H. pylori eradication in the prevention of gastric cancer

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The incidence of gastric cancer has been falling in the developed world over the past fifteen years, however, it remains high or rising in many part of the developing world. The great majority of cases of gastric cancer have reached an incurable stage by the time of diagnosis and the condition is therefore an important cause of premature death throughout the world. Significant advances have been made in our understanding of the aetiology and pathogenesis of gastric cancer over the past fifteen years, particularly with respect to the role of *H. pylori* infection. It is timely therefore to consider whether it is now appropriate to eradicate this infection in the general population as a means of reducing the global incidence of gastric cancer.

It is important to recognise that *H. pylori* infection is a risk factor for cancer of the non-cardia region of the stomach but not of the proximal cardia region of the stomach.[1] Indeed, some studies indicate that the infection may be protective against cardia cancer.[2] The evidence for the association between *H. pylori* infection and non-cardia gastric cancer has increased over recent years. This is due to the recognition that the infection is often lost prior to the development of cancer and studies which have examined *H. pylori* status several years prior to development of the cancer have shown a very strong association.[3] It is now generally accepted that chronic *H. pylori* infection is an essential factor for the vast majority of cancers of the non-cardia region of the stomach.[1]

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H. pylori infection still affects about 50% of the world's population. However, less than 1% of the world's population develop gastric cancer. This indicates that although *H. pylori* infection may be an essential factor in the development of most cases of non-cardia gastric cancer, it is not a sufficient factor and other co-factors are required. Our understanding of the mechanism by which *H. pylori* infection may interact with the host and result in gastric cancer has increased over recent years.[4] The outcome of *H. pylori* infection depends upon the pattern of gastritis induced by the infection in the stomach. In some subjects the inflammation induced by the infection involves mainly the acid secretion body region of the stomach and results in atrophy and the development of intestinal metaplasia. This pattern of gastritis is referred to as a body predominant atrophic gastritis. The inflammation and atrophy markedly reduces the ability of the stomach to secrete acid and many patients with this pattern of gastritis may be completely achlorhydric. It is this pattern of gastritis which is associated with an increased risk of gastric cancer.[5] A variety of factors are known to influence the pattern of gastritis which develops in response to *H. pylori* infection. The factors promoting this pattern of gastritis include infection with the more virulent CagA positive strains of *H. pylori,* environmental factors such as smoking, high salt intake and low antioxidant intake and host genetic polymorphisms promoting a pro-inflammatory response such as those affecting the interleukin-1 gene.[6]

As originally proposed by Corea et al, the development of non-cardia gastric cancer is a multistage and multifactorial process.[7] It starts with *H. pylori* superficial gastritis which then progresses to atrophic gastritis with intestinal metaplasia and hypochlorhydria and this in turn progresses to dysplasia and then finally on to cancer. This pathway leads to cancer of both the intestinal and diffuse histological subtype. *H. pylori* infection is usually contracted in the first few years of life yet gastric cancer usually does not present until more than 60 years of age. This pathway from *H. pylori* infection to cancer thus takes many years, usually more than 50.

When considering the value of eradicating *H. pylori* infection to prevent gastric cancer, it is important to consider whether removing the infection will remove the risk of cancer or whether the process proceeding from the infection to cancer may pass a point of no return. Several recent observations indicate that eradication of *H. pylori* infection in adults rarely restores the gastric mucosa to its pristine condition and thus is unlikely to completely remove the risk of gastric cancer. As mentioned above, *H. pylori* infection often disappears as the gastritis progresses to become atrophic and associated with achlorhydria. The fact that patients go on to develop gastric cancer after the infection has spontaneously cleared is evidence that removal of the infection does not stop the pathology progressing. In addition, a number of studies have examined the effect of eradicating the infection in patients with pre-neoplastic gastric lesions.[8] Mera et al examined 755 Columbian adults with *H. pylori* infection and pre-neoplastic gastric lesions. Half were randomized to *H. pylori* eradication therapy and the others to placebo. After

twelve years there was only 12% reduction in progression of gastric histology in those eradicated of the infection compared to those remaining infection. In a study from China by Leung et al, 405 patients were randomized to *H. pylori* eradication therapy or placebo and followed for five years.[9] Intestinal metaplasia deteriorated in 45% of the *H. pylori* treated patients and 55% of the placebo-treated patients. There was only evidence of slight slowing of the progression of intestinal metaplasia by eradication of the infection. Ley et al found that eradicating *H. pylori* improved the inflammation but not the atrophy.[10] A recent study from Japan examined the effect of eradicating *H. pylori* infection on the restoration of gastric secretion function in patients with severe atrophic gastritis.[11] Again, in these studies, there was some recovery in acid secretion over the first two years but thereafter it plateaud and remained at subnormal levels. All these studies therefore indicate that eradication of *H. pylori* infection in patients with atrophic gastritis may slightly slow progression of pathology but does not restore the mucosa to normal structure and function. This therefore suggests that such treatment will not remove the risk of gastric cancer but at best may only slightly reduce it.

A few studies have examined the effect of eradicating *H. pylori* infection on the risk of gastric cancer itself in high risk regions. Wong et al performed a randomized study of *H. pylori* eradication versus placebo in 1,630 subjects and assessed the outcome at 7 years follow-up.[12] There was no overall difference in cancer between the eradicated and non-eradicated group. However, secondary analysis suggested there might be some reduction in cancer incidence in those with no atrophy or intestinal metaplasia or dysplasia at entry. However, in those dysplasia, intestinal metaplasia entry, there were slightly more cancers in the eradicated group versus the placebo group. Similar results were obtained in the study from Mera et al who performed a randomized study in 755 Columbian patients with atrophy, intestinal metaplasia or dysplasia.[8] In twelve years of follow-up, five cancers developed in the eradicated group versus four in the placebo group.

All these results indicate that eradication of *H. pylori* infection does not reduce the risk of cancer in patients who have reached the stage of atrophic gastritis, intestinal metaplasia or dysplasia. This is unfortunate as these are the patients with the highest risk of going on to develop gastric cancer. Consequently, the patients who most need to have their risk reduced seem to be the ones in whom eradicating *H. pylori* may have little effect. It thus appears that to reduce gastric cancer by treating *H. pylori* infection, the treatment must be given early in life before the process has reached an irreversible stage. The ideal situation would be to prevent infection in the first place.

What are the implications of the above observations for screening and treating the general population for *H. pylori* to prevent gastric cancer? The ability to prevent cancer by simply treating the infection is superficially attractive. In addition, such treatment should have other benefits such as reducing the subsequent risk of developing ulcer disease and its complications. However, there are potential problems with such a strategy. Current

H. pylori eradication treatments have side effects and these become significant when one considers that 50 people would need to be treated to prevent one cancer. Many patients might therefore experience side-effects without experiencing any beneficial effect. There must also be concerns about the development of bacterial resistance to currently available antibiotics, especially as one might have to treat every second person in the world. There would also be cost implications involved in testing, treating and re-testing after treatment and these could be significant in the developing world where gastric cancer is becoming more prevalent. Another negative aspect of all screening programmes is the anxiety they induce in subjects, especially in those in whom the infection is identified but the treatment fails to clear it.

A particular problem associated with eradication of *H. pylori* infection to prevent gastric cancer is the problem related to the point of no return in the pathway from superficial *H. pylori* gastritis to cancer. If one were to screen and treat adult patients at fifty years of age, clearing their infection would be likely to have little impact on their risk of cancer as by this age most have reached the point of no return. In order to ensure a marked reduction in cancer incidence by eradicating the infection, one would need to treat patients at a relatively young age, probably in their teens. At that age, they would not have reached the point of no return and thus removing the infection would presumably prevent them developing cancer. However, the problem with this strategy is that patients do not develop cancer until sixty years of age. Consequently, treating subjects in their teens would not have any impact on the incidence of gastric cancer in the population for 40-50 years. This would therefore involve a substantial investment in the screening programme without any return being seen for a long time. Such a strategy would be particularly unattractive in countries where the incidence of the cancer is reducing and in which the cancer might be rare in 50 years time.

One concern about recommending populations screening and treatment for *H. pylori* infection in asymptomatic subjects is that such treatment might have some long-term adverse effects which are not readily recognised. These adverse effects might outweigh any beneficial effects. One of the very few studies in which *H. pylori* infection were screened and treated in the general population was performed in Leeds.[13] Subjects with *H. pylori* infection were randomized to eradication therapy or placebo. Ten years of follow-up overall mortality and mortality from heart disease was higher in those eradicated of the infection than those treated with placebo. The results did not reach statistical significance but there was a strong trend in the direction of adverse outcomes relating to the *H. pylori* eradication therapy. It is therefore essential that studies are performed to assess the overall impact of eradicating the infection in the general population before such a strategy could be advocated.

Several studies have modeled the cost-effectiveness of *H. pylori* screening of the general population to prevent gastric cancer.[14-16] They suggested that such an approach

would be most cost-effective in regions of high cancer incidence and that the main financial benefit was likely to be prevention of ulcers rather than prevention of cancer. However, each of the studies admitted to having many assumptions and uncertainties and all recommended further randomized trails to assess the efficacy before such a strategy could be recommended in the general population.

On reviewing the evidence, one therefore has to conclude that at present there is inadequate evidence for recommending, testing and treating asymptomatic individuals in the general population as a means of preventing gastric cancer. Randomised trials looking at the effect of such a strategy on overall mortality as well as gastric cancer incidence will be required before such a strategy can be recommended.

It is therefore disappointing that despite the clinical advances in our understanding of the aetiology of gastric cancer and of the role of *H. pylori* infection in this process that this progress has not led to any practical benefit in reducing the incidence of the cancer. Is there any practical steps we can take at present to reduce the incidence of gastric cancer through treating *H. pylori* infection? One practice which we can more widely employ is the use of *H. pylori* test and treat for patients with dyspepsia. This is accepted as a valid strategy in its own right. In addition, dyspepsia is common in the general population and therefore implementing this strategy will eradicate *H. pylori* infection in a significant proportion of the younger population and hopefully reduce their risk of gastric cancer. It also seems reasonable to eradicate *H. pylori* in patients with a strong family history of non-cardia cancer. However, it has to be admitted that we do not have active evidence that such treatment will prevent from developing cancer. It should also be recognised that patients with a very strong history of gastric cancer may have one of the autosominal dominant hereditary diffuse germ cell mutations and these cancers are known to develop in the absence of *H. pylori* infection.

The overall conclusion must be that the ideal way of preventing *H. pylori*-induced gastric cancer would be to prevent *H. pylori* infection in the first place. At present, no vaccine is available but may appear over the next few years. The major risk factor for the development of *H. pylori* infection is low socio-economic status. Improving socio-economic status will therefore eradicate the cause of cancer i.e. *H. pylori* infection.

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