

## Decreasing Incidence of Gastric Cancer and *H. pylori* Infection a 10-Year Study from an Asian Population

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Worldwide, cancer of the stomach is the fourth most common cancer and is the second leading cause of cancer deaths. Gastric cancer is common in many regions of Asia and one of the many factors associated with it is the high prevalence of *Helicobacter pylori* [Hp] infection. Hp has been designated by the WHO as a class I (definite) carcinogen and the association between chronic Hp infection and the development of gastric cancer has been established by numerous publications. Up to 76-95% of gastric cancers are associated with Hp infection [1-3]. Among the many factors expressed by Hp, gastric carcinogenesis via the cag A pathway is the most studied. In individuals infected with CagA-positive strains, a meta-analysis of 16 case-control studies showed a further increase in the risk for gastric cancer by 1.64 fold [4]. However, due to improved sanitation amidst better living conditions, heightened patients and physician awareness and widespread Hp eradication practices, a decreasing prevalence of Hp infection is observed even in previous high-prevalence regions. We have also noted that the number of patients with gastric cancer consulting our institution, a tertiary academic hospital, has diminished remarkably in the last several decades. Thus, we designed a study to determine the incidence of gastric cancer, as well as, Hp infection over a ten-year period as seen in our tertiary referral center and evaluated the relationship between Hp infection and gastric cancer.

In order to determine current Hp infection, we performed rapid urease tests (RUT) and/or histopathology of gastric biopsies taken from the antrum, incisura angularis and gastric corpus on all adult patients who underwent esophagogastroduodenoscopy (EGD) between January 1, 2004 until December 31, 2013. In addition to Hp status, other demographic data were also recorded, i.e., age, sex, height, weight, and BMI. Over a 10-year period, a total of 8,520 patients were included in this analysis. Ninety-six (1.13%) patients were diagnosed with gastric adenocarcinoma (9.6 ± 6.4 cases/year) and 1,708 (20.1%) patients tested positive for Hp infection (170.9 ± 79.0 cases/year). Up to 82% are non-cardia gastric cancers and 42% are infected with Hp (Table 1). The most common clinical presentation of gastric cancer is epigastric pain (30%). Half of the lesions are infiltrating and 11% are completely obstructing lesions at the time of diagnosis. The Chi square test was used to determine whether Hp infection was significantly associated with gastric malignancy while the Pearson correlation test was used to establish a relationship between the annual incidence of gastric cancer and that of Hp infection.

Our analysis revealed that Hp infection is significantly associated with gastric malignancy ( $p < 0.001$ ) among the patients we examined during the last 10 years. In addition, a strong correlation was determined between the decreasing trend in the annual incidence of Hp infection (31.71% to 8.69%) and the corresponding decrease in the incidence of gastric malignancy (1.82% to 0.21%) observed from 2004 to 2013 ( $R = 0.884$ ,  $p = 0.001$ ; Figure 1).

In 2006, a review of 5 meta-analyses showed that *H. pylori* infection is associated with approximately a two-fold increase in the risk of gastric cancer [5,6]. A meta-analysis of 15 papers, 10 of which were from Japan, revealed that *H. pylori* eradication therapy statistically diminished

the prevalence of clinical gastric cancer by approximately one third [7]. Studies by Uemura et al showed that recurrence of early gastric cancer can be prevented by Hp eradication [8]. In the West reports of a diminishing incidence of gastric cancer related to a decrease in Hp prevalence have been published several decades ago [9].

Experts believe that a recent report of the global decrease in gastric cancer incidence is largely attributed to Hp eradication. This is probably true in the areas of the world where most patients have easy access to medical care and Hp eradication is aggressively pursued by both primary care physicians and by national health services.

The result of this study describes the real world observations on how the incidence of gastric cancer is significantly influenced by the diminishing number of Hp-infected patients in the developing world - where Hp infection used to be prevalent. In Asia, access to care, as well as, health services is generally poor, yet a phenomenon similar to what is observed in the West is slowly unfolding currently [10,11].

Among other factors, increasing awareness of both the public and medical colleagues about the risks of gastric cancer associated with Hp infection and timely and aggressive Hp eradication treatment of infections diagnosed during opportunistic Hp testing in the primary physicians' clinics may be additional factors contributing to these observations. In 2005, we also reported a significant reduction in peptic ulcer disease and Hp prevalence in our center over a seven-year period [12,13]. These time-trend observations in gastric malignancy and Hp are similar with those noted with peptic ulcer disease whereby a strong correlation with the decreasing trend in the annual incidence of Hp infection was determined earlier.

Major clinical practice guidelines recommend strongly the testing for and subsequent eradication of Hp infection among those who have tested positive for the infection, most notably in regions where the Hp prevalence is high, in those with severe gastric atrophy, prior history of resected gastric cancer, those who have had a history (and complications) of peptic ulcer disease, etc. The Maastricht IV recommends to eradicate Hp infection because it is the most consistent risk factor for gastric cancer. Hp eradication abolishes the inflammatory response and slows, arrests and in some cases reverses the progression of atrophy. Its elimination is therefore the most promising strategy to reduce the incidence of gastric cancer because there is strong evidence

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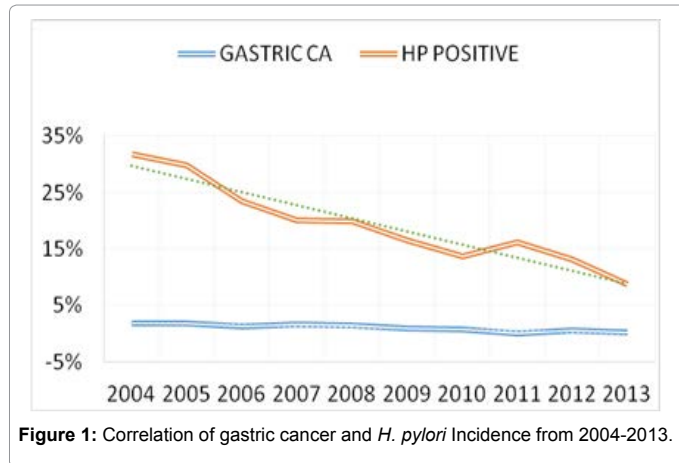
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	Hp positive	Hp negative	P value
Gastric cancer	36	59	0.001
No gastric cancer	1673	6752	

**Table 1:** Distribution of patients according to gastric cancer and Hp Status.



**Figure 1:** Correlation of gastric cancer and *H. pylori* Incidence from 2004-2013.

that its eradication reduces the risk of gastric cancer development.

While, as shown above, an effective eradication treatment has always to be pursued, an issue of growing concern is not only the rising incidence of adverse effects by administering high dosage of antibiotics (up to about 30%), but also the antibiotic resistance. This is significantly affecting the success of triple therapies eradication rates. In particular, between 38% and over 50% of eradication treatment with either metronidazole or clarithromycin, respectively, have been reported [14]. Despite several reports suggesting the potential use of herbal compounds either in adjunct [15] or as a sole treatment [16] for eradication of HP, to date no firm conclusion can be drawn due to the wide heterogeneity and often poor design of such studies [17]. Ourselves, few years ago, did stool culture of HP, tested it in vitro against multiple potential herbal extracts and administered subjects with such would-be “specific” formulations shown to be the most bactericidal (Marotta et al. unpublished). Although our population consisted of naïve subjects but also a group which had failed the first eradication attempt with conventional regimes, the eradication rate in both was poor (below 45%) and the study had to be abandoned for ethical implications.

While the search of any either pharmacological or phytopharmacological optimization of eradication treatments moves on, for the time being, a strict application of the above guidelines deserves the highest attention from medical practitioners.

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