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Gastric Cancer: Epidemiology (including GE junction) and clinical presentation

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EMSO Preceptorship Programme 2017

Research

Clinical Care

Education

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NUH National University Hospital

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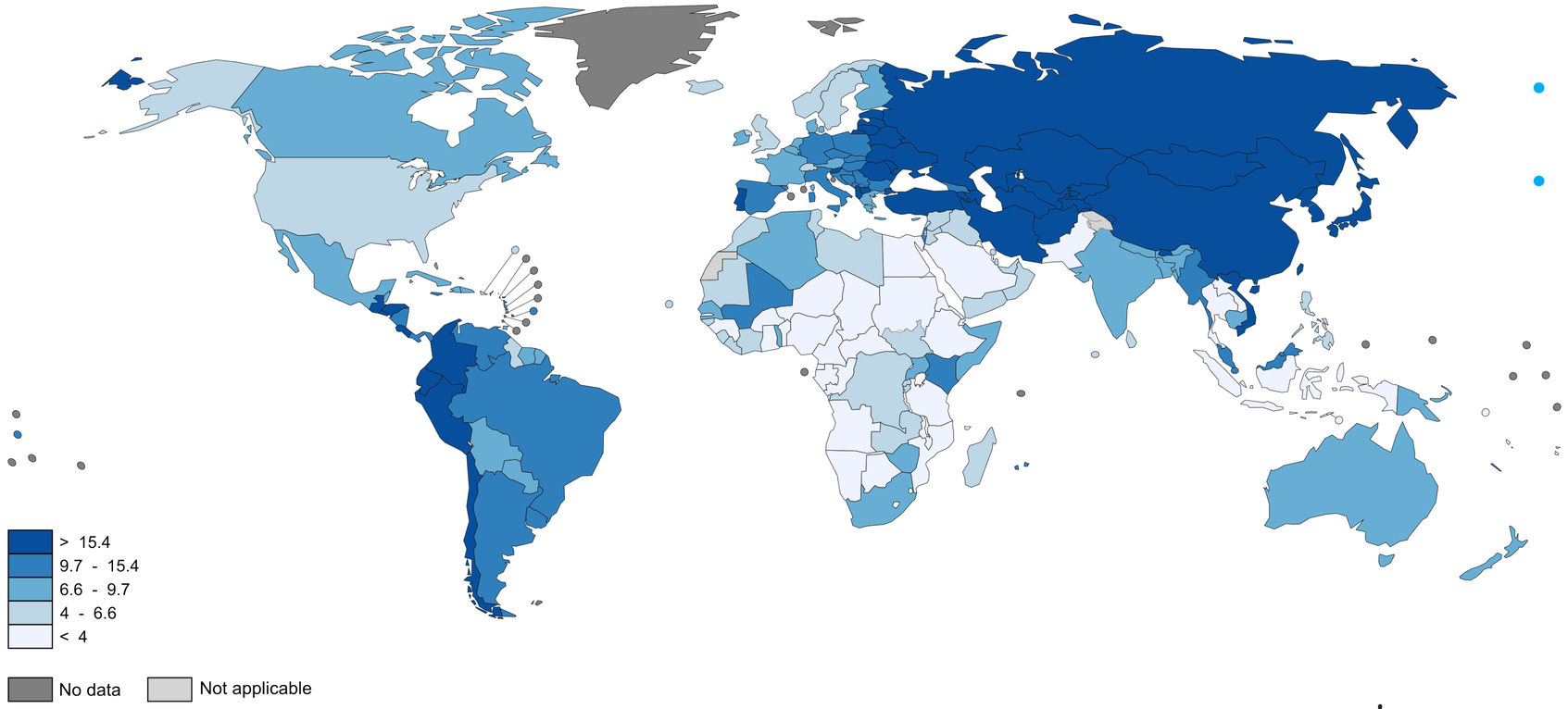
Incidences of GC worldwide



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

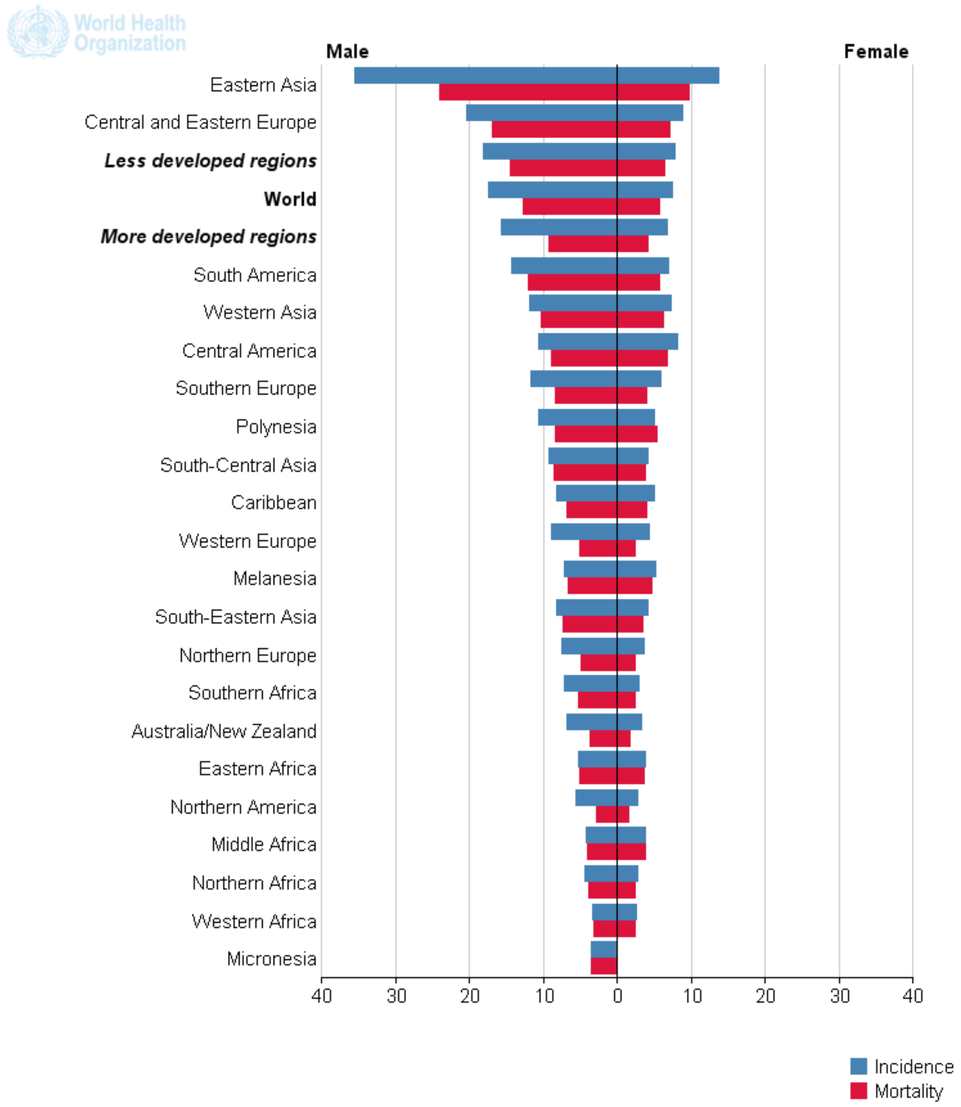
Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

- Nearly 1 million new cases a year
- 3rd leading cause of cancer death

GLOBOCAN 2012 (IARC)

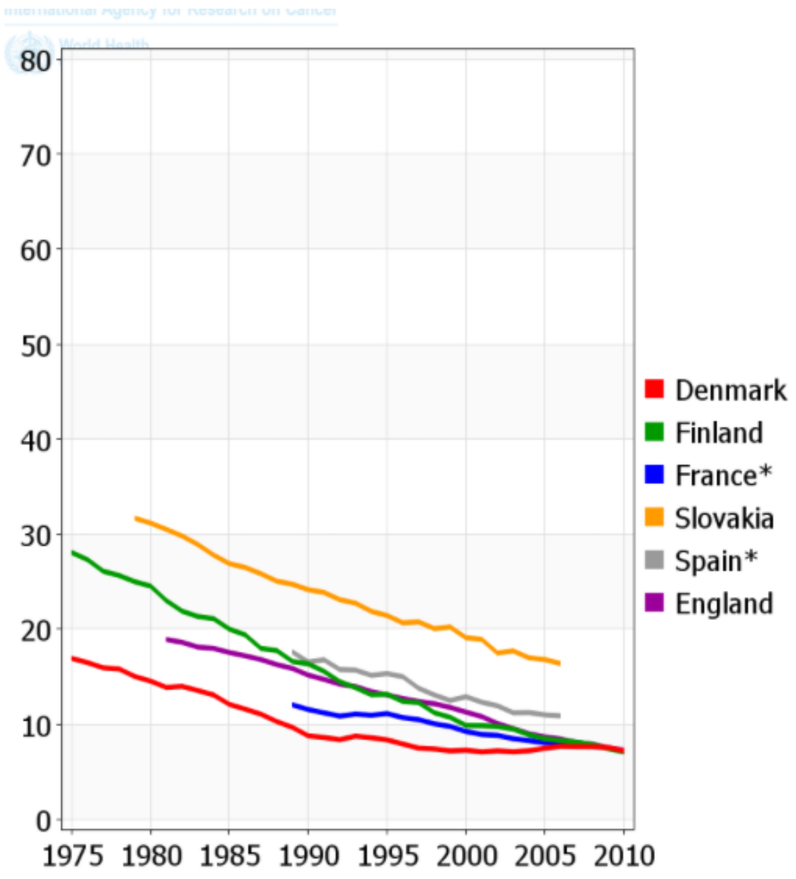
Mortality of GC worldwide

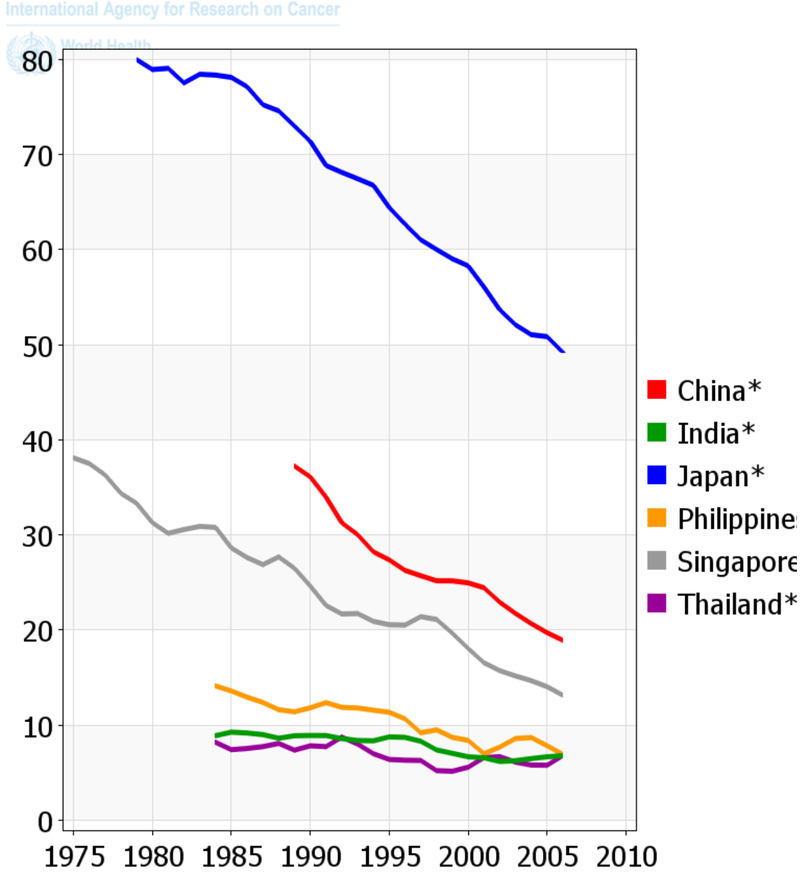


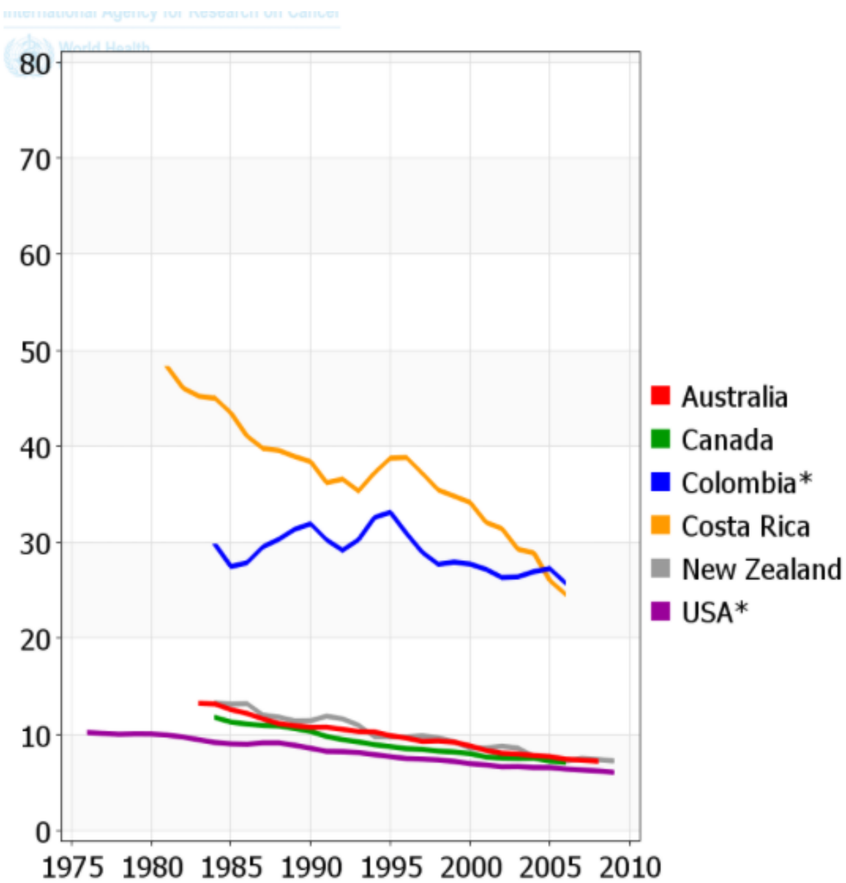
- The highest estimated mortality rates are in Eastern Asia (24 per 100,000 in men, 9.8 per 100,000 in women).
- High mortality rates are also present in both sexes in Central and Eastern Europe, and in Central and South America.

GLOBOCAN 2012 (IARC)

Trends in incidences of GC







- In 1975, stomach cancer was the most common neoplasm
- Currently the 5th most common malignancy

GLOBOCAN 2012 (IARC)

Causes for reduction in incidence and mortality

- Improved food preservation practices
  - use of refrigeration
  - less salt-based preservation of food
  - reduction of bacteria and fungal contamination

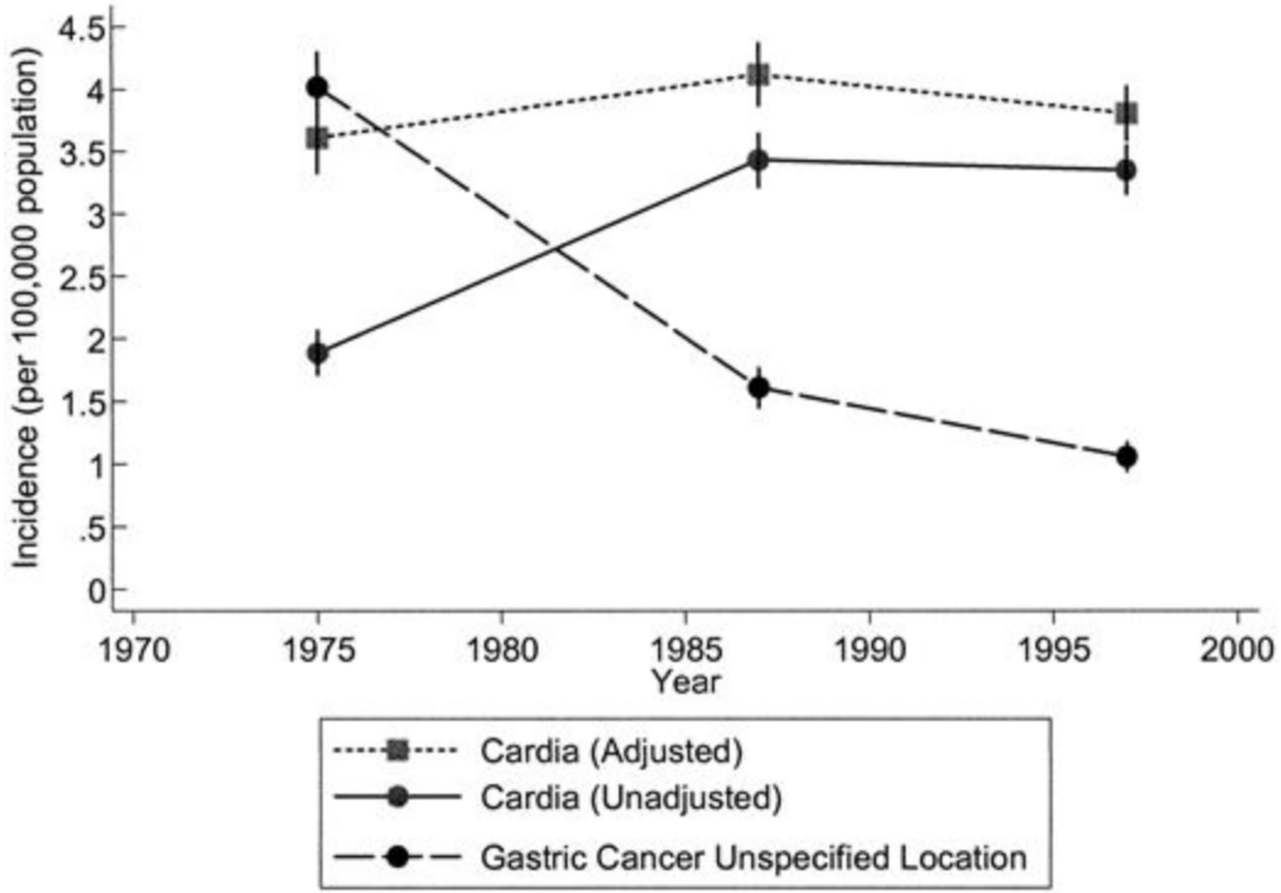
- Reduction in H Pylori infection

- Early cancer detection

- Surgical and oncologic advances

Cardia cancer

- **Incidence and proportion of cardia cancer increased with time in Western countries**



Corley DA JNCI 2004

Risk factors for GC

non cardia GC

Risk Factors	Odds Ratio	Prevalence of risk factors	Reference
Male	1.5 - 2	49%	Annemarie 2008, SCR 2002-2006
Family hx of GC	2.5-5.1	9-16%	Yatsuya 2004, Chen 2004
Low level of education	1.6	24%	Nagel 2007
Alcohol	1.4 – 1.5	24 - 43%	Moy 2010, Li 2011
High intake of salt, salt-preserved food	1.5 – 1.7	-	Brandt 2003, Tsugane 2004
H.pylori infection	2 - 5.1	46 - 82 %	Cho 2010, Sasazuki 2006, Uemura 2001, Watabe 2005
Atrophy gastritis	6 - 25	24%	Sipponen 1985, You 1993
Intestinal metaplasia	6.4 – 12.8	67%	Filipe 1994, Wu 1998

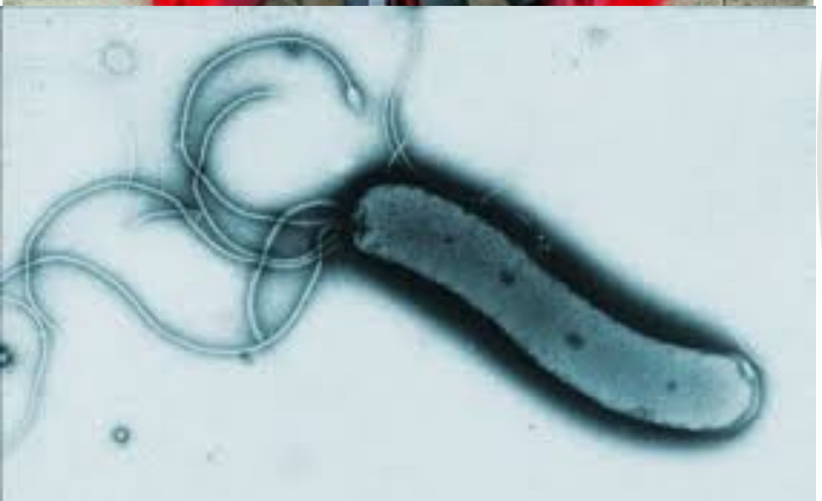
Risk factors for GC

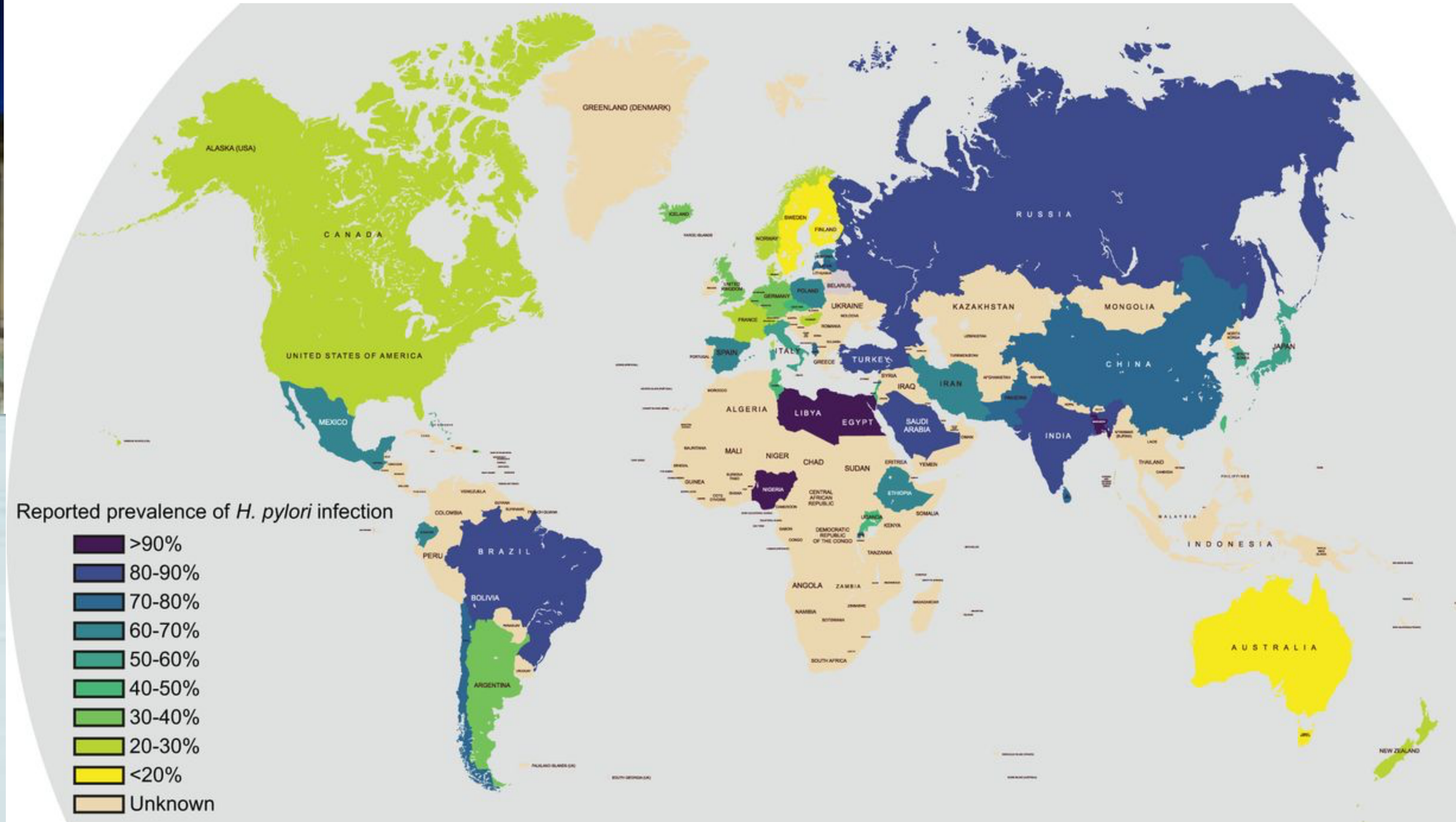
cardia GC

Risk Factors	Odds Ratio	Prevalence of risk factors	Reference
Obesity	1.6-2.61	NR	Yang 2009
Smoking	1.5 – 2.5	49 - 71%	Moy 2010, Sjodahl 2006, Gonzalez 2003

H. Pylori infection

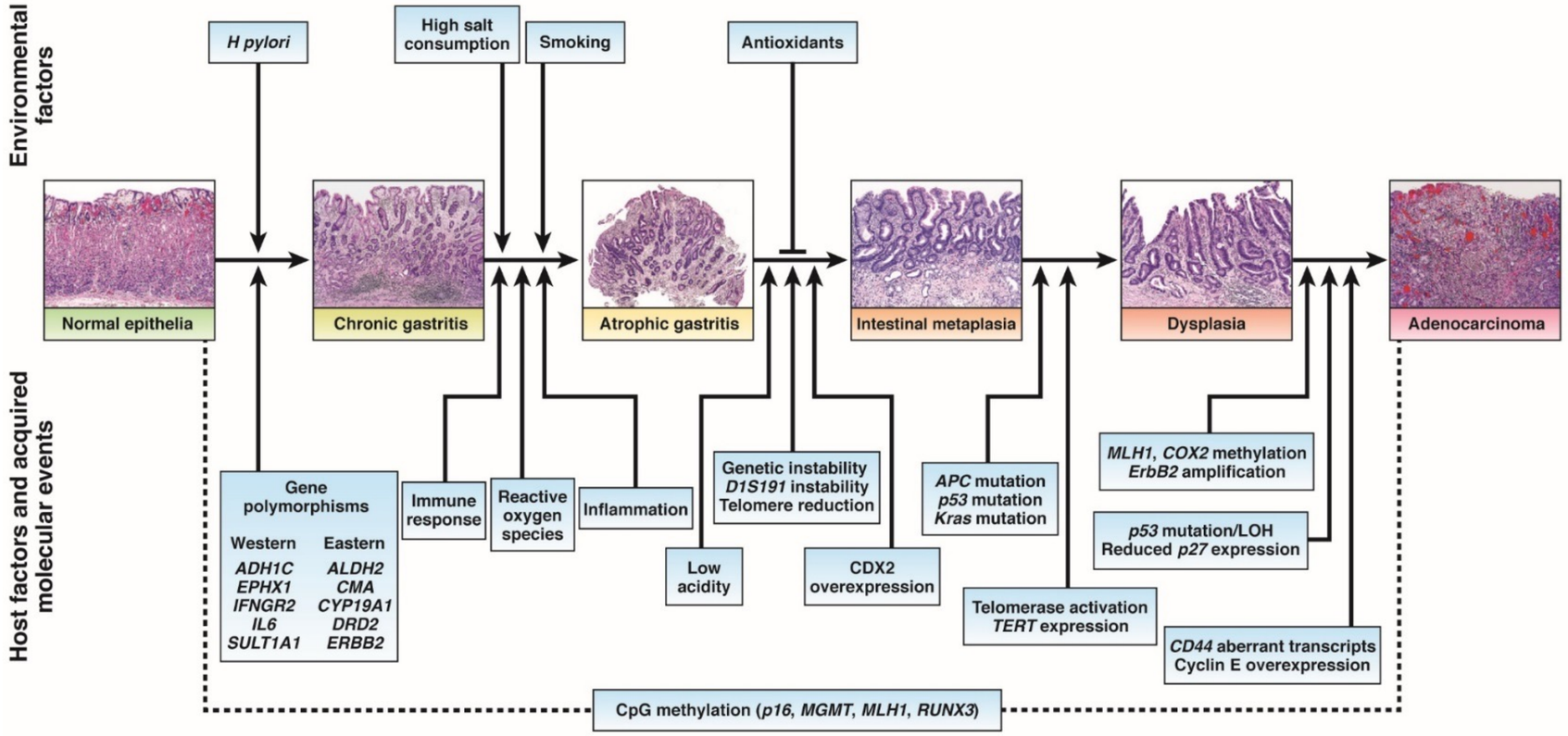
Discovered in 1982.
Group 1 carcinogen for gastric cancer by International Agency for Research on Cancer (IARC) in 1994





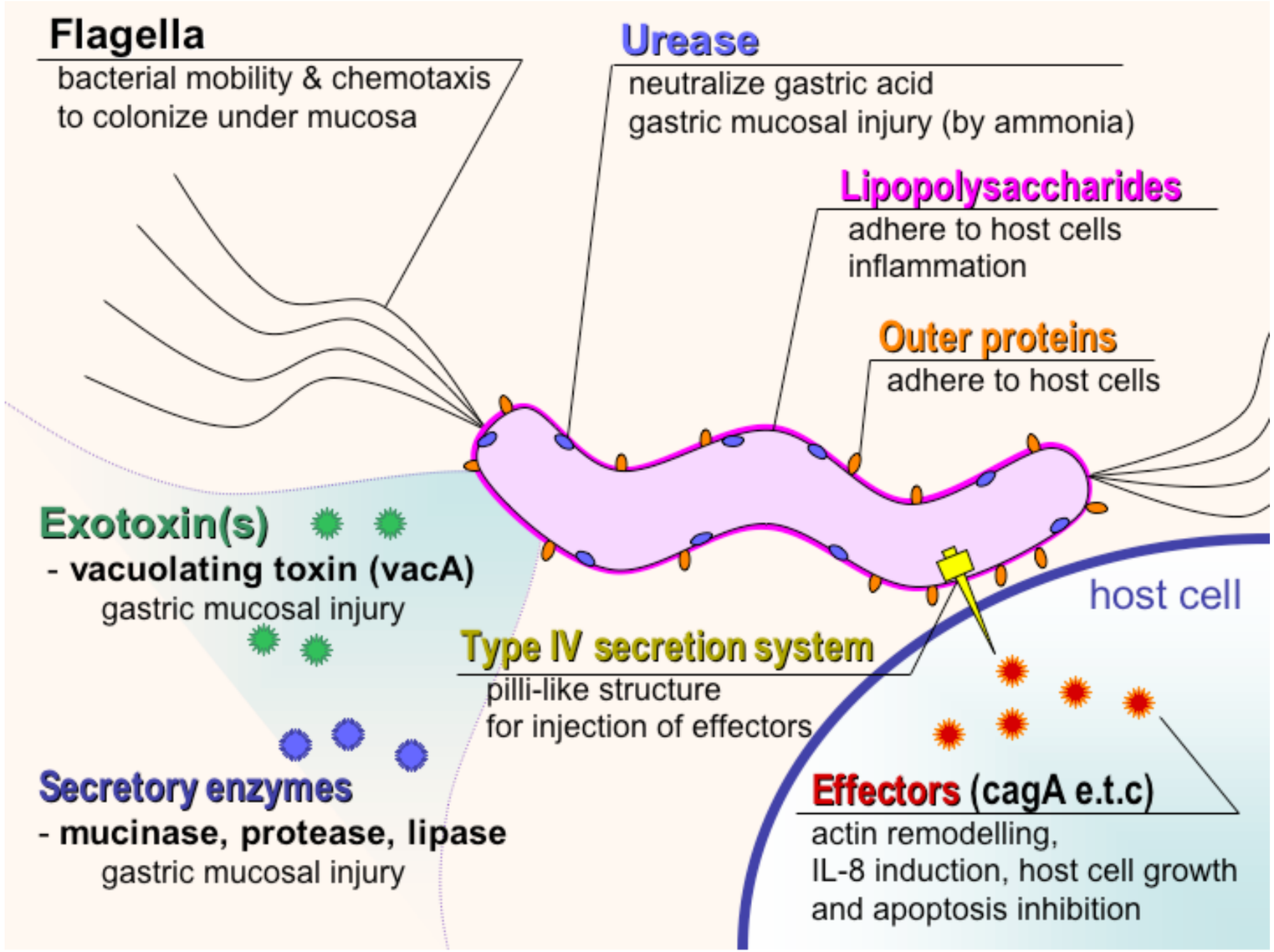
Pathogenesis of gastric cancer

- *H. pylori* infection contributes to the pathogenesis of intestinal-type gastric cancer, along with other host and environmental factors
- *H. pylori*-induced chronic inflammation precedes atrophic gastritis, IM and gastric adenocarcinoma



P Tan and KG Yeoh, Genetics and Molecular Pathogenesis of Gastric Adenocarcinoma. Gastroenterology 2015;149:1153–1162

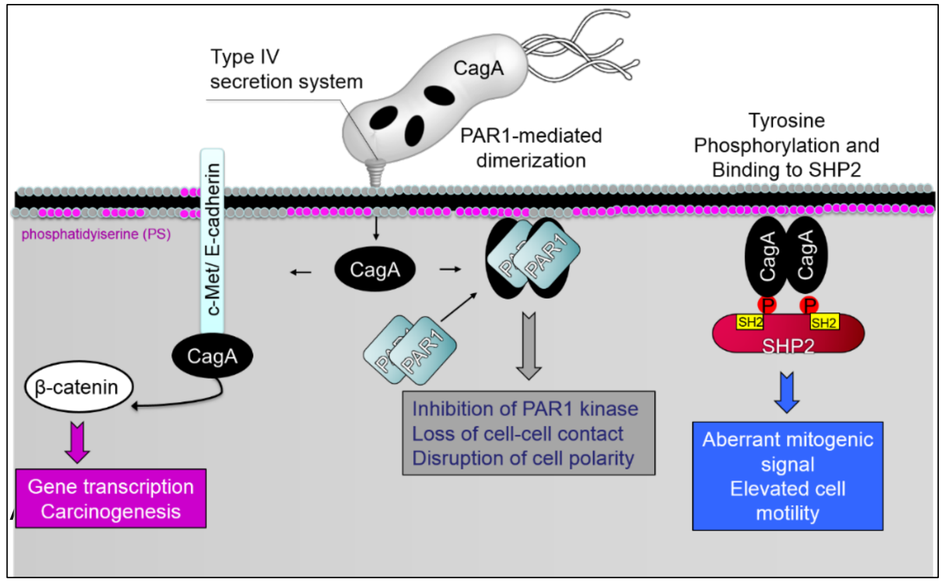
Chronic inflammation from H Pylori



CagA is a major virulence factor of H.pylori

- *H. pylori* virulence and oncogenic ability is contributed by the expression of CagA (cytotoxin-associated gene A)
- Present in 50-70% of *H. pylori* strains

<u>Molecular mechanism for CagA-associated pathogenesis:</u>

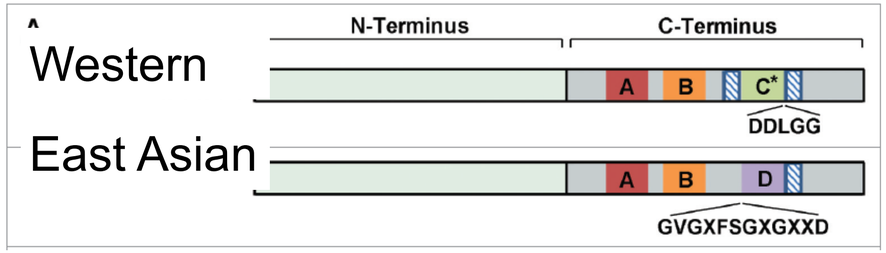


- CagA disrupts tight junctions and cell-cell adhesion by altering cell polarity via interaction Par1/MARK kinase
- Phosphorylation of CagA by Src kinase → binding and activation of SHP-2 → activation Ras-ERK pathway → cell proliferation, adhesion and migration.
- CagA interacts with Met and E-cadherin → displacing β-catenin and driving β-catenin-dependent transcription and cellular transformation, contribute to cancer progression

Huang, J. Q., et al. (2003). "Meta-analysis of the relationship between cagA seropositivity and gastric cancer." Gastroenterology 125(6): 1636-1644.
Hatakeyama, M. (2002). "Deregulation of SHP-2 tyrosine phosphatase by the Helicobacter pylori virulence factor CagA." Keio J Med 51 Suppl 2: 26-32.
Hatakeyama, M. (2008). "Linking epithelial polarity and carcinogenesis by multitasking Helicobacter pylori virulence factor CagA." Oncogene 27(55): 7047-7054.

H.pylori in Western and East Asian Isolates

- ~ 60% of *H. pylori* isolates in Western countries are cag-positive while almost all in East Asia are cag-positive



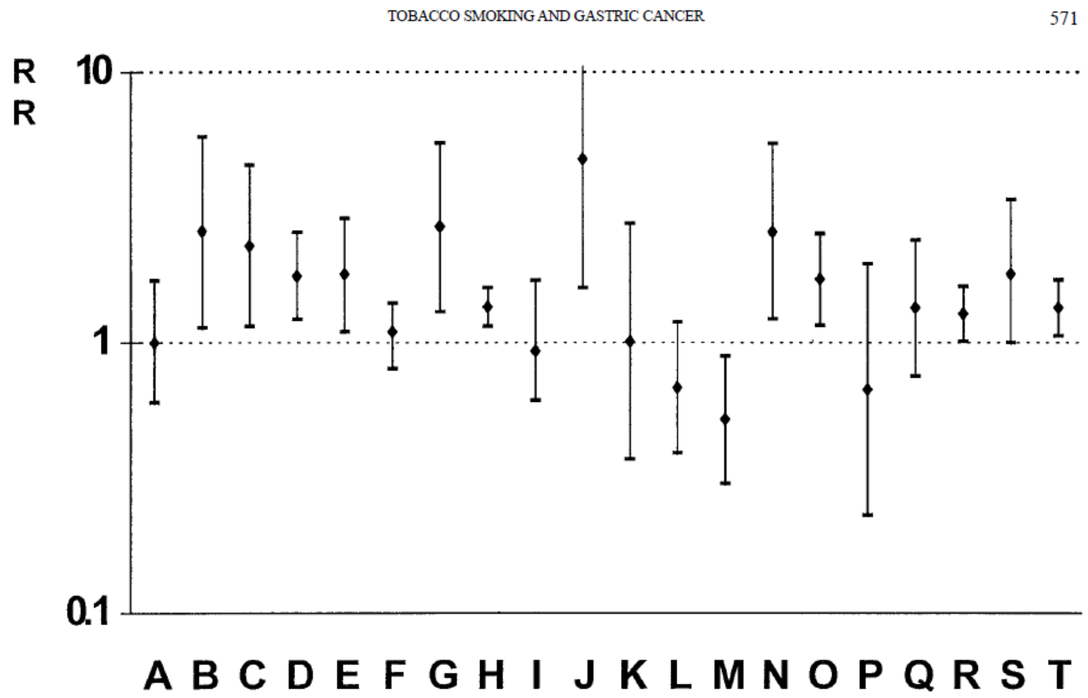
Bridge et. al (2013) Polymorphism in the Helicobacter pylori CagA and VacA toxins and disease.

- CagA phosphorylation occurs within the EPIYA (Glu-Pro-Ile-Tyr-Ala) motif at the C-terminus
- Different segments of EPIYA motifs due to their flanking sequences – EPIYA-A, B, C and D
- EPIYA-C is the main phosphorylation site in Western isolates of CagA; EPIYA-D is the main phosphorylation site in East Asian isolates
- EPIYA-D binds stronger to SHP2 compared to EPIYA-C, eliciting a stronger morphogenetic response
- Patients infected with East Asian isolates of H. pylori exhibit more severe inflammation and atrophy, may have an increased risk for developing GC.

Higashi H *et al.* Biological activity of the *Helicobacter pylori* virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. *Proc Natl Acad Sci USA* 2002; 99: 14 428–33.
Hatakeyama, M. and H. Higashi (2005). "Helicobacter pylori CagA: a new paradigm for bacterial carcinogenesis." Cancer Science 96(12): 835-843.
Azuma T *et al.* Association between diversity in the Src homology 2 domain-containing tyrosine phosphatase binding site of *Helicobacter pylori* CagA protein and gastric atrophy and cancer. *J Infect Dis* 2004; 189: 820–7.

Smoking

A risk of stomach cancer among smokers was 1.5–1.6 times higher as compared to non-smokers

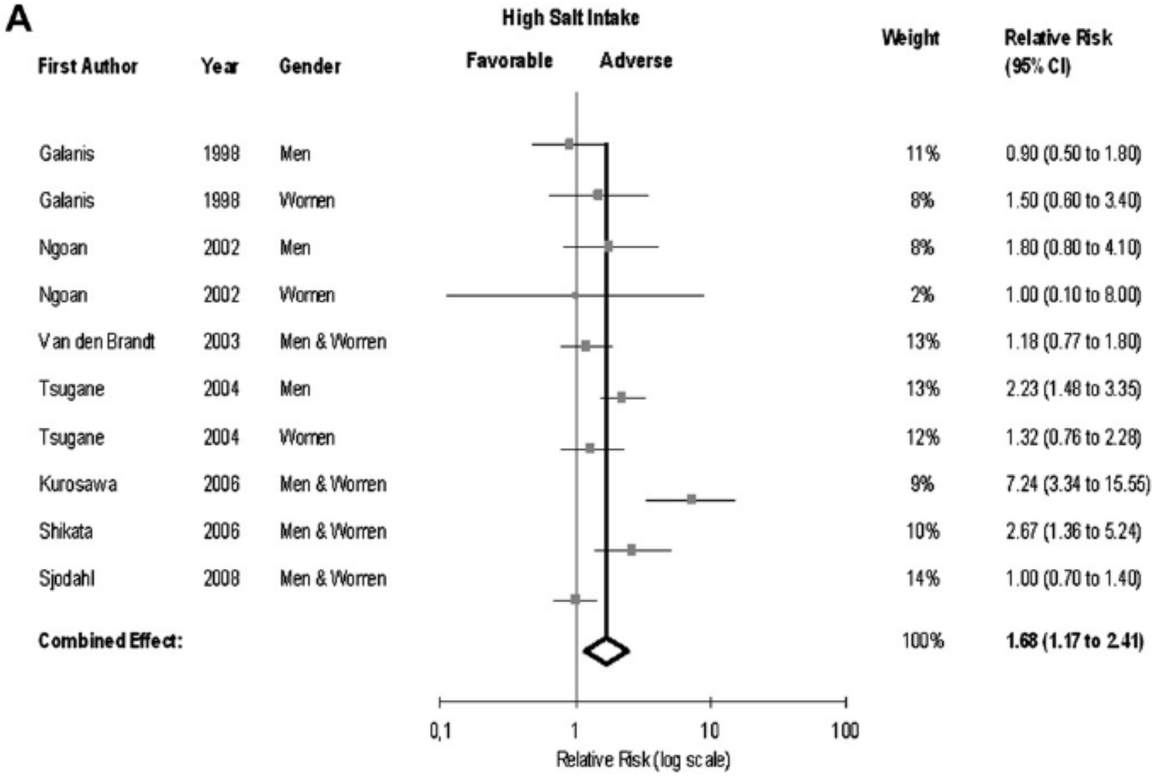


- Similar effect in both the Western and Asian countries
- Higher odds ratio in cardia GC compared to distal one
- Decrease of risk after 10 yrs of quitting smoking
- Carcinogens in tobacco smoke, nitrosamines and other nitroso compounds, exert mutagenic effects, increasing GC risk
- Smoking also increases the risk for precancerous lesions such as intestinal metaplasia and dysplasia

Jean TRE´DANIEL et al.Tobacco Smoking And Gastric Cancer: Review And Meta-analysis. ***Int. J. Cancer* 72:565–573, 1997**
Carlos A. GONZ´ALEZ et al. Smoking And The Risk Of Gastric Cancer In The European Prospective Investigation Into Cancer And Nutrition (EPIC). *Int. J. Cancer:* **107,** 629–634 (2003)

Salt and Salt-preserved Food

Meta-analysis: High salt intake was associated with increased risk of GC with RR 1.68 (95%CI 1.17-2.41)

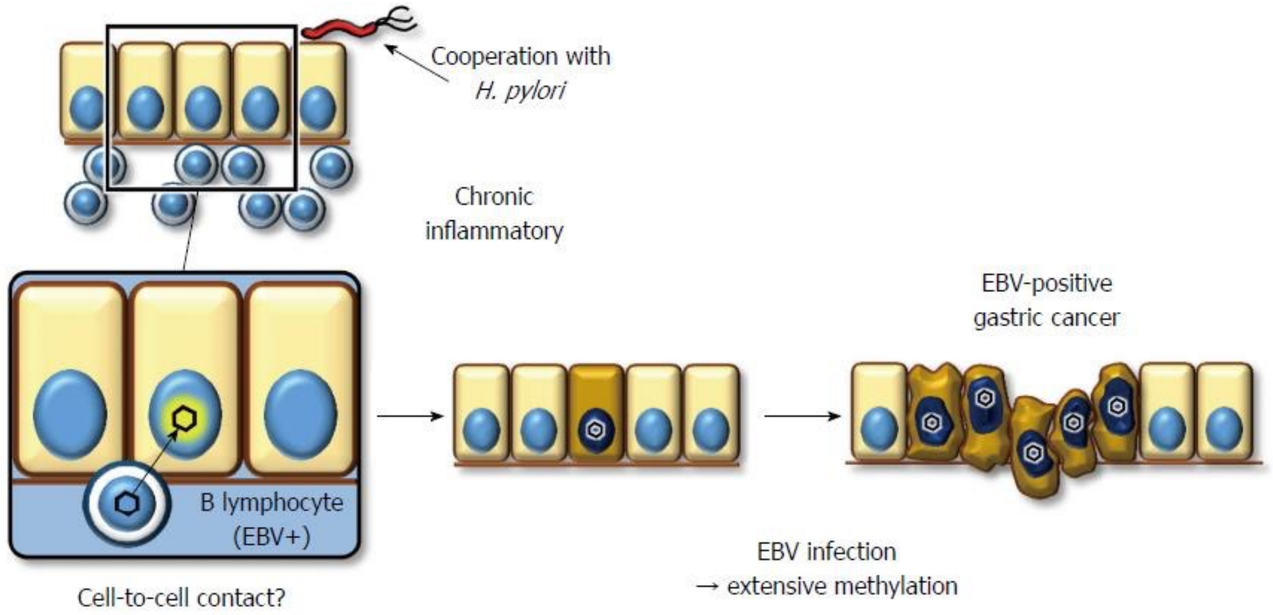


- Increased the risk of *H.pylori* infection
- Enhance the effect of known carcinogens, eg MNNG
- Promote damage of gastric mucosa, hypergastrinemia and cell proliferation

L. D'Elia et al. Habitual salt intake and risk of gastric cancer: A meta-analysis of prospective studies. Clinical Nutrition 31 (2012) 489-498.

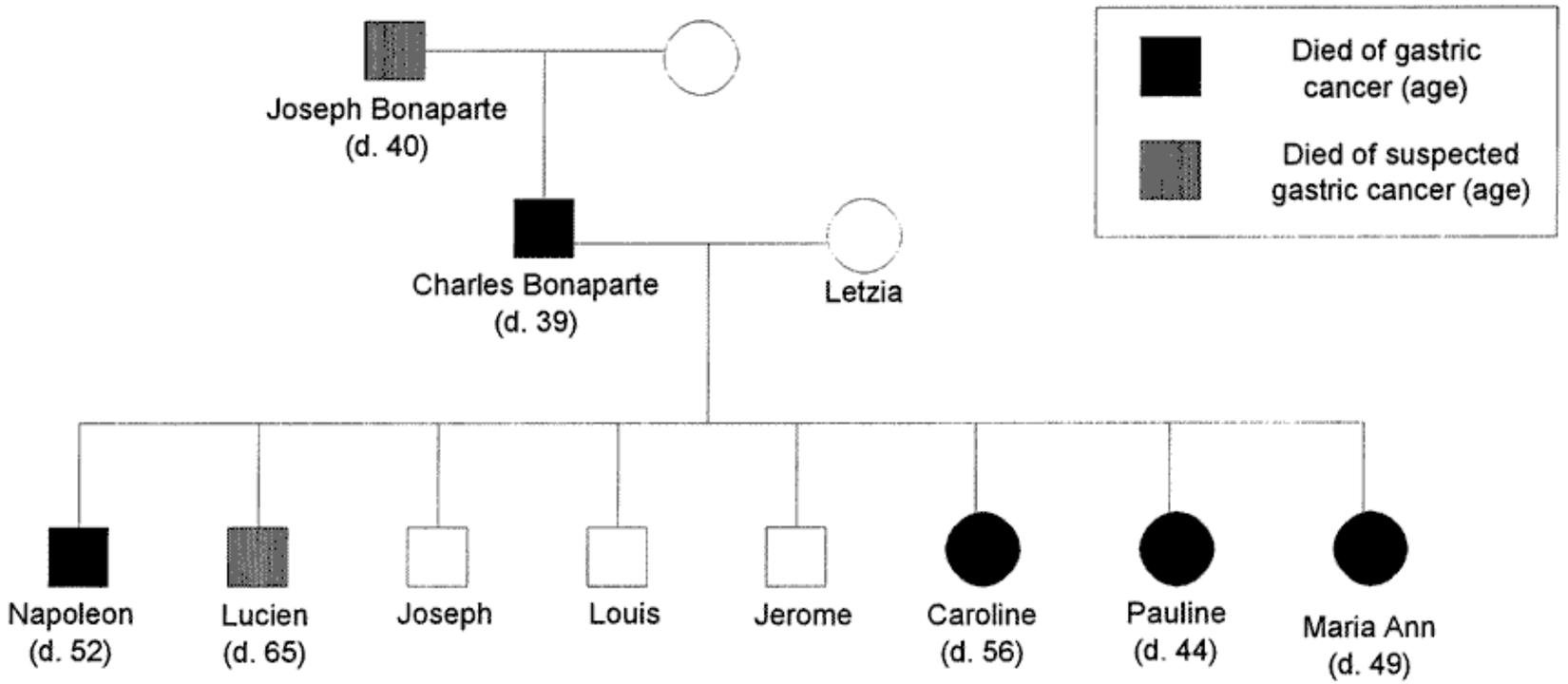
EBV infection

- EBV-encoded genes enhance oncogenesis, eg. small ribonucleic acid 1 (EBER1) inhibits apoptosis and induces IGF-1
- EBV induces extensive methylation that contributes to cancer progression.



Iizasa, Hisashi et al. “Epstein-Barr Virus (EBV)-Associated Gastric Carcinoma.”*Viruses* 4.12 (2012): 3420–3439. *PMC*. Web. 22 Feb. 2016.
Matsusaka K et. al DNA methylation in gastric cancer, related to Helicobacter pylori and Epstein-Barr virus. *World J Gastroenterol* 2014; 20(14): 3916-3926

Familiar gastric cancer syndrome



Familiar gastric cancer syndrome

- 10% of gastric cancers show familial clustering
- Hereditary Diffude Gastric Cancer (E-cadherin mutation),
- Elevated risk of lobular breast cancer and possibly colorectal cancer.
- Histologically, gastric tumors are highly invasive, poorly differentiated, and display occasional signet ring cells.
- The lifetime penetrance of HDGC is about 65%,
- age of onset shows from 14 years upward with a median age in the late thirties.

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Listen to the FDA D.I.S.C.O. podcast about this approval

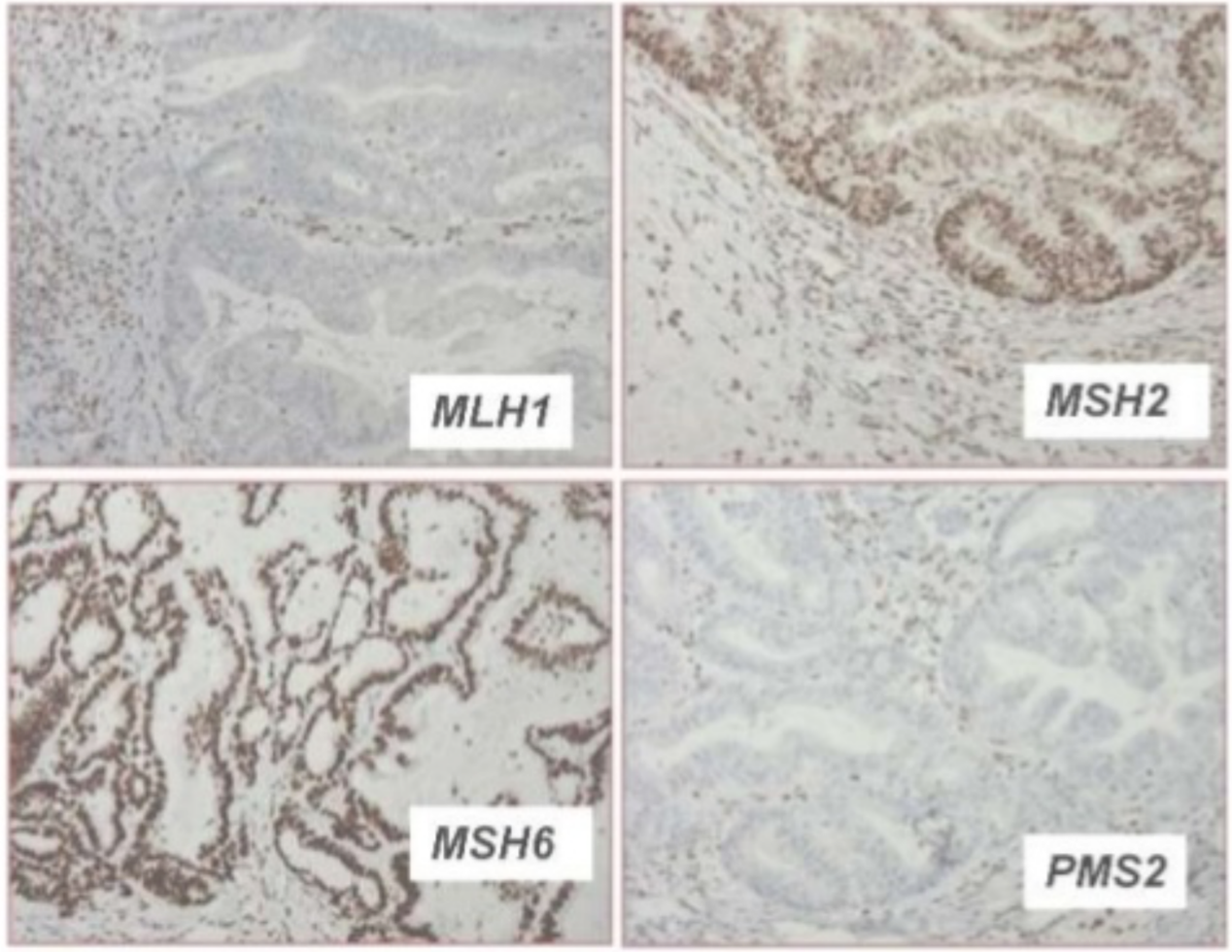
On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This is the FDA's first tissue/site-agnostic approval.

The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-center, single-arm clinical trials. Ninety patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types. Patients received either pembrolizumab, 200 mg every 3 weeks, or pembrolizumab, 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity, or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or associated with a decline in performance status. A maximum of 24 months of treatment was administered.

The major efficacy outcome measures were objective response rate (ORR) assessed by blinded independent central radiologists' review according to RECIST 1.1, and response duration. ORR was 39.6% (95% CI: 31.7, 47.9). Responses lasted six months or more for 78% percent of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses. ORR was similar irrespective of whether patients were diagnosed with CRC (36%) or a different cancer type (46% across the 14 other cancer types).

Diagnosis of MMR deficiency by IHC



- Short turnaround
- No need normal germline tissue
- Cheaper
- Good concordance with MSI testing (>90%)

Diagnosis of MMR deficiency by PCR

- MSI-H if 2 or more markers with instabilities
- MSI-L if 1 marker with instabilities
- MSS if no instability

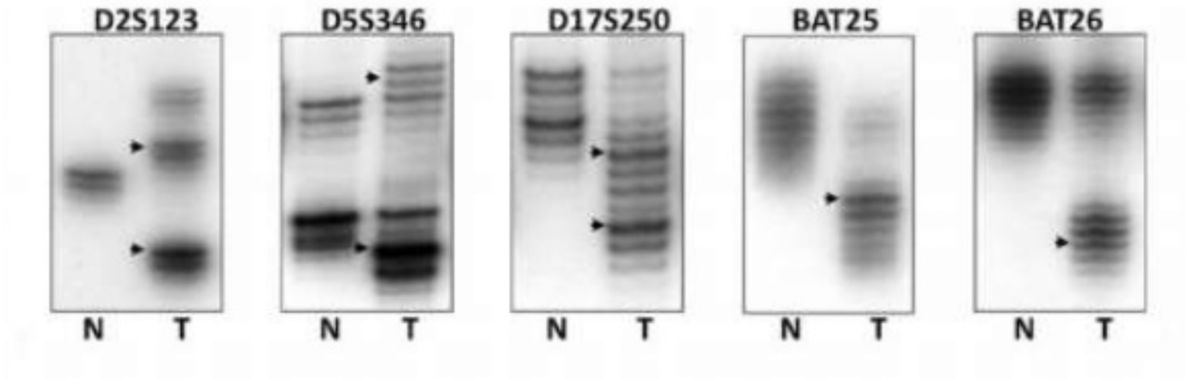


Table 1 Panel with five microsatellite markers

Microsatellite		Forward primer	Reverse primer
BAT25	mononucleotide loci	5′-TCGCCTCCAAGAATGTAAGT-3′	5′-TCTGCATTTTAACTATGGCTC-3′
BAT26		5′-TGACTACTTTTGACTTCAGCC-3′	5′-AACCATTCAACATTTTTAACCC-3′
D2S123	dinucleotide loci	5′-AAACAGGATGCCTGCCTTTA-3′	5′-GGACTTTCCACCTATGGGAC-3′
D5S346		5′-AGCAGATAAGACAGTATTACTAGTT-3′	5′-ACTCACTCTAGTGATAAATCGGG-3′
D17S250		5′-GGAAGAATCAAATAGACAAT-3′	5′-GCTGGCCATATATATATTTAAACC-3′

Other Risk Factors

Fruit and vegetable (protective)

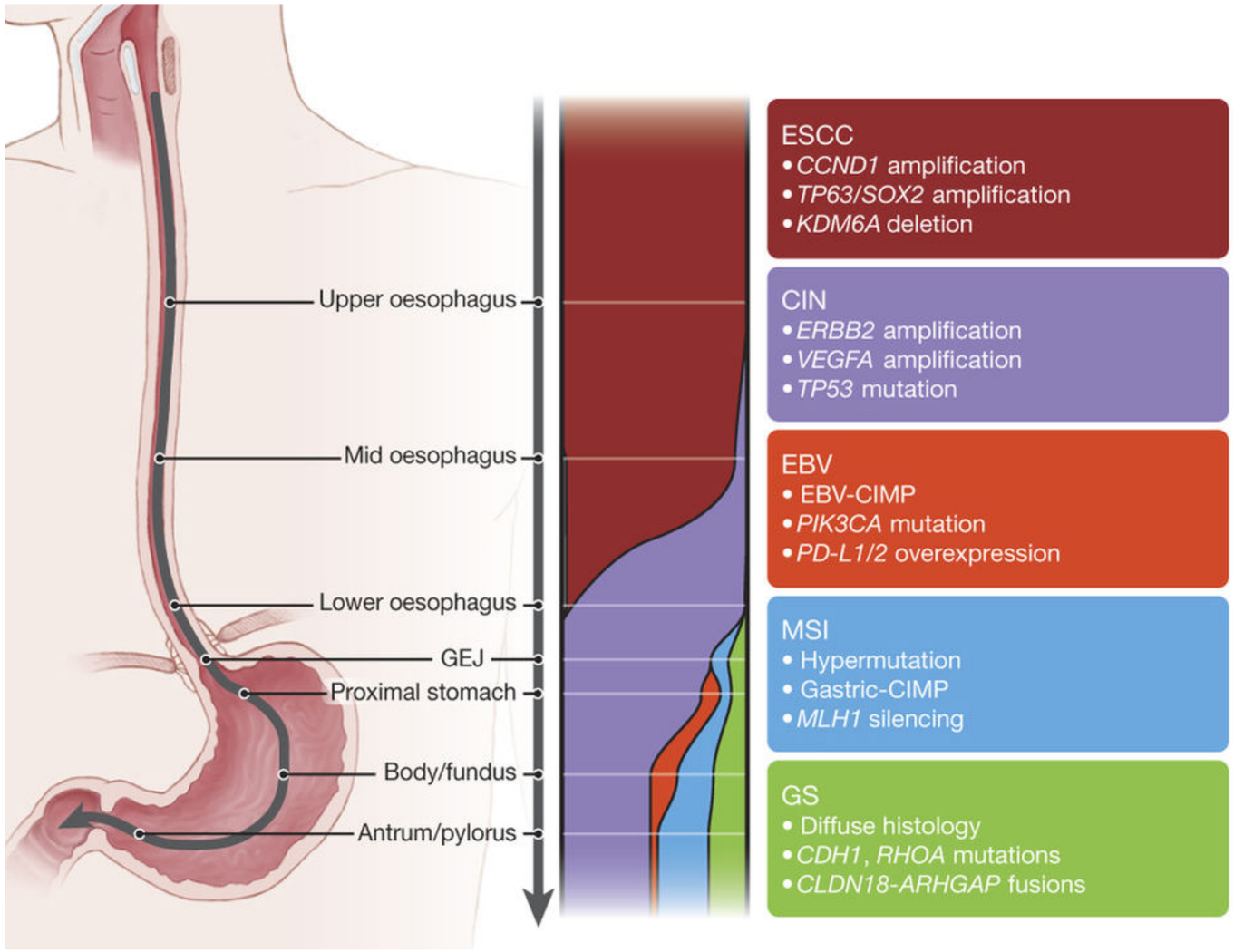
Vitamin C (protective)

Alcohol consumption

Obesity with cardia gastric cancer & oesophagus caner

IL1B, IL1RN2 TNFA-1082G polymorphisms

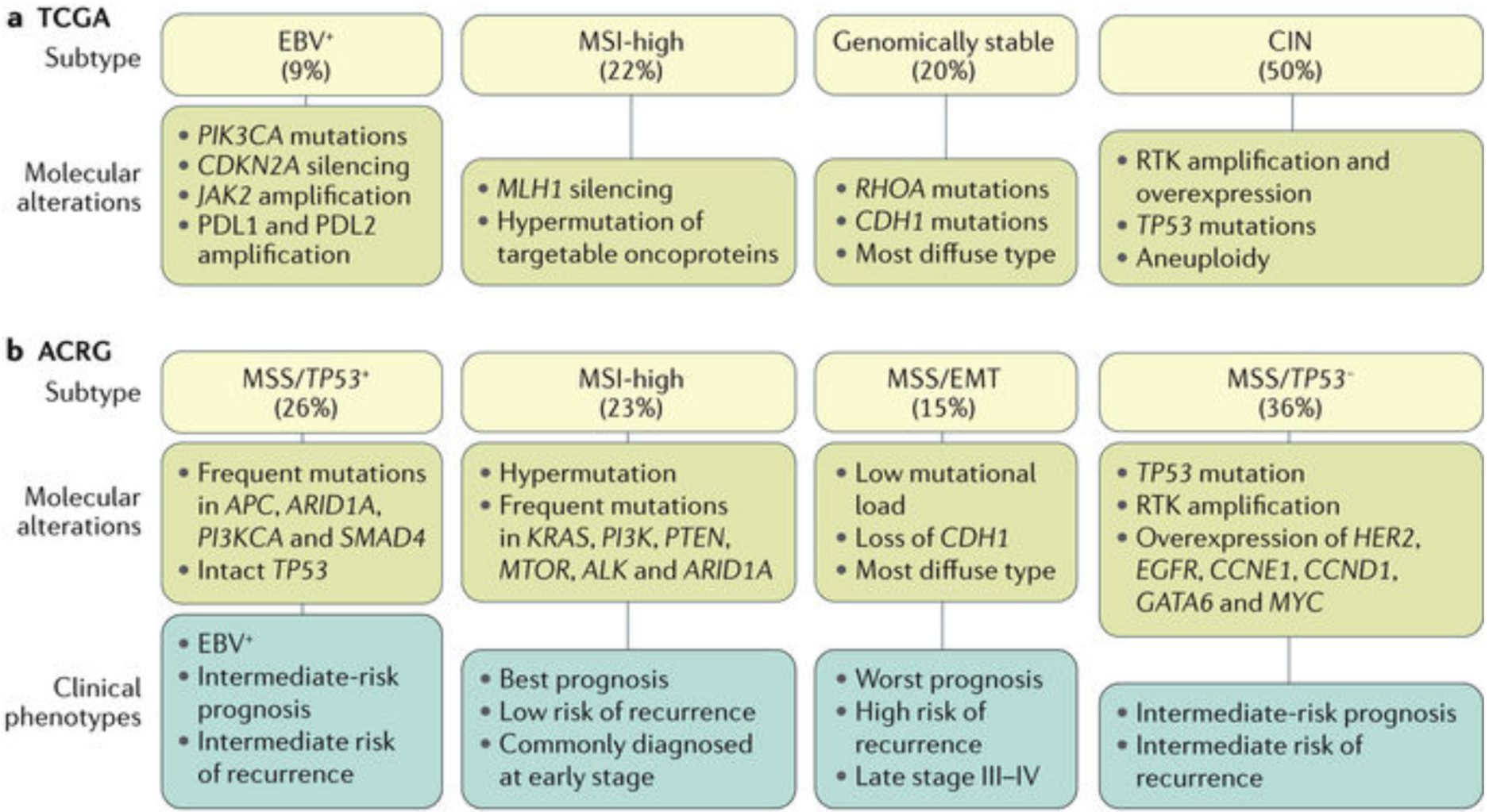
Aetiology and Molecular classification of AGC and EC



- **Diversity in aetiologies lead to molecular heterogeneity in GC**
- **GE junction adenocarcinoma is more molecularly more closely related to gastric cancer than ESCC**

TCGA Nature. 2017

Molecular classification and clinical phenotype



Ajani. Nature Reviews Disease Primers 2017 TCGA Nature. 2014

Clinical presentation of gastric cancer

- Early disease has no associated symptoms

- Patients may complain of one or more of the following:
  - indigestion, nausea or vomiting, dysphagia, postprandial fullness, loss of appetite, weight loss.

- Late complications:
  - Obstruction of the gastric outlet, gastroesophageal junction, or small bowel
  - Abdominal pain
  - Melaena, hematemesis,

Conclusions

- The incidence and mortality of GC is decreasing worldwide.
- HP infection is the most important cause for GC
- Epidemiology of GC reflects changing risk factors over time and places.
- Diversity in the aetiologies resulted the molecular heterogeneity seen in GC and have huge implication in the clinical phenotype and response to therapy.

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THANK YOU!

Research

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