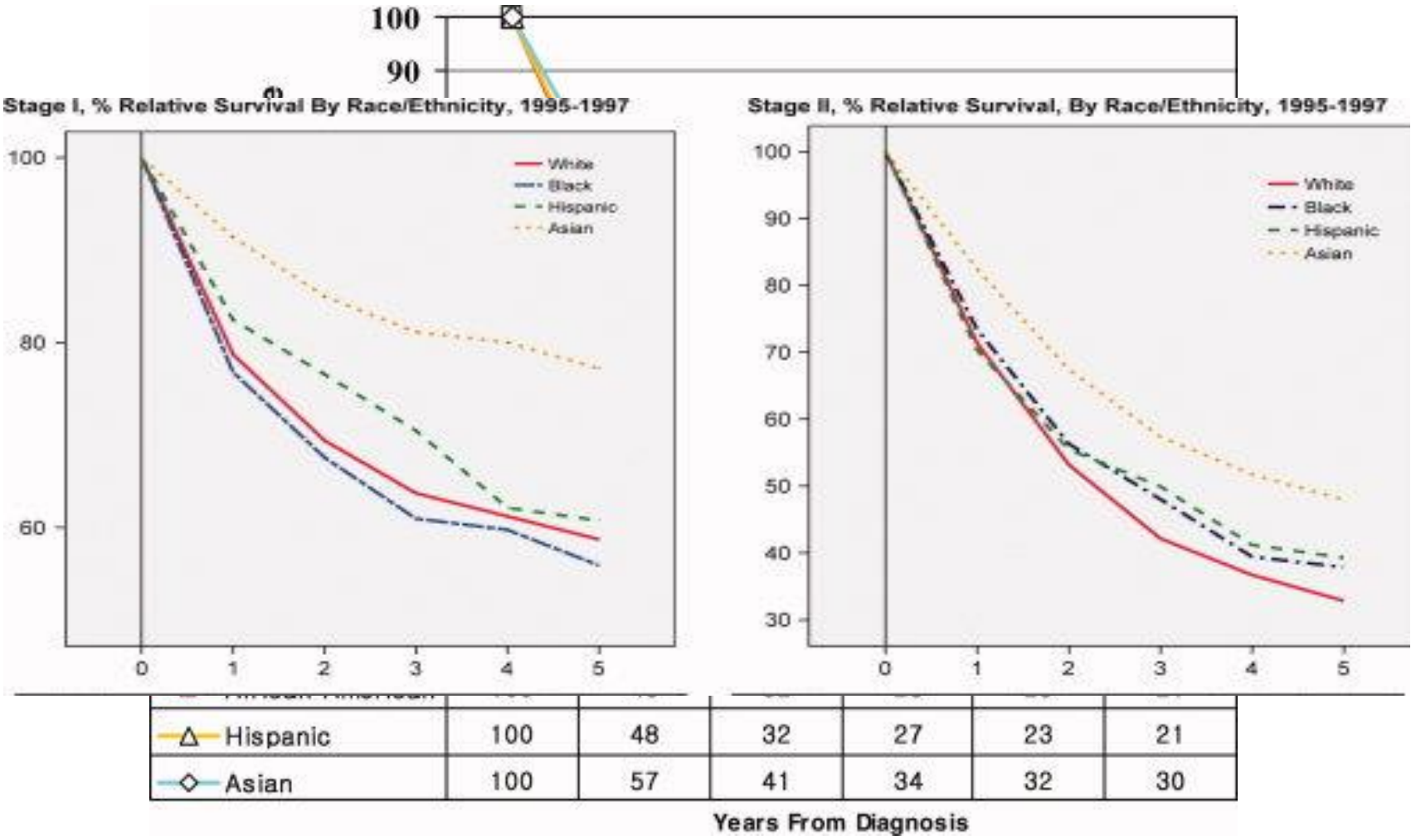
Gastric cancer in Asian patients

- **Younger** age at diagnosis
- **More localized disease** at presentation (53% in Japan vs 27% in U.S.)
- More common in **distal (lower) portion** of stomach
- Greater proportion of **signet ring** histology

- National Cancer Center, Japan (Ohtsu, Gastrointest Cancer Res 2007, suppl 1:S10-15
- British Columbia Cancer Agency (Gill et al, J Clin Oncol 2003, 21:2070)
- California Cancer Registries (Theuer et al, Cancer 2000, 89:1883)

impact of ethnicity on prognosis in gastric cancer: results from the national cancer database

(Al-Refaie, *Cancer* 2008;113:461-9)

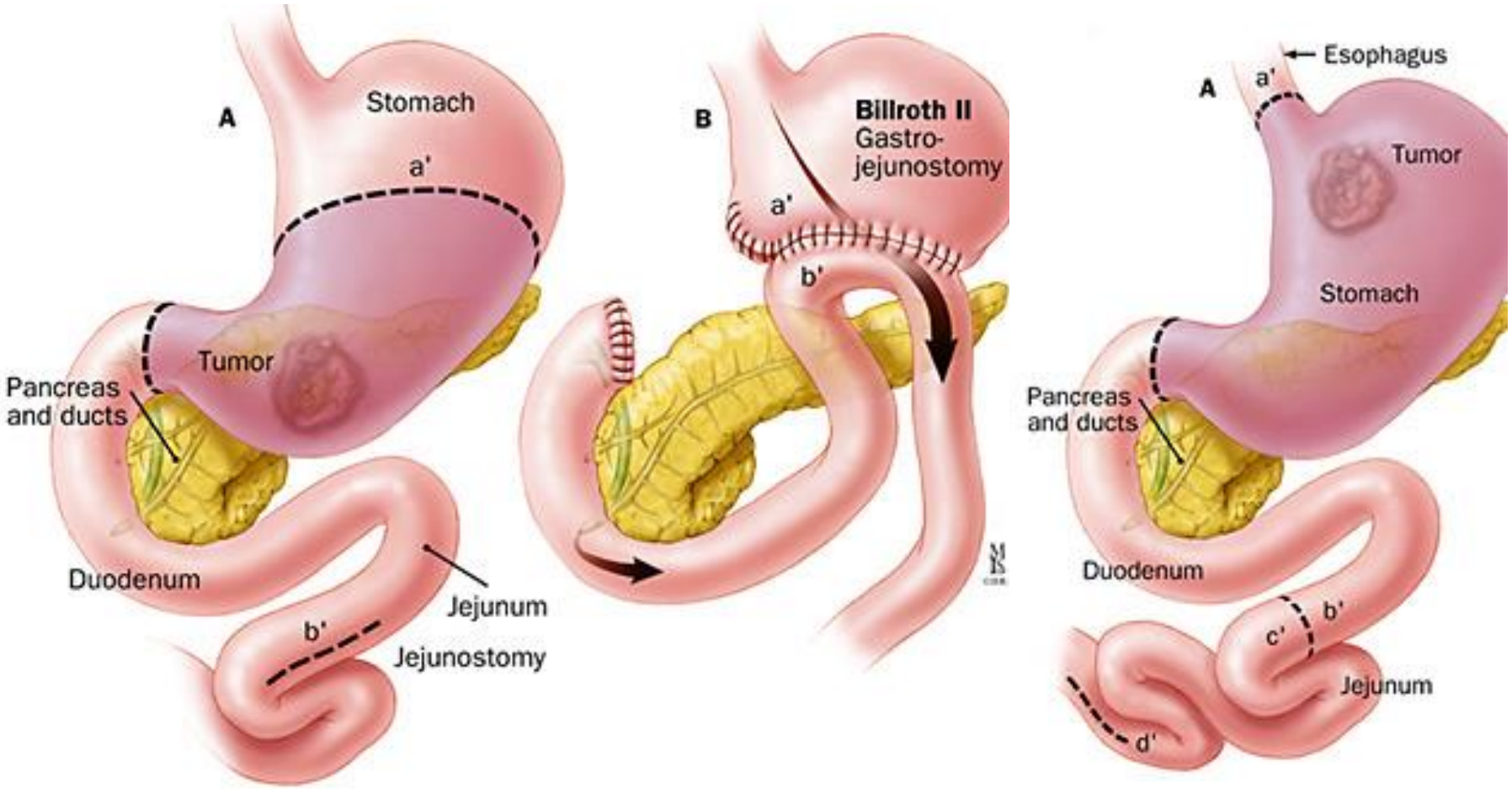


How to explain differences in outcomes between asians and non-asians?

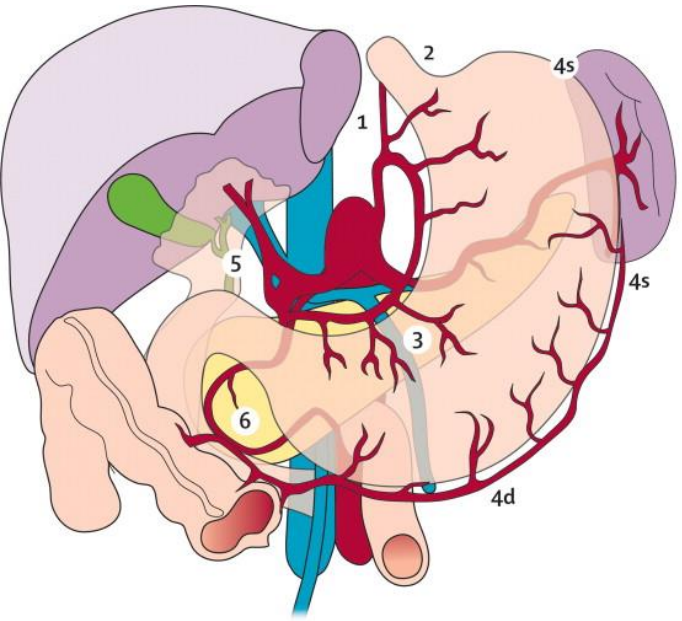
- Tumor biology and disease behavior?
  - Japanese patients' stage-stratified survival: Tokyo > Honolulu (Hundahl et al, Arch Surg 1996, 131:170-5)

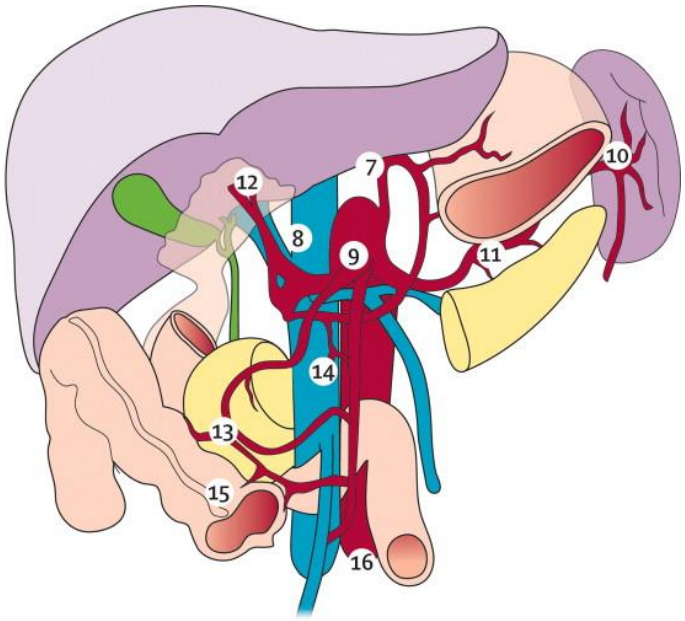
- Practice patterns and treatment differences between East and West
  - Surgical approaches
  - Exposure and responsiveness to chemotherapy

Example #1: differences in surgical approaches



Which lymph nodes need to be removed during a gastric cancer operation?





N1 Lymph nodes (perigastric)

1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along the lesser curvature
4d Lymph nodes along the short gastric and the left gastroepiploic vessels
4s Lymph nodes along the right gastroepiploic vessels
5 Suprapyloric nodes
6 Infrapyloric nodes

N2 Lymph nodes (branches coeliac axis)

7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around coeliac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes

12 Nodes at the hepatoduodenal ligament
13 Retropancreatic (peridoudenal) nodes
14 Nodes at the root of the mesentery

N4 Lymph nodes

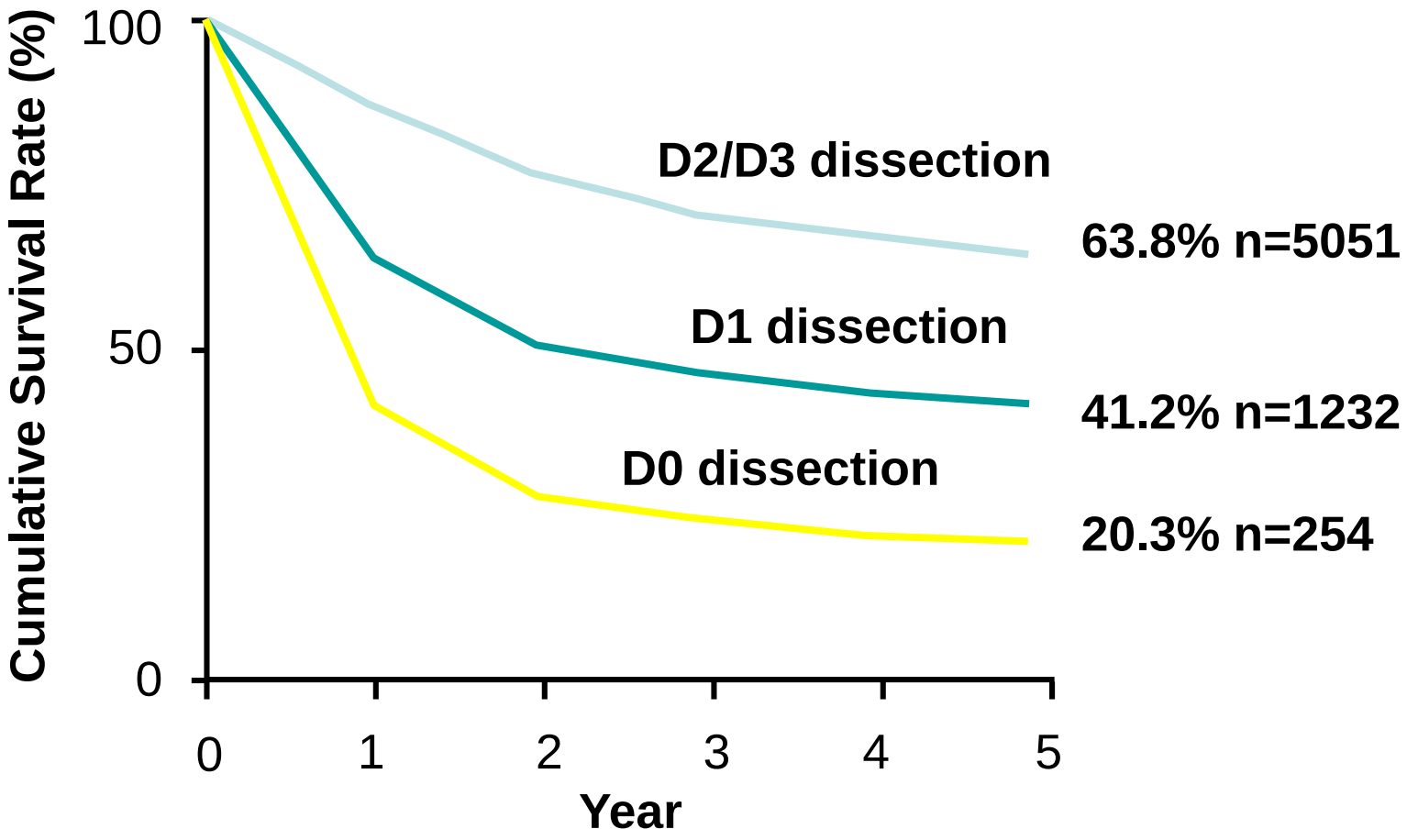
15 Nodes along the middle colic vein
16 Para-aortic nodes

LYMPH NODE DISSECTION

- D0 (suboptimal)
- D1 (standard)
- D2 (extended)
- D3 (super-extended)

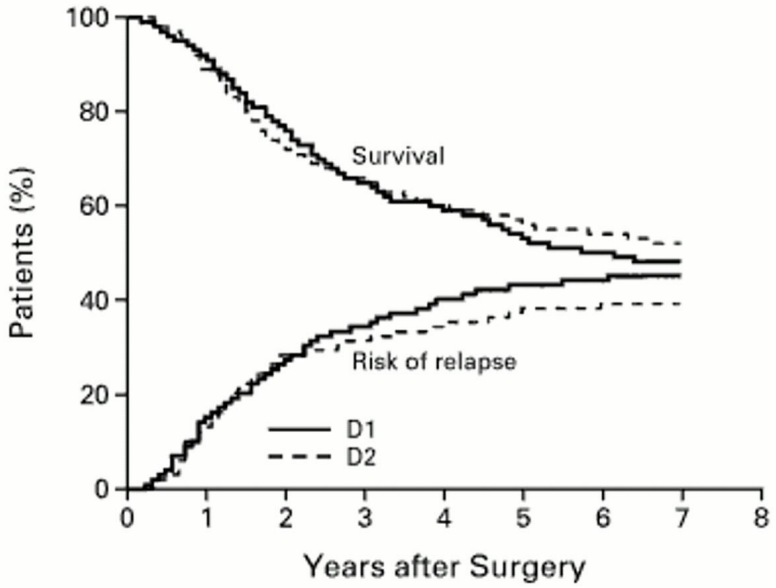
Sungun et al, Lancet Oncol 2010; 11:439-49.

Early Japanese data supported more extensive lymph node dissection



National Cancer Center, Tokyo. 1969-1991. Maruyama et al. *Sem Oncol.* 1996;23:360-368.

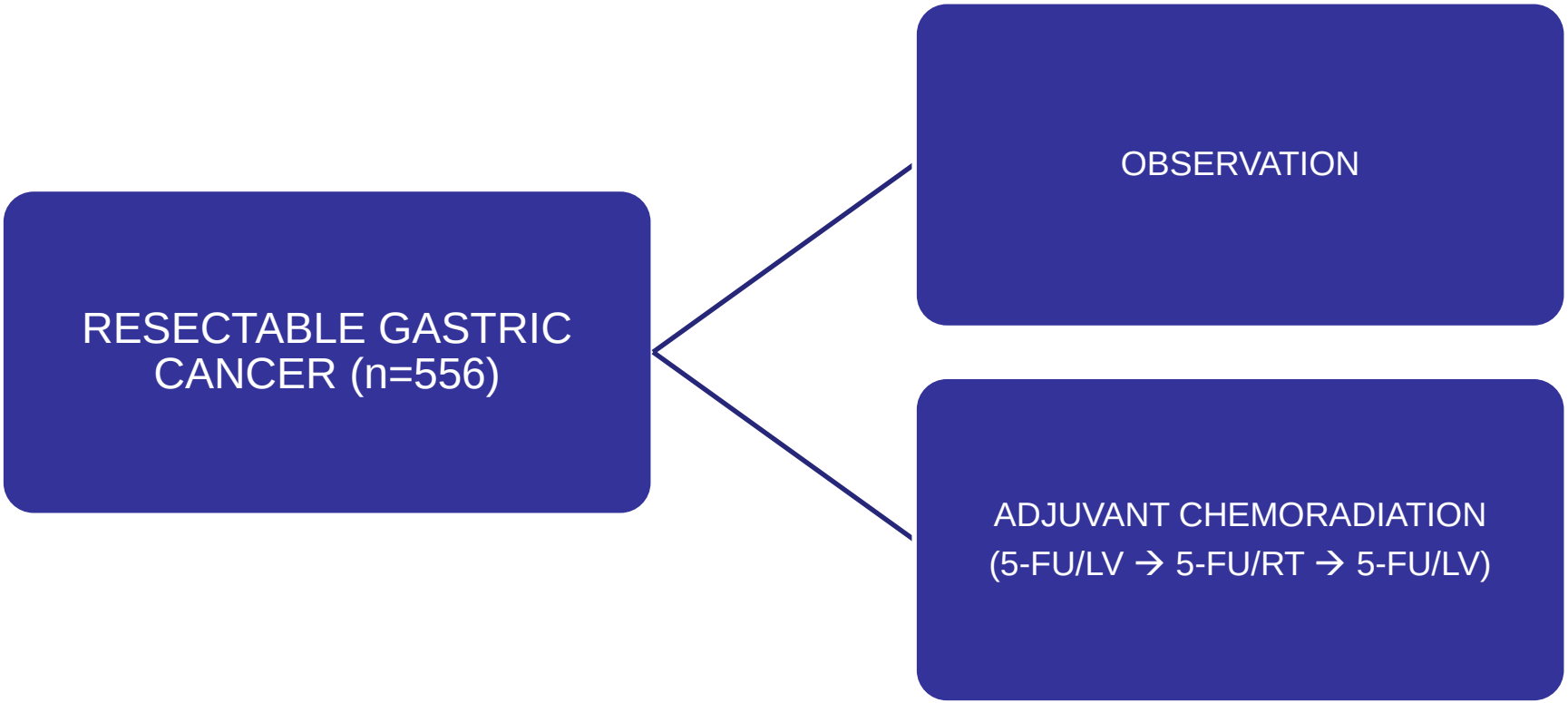
Dutch trial of D1 vs. D2 dissection for gastric cancer (Bonenkamp J et al. *N Engl J Med* 1999;340:908-914)



	15-year survival rate	Complication rate	Gastric cancer-related death	Postop deaths	Locoregional recurrence	5-year survival rate
D1	25% 21%		4% 48%		45% 41%	
D2	43% 29%		10% 37%		47% 25%	

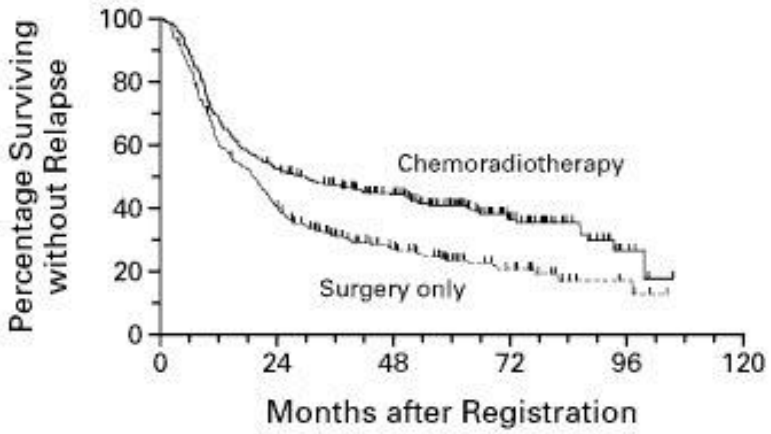
Why does the extent of Lymph node resection matter?

U.S. INTERGROUP 0116 STUDY

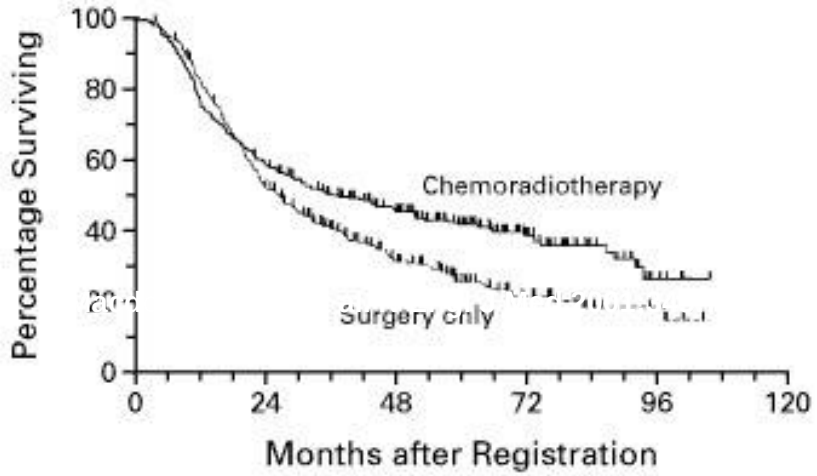


MacDonald et al, N Eng J Med 345:725, 2001

Results of int-0116 led to **chemo + Radiation** becoming standard of care in the U.S. for post-op adjuvant therapy



Relapse-free survival
19 vs. 30 months
($p < 0.001$)



Overall survival
36 vs. 27 mos.
($p < 0.001$)

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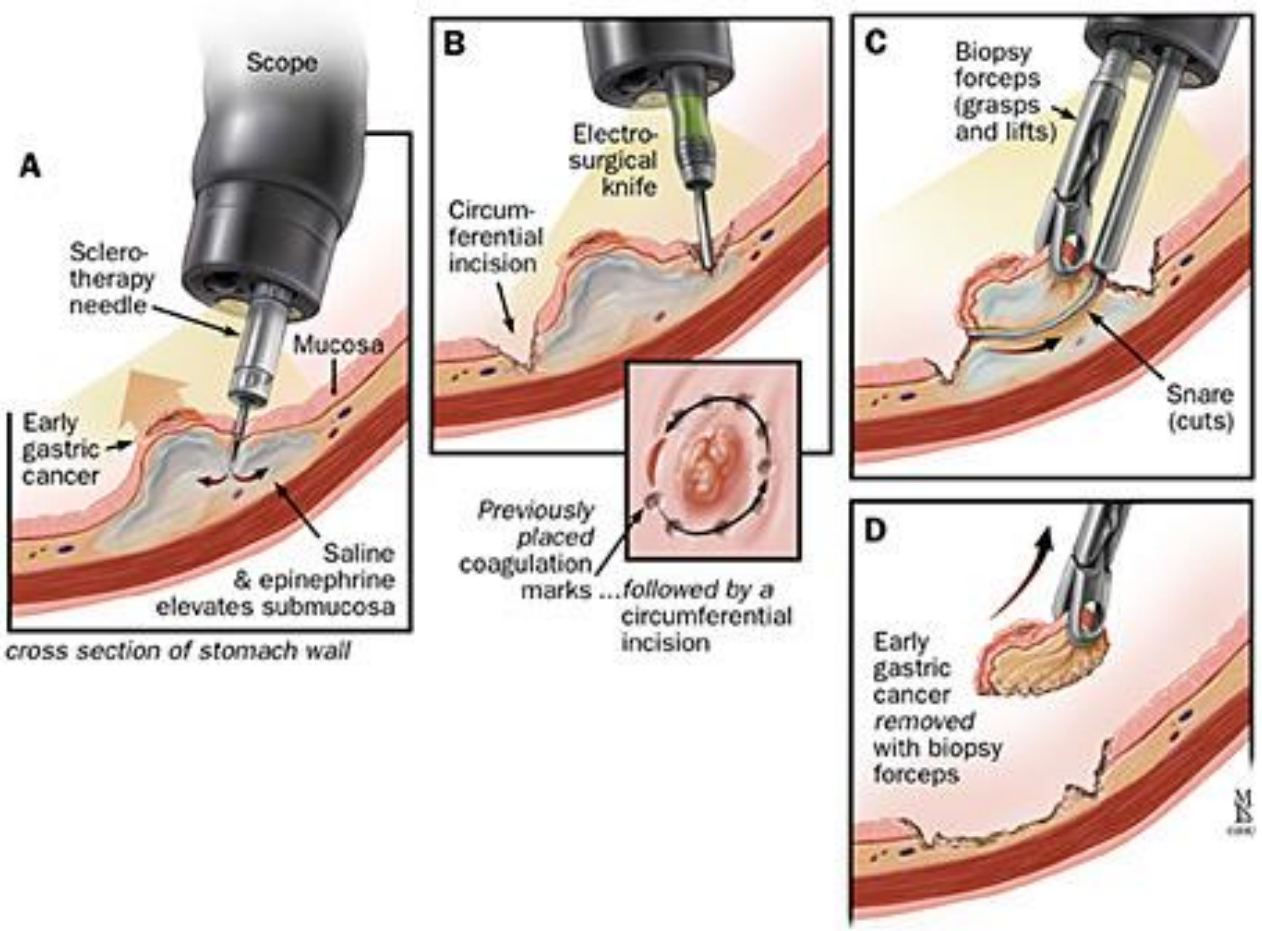
So Why didn't asians accept these data?

- Surgery Q/A performed
- Types of lymph node dissection performed on study patients:
  - 10% D2
  - 36% D1
  - 54% D0 (!!) ⟶ *Therefore, with better surgery, Is chemoXRT necessary??*

surgical outcomes between western vs. asian patients in adjuvant trials: differences attributable to tumor biology… or adequacy of operation?

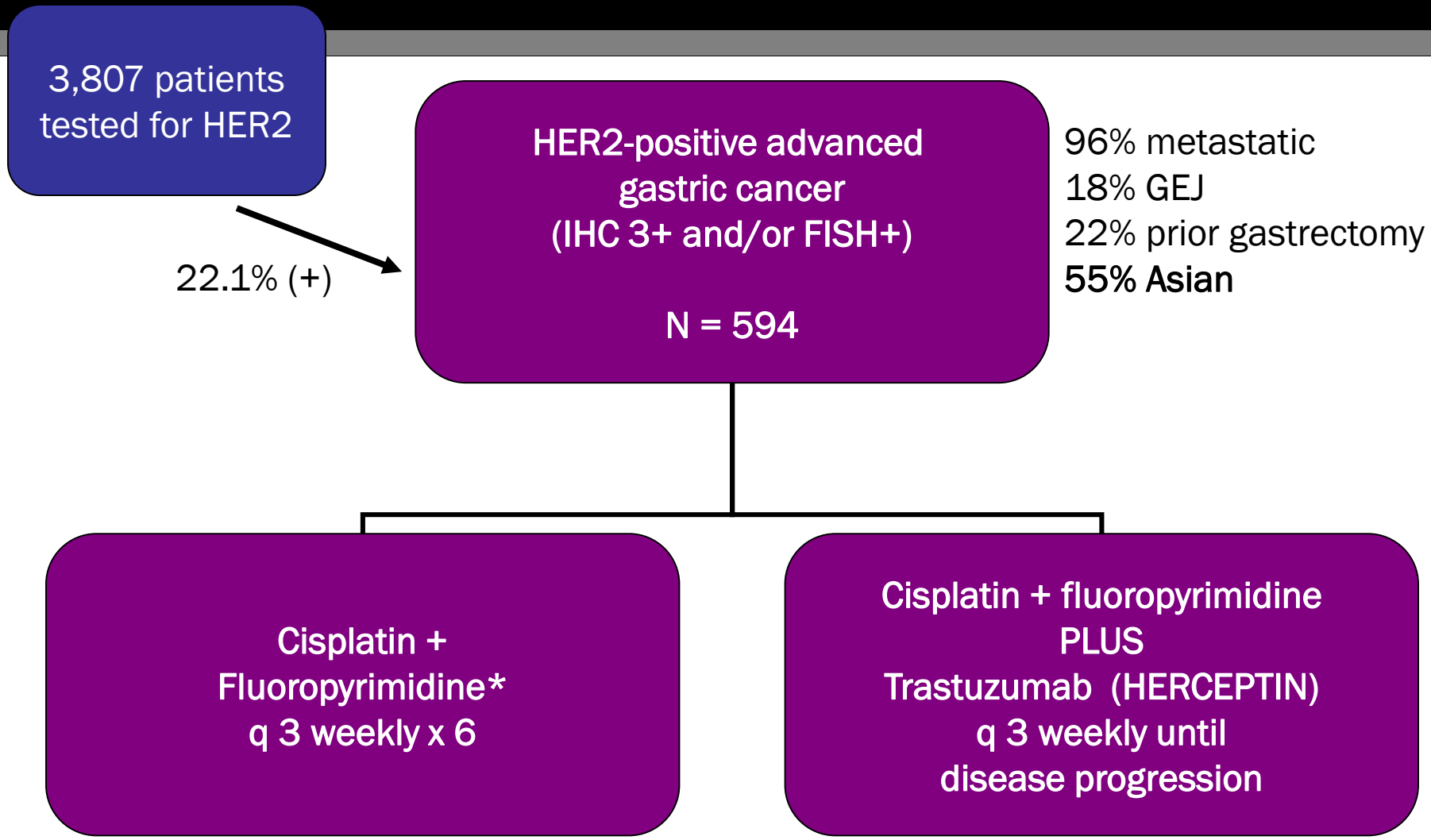
	Median age	D2 dissection (or greater)	3-year overall survival	3-year relapse-free survival
		(CONTROL ARMS ONLY – NO ADJUV RX)		
United States	59 yrs	10%	**41%**	**31%**
Japan	63 yrs	100%	**70%**	**60%**
Korea/Taiwan/ China	55.8 yrs	100%	**78%**	**59%**

endoscopic mucosal resection (EMR) is also a more common approach in asia for early-stage disease



- Should only be used for early gastric cancers (confined to mucosal layer)
- Contraindications: > 2 cm in size, LN metastases, lymphovascular invasion, or poor differentiation

Example #2: Ethnic differences in sensitivity to anti-cancer drugs



* Capecitabine or 5-FU

Van Cutsem et al, Lancet 2010, 376:687-97.

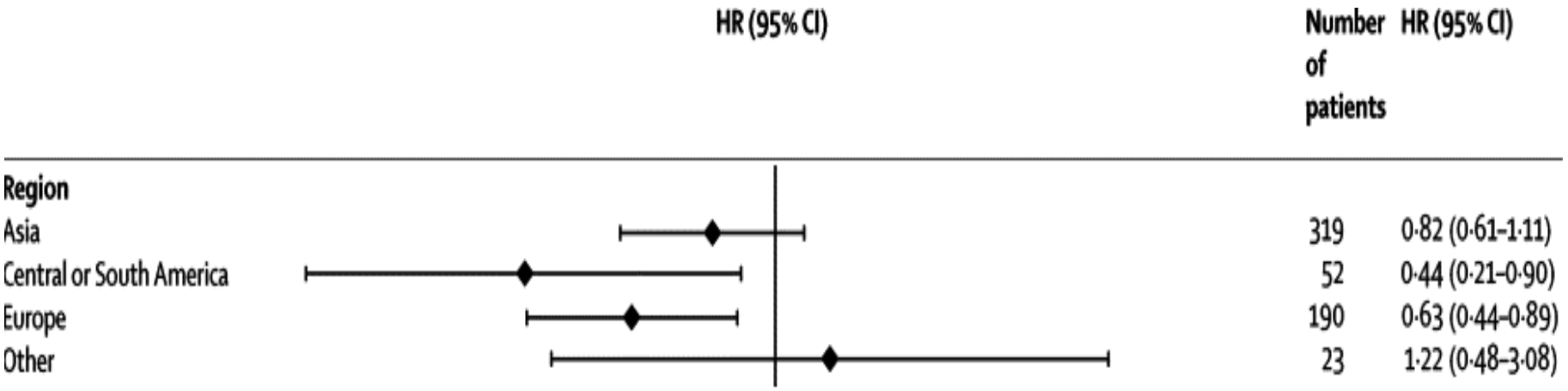
ToGA trial in advanced gastric cancer: efficacy results

	Chemo alone	Chemo + trastuzumab	P value
ORR	34.5%	47.3%	P=0.0017
Median PFS	5.5 months	6.7 months	P=0.0002, HR 0.71
Median survival	11.1 months	13.5 months	P=0.0048, HR 0.74

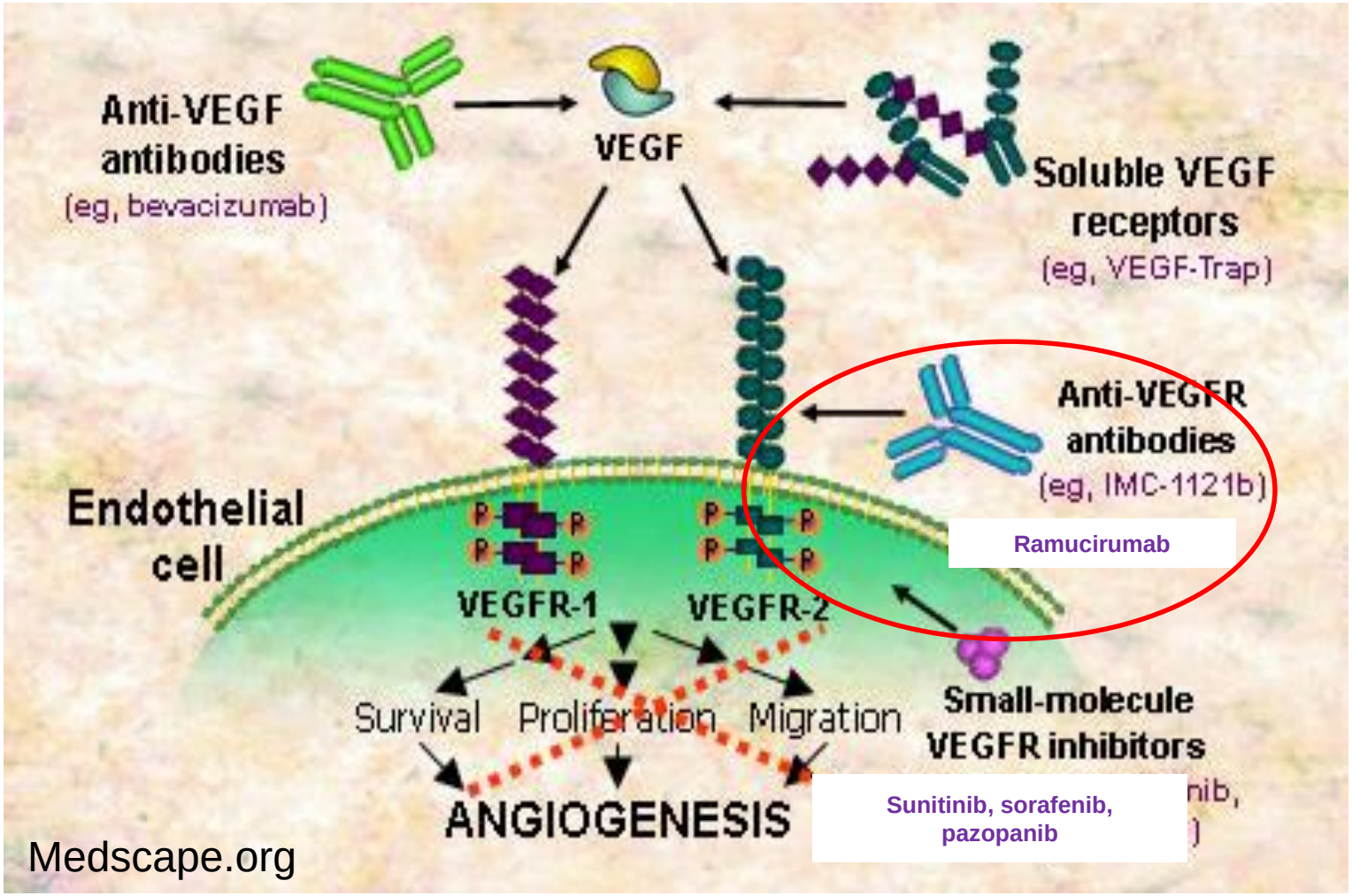
No major increase in treatment-related toxicities; decrease in LVEF in < 5% of patients

Led to first targeted therapy being approved for gastric cancer!

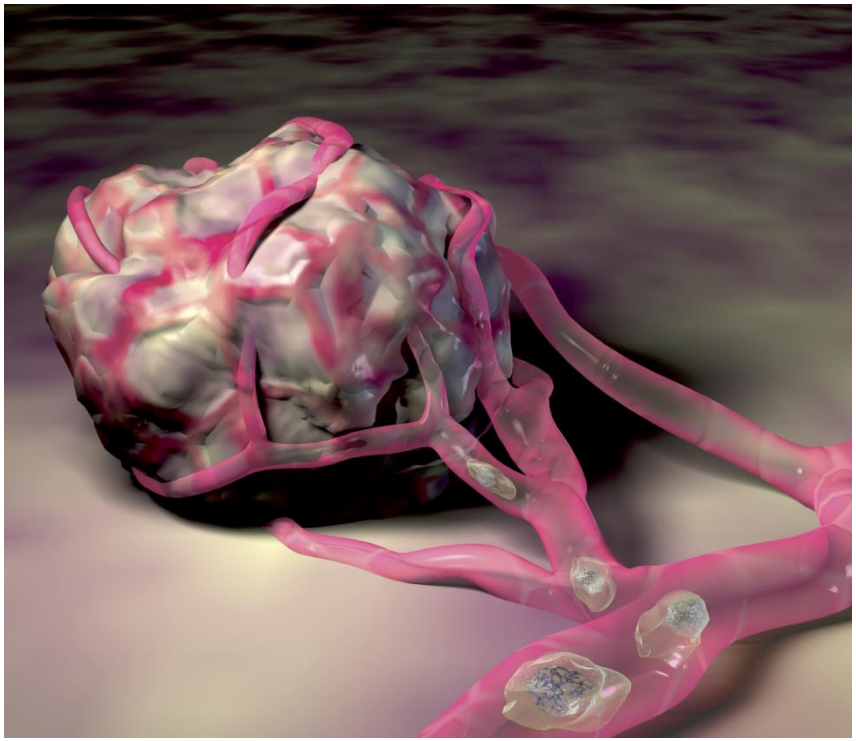
DID TRASTUZUMAB BENEFIT ASIAN AND NON-ASIAN PATIENTS EQUALLY?

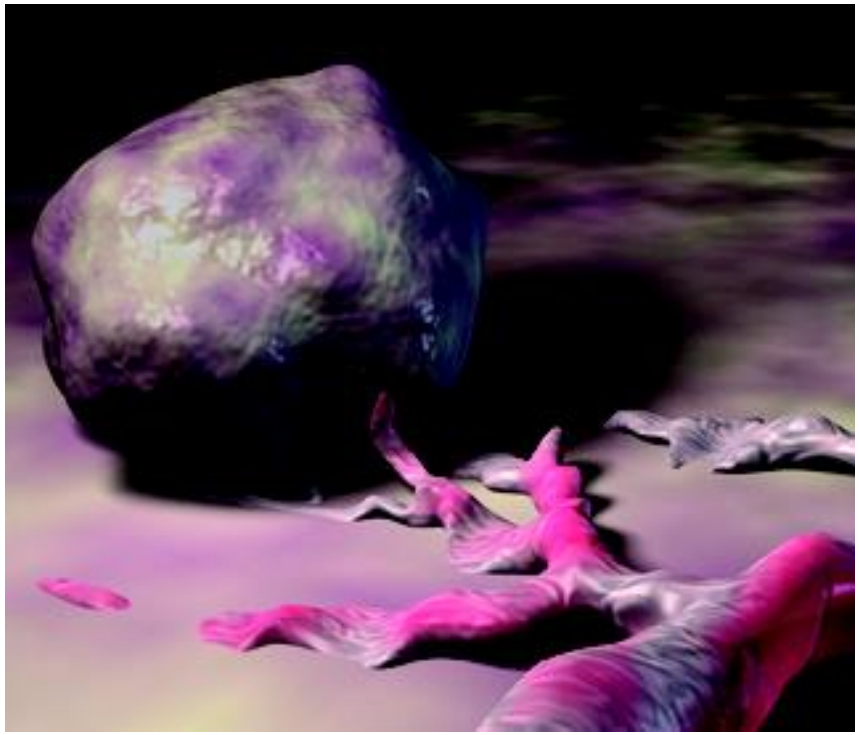


Ramucirumab: a new treatment option for advanced gastroesophageal cancer



Ramucirumab: anti-VEGFR antibody

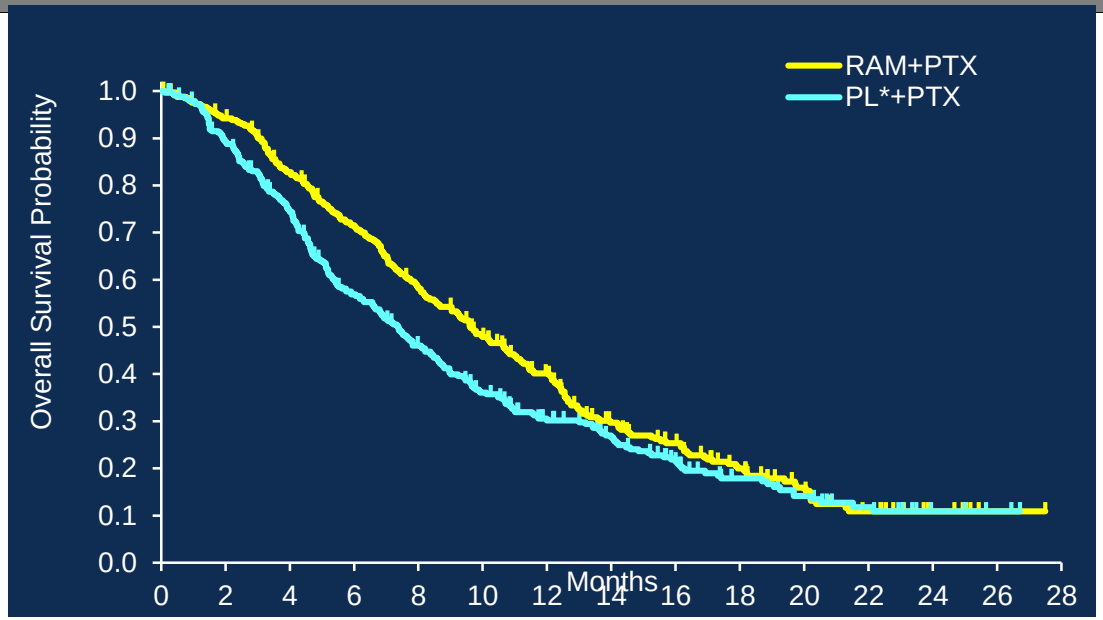




Courtesy of Genentech.

Phase III RAINBOW trial

Wilke H, et al. *J Clin Oncol* 2014 (LBA7)



	RAM+PTX N=330	PLACEBO+PTX N=335	Signif?
Median OS	**9.63 months**	**7.36 months**	P=0.017 (HR 0.81)
Median PFS	**4.40 months**	**2.86 months**	P<0.0001 (HR 0.64)
ORR	**28%**	**16%**	P=0.0001

Differences in ORR and PFS, Japanese vs Western patients

	Japan		West	
	RAM + PTX N = 68	**PL + PTX N = 72**	**RAM + PTX N = 198**	**PL + PTX N = 200**
ORR, %	41	19	27	13
p-value	0.0035		0.0004	
Median PFS	5.6 mos			os
p-value	0.0002 (HR 0.[illegible]03)		<0.0001 (HR 0.631)	
Median OS	11.4 mos	11.5 mos	8.6 mos	5.9 mos
p-value	0.51 (HR 0.880)		0.005 (HR 0.726)	

Probably because many more Japanese patients received post-progression therapy! (75% vs. 37%)

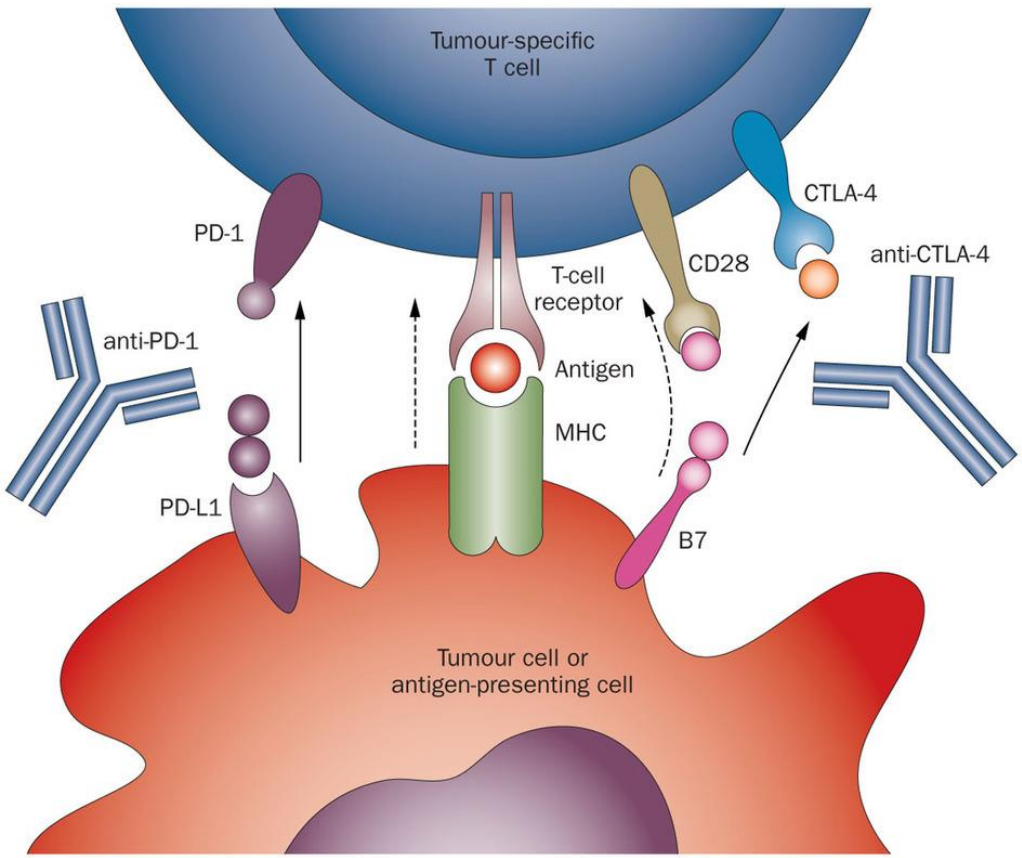
Wilke H, et al. *J Clin Oncol* 2014 (LBA7)

What to make of these data?

- Do clinical trials of new (cancer) therapies need to be validated in different ethnic groups given potential for differential responses and toxicity?
  - *Do pivotal studies conducted in Asia need to be duplicated in the U.S. (and vice-versa)?*
- Should clinical trials at least be stratified by ethnicity/race/nationality?
- How practical/feasible/ethical is this?

Finally, A GLIMPSE INTO THE FUTURE…

The immunotherapy revolution in cancer

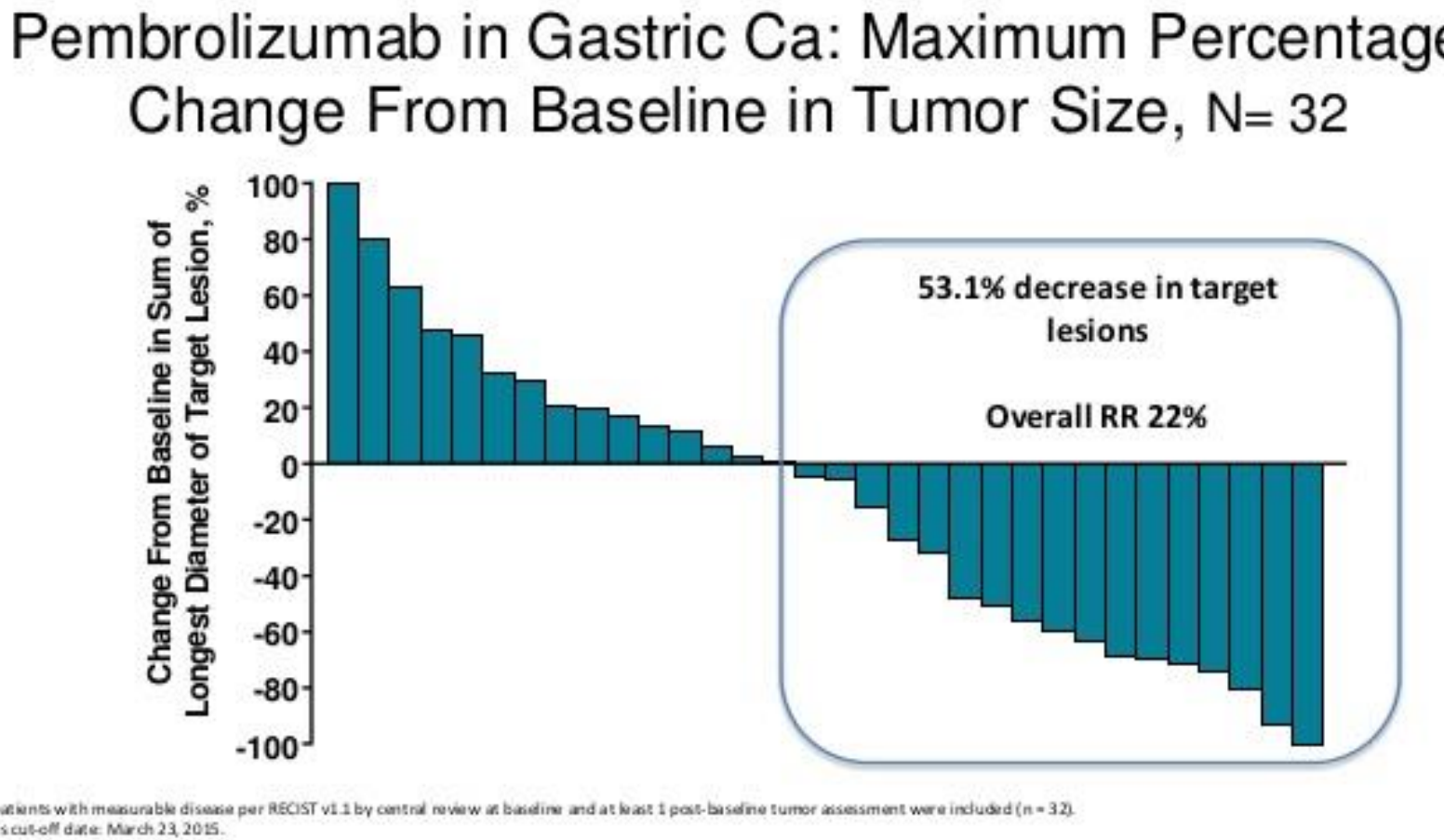


Nature.com

Immunotherapeutic approaches have transformed the way we treat many cancer patients, including:

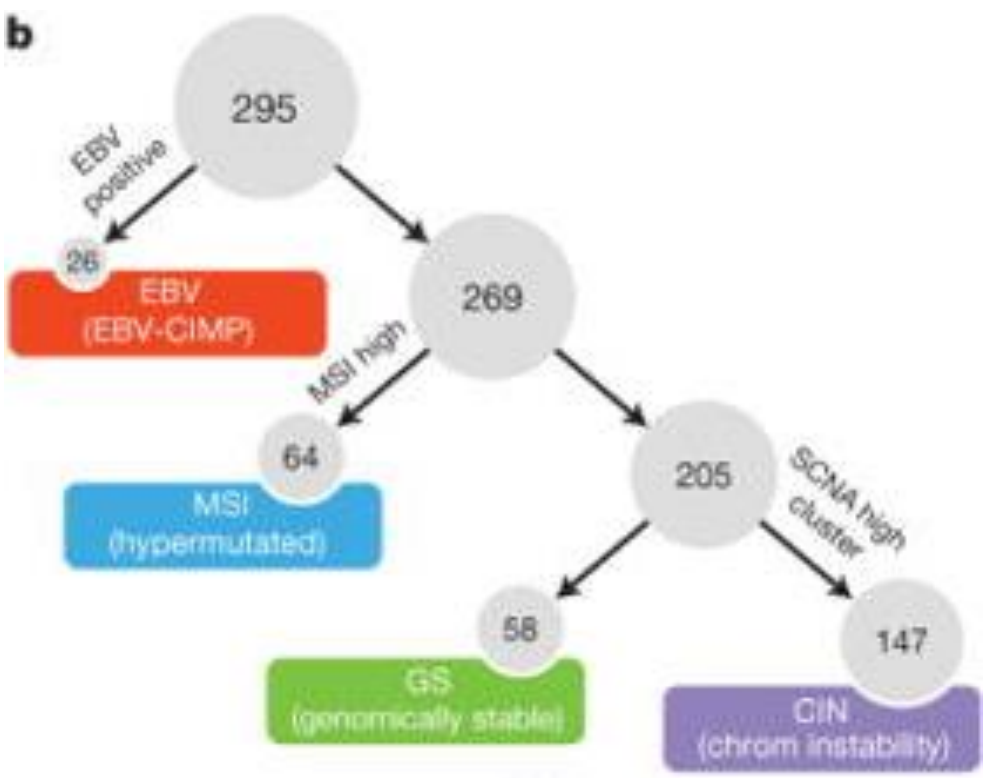
- *Melanoma*
- *Lung cancer*
- *Bladder and renal cell cancer*
- *Head and neck cancer*

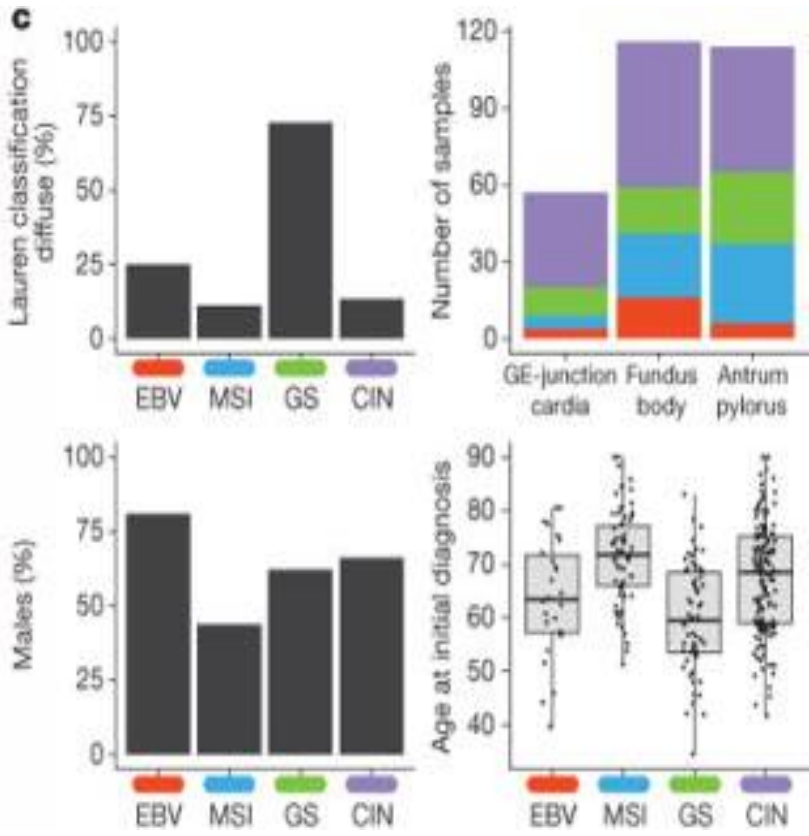
Does immunotherapy work in gastric cancer?



Bang, J Clin Oncol 33, 2015 (suppl, abstr 4001)

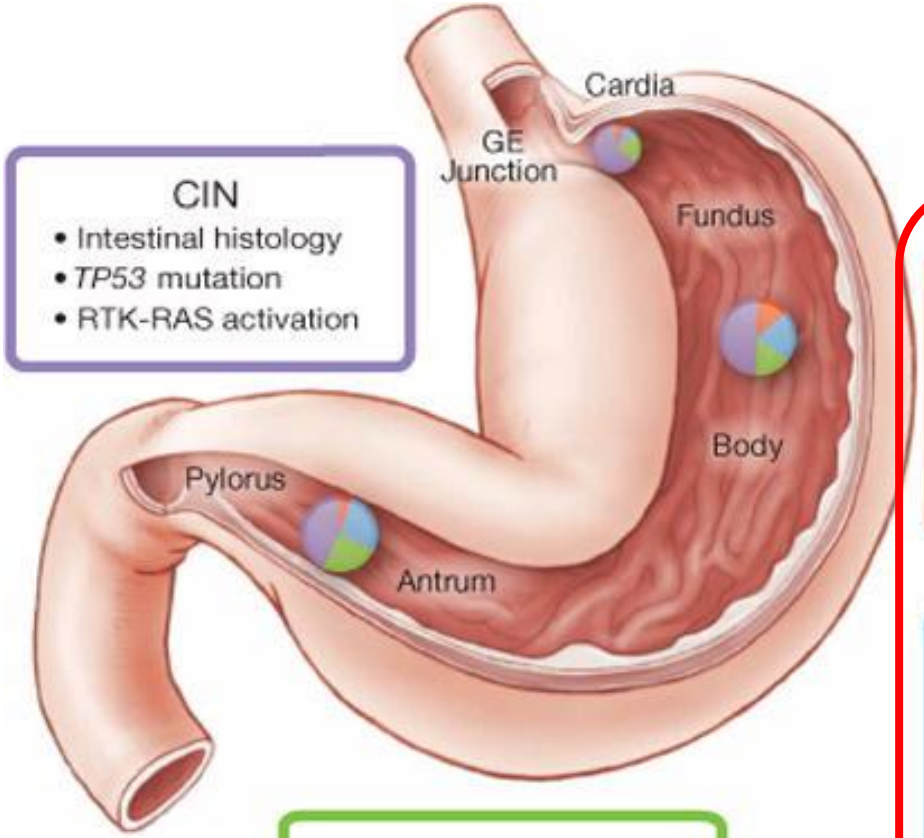
Clues from the Cancer Genome Atlas: Gastric cancer can be categorized into four molecular subtypes





Bass et al, Nature 2014, 513:202-9.

4 distinct molecular subtypes of gastric cancer



CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

Particularly sensitive to immunotherapeutic approaches?

Bass et al, Nature 2014, 513:202-9.

CONCLUSIONS

- The burden of gastric cancer is declining both in the United States and worldwide -- but remains 2nd leading cause of cancer mortality throughout the world
- Gastric cancer represents an ideal disease to demonstrate the differences between Asian and Western patients in terms of:
  - Incidence
  - Prognosis/clinical outcomes
  - Therapeutic approaches
- Need for greater understanding of the biologic/genetic differences in gastric cancer arising from different ethnicities
- Exciting new ways of categorizing and treating patients with gastric cancer are in the horizon!


THANK YOU
NASA