

Original article

## Opposing time trends of gastric cardia cancer and duodenal ulcer

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### SUMMARY

**Background:** Most countries have registered decline in distal (antrum and corpus) gastric cancer incidence and mortality. On the other hand, adenocarcinoma of the gastric cardia has been increasing with the unknown risk factor being responsible. This observation may or may not be in the relation to the *Helicobacter pylori* infection.

**Aims:** To study the time trends of *Helicobacter pylori* related diseases in the past decade

**Material and methods:** This study was based on endoscopy reports of the hospitalized patients collected in the Department of the diagnostic endoscopy; Clinic of gastroenterology and hepatology- Belgrade between 1987 and 1997.

**Results:** From 1987 to 1997, hospitalisation rates for gastric ulcer as well as distal gastric cancer fell, while the hospitalization rate for gastro-oesophageal reflux disease and duodenal ulcer didn't change. At the same time hospitalisation rate for gastric cardia cancer rose. When this is compared to the time trend of the duodenal ulcer significant difference between those two trends was observed ( $P < 0.01$ ).

**Conclusion:** Opposing time trends of duodenal ulcer versus gastric cardia cancer is consistent with hypothesis that the declining infection rates for *Helicobacter pylori*, due to the active therapy, in the general population may actually

have led to a rise in the occurrence of proximal gastric cancer. New developments in molecular biology may provide better understanding of the topographic variants of gastric cancer and the potential role of *Helicobacter pylori*-associated gastritis with atrophic and metaplastic sequelae, distinct from Barrett's oesophagus.

**Key words:** gastric cardia cancer, *Helicobacter pylori*, gastroesophageal reflux disease (GERD), time trends

### INTRODUCTION

Ever since 1994, *Helicobacter pylori* is considered to be I group carcinogen- International Agency for Research on Cancer<sup>1</sup> causing gastric cancer. Relationship between *Helicobacter pylori* infection and gastric cancer can be studied through either: a) epidemiological studies or b) morphological aspects of the gastritis- cancer cascade or c) molecular mechanisms of cancer genesis. Most countries have registered for the past three decades notable decline in incidence and mortality rates for gastric and duodenal ulcer as well as for the gastric cancer (1-1).<sup>2,7</sup> It appears likely that observed decline in the occurrence of these diseases is epidemiologically associated with underlying decline in the infection rates with *Helicobacter pylori*.

Recent reports show increase in incidence rates for adenocarcinoma of the gastric cardia. This trend parallels the one of the lower esophageal adenocarcinoma, frequently linked with Barrett's esophagus, reflux oesophagitis, a gastric hypersecretion and history of duodenal ulcer.<sup>2,3</sup>

We hypothesised that the decline in the *Helicobacter pylori* infection rates of the general population resulted not only in a fall in peptic ulcer and gastric cancer, but also in a concomitant rise in gastric cardia cancer.

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## PATIENTS AND METHODS

Hospitalisation rates were studied using the data of the Clinic of gastroenterology and hepatology-University Clinical Center of Belgrade. The data files contained the records of all inpatients including upper endoscopy reports. It was started in 1987, and files were available for each year until 1997. During this period, 37 369 upper endoscopy examination were performed. Endoscopy findings were classified according to the currently accepted classifications for the upper gut diseases<sup>8-12</sup> and the discharge diagnosis according to ninth revision of the International Classification of Diseases (ICD9) (1-2). For every year from 1987 to 1997 following hospital discharge diagnosis were taken into account: gastric ulcer and duodenal ulcer, GORD, cancer of the gastric corpus and antrum and gastric cardia cancer. To calculate proportional hospitalisation rates, the number of hospitalizations for a particular diagnosis was divided by the total number all hospitalisations during the same period. Since the hospital data base covers the entirety of Belgrade city population and minority of Serbian population, calculation of common statistical parameters such as standard error or standard deviation is not feasible.

The observed changes have tendency best represented by polynomial equation of the higher rank III-IV. In order to compare different time tendency linear trend approximation was applied.

Statistical analysis was done applying time trend lines and calculating the angle between two trend lines. If this angle is less than a  $< 33^\circ$  difference is considered not being significant. Angle  $33^\circ < \alpha < 67^\circ$  is considered to be significant ( $P < 0.05$ ) and for the  $\alpha > 67^\circ$ ;  $P < 0.01$ . All the statistics was done by means of software packages *SPSS* and *Statistics*.

## RESULTS

During past eleven years 37 369 endoscopy examination were done in the diagnostic endoscopy unit of the Clinic of Gastroenterology and Hepatology. Because of the large size of population hospitalized, all diseases

appeared frequently, (Table 1).

Number of patients each year, diagnosed as having gastric or duodenal ulcer is represented in table 1.

There was significant decreasing linear trend for the gastric ulcer (Figure 1) and distal gastric cancer (Figure 2) for the past eleven years, but not for the duodenal ulcer (Figure 3).

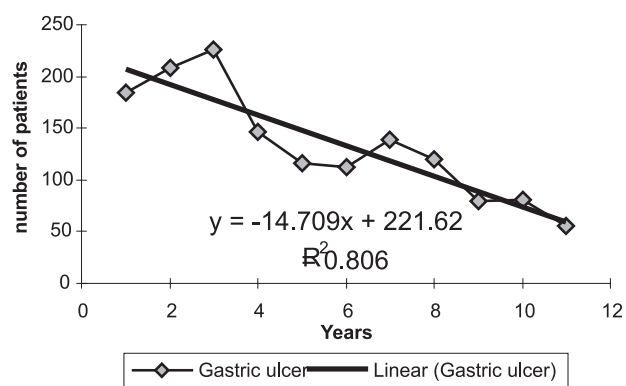
At the same time there were no significant changes in gastroesophageal reflux disease incidence over time, even though absolute number was lower (Figure 4).

Time sequence analysis indicates statistically significant opposing time trend of duodenal ulcer and gastric cardia cancer (Figure 5) that matches active anti *Helicobacter pylori* therapy.

## DISCUSSION

Although the incidence of the distal (antrum and corpus) gastric cancer is declining, there are data emerging that the incidence of the carcinoma localized to the gastric cardia has risen dramatically.<sup>13</sup>

*Helicobacter pylori* eradication carries certain risk of developing reflux oesophagitis. In the studies of Labenz and Sacca this was an early event.<sup>14,15</sup> There are also stud-



**Figure 1.** Time trend of gastric ulcer for the period 1987-1997. For the value of  $R^2 = 0.806$ ;  $P < 0.01$

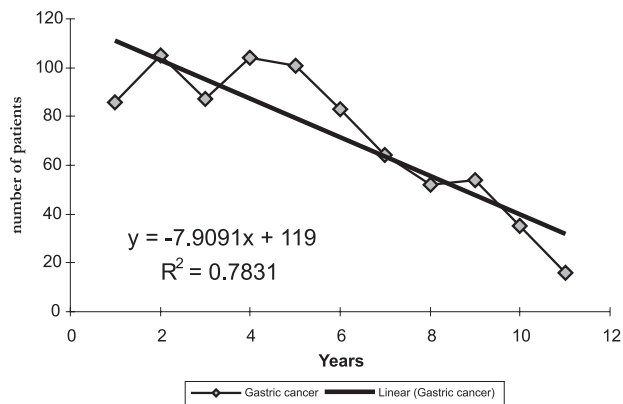
**Table 1.** Number of patients diagnosed as having gastric or duodenal ulcer between 1987-1997.

	Years										
	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Number of endoscopy performed	1828	2257	2397	2684	2848	2303	2321	2236	1656	1681	1634
Gastric ulcer	184	208	226	146	116	112	139	120	79	81	56
Duodenal ulcer	251	296	318	336	381	253	380	336	226	255	231

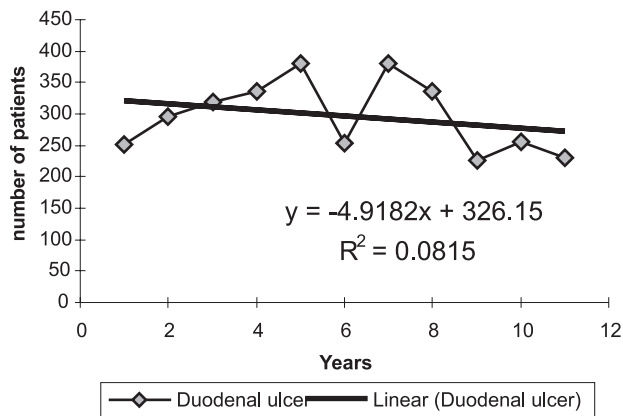
ies suggesting that GERD patients are less often infected with *Helicobacter pylori*.<sup>16-18</sup>

Second argument for the hypothetical protective role of *Helicobacter pylori* infection comes from negative correlation between *Helicobacter pylori* infection and severity of gastro-oesophageal reflux disease (GERD).<sup>19</sup>

Moreover, patients with acid reflux disease have a significant prevalence of oesophageal complications. These include oesophageal ulceration, which occurs in 2-7% of patients with the diseases, Barrett's oesophagus, which has a prevalence of 10-15%, and oesophageal stricture, which occurs in 4-20% of patients.<sup>20,21</sup> Furthermore, the risk of malignancy in-patients with Barrett's oesophagus may be as much as 30-40 times that of the



For the value of  $R^2 = 0.7831$ ;  $P < 0.01$   
**Figure 2.** Time trend of the gastric carcinoma. For the period 1987-1997.



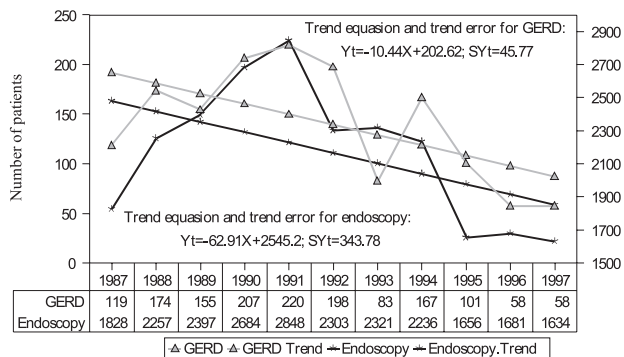
For the value of  $R^2=0.0815$ ;  $P > 0.05$   
**Figure 3.** Time trend of the duodenal ulcer in period 1987-1997.

general population. But the most important issue is whether this sequence of the events heightens the risk of gastric cardia cancer development.

Data from USA shows significant drop of *Helicobacter pylori* infection in the past 25 years, but also there was sevenfold increased of the frequency of hospital admission for erosive oesophagitis as well as for cancer of the cardia and distal oesophagus.<sup>22</sup>

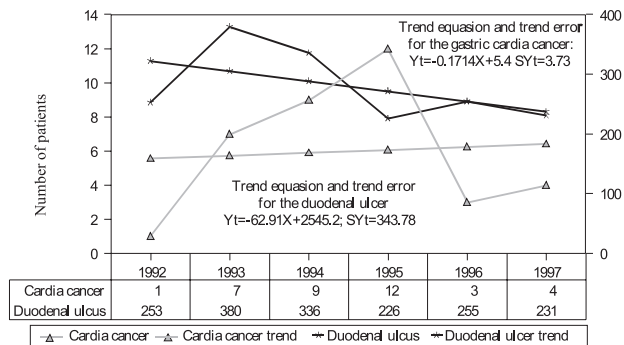
Along with these observations, *Helicobacter pylori* may actually play a protective role against cardia and distal oesophagus malignancy.

Pathophysiological observations suggest that CagA strains of *Helicobacter pylori* are in negative correlation with the presence of Barrett's oesophagus.<sup>23,24</sup> It seems that location of *Helicobacter pylori* induced gastritis plays a certain role in development of GERD. Pangastritis with multifocal mucosa atrophy leads to decrease in acid se-



Comment: number of endoscopy verified GERD follows the number of endoscopies  
 Angle between trend lines: for the  $\text{tg}\alpha = -0.0798$   $\alpha = 4.5$ ;  $p > 0.05$

**Figure 4.** Time trend of endoscopy verified GERD for the period 1987-1997.



Angle between trend lines: for the  $\text{tg}\alpha = -8.9724$   $\alpha = 83.6$ ;  $P < 0.01$

**Figure 5.** Time trend of the gastric cardia cancer and duodenal ulcer for the period 1992-1997.

cretion and more production of ammonia ion due to the increased density of bacteria. On the contrary, antrum predominant gastritis leads to increased acid secretion via gastrin production, more tissue damage due to the pro-inflammatory agents' production (cytokines, prostaglandins, nitric oxide etc.).

Interesting observation was made by Hackelsberg who pointed out that 97.7% of all patients with antral gastritis also had gastritis of the cardia, although with smaller bacterial density and inflammatory response than in antrum.<sup>25</sup> This was confirmed later one in couple of other studies.<sup>13,26,27</sup> It is not yet clear whether cancer of the gastric cardia arises from premalignant lesion such as intestinal metaplasia.

In the article of Morales et al 23% of the examined patients had intestinal metaplasia of the cardia and 37.5% of them had concomitant intestinal metaplasia else where in the stomach. There was significant association between *Helicobacter pylori* and intestinal metaplasia of the gastric cardia.

These findings suggest that antrum predominant gastritis and duodenal ulcer patients may be at more risk of developing gastric cardia cancer through out life long gastritis of the cardia, intestinal metaplasia and dysplasia. But this hasn't been proven yet.

As a matter of fact, results of our study show that frequency of duodenal ulcer is pretty stable over time with insignificant decline and the gastric cardia cancer is increasing for the past six years matched with active anti *Helicobacter pylori* therapy. This opposing tendency is of significant value ( $P < 0.01$ ).

At the same time, both, distal gastric cancer and gastric ulcer are significantly decreasing suggesting *Helicobacter pylori* eradication being beneficial.

Number of patients with endoscopy verified reflux disease decreased for the past eleven years, specially for the past five years 1987-92:1993-98=1073:467), but this is of relative value since number of endoscopies also dropped.

If we assume that *Helicobacter pylori* infection is declining as a result of active treatment for the past decade, eradication of infection should be called beneficial in terms of gastric ulcer and distal gastric cancer.

Apart from the well-understood cascade gastritis-intestinal metaplasia-dysplasia-cancer, relationship between *Helicobacter pylori* and distal esophagus and gastric cardia cancer needs deeper look inside.

It seems that *Helicobacter pylori* infection affects gastric cardia site in two different ways, both with similar end-point. One that goes along with *Helicobacter pylori* infection and may be related to the bacterial strains inducing antrum predominant gastritis. The other one is triggered by *Helicobacter pylori* eradication of the strains causing gastritis with multifocal atrophy predominantly situated in the gastric corpus.

There are very little information regarding risk factors that might be responsible for the increasing time trend of gastric cardia cancer. Further confirmations are needed and long-term follow-up studies will be necessary. New developments in molecular biology may provide better understanding of the topographic variants of gastric cancer and the potential role of *Helicobacter pylori*-associated gastritis with atrophic and metaplastic sequelae, distinct from Barrett's esophagus.

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