Editorial

Gastric Cancer Prevention through Eradication of *Helicobacter pylori* Infection: Feasibility and Pitfalls

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Cite this article as: Derakhshan MH, Lee YY. Gastric cancer prevention through eradication of *H. pylori* infection: Feasibility and pitfalls. *Arch Iran Med*. 2012; **15(11):** 662 – 663.

A recent review and systematic analysis revealed that over two million new cancer cases were attributable to various infections in 2008.[1] *Helicobacter pylori* (*H. pylori*) is expectedly the leading infection accounting for as many as 650,000 new cases annually of non-cardia gastric cancer worldwide.[1] After the discovery of *H. pylori* by Warren and Marshall in 1982, accumulating evidence has unmasked a string of associations between the infection and gastric cancer.[2] Now, the central role of *H. pylori* infection in the pathogenesis of gastric cancer, including both the intestinal and diffuse histological subtypes, is not to be ignored. Although gastric cancer is the outcome of a multi-factorial pathway, the crucial role of an infectious agent involved in its pathogenesis makes it potentially preventable through eradication therapy that utilizes effective antibiotics.

Successful clinical recovery from the peptic ulcer disease model following eradication of *H. pylori* has prompted researchers to investigate whether this would be applicable for the gastric cancer model. The first well-designed trial was performed in 1991 by Correa et al., in a study that recruited individuals at high risk for gastric cancer in Colombia.[3] The result from this study was disappointing in that the reported cancer incidence was similar in both treated and untreated groups after six years of follow-up. Later studies from other high-risk regions which included four Chinese and two Japanese trials failed to demonstrate any statistically significant improvement in the cancer incidence in the eradicated groups.[4–9] In fact, all these studies except for two[5,9] were designed to test the effect of *H. pylori* eradication on the progression or regression of "precancerous" lesions rather than change in cancer incidence. However in doing so, these studies possibly did not have sufficient power to detect any reduction in the incidence of gastric cancer. Two main limitations in the above studies were the small number of participants allocated to each arm at baseline and the relatively short follow-up period. The best evidence for the short follow-up period was the result of an extended study which showed a remarkable reduction in the incidence of gastric cancer by lengthening the period of follow-up from 7.5 years to 15 years in the Shandong Interventional Trial. In this trial the relative risk changed from null to 0.61 (95% CI: 0.38 – 0.96).[6,10] In a pooled analysis of six studies by Fuccio et al. who analysed a total of 6695 participants followed over a 4 – 10 year period, the relative risk for gastric cancer was 0.65 (95% CI: 0.43 – 0.98) after eradication.[11] Interestingly, none of the studies included in the meta-analysis showed any significant reduction of cancer incidence per se, which indicated that an insufficient number of participants might have masked the real effect of eradication.

To overcome the above limitations in gastric cancer prevention trials, we need to recruit thousands of *H. pylori*-positive volunteers and follow them up for over ten years after eradication. Obviously this is not attainable in most population studies and may not be logistically justifiable. An alternative approach is to utilize any progression or regression of precancerous lesions as the main outcome of intervention instead of cancer per se. A higher incidence of gastric adenocarcinoma (mainly non-cardia, and cardia to a lesser extent) has clearly been shown in those with atrophic gastritis in the Iranian population.[12] Targeting those with atrophic gastritis and/or intestinal metaplasia (IM) will reduce the required sample size and the duration of follow-up. Most interventional trials mentioned earlier have utilized the regression and progression of precancerous lesions as the main outcome and have achieved desirable results.[2,3,4,6,7] In this issue, Massarrat et al. have reported an excellent interventional study, in which they applied a similar methodology. However unlike other trials, they recruited first degree relatives of patients with gastric cancer.[13] Inclusion of volunteers with pan-gastritis regardless of any other histological variables allowed them to have a broad range of baseline histological abnormalities to explore the effects of eradication therapy. Enrolled subjects were allocated to either eradication or placebo arms and were followed for a reasonable time period. Although the authors employed an apparently less effective anti-*H. pylori* combination but this "oversight" did not affect the overall outcome of the study.

Histological scores of atrophic gastritis were downgraded in both antral and corpus biopsies in the *H. pylori*-eradicated group. Considering a relatively short follow up period in the time of interim analysis, this was a remarkable achievement that favoured eradication therapy. The regression of atrophic gastritis after *H. pylori* eradication has been shown by several controlled [2–4,6,7] and un-controlled studies.[14] Atrophic gastritis at the gastric body is of particular interest as it may pose a higher risk of cancer, and fortunately the evidence of its regression with eradication seems to be superior.

The presence of IM in *H. pylori*-associated chronic gastritis may suggest a less reversible stage than atrophic gastritis alone. Evidence suggests that eradication instituted at the IM stage is less

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Accepted for publication: 25 July 2012

effective and more likely to progress.[14,15] In the current study, it is probably not surprising that despite eradication, IM did not regress even after 4.5 years. Progression of gastritis with age and the "birth-cohort effect" of Sipponen have been well documented.[16] The age of recruited subjects in the current study ranged from 40 to 65 years of age. This and the fact that first-degree relatives represented a "higher risk" category for gastric cancer further reduced the chance for regression of their IM lesions.

Having accepted the multi-factorial nature of gastric carcinogenesis, interactions between *H. pylori* infection and smoking, excess dietary salt and lack of anti-oxidants should be addressed appropriately in future prevention trials. Interestingly all of these factors will not drive the carcinogenesis cascade in an un-inflamed mucosa and *H. pylori* is the only major cause of widespread and long term inflammation of gastric mucosa in the Iranian population.[17] Ethnic Malays from the north-eastern region of Peninsular Malaysia have consistently reported an exceptionally low incidence of *H. pylori* infection as well as gastric cancer.[18] The exposure to certain environmental factors, particularly diet, have been shown to "protect" the Malays from infection.[19] A study from the same population also demonstrated that only those infected subjects developed IM and dysplasia.[20] What can we infer from these studies? If eradication of *H. pylori* can be done effectively, possibly over a long period of time and at an early age, the chances for prevention of gastric cancer are therefore much higher.

The role for genetic variations in the predisposition of pre-cancerous lesions has recently been documented in both the host and bacteria.[21] First degree relatives of patients with gastric cancer may have an increased chance for having susceptible genes to gastric cancer and therefore are less likely to respond to eradication therapy. Further studies are however needed to confirm the presence of these genetic variations in the Iranian population.

What lessons could we learn from the current study? Before commencement of any new trial we suggest the following: a) a more reliable and consistent method for histological diagnosis and grading of atrophic gastritis, along with strict criteria for inter- and intra-observer agreement is warranted. The Sydney Classification is undoubtedly comprehensive but it is not without limitations. It is not widely practiced, especially in the clinical setting and as evidenced in the current study, the agreement between pathologists is often poor. b) Employing an internationally and locally validated method for serological diagnosis of atrophic gastritis is essential. Although the current study did not appreciate it, but serum pepsinogen I, II and their ratio are well established surrogate markers of atrophic gastritis in Japanese and other populations. Currently, no standard serological marker is available for IM. c) An optimal anti-*H.pylori* combination that has an almost 90% eradication rate should be considered. d) Strict control for life-style factors associated with gastric cancer is warranted as these factors are likely to be changed during follow-up, and finally, e) perhaps the inclusion of two or more life-style risk factors as part of the intervention (i.e., smoking cessation and reduction in salt intake) along with *H.pylori* eradication will enhance the magnitude of risk reduction.

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