

Epidemiology:

Gastric cancer carries a significant morbidity and mortality. Roughly 80% of patients are diagnosed at an advanced stage with a 5-yr survival rate of 24%ⁱ. Though the incidence of gastric cancer has decreased over the past decade (it once was the 2nd most common cancer in the world), it still continues to disproportionately affect poorer countries and specific populations such as certain Latin American countries, Japanese, Korean, and Chinese people.

In the United States, 1 in 114 people will be diagnosed with stomach cancer in their lifetimeⁱⁱ. According to SEER data, Asian/Pacific Islander populations are disproportionately affected, even in the US, compared to the rest of the population.

Risk Factors/Protective Factors:

H. pylori is considered a group I carcinogen by IARC

- OR 3.0 (2.3-3.8)ⁱⁱⁱ

Environment and country of origin

- rates of gastric cancer decrease in subsequent generations after immigration^{iv}

Diet with fresh fruits and veggies is protective^v

Age – Peak incidence is between 40-60 years old

- Most experts suggest screening for GC starting at age 40.

Diet w/ high salt and preserved foods^{vi}

Smoking

- RR 1.60 (1.41-1.80) for non-cardia and RR 1.87 (1.31-2.67) for cardia cancer^{vii}
- Dose response relationship^{vii}

Male > Female

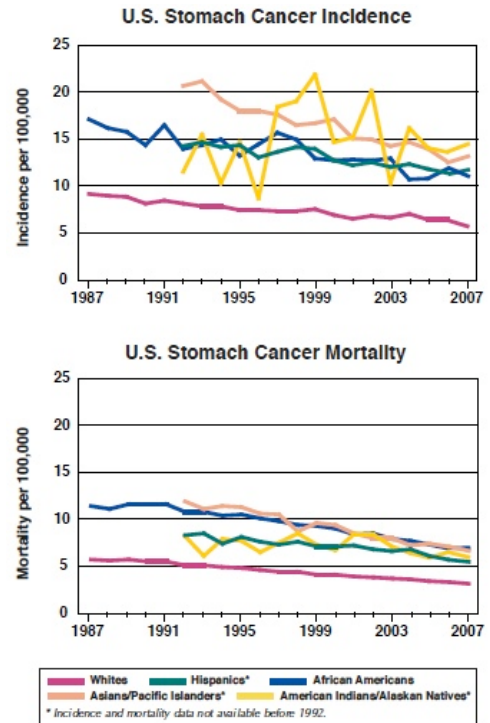
- Male prevalence is 2x female^{viii}
- Female rate trails male by 10 years and peaks after menopause^{viii}

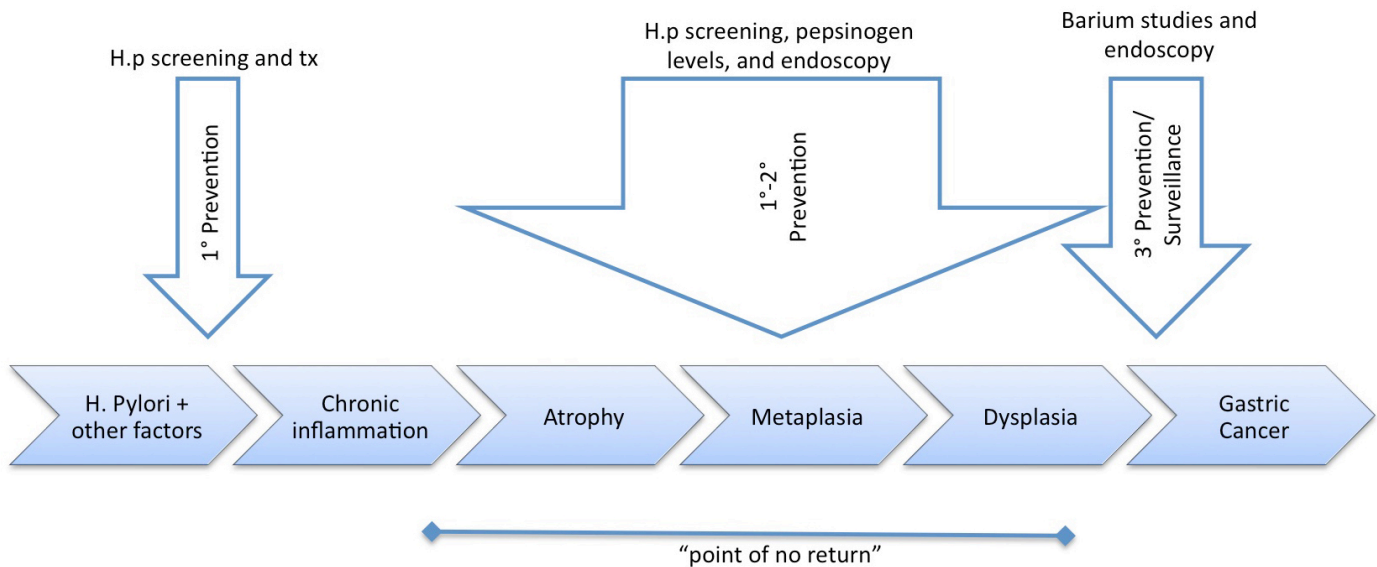
FH

- RR of 2.0 (1.3-6.5) most studies show 1.5-3.5^{viii}
- FH + *H. pylori* positive RR to 8x^{viii}
- Familial clustering of 10% and hereditary 1-3%^{viii}

Natural History of *H. pylori* and Gastric Cancer:

It takes approximately 44 months to develop from early cancer to advanced stage cancer.^{ix} It is estimated that 65-80% of gastric cancer is associated with *H. pylori*ⁱⁱⁱ. However, only a minority of *H. pylori* patients will ever develop gastric cancer. Multiple studies suggest that there is a “point of no return” at which even with successful eradication of *H. pylori*, the patient will progress to gastric cancer.





The Gestalt:

In 2006 the “Asia-Pacific consensus guidelines on gastric cancer prevention” was published^x. Here are their Grade I Evidence/Recommendation Strength A guidelines:

- *H. pylori* eradication decreases the risk of gastric cancer
 - Meta-analysis done for consensus meeting found RR of developing gastric cancer after *H. pylori* eradication was 0.56 (0.40-0.80).
- *H. pylori* eradication decreases risk even at a late stage of gastric cancer
 - *H. pylori* eradication is standard of care after resection.
- Gastric cancer can still occur after successful eradication.
- *H. pylori* screening and treatment is the strategy of choice in high risk populations and should be done
 - Research suggests that appropriate screening age is somewhere between 35 and 50 years old. One cost-analysis suggested 20 was the optimal age^{xi}.
 - Evidence suggests that it is more cost-effective than surveillanceⁱ.

Caveats to the Conclusions Drawn from the Current Research:

- Data largely limited to East Asian countries and in high-risk populations.
- There is strong evidence that *H. pylori* is associated with and, likely, causal of gastric cancer. Obviously, a RCT will never be done.
- *H. pylori* eradication, when done early enough in the disease course seems to reduce the incidence of gastric cancer. However, the evidence for this is weaker.
 - *H. pylori* was only discovered in 1984. Given the long natural history of *H. pylori* and gastric and its incidence it’s not surprising that no adequately powered, RCT of eradication and gastric cancer have been done.
 - The conclusion of eradication decreasing GC incidence is from drawn from:
 - Subgroup/post-hoc analysis of studies
 - Studies on eradication’s affect on precancerous lesions and dysplasia

A Paper on *H. pylori* Eradication and Gastric Cancer:

You WC, Brown LM, Zhang L, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J. Natl Cancer Inst.* 2006; **98**: 974-83.

Study Population:

- 3365 adults 35-64 years old in 13 randomly selected villages in Shandong Province, China.
- High-risk province where 42% of cancer deaths due to gastric cancer.
- 67% of adults have antibodies to *H. pylori*.

Intervention: blinded, randomized, placebo-controlled, intention to treat

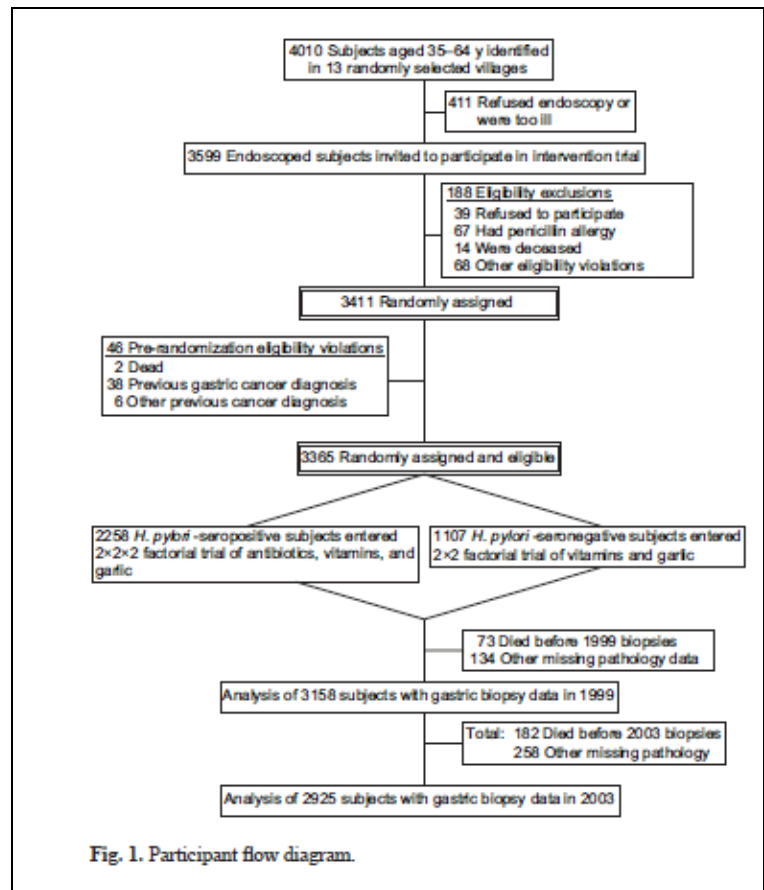
- Amoxicillin and omeprazole for 2 weeks (w/ retreatment for failure)
- Vit E, vit C, selenium
- Garlic supplement

Data Collection:

- Baseline endoscopy in 1994
- Repeat endoscopy in 1999 and 2003.
- Histopathology scale:
0 normal, 1 superficial gastritis, 2 mild/mod chronic atrophic gastritis, 3 severe chronic atrophic gastritis, 4 superficial intestinal metaplasia, 5 deep intestinal metaplasia, 6 mild dysplasia, 7 moderate dysplasia, 8 severe dysplasia, 9 gastric cancer.

Endpoints:

- Prevalence of dysplasia or gastric cancer (score ≥ 6)
- Prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer (score ≥ 3)
- Average severity score
- Powered to detect decrease of 5% in prevalence of dysplasia or gastric cancer .



Results:

- From 1994 to 2003, the percentage of subjects with at least mild dysplasia doubled, regardless of the arm of the trial.
- *H. pylori* arm:
 - 62% initial eradication with 73% combined eradication. In 2003 43% remained infection free and 10% of placebo group was free of infection.
 - No statistical difference in dysplasia or gastric cancer (severity score ≥ 6).
 - *H. pylori* treatment decreased OR for an advanced lesion (severity score ≥ 3) to 0.77 (0.62-0.95) in 1999 and 0.60 (0.47-0.75) in 2003.
 - *H. pylori* treatment decreased average severity scores in 2003 by -0.24 (-0.40 to -0.09).
 - Eradication treatment increased disease regression (17% versus 12%) and decreased disease progression (45% versus 49%) in 2003 ($p=.006$). No statistical difference in 1999.
 - Subgroup analysis of affect of treatment on each lesion were reported without p values therefore are not discussed here.
 - In both 1999 and 2003, placebo and *H. pylori* group differed significantly ($p=.009$ and $p=.0001$ respectively).
 - *H. pylori* group had higher proportions of mild gastritis in 1999 and 2003 and superficial gastritis in 2003. Correspondingly lower proportion of deep intestinal metaplasia in 1999 and 2003.

Discussion:

- Authors conclude that eradication decreases prevalence of precancerous gastric lesions, which would suggest that this also would have a positive impact on gastric cancer. Their study did not detect a change, however, it was not necessarily powered to do so. Also would not be able to distinguish between prevented cases versus simply delayed cases of GC/precancerous lesions.
- Was their impact underestimated?
 - Treatment had only 73% successful eradication and they used a treatment regiment that is no longer standard of care. More effective treatment might have created a bigger impact.
 - Study population was considered high-risk based on population rather than individual risk factors. Would better selection have created a bigger impact?
 - Eradication was done at the entry of the study which might have been past of the point of no return. They did do subgroup analysis but without p-values and clearly with dubious power at that level.
- Is it generalizable to Asian Americans?
 - Re-infection rate was probably higher than it would be in the US.
 - Study does not take in account other environmental differences once someone has immigrated to the US.
- Even with the statistical differences, mild dysplasia across all treatment groups still doubled. This is not a magic bullet.
- The fact that many of the interventions did not show statistical benefit until 2003 reinforces that the change in gastric mucosa is a slow one.

References:

- ⁱ Bornschein J, et al. "*Helicobacter pylori* and Clinical Aspects of Gastric Cancer." *Helicobacter*. 2009;14(Suppl. 1):41-45.
- ⁱⁱ Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics.
- ⁱⁱⁱ Webb PM, et al. "Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nest within prospective cohorts." *Gut*. (2001) 49:347-353.
- ^{iv} Haenaszel W, Kurihara M. "Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst*. 1968;40:43-68.
- ^v Lunet N, Lacerda-Vieira A, Barros H. "Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies." *Nutr Cancer*. 2005;53(1)1-10.
- ^{vi} Joossens JV, Hill MJ, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol* 1996; 25: 494-504.
- ^{vii} Laderira-Lopes R, et al. "Smoking and gastric cancer: systematic review and meta-analysis of cohort studies." *Cancer Causes Control*. (2008) 19:689-701
- ^{viii} Fuccio L, Eusebi L, Bazzoli F. "Gastric cancer, *Helicobacter pylori* infection and other risk factors." *World Jour of Gastrointestinal Onc*. 2010 Sept 15;2(9): 342-347.
- ^{ix} Leung WK, et al. "Screening for gastric cancer in Asia: current evidence and practice." *The Lancet*. 2008 Mar;9:279-287.
- ^x Fock KM, et al. "Asia-Pacific consensus guidelines on gastric cancer prevention." *J Gastroenterol Hepatol*. 2008 Mar;23(3):351-65.
- ^{xi} Yeh J, et al. "Exploring the cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer in China in anticipation of clinical trial results." *Int J Cancer*. 2009 Jan 1; 124(1):157-166.