LEADING ARTICLE

# The time to eradicate gastric cancer is now

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Worldwide gastric cancer remains one of the most common cancers, killing upwards of one million people each year. While the molecular pathogenesis remains unclear, infection with the bacterium *Helicobacter pylori* is considered a ''necessary but not sufficient'' cause, not surprisingly as gastric cancer has long been known to be associated with atrophic gastritis. Eradication of *H pylori* is expected to virtually eliminate gastric cancer and *H pylori* associated peptic ulcer within approximately 40 years and thus reduce overall mortality. In the USA, the incidence of gastric cancer in the general population is low, reflecting the change in the pattern of gastritis from atrophic to non-atrophic and in the low and decreasing prevalence of *H pylori* infection in the middle and upper classes. However, the plan for eradication of this important pathogen must be considered within the context of the prevalence and outcome within specific populations.

Worldwide gastric cancer remains one of the most common cancers, killing upwards of one million people each year. While the molecular pathogenesis remains unclear, a ''necessary but not sufficient'' cause has been clearly established (that is, infection with the bacterium *Helicobacter pylori*).[1–3] This was not surprising as gastric cancer had long been known to be strong associated with atrophic gastritis.[4–7] One would have thought that identification of *H pylori* and proof it was the main cause of gastritis would have resulted in worldwide eradication programmes.[8] This has yet to happen. Possibly, part of the resistance was methodological as epidemiologists systematically underestimated the attributable risk related to *H pylori*, which resulted in underestimation of the potential benefits from *H pylori* eradication. As atrophic gastritis progresses to atrophy (and the risk of cancer increases), the stomach becomes inhospitable to *H pylori*, resulting in loss of infection and seroreversion with antibody tests becoming negative.[1 9–11] The possibility that seroversion was a common event among those with gastric cancer has not been addressed and studies to test the validity of serology to categorise patients with regard to *H pylori* history in the study groups have not been done. Prospective or retrospective studies to test the validity of serology were not done, despite the extensive pre-*H pylori* literature showing a strong association between atrophic gastritis and gastric cancer. It is likely that examination of the gastric mucosal histology of any group of patients with gastric cancer would have confirmed the close association with atrophic gastritis.[12]

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## ATROPHIC GASTRITIS AND GASTRIC CANCER

*H pylori* induced gastritis is typically acquired in childhood and results in progressive damage to the stomach. Paralytic polio, infectious hepatitis (hepatitis A), and duodenal ulcer all made their appearance in the latter 1800s. A change in the age of acquisition was responsible for the appearance of polio and infectious hepatitis as clinical syndromes, and we suggested that the change in the pattern of gastritis and thus the outcome of *H pylori* infections might also reflect a change in the age of acquisition.[13 14] This hypothesis was rapidly disproved.[15]

The degree of gastric damage is initially more severe in the non-acid secreting gastric antrum but over time the damage progresses into the gastric corpus and can be visualised as an advancing atrophic border which involves the lesser curvature more rapidly than the greater curvature.[16–18] As parietal and chief cells in the corpus are replaced by mucus cells, the mucosal biopsy appears phenotypically like antral mucosa and is called mucus metaplasia or pseudopyloric metaplasia.[19 20] Islands of intestinal metaplasia are typically found within the atrophic mucosa.[20] Intestinal metaplasia was considered as a direct precursor to gastric cancer but recent data suggest that cancer arises from a different cell linage and intestinal metaplasia is rather a marker for atrophy.[21–24]

## GASTRIC CANCER PREVENTION PROGRAMMES

One approach to reducing the mortality of gastric cancer has been to attempt to identify cancer at an early and curable stage.[7] Screening and surveillance programmes, as adopted in Japan, have generally resulted in a reduction in cancer mortality among the population screened but are costly and inefficient.[9 25–28] It is possible to increase the yield of cancer within the screened population by focusing on those with atrophy identified by abnormal serum pepsinogen levels.[29] Pepsinogens are proteolytic enzymes produced by the chief cells in the stomach. Pepsinogen I is found only in the gastric corpus whereas pepsinogen II is present in the antrum and corpus. Progressive mucosal damage results in a progressive decline in ppsinogen I levels and in the ratio of pepsinogen I to pepsinogen II[29] such that measuring pepsinogen levels can non-invasively identify the presence of atrophic gastritis and enhance the detection of positive cases in gastric screening programmes.[30]

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Cancer risk is negligible in those with a normal gastric mucosa and increases stepwise, with the increase in atrophic gastritis being highest in those with the most severe atrophy associated with spontaneous loss of *H pylori* infection.[31] In this issue of *Gut*, Watabe and colleagues[32] report on their findings of combining *H pylori* testing and pepsinogen testing to identify subgroups with different risks of developing gastric cancer ***(see page 764)***. Their results confirmed and extended prior observations showing that the highest incidence of gastric cancer was associated with the risk factors male, age greater than 60 years, severe atrophic gastritis (based on pepsinogen levels), and loss of *H pylori* antibody.[32] The annual risk for their highest risk group was extremely high, being approximately 2000/100 000 per year, or 2% per year.

The actual incidence of gastric cancer in any population is dependent on a number of variables, including the proportion with *H pylori* infection, the proportion with atrophic (versus non-atrophic) gastritis, the severity of atrophy, and the rate with which atrophic gastritis develops. Factors which influence the development of atrophic gastritis and the rate in which it progresses include environmental factors such as diet (salt increases the risk, fresh fruits and vegetables reduce it), the virulence of the infecting strain, and host factors, especially polymorphisms in genes that enhance or reduce the inflammatory response to the infection.[1] The relative importance of any one factor varies within populations and individuals. The lessons learned regarding the interactions between bacterial, host, and environmental factors by those studying periodontal disease are now being learned by those studying gastric cancer (reviewed by Dore and Graham[33]).

## EFFECT OF *H PYLORI* ERADICATION

While no *H pylori*, no gastric inflammation, no atrophy, no gastric cancer is generally true, eradication of *H pylori* will not immediately result in elimination of gastric cancer. Because *H pylori* is the necessary cause of gastric cancer, eradication of *H pylori* will eventually lead to gastric cancer becoming a rare disease. The important question from treatment studies is what is the effect of *H pylori* eradication on progression to cancer among those at risk. Figure 1A shows the incidence of gastric cancer in Japan in 1986. In a theoretical experiment, consider the possible effects of eradication of *H pylori* infection in a subpopulation of 55 year old men. *H pylori* eradication is done at point ''A'' and patients and a suitable control group are followed for 10 years, to point ''B''. During this interval, the incidence of cancer in the control group would be expected to approximately double (from 200/100 000/year to 400/100 000/year). The sample size calculation is then dependent on the effect of *H pylori* eradication in the treated group. Studies of *H pylori* eradication after mucosal resection of early gastric cancer[34 35] suggest that *H pylori* eradication would reduce but not eliminate the risk of development of cancer compared with no eradication. Thus the study design might consider cancer risks ranging from 100 to 400/100 000 per year. If *H pylori* eradication reduced the incidence from 400 to 300 (50% reduction in the expected increase) the sample size to detect this difference would be 17 265 in each group with a 10 year follow up.

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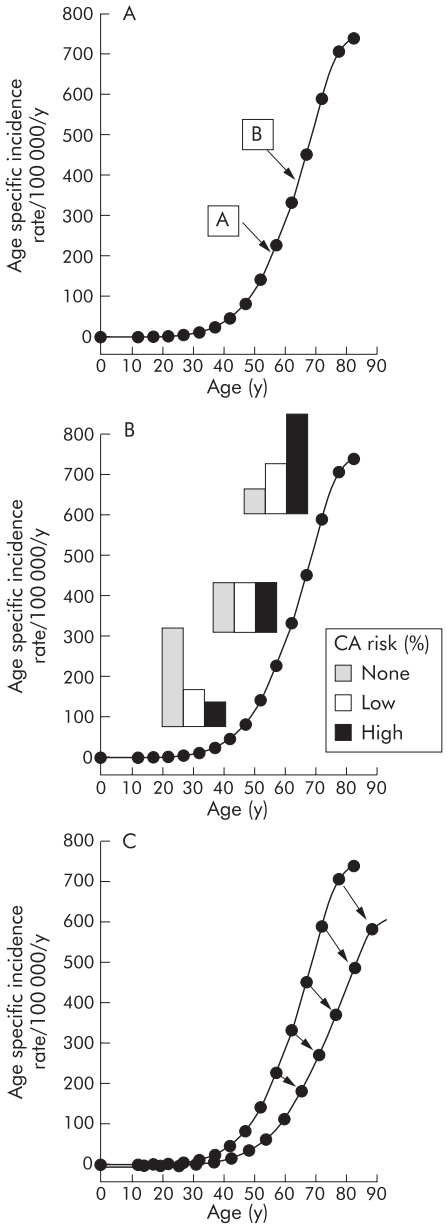


**Figure 1** (A) Age specific incidence of gastric carcinoma among Japanese men in 1986.[45] Point A represents the starting point for a theoretical trial of *Helicobacter pylori* eradication at age 50 years, when the incidence (per 100 000/year) of gastric cancer is approximately 200, and continuing for 10 years where the expected incidence has doubled. The sample size required to detect a difference in the proportion between the two groups (two sided at 0.05 significance level with 80% power) is 17 265 per group, making such studies impossible. (B) A model where the increase in cancer incidence with aging actually reflects the ever increasing proportion of the population advancing into higher risk groups. It is proposed that surveillance be targeted to those in the higher risk groups defined by non-invasive testing of pepsinogen levels and not by age. Those in the lower risk groups would undergo *H pylori* eradication with no subsequent surveillance. (C) Effect of the passage of approximately 10 years after a global *H pylori* eradication programme that resulted in a reduction in cancer incidence among those in the high risk groups. Each year the curve would move further to the right such that by approximately 40 years gastric cancer would be a very rare disease, irrespective of whether *H pylori* eradication produced a significant reduction in cancer incidence among those in the higher risk groups.

Most current studies are small and have generally attempted to examine surrogate markers such as changes in intestinal metaplasia or atrophy. Both outcomes are extremely difficult to quantify using random or even targeted endoscopic biopsies such that likelihood of a meaningful result is extremely low.[19 36] Small studies using surrogate markers are likely to achieve positive results because of pre and post therapy biases with regard to diagnosis of intestinal metaplasia or atrophy in the presence of *H pylori* inflammation.[19]

## PROPOSAL

We propose that there are now sufficient data to consider strategies designed to both prevent gastric cancer and to reduce gastric cancer mortality. Screening programmes by themselves are akin to repairing the ceiling after each rain without also fixing the roof. We now know where the leak is as *H pylori* infection is the necessary but not sufficient cause of gastric cancer. While gastric cancer incidence might be reduced by targeting cofactors, elimination of the reservoir of *H pylori* infection is the only method to eliminate the disease.

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We propose a two pronged approach: eradication and targeted surveillance. Firstly, we propose nationwide or high risk population wide *H pylori* eradication in countries and populations with a significant risk of gastric cancer (for example, Japan, Korea, China, etc). Eradication of *H pylori* would eliminate gastric cancer in approximately 40 year as the number of new cases would fall each year as the proportion of the population with ''no risk'' increased. The fall in cases would likely be increased by *H pylori* eradication, resulting in a truncation of the ''natural'' age related increase in incidence. *H pylori* eradications would also be accompanied by a surveillance programme based on risk assessment using non-invasive markers designed to identify those at higher risk for development of gastric cancer. We propose that fig 1A, which shows the age related increasing risk of gastric cancer, actually represents a change in the proportion of the population in the higher risk category. Age is a poor discriminator of risk and we propose that it be replaced with a risk assessment. The population would then be divided into risk groups such as none, low, and high (fig 1B). All with *H pylori* infection would receive eradication therapy and confirmation of cure. Those in the low risk group (defined as *H pylori* infected but with normal pepsinogen levels) would undergo no further testing. Those in the high risk group would be enrolled in a screening programme to identify early cancers.

## RISK MODIFICATION PROGRAMMES

There are a number of research questions arising from the proposal that require additional studies, including identification of risk factors and appropriate cut offs for risk stratification. For example, the paper by Watabe *et al* suggests that a patient with an ''atrophic'' pattern of pepsinogens at age 60 years may have a different risk than a patient aged 50 years.[32] Whether this possible age related risk factor would disappear when pepsinogen values were analysed by actual level (for example, pepsinogen I: pepsinogen II ratio of 1.1 *v* 2.9) or other analyses is a subject for research. Similarly, if one embarked on a follow up cancer screening programme for those in the high risk group (however defined), when could one stop? What is the pattern of change in risk after *H pylori* eradication? What are the predictors of change? For example, *H pylori* eradication in those with hypochlorhydria is expected to eliminate inflammation induced suppression of the remaining parietal cells. Therefore, even thought no new parietal cells may be produced, intragastric pH would be expected to fall, which will be reflected in a fall in gastrin 17 levels[37–40] as well as reduction in overgrowth by non-*H pylori* in the stomach. Those with complete atrophy would not be expected to experience any change in pH or overgrowth such that comparisons might include those whose gastrin remains elevated compared with those in whom it returns to normal.

Other research questions include whether it may be possible to further reduce risks after *H pylori* eradication. Possibilities include the effects of dietary modifications (for example, reducing the amount of salt and increasing intake of fresh fruits and vegetables), smoking cessation programmes, and possibly the use of drugs such as anti-inflammatory agents (that is, cyclooxygenase 2 inhibitors, rebamipide, or other drugs that have an effect on modifying gastric inflammation).

## COST EFFECTIVENESS OF SCREENING

Assessment of cost effectiveness is dependent on determining actual costs, gains, and trade offs needed to achieve the goals.[41–43] As noted above, currently in Japan 5–6 million people are screened annually at a cost of at least $300 million US. The eligible population in Japan is 65 million over 40 years of age, of whom approximately half do not have *H pylori* infections and are thus either not at risk or at very low risk. Studies are needed to define the effect of *H pylori* eradication on subsequent cancer incidence and to identify the most cost effective strategy for post eradication cancer surveillance among high risk groups. Cost savings are obtained by limiting the population undergoing surveillance to those who might benefit, reducing the age specific increase in cancer incidence, more effective resource utilisation by identifying those at highest risk independent of age, and providing surveillance targeted specifically to them. It is important to remember that the costs of *H pylori* screening and eradication for the population are a one time cost, as elimination of the reservoir eliminates transmission and therefore the diseases associated with the infection. In countries such as Japan where infection is uncommon in children, it is likely that screening could be targeted only to children within families where one or more parent had active *H pylori* infection.

## SUMMARY

Eradication of *H pylori* is expected to virtually eliminate gastric cancer and *H pylori* associated peptic ulcer within approximately 40 years (fig 1C) and thus reduce overall mortality and increase the number involved in productive endeavours. Elimination of a cause of death is always associated with an increase in the proportion of problems that the presence of the original disease prevented. Public health measures and the widespread use of vaccines led to an increased average lifespan and thus increased the problems and deaths from diabetes, heart disease, and cancer. No one suggests that we consider withholding vaccines and sanitation to prevent cancer deaths in the elderly. Prevention or lessening of corpus gastritis (the precursor lesion for gastric cancer) will reliably lead to increased acidity and worsening of the severity of gastro-oesophageal reflux disease among those who have abnormal barriers to the reflux of gastric contents into the oesophagus. In the early 1900s in the USA, the incidence of gastric cancer was similar to what it is today in Japan. In the USA today, the incidence of oesophageal adenocarcinoma among the high risk group of men aged 60–69 years is approximately 20 per 100 000/year, which is at least 30-fold less than the risk of gastric cancer among men

of the same age in Japan today and among men in the USA when *H pylori* corpus gastritis was common.

> ''Eradication of *H pylori* is expected to virtually eliminate gastric cancer and *H pylori* associated peptic ulcer within approximately 40 years''

In the USA, the incidence of gastric cancer in the general population is low, reflecting the change in the pattern of gastritis from atrophic to non-atrophic and in the low and decreasing prevalence of *H pylori* infection in the middle and upper classes. None the less, *H pylori*, atrophic gastritis, and gastric cancer remain common in immigrants from countries where gastric cancer is still a problem (for example, lifetime risk among Korean Americans living in Los Angeles is 4.5%)[44] suggesting that like syphilis, the plan for eradication of this important pathogen must be considered within the context of the prevalence and outcome within specific populations.

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