

Decreasing Prevalence of Helicobacter Pylori Infection Parallels: The Incidence of Gastric Cancer in Northwest Italy, During the Last Decade

Lucio L^{1,2*}, Alessandro L¹, Antonella G³, Olga R¹, Manuela M⁴, Bruno T⁴

¹Dpt Gastroenterology, Mauriziano U.Ist Hospital, Turin, Piedmont, Italy

²Currently (from October 2012): Consultant at Poliambulatorio Statuto, Turin, Italy

³Health Physics, Mauriziano U.Ist Hospital, Turin

⁴Pathology Institute, Mauriziano U.Ist Hospital, Turin

Abstract

Background: Although *H.pylori* is a human carcinogen agent, the efficacy of its eradication on gastric cancer prevention is yet to be demonstrated. Piedmont, Northwest Italy, is an area with a relatively high incidence of gastric cancer.

Methods: A retrospective, population-based study was performed among all the dyspeptic outpatients (38,514) afferent to the Gastroenterology Unit of Mauriziano U.I Hospital, Turin, Italy. Exposure to *H.pylori* was assessed using ¹³C Urea Breath test from 1997 to 2008 by means of mass spectrometry. The incidence of gastric cancer was evaluated among all dyspeptic patients (28,900) submitted to upper endoscopy at the same Gastroenterology Unit, over the years 2000-2008. Data were analysed by chi square test and Pearson r correlation.

Results: *H.pylori* infection overall prevalence was 34.5% and decreased from 36% to 32% over the 1997-2008 period. ($p < 0.01$). Among the 12,662 *H.pylori*+ patients, at least 9,530 repeated the test for eradication verification (75.3%). The overall eradication rate was 65%. Gastric cancer incidence decreased from 0.0143% to 0.0089% over the 2000-2008 period. A significant positive correlation ($p < 0.02$) between gastric cancer incidence and *H.pylori* infection prevalence over the studied period was found ($R^2 = 0.621$).

Conclusions: Prevalence of *H.pylori* infection has decreased significantly over the last decade. This trend parallels the incidence of gastric cancer. One of the causes may be the high level of interest in the eradication treatment, not less than 75.3%, with an eradication success rate of 65.5%, which is remarkable in "real life" setting, out of controlled trials. Our data demonstrate that eradication of *H.pylori* is effective in preventing gastric cancer development. Test & treat approach in dyspeptic reveals to be effective on clinical and social basis.

Keywords: Helicobacter pylori infection; Gastric cancer; Epidemiology; Dyspeptic patients

***Corresponding author:** Lombardo Lucio, Poliambulatorio Statuto, Gastroenterology Service, Piazza Statuto 3 ang. Via Manzoni 0, 10100-Turin, Italy, E-mail: lombodilucio@yahoo.it

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that the two over mentioned two large-scale prospective studies in high-risk populations have stated *H.pylori* infection as a definitive risk factor for the development of gastric cancer [3,4], the opposite premise that eradication of *H.pylori* infection is an appropriate target for the prevention of gastric cancer is still to be demonstrated.

Piedmont, Northwest Italy, is an area with a relatively high incidence of gastric cancer [6]. Aims of this study are: 1) Compare the current prevalence of *H.pylori* infection (2007-2008) with that for 1997-1998, in a dyspeptic population in Piedmont. 2) Evaluate the "interest" in the eradication treatment of *H.pylori*-positive patients and its success rate. 3) Correlate the prevalence of *H.pylori* infection with the incidence of gastric cancer, over the last decade, in the same geographic area.

Materials and Methods

A retrospective, population-based study was performed among all the dyspeptic outpatients (38,514) afferent to the Gastroenterology Unit of Mauriziano U.I Hospital, Turin, Italy, from 1997 to 2008. Exposure to *H.pylori* and its eradication were assessed only by ¹³C Urea Breath test using a mass spectrometry method (ABCA-Europa Scientific, Crew, UK). The eradication of *H.pylori* infection was assessed 4±2 months after completion of therapy. The "interest" for the test was inferred from the adhesion to the post-treatment testing, mirroring the willingness to know the treatment outcome. The incidence of gastric cancer was evaluated among all dyspeptic patients (28,900) submitted to upper endoscopy at the same Gastroenterology Unit, on histological basis, over the years 2000-2008. Endoscopic Olympus and Pentax video-instruments were used for morphologic diagnosis. Histologic assessment was performed on endoscopic biopsy samples (not less than 6) and on surgical resected stomachs by standard processing using hematoxylin and eosin staining. Data were analysed by chi square test to evaluate difference among groups and Pearson r correlation. A Value of $p < 0.05$ was considered significant.

Results

From January 1997 to December 2008 *H.pylori* infection overall prevalence in our dyspeptic patients was 34%, decreasing from 36% to 32% over time ($p < 0.01$) (Table 1 and Figure 1). No difference was registered between male and female gender. The highest prevalence was registered in the age range 40-70 years. Among 12,662 *H.pylori*

Introduction

The prevalence of Helicobacter pylori (*H.pylori*) infection varies by geographic locations and it is estimated that approximately 50% of the general population is affected. The distribution varies considerably between developed and developing countries, featuring a decreasing prevalence in some countries over the last decade [1]. Recently, *H.pylori* has been classified as a human carcinogen by the International Agency of Research on Cancer (IARC) [2]. Two key papers have demonstrated a positive association between gastric cancer and *H.pylori* infection [3,4]. In some countries however, as in North India, the prevalence of *H.pylori* in controls resulted slightly higher than in gastric cancer patients (80% vs 78%), supporting the concept that *H.pylori* infection is not directly associated with the pathogenesis of gastric cancer but it may act as a simple co-carcinogen [5]. Moreover, in spite of the fact

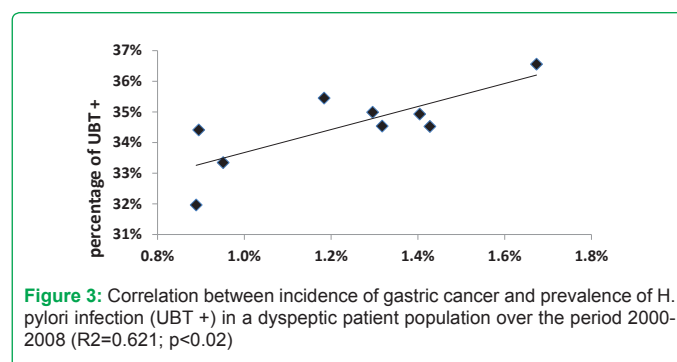
positive patients (32.88%) at least 9,530 repeated the test for eradication assessment (75.3%), indirectly indicating the “interest” in knowledge of the treatment outcome. Patients were treated with triple standard therapy (proton pump inhibitor + amoxicillin+metronidazole/tinidazole) in 80%, with levofloxacin-based therapy in 10% and with quadruple tetracycline-based therapy in 10% of the cases. The overall eradication rate of infection was 65.5%.

The total gastric cancer cases over 2000-2008 time period was 449, (163 females, 242 males) mostly intestinal-type non-cardia adenocarcinoma (99.1%), with an incidence decreasing from 0.0143% to 0.0089% ($p < 0.05$) (Table 2 and Figure 2). Mean age at the diagnosis was significantly higher in female (71 ± 4 years) than in male patients (68 ± 5 years; $p < 0.05$).

A significant positive correlation between gastric cancer and *H.pylori* infection prevalence was found over the studied period ($R^2 = 0.621$; $y = 4.218x - 0.044$; $p < 0.02$) (Figure 3). The total number of gastric lymphoma over the same period was 44 (24 females, mean age 78 ± 9 years; 20 males, mean age 69 ± 8 years), almost uniformly scattered over the decade. The positive, statistically significant, correlation between incidence of adenocarcinoma only and *H.pylori* infection prevalence did not change by eliminating the cases of lymphoma from the calculation ($p < 0.02$). The correlation between gastric lymphoma incidence and *H.pylori* prevalence over the studied period was not significant ($R^2 = 0.0172$), probably because of the paucity of the cases.

Discussion

This study shows that the prevalence of *H.pylori* infection in the dyspeptic population in Northwest Italy has been decreasing significantly over the last decade from 36% to 32 %. These figures parallel those regarding the incidence of gastric cancer in the same



geographic area over the same time period (from $14.3/10^5$ to $8.9/10^5$ subjects), with a statistically significant correlation ($R^2 = 0.621$; $y = 4.218x - 0.044$; $p < 0.02$).

Studies on the prevalence of *H.pylori* infection in gastric cancer from several countries have yielded widely varying results, ranging from 19% to 80% [3,7,8], and epidemiological studies have produced mixed conclusions, stating a mean association between *H.pylori* and gastric cancer in the range of 50% of the patients [9]. In the case of our region, Piedmont, Northwest Italy, the relatively high incidence of gastric cancer [6] is paralleled by a high incidence of chronic atrophic gastritis, recently demonstrated by a population-based survey using GastroPanel test [10], a relatively new, highly reliable serological diagnostic test for the assessment of gastric function [11]. A combined analysis of 12 case-control studies (1,228 gastric cancer cases) showed that the association with *H.pylori* infection was restricted to non-cardia gastric cancers with an odds ratio = 3.0, that increased to 5.9 when infection diagnosis was made 10+ years before cancer diagnosis [12]. Although the so-called “African enigma” remains unexplained [13] and other oncogenes are certainly involved, it is universally accepted that *H.pylori* carries an increased risk for gastric cancer. So far, however, no definitive demonstration has been supplied for *H.pylori* eradication as an efficient prophylactic measure for gastric cancer prevention, on population basis. Three randomized placebo-controlled trials in China and Columbia demonstrated no significant protective effect by *H.pylori* eradication [14-16], whereas contradictory results have emerged from three Japanese studies [17-19]. Although the Japanese studies were neither randomized nor placebo-controlled, they gave common evidence that no gastric cancer developed after eradication treatment in patients without precancerous gastric lesions at entry.

Our data, showing a significant positive correlation between *H.pylori* infection prevalence and gastric cancer incidence, both in decreasing trends in the same geographical area over the same time period, support the concept that *H.pylori* eradication is an efficient prophylactic measure against gastric cancer development. In agreement with these conclusions are the results of a recent study that shows that the eradication of *H.pylori* significantly reduces the incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer [20]. The classical epidemiologic approach to causality postulates that such outcomes depend on the interplay of three factors: the agent, the host and the environment. Studies on virulence factors of the bacterium have shown that the types Cag A and Vac A s1 (a or b) predominate in most population with historically high gastric cancer risk [21]. Host related factors involve genetic susceptibility (or resistance) that may depress (or stimulate) defences against environmental carcinogens [22-24]. Environmental factors linked to gastric cancer risk are excessive use of salt and deficient intake of fresh fruits and vegetables in the diet. Excessive salt may be an irritant

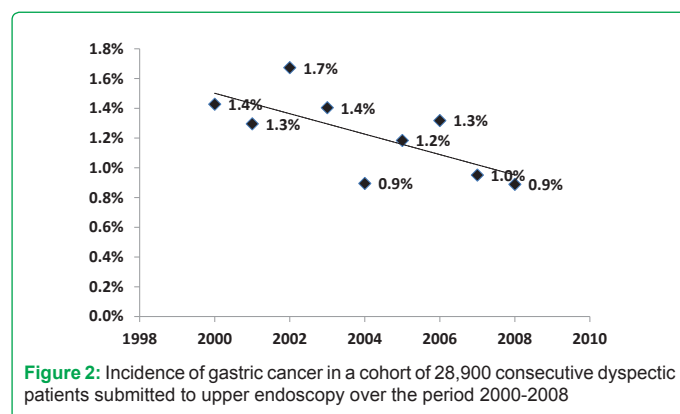
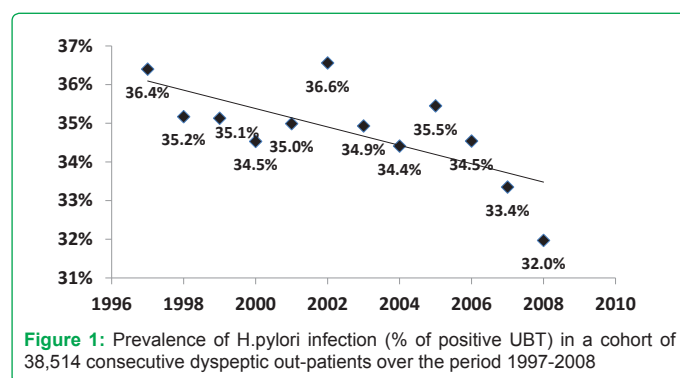


Table 1: Absolute numbers of yearly positive *H.pylori* patients (UBT +) and of tests performed (UBT) over the period 1997-2008; relative percentage of UBT+

year	UBT +	n° of UBT	percentage of UBT +
1997	586	1610	36%
1998	1632	4640	35%
1999	1649	4694	35%
2000	1495	4330	35%
2001	1422	4064	35%
2002	1194	3266	37%
2003	1006	2880	35%
2004	999	2903	34%
2005	926	2612	35%
2006	1118	3237	35%
2007	819	2456	33%
2008	950	2972	32%

Table 2: Absolute numbers of gastric cancer (g.ca) and upper endoscopies over the period 2000-2008; relative percentages

year	n° of g.ca.	n° of endoscopies	percentage of g.ca.
2000	43	3012	1.4%
2001	39	3010	1.3%
2002	50	2988	1.7%
2003	41	2920	1.4%
2004	27	3017	0.9%
2005	34	2872	1.2%
2006	37	2808	1.3%
2007	30	3154	1.0%
2008	33	3712	0.9%

to the gastric mucosa; fresh fruits and vegetables have been linked to antioxidants such as ascorbic acid, β -carotene, vitamin E, folates and non-nutrients such as polyphenols [25,26]. All these factors may be conceived as “dominated” by the *H.pylori* infection. The infection results in chronic inflammation that lasts for decades. Multiple forces, genetic and environmental in nature, can modulate the inflammatory process.

A key issue regarding the influence of *H.pylori* eradication on gastric cancer prevention is the acquisition that atrophic gastritis may be reversible after *H.pylori* eradication. Reversibility of gastric atrophy or intestinal metaplasia can be demonstrated by sophisticated analytical techniques including micro array or proteomics [27] or, more simply, by the assessment of serological pepsinogen I value [11]. However, from a practical point of view, the easiest way to prevent gastric atrophy/metaplasia progression toward neoplasia seems to be the eradication of *H.pylori* infection as early as possible. As a matter of facts, a clue factor influencing the deflection of both *H.pylori* infection prevalence and gastric cancer incidence in our study is the high level of “interest” for the eradication treatment (not less than 75.3%). The effectiveness of *H.pylori* eradication treatment in the Italian population has been stressed in a previous study by our group [28]. The overall eradication rate of *H.pylori* infection was not less than 65.5% that is a remarkable achievement in real life setting, out of controlled trials. The gastric lymphoma incidence failed to show significant variations over the last decade, probably because of the paucity of the cases. Although primary gastric mucosa associated lymphoid tissue (MALT) lymphoma can regress after anti-*H.pylori* co-treatment [29], only marginal and contradictory data exist in literature about the role of *H.pylori* infection treatment in preventing primary non-Hodgkin gastric lymphoma [30]. Taken together, our data support the thesis that *H.pylori* eradication might reverse, or at least delay gastric carcinogenesis before it reaches the point of no return (dysplasia/neoplasia). Consequently, the earlier

the eradication the higher the benefit towards the prevention of gastric cancer could be, especially in high-risk population [31].

Limitations of the present study include solely observational retrospective study design, lack of evaluation of environmental factors and lack of characterization of *H.pylori* subtypes. Nonetheless, we think that it has the major value for having demonstrated, a positive correlation between the eradication of *H.pylori* infection and the incidence of gastric cancer, for the first time in our country, in a population-based study, over a long enough observational period. It is conceivable that the possible concomitant etiologic factors present in our population (salt consumption, smoking, alcohol etc) have remained substantially constant, over the studied period, so that they don't are expected to significantly modify the final result of the study [32,33].

In conclusion, our data, in agreement with the results of other studies [17-20] demonstrate, for the first time in Italy and in Europe as a whole, at our knowledge, the beneficial effect of *H.pylori* eradication as a prophylactic measure against gastric cancer development. They confirm, on epidemiologic basis, that test & treat policy is clinically effective and of outstanding social impact in dyspeptic patients. **Conflict of Interest: None**

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