Helicobacter pylori Update: Gastric Cancer, Reliable Therapy, and Possible Benefits

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Abstract

Helicobacter pylori infection contributes to development of diverse gastric and extra-gastric diseases. The infection is necessary but not sufficient for development of gastric adenocarcinoma. Its eradication would eliminate a major worldwide cause of cancer death, so there is much interest in identifying how, if, and when this can be accomplished. There are several mechanisms by which *H pylori* contributes to development of gastric cancer. Gastric adenocarcinoma is one of many cancers associated with inflammation, which is induced by *H pylori* infection, yet the bacteria also cause genetic and epigenetic changes that lead to genetic instability in gastric epithelial cells. *H pylori* eradication reduces both. However, many factors must be considered in determining whether treating this bacterial infection will prevent cancer or only reduce its risk— these must be considered in designing reliable and effective eradication therapies. Furthermore, *H pylori* infection has been proposed to provide some benefits, such as reducing the risks of obesity or childhood asthma, although there are no convincing data to support the benefits of *H pylori* infections.

Keywords

bacteria; stomach cancer; prevention; Barrett's esophagus; esophageal adenocarcinoma

Helicobacter pylori infection is etiologically related to gastric cancer. Elimination of *H pylori* will dramatically reduce the incidence of gastric cancer. However, it is not clear how to reliably cure the infection or whether there might be populations in which *H pylori* might provide some benefit. There are several animal models of *H pylori*-induced carcinogenesis[7-9], but unless the bacteria are combined with a chemical carcinogen, none of

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these models reliably produce a malignancy similar to that observed in humans. More importantly, curing the infection in animal models frequently results in resolution of the malignancy or dysplastic changes, calling into question their relevance to human gastric adenocarcinoma [9, 10]. We review the effects of *H pylori* infection and challenges to and benefits of its eradication. For reviews of basic issues related to the ability of *H pylori* to survive on the surface of the stomach, the role of virulence factors in the pathogenesis of gastric cancer, H pylori induced inflammation and genetic instability in the gastric mucosa, and on the history of H pylori-related disease see [1, 2, 3, 4,5, 6].

H pylori as the Primary Cause of Gastric Cancer

H pylori infection is necessary but not sufficient for development of *H pylori*-associated gastric cancer [11], similar in concept to hepatitis B and C viruses and human papilloma virus. The infection is required for gastric cancer to develop, but *H pylori* infection alone is not sufficient for gastric carcinogenesis—other events are also involved. However, *H pylori* is not the only cause of gastric cancer—other less common causes account for 3%–5% of gastric adenocarcinomas and include infection with Epstein-Barr virus, genetic abnormalities in the host, autoimmune gastritis, and possibly proximal cancers related to esophageal adenocarcinoma. Therefore, even in the absence of *H pylori*, gastric adenocarcinoma would almost but not completely disappear.

Gastric cancer is a major cause of cancer death worldwide. Japan has a particularly high burden of gastric cancer, so in February 2013 the Japanese government approved insurance coverage for a gastric cancer prevention program [12, 13] that includes *H pylori* screening and treatment (primary prevention), as well as post-treatment surveillance (secondary prevention for people with atrophic gastritis). In November 2014 the World Health Organization published an IARC working group report entitled H pylori Eradication as a Strategy for Preventing Gastric Cancer; this report resulted from a conference held in December 2013 [14]. In addition, recommendations of the Kyoto Global Consensus Conference on *Helicobacter pylori* gastritis (held in January 2014) were published in early 2015 [15]. Those recommendations state: "*H pylori* gastritis should be defined as an infectious disease, even when patients have no symptoms and irrespective of complications such as peptic ulcers and gastric cancer", "*H pylori*-infected individuals should be offered eradication therapy, unless there are competing considerations", and "eradication of *H pylori* reduces the risk of gastric cancer. The degree of risk reduction depends on the presence, severity, and extent of atrophic damage at the time of eradication" [15].

Overall, it appears the tide has turned toward *H pylori* eradication and the question of whether it can eliminate gastric cancer has become moot—similar to asking whether eradication of polio virus infections would eradicate polio. The current issue is how to eradicate *H pylori* in the most efficient and cost-effective manner. For example, should the entire population of Japan be treated for infection? Should high-risk and high-prevalence groups in regions of low gastric cancer incidence, such as the United States (US), be treated? The magnitude of the problem is illustrated by the fact that Japan and Korea alone, which each have a high prevalence of gastric cancer, have approximately 80 million *H pylori*-infected individuals. Whereas *H pylori* eradication may be possible in Japan and Korea,

eradication in other countries with many infected people, such as India, is probably unlikely due to costs, the presence of other important infectious diseases, and the immense numbers of people that would require treatment. In addition, in India and other developing countries, there is high risk for reinfection due to poor sanitation and low standards of living. Vaccination is a possibility, but progress toward a preventive or preventive and therapeutic vaccine has been disappointing and funding for vaccine research is scarce [16]. So far in the 21st century we have greatly increased our understanding the pathogenesis of *H pylori*-related diseases and mucosal immunology, so many problems of *H pylori* vaccine development no longer seem insurmountable.

H pylori-associated Gastric Cancer

Atrophic gastritis, the precursor to gastric cancer, leads to little or no secretion of acid, which alters the gastric microbiome [6]. The outcome of each individual infection is unpredictable, as is the rate of progression of the gastric mucosal damage. However, further progression is stopped by eradication. Eradicating *H pylori* before the development of atrophic changes can essentially eliminate cancer risk. Depending on the degree and extent of atrophic changes, eradication can stop and possibly partially reverse, the changes that occurred with atrophy and thus reduce associated cancer risk. As such, there is a point in the progression of the disease when a significant risk of cancer development remains despite *H pylori* eradication. It is at this point that secondary prevention (eg, endoscopic surveillance) programs may become cost-effective in reducing gastric cancer deaths [15, 17, 18]. Candidates who might be suitable for non-invasive, secondary prevention surveillance programs can be identified based on serum levels of pepsinogen, which can be used to determine their risk for gastric cancer (Figure 1). Such an approach obviates the need for endoscopy for most subjects; those potentially at risk can then be specifically identified using validated histologic staging systems such as the Operative Link on Gastritis Assessment (OLGA) or OLGIM (Figure 1) [6, 15, 19, 20]. Importantly, assays that measure serum levels of pepsinogen cannot accurately identify patients with gastritis if they are receiving proton pump inhibitors or following *H pylori* eradication [6, 21, 22].

The ability of *H pylori* eradication to prevent gastric carcinogenesis depends on a patient's level of cancer risk at the time that *H pylori* is eradicated. Patients with non-atrophic gastritis can expect complete or nearly complete protection. Those with irreversible changes to the gastric mucosa have a significant risk, but can be assured that their risk will not increase and will likely decrease. Risk stratification also allows for identification of patients who might benefit from a post-*H pylori* eradication secondary cancer prevention program. The benefits of *H pylori* eradication extend also to those at highest risk for cancer death, such as patients who have early gastric cancer (gastric adenocarcinoma confined to the mucosa and submucosa of the stomach, with or without regional lymph node metastases). Among patients who have had successful endoscopic removal of an early gastric tumor but remain infected with *H pylori*, the risk of metachronous gastric cancer ranges from 1% to >4% per year. *H pylori* eradication reduces that risk approximately 3-fold [23, 24].

The evidence that *H pylori* eradication reduces gastric cancer risk has led to questions of what *H pylori* eradication accomplishes and how to best to use this knowledge. *H pylori*

contributes to gastric carcinogenesis by producing persistent acute-on-chronic inflammation and genetic and epigenetic changes that contribute to genetic instability in the gastric epithelium. During tumor progression, gastric cancer cells acquire the ability to evade immune destruction, suppress the immune response, and begin to invade surrounding tissues[3, 6, 25]. Interactions between *H pylori* and other members of the gastric microbiome, endogenous factors, and exogenous factors can also produce carcinogens within the stomach [6]. Environmental factors, especially diet, are important determinants of risk for populations (i.e., different diets or methods of food preservation can affect the severity of *H pylori*-induced gastric mucosal damage and cancer risk) [5, 26].

H pylori-induced inflammation leads to high gastric endothelial cell turnover and a microenvironment that is high in reactive oxygen and nitrogen species, increasing opportunities for DNA damage and somatic mutations [3, 27-29] (Figure 2). *H pylori* can induce methylation of multiple CpG islands, especially at sites encoding tumor suppressors such as E-cadherin [30]. *H pylori* also stimulates activation-induced cytidine deaminase, which alters nucleotides [31-33]. Furthermore, *H pylori* infection can lead to double-stranded breaks in DNA and alter expression of microRNAs to increase genetic instability [3, 6]. Many, if not most, of these *H pylori*-related events (such as hypermethylation) are reversed following *H pylori* eradication [34-36] (Figure 3). Any increase following *H pylori* eradication would also reduce overgrowth of non-*H pylori* bacteria and potentially reduce or eliminate their deleterious effects [6].

Gastric cancer risk increases with infection with more virulent strains of *H pylori*, such a CagA-positive strains [2]. Attempts to associate a specific *H pylori*-related disease with an individual putative virulence factor have produced inconsistent results, possibly because most virulence factors are frequently found together in the more virulent strains [2]. None of the recognized virulence factors have been associated with a specific disease. However, they are typically associated with an increase in the inflammatory response and possibly can best be considered as markers for the severity of inflammation [2]. Importantly, all *H pylori* strains cause gastric inflammation and disease; no avirulent strains have been identified. The difference in gastric cancer risk between the most- and the least-virulent strains is probably less than 3-fold, prompting the recommendation that all *H pylori* infections be eradicated, irrespective of virulence factors [2, 15].

Clinical Research Findings

H pylori eradication eliminates the noxious stimulus and promotes resolution of inflammation. However, resolution of inflammation is a highly coordinated process regulated by anti-inflammatory molecules, including lipid mediators such as lipoxins and resolvins. This brings up the issue of whether and/or when *H pylori*-induced inflammation has resolved [37]. Gastric cancer development is associated with inflammation. Increasing our ability to identify whether inflammation has resolved (or not), and why, should provide new insights factors that determine cancer risk after *H pylori* eradication and help identify strategies to further reduce cancer risk.

People who have undergone removal of an early gastric tumor have a high rate of metachronous cancer, and could provide a high-risk population for clinical studies, which could be performed in a reasonable period of time with a reasonable sample size. For example, this population may be ideal for studies of risk factors for metachronous cancers or for randomized controlled trials of gastric cancer prevention (such as with anti-oxidants, cyclooxygenase II inhibitors, etc). These individuals might also be studied to identify biomarkers of disease recurrence and progression.

There is evidence that it might be possible to reverse atrophic gastritis or gastric atrophy. For example, studies performed before *H pylori* was discovered found that corticosteroid therapy for patients with atrophic gastritis or atrophy (autoimmune and *H pylori*-associated diseases) produced a partial recovery of parietal and chief cells [38-41]. These observations have not been confirmed since patients began receiving *H pylori* eradication therapy. It might be unethical to use high-dose steroid therapy to attempt to reverse atrophic changes, but it might be possible to study patients with atrophic gastritis who receive steroids for other conditions.

Studies in patients and animals receiving tamoxifen showed regression of intestinal metaplasia. Partial reversal of intestinal metaplasia was also observed in animals given ADP ribosylation inhibitors, such as Olaparib, or prostaglandin E_2 [42, 43]. However, prostaglandin E2 is believed to be involved in development of colon cancer, so it probably shouldn't be given to patients [37]. Nonetheless, these intriguing findings indicate that it may be possible to at least partially reverse atrophic gastritis [42, 44]. Evidence for a direct role of intestinal metaplasia or spasmolytic polypeptide-expressing metaplasia in gastric carcinogenesis is circumstantial; it is possible that reversal of atrophy may result in detectable changes (eg, related to transdifferention) that do not, however, significantly modify cancer risk [45]. Studies designed to reverse atrophic changes therefore must also assess changes in cancer risk such, as reduced genetic instability in the involved mucosa.

Finally, whole-genome sequencing analyses of gastric cancers have begun to identify factors that promote gastric carcinogenesis. This information has been used to develop tiered molecular classification systems that relate genetic changes to different etiologies of gastric cancer (eg, *H pylori* or Epstein Barr virus) [46, 47]. These types of studies could lead to better design of cancer treatment and pathogenesis.

Eradication Therapy

Reducing gastric cancer from a major clinical problem and cause of cancer death to a rare disease requires that we reliably eradicate or prevent of *H pylori* infections. Theoretically, *H pylori* cause a relatively straight-forward gastric infection—they are an organism that is susceptible to many antibiotics. Traditionally, studies of antimicrobial therapy for other infections have been performed and interpreted under conditions of well-defined drug susceptibility. In other infectious diseases the development of antimicrobial resistance produces rapid changes in recommendations and practice. *H pylori* has been an exception in that treatment regimens that vary in dose, duration, and composition are often compared,

and data have been interpreted without consideration for patterns or effects of drug resistance.

The rapid decrease in efficacy of clarithromycin-containing regimens has produced a clinical dilemma, because these are often the only therapies approved by local regulatory authorities. In response to this decrease in efficacy, new combinations of the drugs, such as sequential therapy, were introduced and claimed to be superior. However, in the absence of clarithromycin resistance, the new 4-drug clarithromycin and metronidazole-containing regimens (eg, sequential, concomitant, or hybrid regiments) all have similar high levels of efficacy. New formulations, such as sequential therapy, contain a third antimicrobial agent (metronidazole or tinidazole), so it can only appear to be superior to triple therapy in populations in which the level of clarithromycin resistance is modest and metronidazole resistance is low. After repeatedly proving that sequential therapy was superior to triple therapy in an Italian population, researchers tested sequential therapy in populations with higher levels of metronidazole resistance, and found it to be ineffective (78% eradication in a study in Korea, 85% in a study in France, and 84% in a study in Spain). A regimen is considered to be effective only if it reproducibly eradicates the infection in 90% or more of the treated patients. So, sequential therapy is not superior to triple therapy in only certain populations [48].

The focus on testing for superiority via comparative studies with a regimen known to be ineffective in a specific population (eg, because of clarithromycin resistance), instead of a focus on understanding the mechanisms of efficacy (such as differences in resistance), has delayed our understanding the factors responsible for the efficacy and failure of the 4-drug combinations by more than a decade. We now recognize that we must collect data on the effects of resistance to each antimicrobial agent, separately and in combination, before we collect data on patient outcomes, to determine if the results are generalizable rather than population specific. During this learning process many thousands of patients were randomly assigned to groups given regimens known to be ineffective in those populations and thereby experienced unnecessary treatment failures and their consequences.

Lessons learned

Study participants are randomly assigned to groups to produce study populations that are equivalent in all respects. In retrospect, in many comparative studies, the outcome was entirely dependent on the pattern of drug-resistance in the population studied. In a population with a low prevalence of resistance to 14-day treatment with clarithromycin, 10-day sequential therapy would be either equivalent or triple therapy slightly superior. Sequential therapy could therefore be considered to be effective and superior to other treatments in Italy, yet ineffective in Korea. These results are entirely explained by differences in patterns of drug resistance, which were typically not assessed before studies were initiated. Findings from many, or even most comparative studies, cannot be applied to other populations unless they are accompanied by resistance data. Meta-analyses have compounded these errors by combining studies from the same geographic location and then making general conclusions about efficacy.

Potentially inaccurate conclusions

In analyzing the results of any study of antimicrobial agents, it is important to determine the effect of drug resistance on efficacy. Efficacy should be presented in terms of proportions of subjects cured, with 95% confidence intervals. Some comparative trials and meta-analyses provide results in terms of odds ratio and discuss superiority, even though no regimen produced an acceptable cure rate[49]. To be clinically useful, a reagent must eradicate strains susceptible to the antibiotics tested in at least 90% of subjects. Any claim of superiority from a comparison of 2 otherwise good or excellent drugs must be accompanied by an explanation of an otherwise unexpected result. Differences in effectiveness often appeared because the bacteria were resistant to 1 of the drugs tested.

In the past, claims of superiority often resulted when a new combination was compared with a drug already shown to provide an unacceptably low rate of cure in the study population. The suspicion that investigators may have chosen a known inferior regimen in an attempt to make their study regimen look more effective can be tested by examining the justifications for sample sizes. Randomization would reliably produce study groups that differed in relation to the effects of resistance on only 1 regimen, so there would be no valid hypothesis.

The principles of informed consent also require that potential subjects be informed of all that is known by the investigators and all published information on issues that might influence their willingness to participate (including they might receive a regimen known to have an unacceptably low cure rate in that population). In 1952, Sir Heneage Ogilvie called the process of disguising (eg, calling an inferior regimen "standard therapy") or withholding information that might influence participation "medical fraud" [50]. In either instance (i.e., no valid hypothesis or lack of truly informed consent) the study would be unethical[51].

Patient-specific Therapy

H pylori eradication therapy is relatively simple; health-care workers must consider only drug availability, acceptability (such as whether patients might have allergies or the drugs have side effects), cost, and known or suspected patterns of resistance, based on prior experience with the drug in the same population. Whenever possible, only regimens that reliably yield >90%, preferably >95%, treatment success should be used. Data on which drugs each patients' infection is likely to be resistant or susceptible to should be considered. Pretreatment tests are not widely available, although rapid molecular tests for clarithromycin resistance are practical and commercially available [52]. The best advice for areas where susceptibility tests are not yet available is to use what works reliably locally and the follow up with patients to insure eradication of infection and to detect trends of antimicrobial resistance. There are now many regimens available that will reliable provide 95% or greater treatment success per protocol when used to eradicate susceptible strains. These include 14-day therapy with clarithromycin or metronidazole triple therapy, sequential therapy, concomitant therapy, and levofloxacin triple therapy (see Table 1 and supplemental material) [53, 54].

In most of the US, resistance to the combination of clarithromycin and metronidazole is rare, making it our first choice. If the patient's infection does not respond to this therapy, bismuth

quadruple therapy is given. Infections that are not eradicated by either regimen should be cultured and tested for susceptibility or the patient should be sent to a center with expertise in resistant infections. It is possible to predict the outcome of most therapeutic regimens, provided there is local or regional data available on drug susceptibility (see supplemental data).

Identifying Treatment Failure

^{13}C urea breath tests are frequently used to detect *H pylori* infection. However, false-positive results have been reported from Spain and Korea [55, 56]. These occurred for results were near the cut-off value, such as between a delta over baseline between the cut-off (such as 3) and 10 [55-57]. The problem is most common for patients with atrophic gastritis, likely due to the presence of non-*H pylori* urease containing organisms [55-57]. It was proposed that the addition of citric acid, which suppresses the delta over baseline value in uninfected individuals and increases the value in subjects with *H pylori* infection, should reduce the problem but this strategy requires direct testing [55, 56, 58]. False-positive results lead to the erroneous conclusion that antibiotic treatment failed, frequently in subjects who have already experienced multiple treatment failures [56]. As such, in areas where atrophic gastritis is common, patients with results from a ^{13}C- urea breath tests between the cut-off and a delta over baseline value of approximately 10 should not be considered as treatment failures until the finding is confirmed with a different test, such as a stool antigen assay or histologic analysis. In regions where atrophic gastritis is common and the urea breath tests does not contain citric acid, urea breath tests results may fall into this gray zone for more than 10% of cases [56]. Studies are needed to determine whether citric or malic acid adjuvant therapy can reduce the frequency of false-positive results.

Future studies should provide more data to guide selection of patient-specific therapy. New molecular methods that detect specific resistance using stool or biopsy specimens will likely be developed to allow therapy to be tailored based on susceptibility. We predict a renewal of interest in amoxicillin and high-dose proton pump inhibitor dual therapy. This regimen to be appears highly successful in Asia, but they have fared less well in western populations. Areas for potential advances include more reliable control of intragastric pH and a better understanding of outcome in relation to amoxicillin pharmokinetics. Tetracycline continues to be unavailable or difficult to obtain in many countries; studies are needed to learn whether doxycycline can be reliable substituted. Until such studies are available it is best still avoided. New drugs such as solithromycin could eventually prove useful.

Is the Only Good *H pylori* a Dead *H pylori*?

Any claim that a major human pathogen might also provide a meaningful health benefit, and that plans to eradicate it should be reconsidered, is guaranteed to elicit interest from the press. *H pylori* was no exception and the press has continued to carry stories regarding a possible relationship between reductions in *H pylori* infections and the increased prevalence of esophageal adenocarcinoma, childhood asthma, and obesity. *H pylori* infection has been proposed protect against these disorders. In this instance, the term protection means that there is an inverse correlation in an epidemiology study. However, just because 2 events are

associated does not mean that one causes the other. For example, a study reported a correlation between the number of storks in Brandenburg, Germany, and the birth rate in Berlin [59].

It could be possible that factors associated with decreases in *H pylori* infection also led to the recognition of unrecognized positive associations. For example, there has long been an interest in a possible role of chronic infection with atherosclerosis [60]. The journal *Global Heart* devoted a large portion of the June 2014 issue to atherosclerosis in ancient humans. Computed tomography studies found that ancient humans had extensive atherosclerosis, even though the people analyzed were from different locations, had a wide range of diets and lifestyles, and died at relatively young ages [61, 62]. The researchers proposed that chronic inflammation induced by microbial and parasitic diseases might have been responsible [61, 62]. The incidence of myocardial infarctions decreased significantly in the second half of the 20th century in the US, indicating a concomitant change in an important environmental factor(s) involved in arthrosclerosis [63]. Could on of those factors have been *H pylori* infection?

H pylori has been with humans since we traveled out of Africa more than 50,000 years ago [5, 64]. The bacteria have been proposed to cause a variety of extra-gastric diseases and metabolic derangements, either directly, through molecular mimicry, or indirectly, by producing chronic inflammation [65-67]. The *H pylori*-related disease peptic ulcer has long been associated with an increased risk for cardiovascular disease [68]. The decrease in cardiovascular mortality was recently linked with the prevalence of *H pylori* in the US [69]. Examination of the hearts of young soldiers who died during the second half of the 20th century (i.e., during the Korean, Vietnam, and Gulf wars) revealed a progressive decrease in significant coronary atherosclerosis. Over the same time period, there has also been a decrease in the prevalence of *H pylori* infection in the US population (Figure 4) [70-73]. Although these 2 events might be unrelated, *H pylori* infection has been linked with systemic inflammation, atherosclerosis, lipid disorders, heart disease, alternations in vitamin B12 metabolism, and changes in the microbiome. We provide a testable hypothesis that coronary arthrosclerosis might be associated with a preventable factor.

In a review article, Julie Parsonnet considered the evidence that *H pylori* reduces the risk for of immune regulator disorders such as asthma, esophageal cancer, Barrett's esophagus, gastroesophageal disease, inflammatory bowel disease, infectious diseases such as tuberculosis and gastroenteritis, and obesity [74]. Overall, she was skeptical of the associations and concluded "the mere fact that *H pylori* is disappearing from the human host without substantive intervention might indicate that, in many countries, it is providing little benefit". [74].

Esophageal disease

The role of *H pylori* in development of esophageal adenocarcinoma, Barrett's esophagus, and gastroesophageal reflux disease was discussed in the most recent Maastricht consensus report (see [75]). These esophageal problems are all are acid reflux-related diseases. *H pylori* infection can promote and inhibit acid reflux; antral predominant gastritis is associated with increased acid secretion and an increased risk for reflux esophagitis, whereas *H pylori*-

induced corpus gastritis reduces acid secretion and thereby prevents or reduces the severity of reflux. According to the model, the bacterium behaves as a biologic secretory or anti-secretory agent [76, 77] that promotes, prevents, or has no effect on gastroesophageal reflux, depending on the pattern and extent of gastritis. Importantly, the more *H pylori* reduces acid secretion, the more protection it provides against acid reflux and the greater the risk of gastric cancer. Gastric cancer is a common disease that affects all races and both sexes and, until the mid-20th century was the leading cause of cancer deaths worldwide. Esophageal adenocarcinoma is primarily a rare disease of white men (i.e., the incidence of esophageal adenocarcinoma is more similar to that of small bowel adenocarcinoma) (Figure 5) [78]. Despite the continuing decrease in the incidence of gastric carcinoma in the US, the risk of developing adenocarcinoma of the stomach remains higher than the risk of adenocarcinoma of the esophagus in the highest risk group (i.e., men in the US) (Figure 6) [79].

Non-esophageal Diseases

Ptolemy proposed that the earth was the center of the universe. He had observed that when he looked at the northern sky he (and everyone after him) saw that the stars circled around the earth. Thomas Henry Huxley said in 1870 "The great tragedy of science is the slaying of a beautiful hypothesis by an ugly fact". Although thousands of experiments can support a hypothesis, it only takes 1 finding to disprove it. For example, despite countless observations over more than a thousand years that supported Ptolemy's model, experiments performed with the first telescopes rapidly disproved it. We will therefore not review each association for validity but provide evidence that *H pylori* infection does not cause non-esophageal diseases such as asthma or obesity.

Asthma

The initial studies relating *H pylori* prevalence with asthma were based on the concept that the incidence of asthma was increasing and it would be useful to search for the cause [80]. The most-recent studies found that asthma incidence has peaked or is decreasing [81, 82]. A study of asthma trends in England from 2001 to 2005 involved 333,294 individuals from all socioeconomic groups and all ages. Their results can be used to test whether there was a link between *H pylori* infection and changes in asthma incidence [82]. The UK, as a developed country, has experienced a steady reduction in the prevalence of *H pylori* infection, which is currently likely concentrated in immigrants and the lower socioeconomic strata. We would therefore predict that any changes related to the decrease in *H pylori* infection would tend to be concentrated in the higher socioeconomic strata. In that study, the incidence rate of asthma decreased significantly in all groups over the interval studied (from 6.9/1000 patient-years; 95% confidence intervals [CI], 6.8–7.0 to 5.2/1000 patient-years; 95% CI, 5.1–5.3) ($P<.001$).

The decrease occurred in all socioeconomic groups, as assessed by deprivation quintiles. For example, the incidence in quintile 5 (the least affluent and most likely to have *H pylori* infection) decreased 24.2%, from an age-standardized rate/1000 patient-years in 2001 of 8 (95% CI, 7.7–8.2) to 6.0 in 2005 (95% CI, 5.8–6.2), whereas in quintile 1 (the most affluent) the incidence rate decreased 26.5%, from 6.3 (95% CI, 6.1–6.5) to 4.6 (95% CI, 4.4–4.8). The greatest effect was in children under 5 years of age (a decrease of 38.4%). A decrease in

childhood asthma, compared with other developed countries, has also been observed [83, 84]. Overall, these data are not consistent with the hypothesis that *H pylori* infection protects against childhood asthma.

The asthma association studies led to studies in mice showing that *H pylori* infection protected against asthma, possibly by promoting immune tolerance [85]. Further studies showed that 2 *H pylori* antigens (Y-glutamyl transpeptidase and VacA) induced T-regulatory cells in the gastric mucosa of mice, resulting in development of tolerance and reduced allergic responses [86]. Of interest, induction of T-regulatory cells in the gastric mucosa was also an important step in the establishment and maintenance of *H pylori*-induced gastric adenocarcinoma [87, 88].

Overall, animal studies showed that *H pylori* possess specific antigens that might mediate alterations in the immune system to promote tolerance and reduce asthma. An alternate possibility is that since *H pylori* infection correlates with poor household hygiene, any protection observed was likely related to differences in household hygiene (the hygiene hypothesis), with the presence of *H pylori* serving as a marker for poor household hygiene. This hypothesis has been tested in vivo and in vitro. The first test was designed to separate *H pylori* from other elements in the hygiene hypothesis. In Malaysia, very few Malay people have *H pylori* infections but in many areas, hygiene is substandard. According to the *H pylori* hypothesis, childhood asthma should be a common problem among the Malay because of the absence of *H pylori*. It is not [89].

A second test included mouse models and was designed to examine the observation that the presence of dogs in a home was associated with a reduced risk of asthma [90]. Investigators collected house dust from a residence with a pet dog and from 1 with no pets and used the 2 house dust samples to try to protect mice from asthma. The dust from the family with the pet dog protected mice from asthma, and was associated with remodeling of the gut microbiome related, at least in part, to the presence of *Lactobacillus johnsonii.* The authors concluded that protection against asthma "is likely a combinatorial effect based on multiple pathways and resulting microbial products encoded by co-colonizers resulting in presentation of a specific suite of microbial ligands and a distinct profile of microbial metabolites to the innate and acquired components of the host immune system".

For a more detailed discussion of models of asthma, differences in the immune responses of mice vs humans, and roles of environmental factors (diet and commensals) in allergy and asthma development, see [91]. Overall, the studies do not support the hypotheses that increases in childhood asthma were related to the absence of *H pylori* or reduced immune system stimulation by specific *H pylori* antigens. One must therefore conclude that the hypothesis is wrong.

Obesity

Obesity is an extremely complicated problem. Fundamentally, obesity develops via an imbalance between energy intake and expenditure. In the 20th century, there were enormous changes in the production and availability of food, related to the green revolution, to increases in standards of living, and to improvements to the transportation infrastructure.

Giant companies began producing calorie-dense processed foods, sugary soft drinks, and fast foods while the proportion of the population that performed intensive physical work decreased. In 1939 E. Parmalee Prentice wrote *Hunger and History* in which he reviewed the world's literature on hunger from antiquity to the 1930's, discussing famines, hunger, and food production [92]. He stated that a history of hunger had become possible because for the first time the world had entered a phase in which there were large regions without risk of famine.

This book was followed in 1952 by *The Geography of Hunger*, in which Josue de Castro examined the problem of world hunger (two-thirds of the world's population was thought to suffer from hunger at that time) [93]. He related a study by Rigoberto Aguillar, who in 1944 examined 10,000 poor children in Mexico City. Aguillar found 5000 children to have clear signs of dietary deficiency; children 10 to 12 years old appeared to be no older than age 4 or 5. In 1945 de Castro visited Mexico City where he found "innumerable cases of vitamin deficiency in children" [93]. A half century later the problem had changed to an increasing concern about obesity among Mexican children [94-96].

It has been proposed that the increasing widespread obesity might be related to alterations in gastric physiology, due to the absence of *H pylori* [74, 97]. However, there is little data to support that hypothesis other than conflicting data from comparisons of obesity rates among those with and without *H pylori* infection [98, 99]. Obesity is a manifestation of an imbalance between energy intake and expenditure, so the absence of *H pylori* might increase appetite and intake. However, it not clear whether absence of *H pylori* might also encourage behaviors that reduce energy consumption.

The natural decrease in the prevalence of *H pylori* occurred first in the proportion of the population with high socioeconomic status, and that decrease continues among people of low socioeconomic status, especially during childhood. The infected and uninfected populations differ in many ways, some of which might affect obesity. These differences include the consumption of processed foods and high-calorie fast foods, as well as in the amount of physical activity. Available studies have rarely considered variables other than *H pylori* prevalence and body mass index, and none have taken into account the marked changes in the food industry and its effects on eating habits.

The food industry has had remarkable effects on human behavior (eg, on a mother's choice of breakfast food for her school children). The industry has steadily improved its ability to produce delicious high-calorie foods. Innovations that encourage consumption include the discovery of bliss points, and how to combine ingredients to largely negate satiety signals, which normally limit consumption [100, 101]. These innovations by the food industry have resulted in increased consumption of processed foods dense in sugar and fat, and of extra calories contained in soft drinks and fast foods [100, 101]. The modern life style also encourages sedentary activities due to television, computers, video games, and smart phones, all of which also increase opportunities to snack. In addition, overall physical activity has decreased (i.e., most ride rather than walk).

H pylori infection has long been rare among Malays (~60% of the population of Malaysia) but was common and is now decreasing among Chinese (~30% of the population) and Indians (~10%) subpopulations. Malaysia might be considered a poster child of a developing country as it has undergone rapid industrialization and urbanization with rapid increases in standards of living. However, these changes been associated with westernization of the diet, increased caloric intake, and reduced energy expenditure [102, 103]. The change to a sedentary lifestyle with increased intake of calorie-dense foods (eg, McDonald's entered in 1982, Pizza Hut in 1984, and Domino's Pizza in 1997) has resulted in an increasing prevalence of obesity (eg, 0.7% in 1990 to more than 10% in 2004) and this has occurred in among the Malays, Chinese, and Indians, irrespective of differences in *H pylori* prevalence [89, 102-104]. The recent increase in obesity is a complex issue and there is only weak circumstantial evidence for a significant role of decreasing *H pylori* infection in the obesity epidemic. A meaningful causative association between *H pylori* and obesity is unlikely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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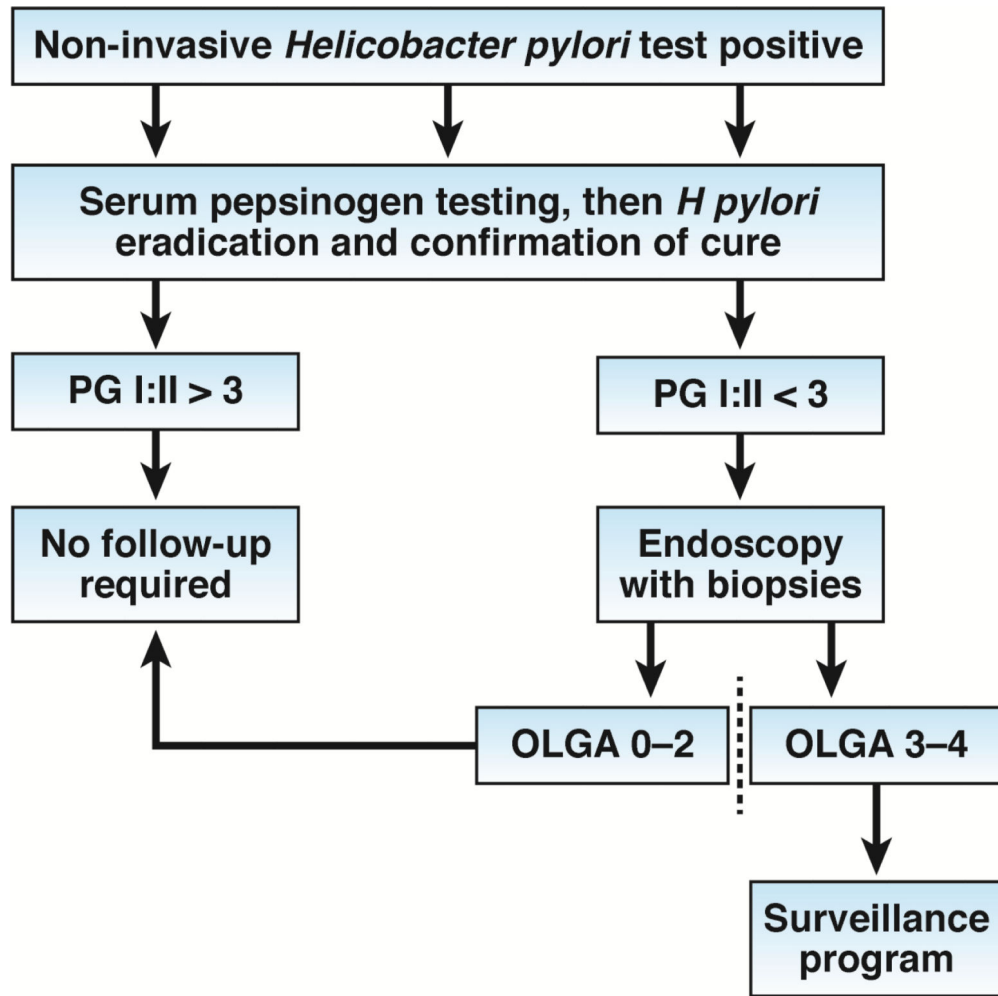
Figure 1. Screening and Follow-up Approaches

The approach is based on initially identifying those with *H pylori* infections and assessing the health of the gastric mucosa using non-invasive testing with a locally or regionally validated IgG *H pylori* serology and serum pepsinogen tests. Those without *H pylori* infection or atrophic gastritis would require no further evaluation or follow up. All those with *H pylori* infections would undergo eradication therapy; eradication can be confirmed using non-invasive tests such as the urea breath or stool antigen assays. After *H pylori* eradication, those with non-atrophic gastritis would require no further follow up. Those with suspected atrophic gastritis (based on pepsinogen level) would undergo endoscopy for further risk stratification by a validated histologic staging system. Patients cured of *H pylori* infection and healed, non-atrophic gastritis would require no further follow up. Those with confirmed atrophic gastritis (e.g., OLGA stage III or IV) would enter a long-term endoscopic surveillance program. Because their cancer risk if likely to decrease with time, these patients might also be included in studies of surveillance intervals or to determine whether anti-inflammatory or anti-oxidant adjuvant therapies could further reduce the risk. There are not enough data available to make recommendations for patients who have undergone *H pylori* eradication therapy but still have mild atrophy (e.g., OLGA I and II

scores). Further studies are needed to determine the best management strategies for these individuals.
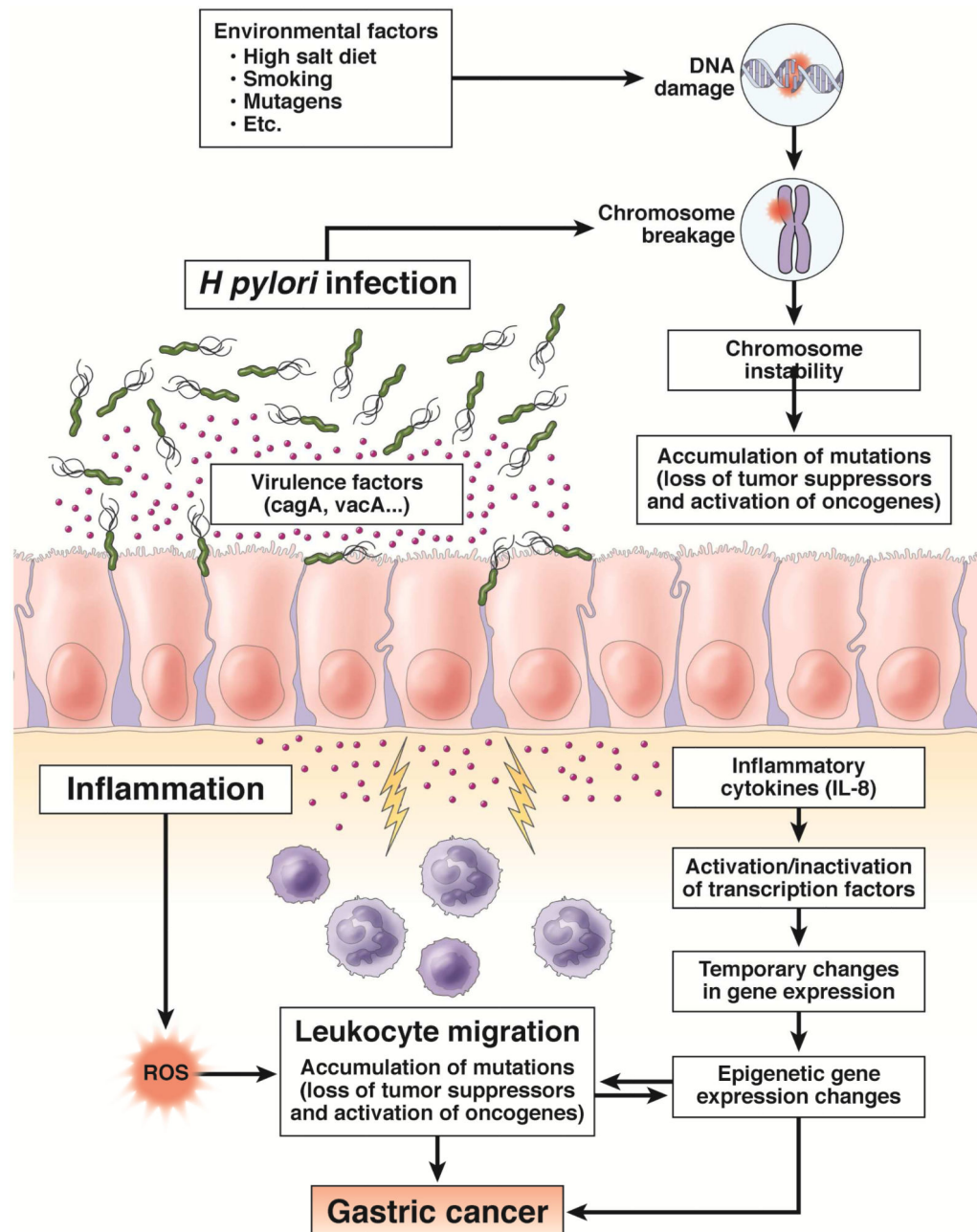
Figure 2. Interactions Among Inflammation, Bacteria, and the Epithelium Leading to Gastric Cancer

We show the interaction of *H pylori,* environmental factors, and inflammation in the pathogenesis of gastric cancer. Each plays important roles leading to progressive chromosome instability. *H pylori*-induced inflammation leads to high gastric endothelial cell turnover and a microenvironment that is high in reactive oxygen and nitrogen species, increasing opportunities for DNA damage and somatic mutations. ROS = Reactive oxygen species. Adapted from references [3, 28]
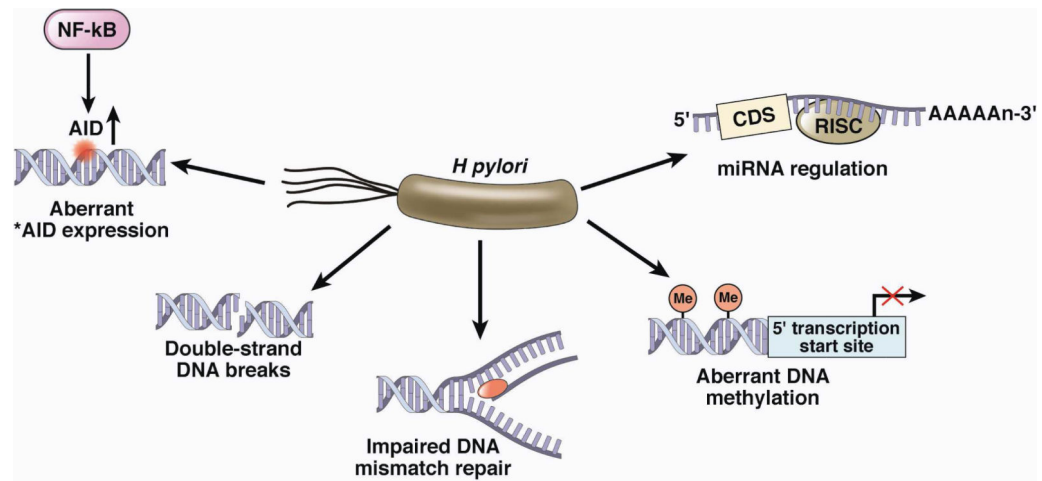
Figure 3. *H pylori* Infection Leads to Genetic Instability of Epithelial Cells
H pylori can induce methylation of multiple CpG islands and also acting through stimulation of NF B stimulates activation-induced cytidine deaminase (AID), which alters nucleotides. Furthermore, the interaction of *H pylori* with the cell can result in double-stranded breaks in DNA as well as alter the expression of microRNAs and impair DNA mismatch repair all of which serve to increase genetic instability. Adapted from reference [6], with permission
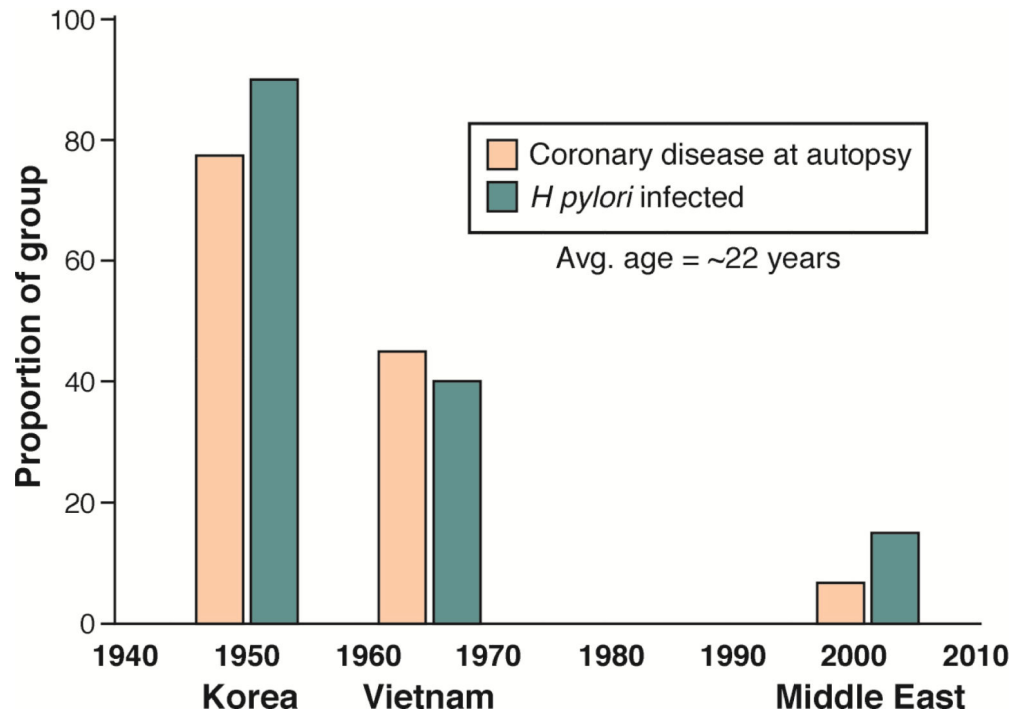
Figure 4. Relationship Between Coronary Artery Disease and *H pylori* Infection in the US
Data on coronary artery disease were collected from histologic analyses of autopsies performed on soldiers who died in the Korean, Vietnam, and Middle East wars [70-72]. They are compared with the prevalence of *H pylori* infection in the US population during the same time periods, based on the premise that infection at age 22 did not change during the lifetimes of this cohort [73].
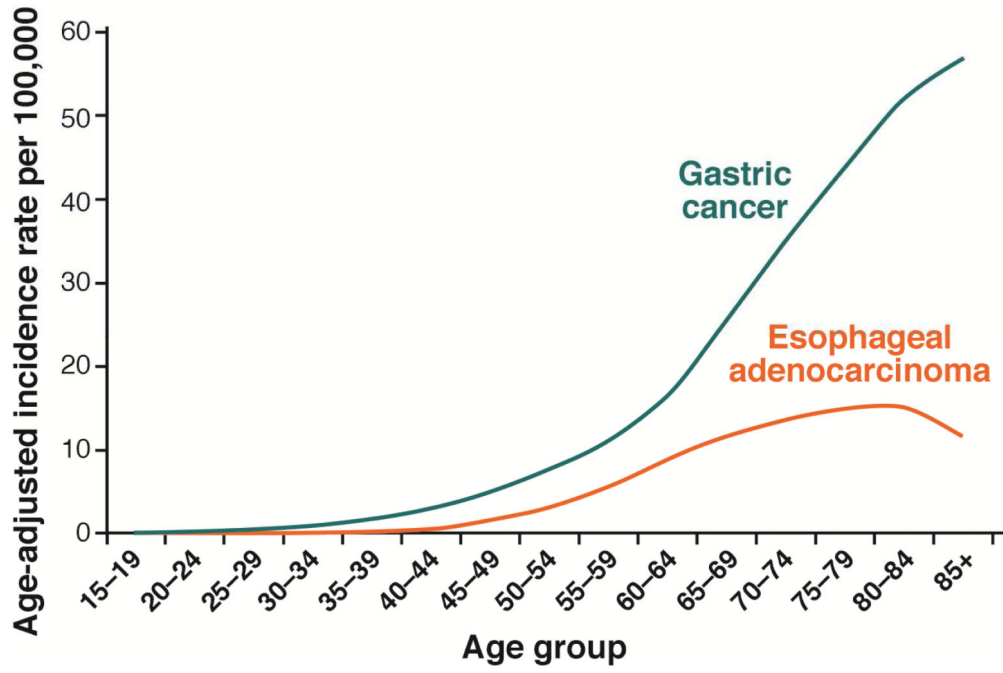
Figure 5. Age-adjusted US Incidence Rates of Gastric and Esophageal Adenocarcinoma (2006–2010)

Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973-2011) National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission. [79]
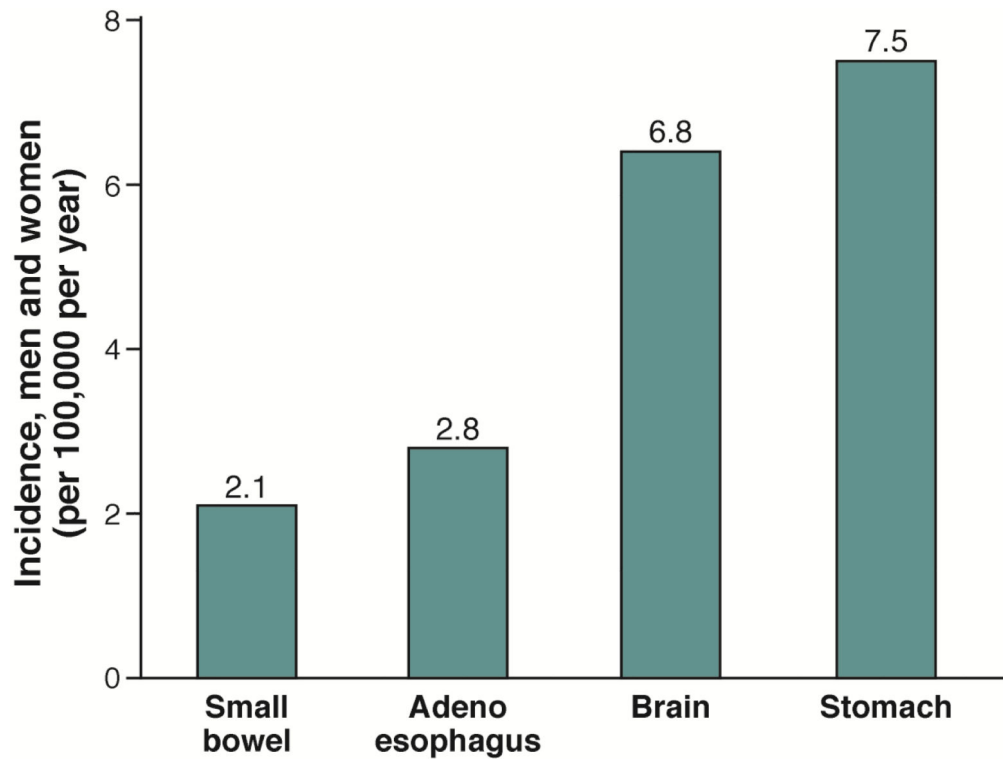
Figure 6. Incidence of Cancers in the US
Incidence values are based on data collected in 2011 by the Surveillance, Epidemiology, and End Results Program .

Table 1

Common Eradication Regimens and Resistance

Therapy	Clari Susceptible	Clari Resistant	Met Resistant	Met-Clari Resistant	Levo^ Resistant	Population result^^ <90% cures**
Clari Triple 7 * 93%	0-10%**	93%	0-10%**	93%		Clari >4%
Clari Triple 14 98%	0-49%**	98%	0-49%**	98%		Clari >10%
Sequential 10 94%	80%	75%	0-10%**	94%		Met and with dual resistance
Sequential 14 * 98%	88%	75%	0-49%**	98%		Met and with dual resistance
Concomitant 4 *	98%	97%	98%	0-49%**	98%	only with dual resistance
Levo Triple 14 *	97%	97%	97%	97%	0-49%**	Levo >10%
Bismuth quad 10	93%	93%	85%	85%	93%	Met >37%
Bismuth quad 14	98%	98%	95%	95%	98%	Adherence issues primarily

Note: In the US, treatment naïve patients are expected to be resistant to clarithromycin (10%–20%) or metronidazole 20%–40%), levofloxacin (more than 30%), but not amoxicillin, tetracycline, or rifabutin <1%. Patients previously treated with macrolide, metronidazole, or quinolone are expected to have high rates of resistance, so susceptibility testing is recommended.

^^ The cure rate for a population will fall below 90% when resistance exceeds the percent shown using the therapy shown.

* 7 and 10 day therapies not recommended as they either ineffective (levo) or are less effective (clari)

** 7 day 10%, 14 day 20% success with PPI + amoxicillin used for calculations when resistance was present as the represent western populations. Results depend in part of prevalence of CYP2Y19 polymorphisms as poor PPI metabolism tends to increase treatment success with this dual therapy.

^ Levofloxacin