Helicobacter pylori infection, premalignant gastric lesions and gastric cancer in the Baltic States: a review

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Helicobacter pylori (H. pylori) infection has been recognized as a human class I carcinogen in 1994 and linked with the development of gastric cancer in numerous studies. Gastric cancer still ranks as the second leading mortality cause among all cancers in the world and in the fourth place in Europe. High prevalence of H. pylori infection and high incidence of gastric cancer in adults are still characteristic of the Baltic States and resemble patterns in the Western and Northern European countries several decades ago. The recent decline in gastric cancer incidence and mortality as well as H. pylori prevalence in Lithuania, Latvia and Estonia reflects the worldwide trends. H. pylori-induced diseases, however, still remain a significant burden for health care systems in the Baltic States. The relevance of H. pylori induced gastric diseases in the Baltic States has stimulated epidemiological, clinical as well as fundamental research on H. pylori infection, premalignant gastric conditions and gastric cancer. This paper reviews original research on H. pylori infection and related diseases in Lithuania, Latvia and Estonia during the period 1992–2011.

Key words: Helicobacter pylori, atrophic gastritis, gastric cancer, Baltic States

INTRODUCTION

Helicobacter pylori (H. pylori) infection is now recognized as the main cause of most stomach and duodenum diseases. H. pylori was found to trigger chronic inflammation in the stomach, further leading to premalignant and malignant changes (1). This bacterium has been initially linked with the development of atrophic gastritis and peptic ulcer disease. Later evidence has shown that H. pylori plays a role in the development of the mucosa-associated lymphoid tissue (MALT) in the stomach. Furthermore, as proven by numerous studies, H. pylori is the main risk factor for the development of gastric carcinoma (2). Despite the decreasing incidence of H. pylori infection in the Baltic States in the recent years, H. pylori induced diseases still remain a significant challenge for health care systems in Lithuania, Latvia and Estonia. This paper reviews epidemiological, clinical and fundamental research on H. pylori infection and associated diseases in the Baltic States during the period 1992–2011.

PATTERNS OF H. PYLORI INFECTION IN BALTIC STATES

The high prevalence of H. pylori infection in adults is still characteristic of the Baltic States; however, recent data suggest that the prevalence of this bacterium has rapidly decreased during the last decade, following the cohort phenomenon. The prevalence of H. pylori has been linked with socioeconomic factors in numerous studies. During the years 1990–2011, the Baltic States have gone through dramatic changes in the quality of life. The improved living conditions and hygiene standards are reflected in the decreasing H. pylori prevalence among children, since this
bacterium is acquired early in childhood. The high prevalence of *H. pylori* and associated disorders in Lithuania, Latvia and Estonia has been under constant monitoring of different research groups in the Baltic States.

Data on *H. pylori* prevalence in the last decades in the Baltic States reflect the high rate of infection among adults. In Lithuania (1999), 78.5% of 18–60-year-old blood donors were contaminated with *H. pylori* infection (3). In 2005–2006, *H. pylori* was established in 65.5% of Latvian patients and in 69.7% of Lithuanian patients aged 55 and above, referred to upper endoscopy due to dyspeptic symptoms (4). In a recent comparative study, the prevalence of *H. pylori* antibodies was 69% in Tartu, 36% in Reykjavik and 11% in Uppsala (5). These data provide a clear evidence that the prevalence of *H. pylori* in the Baltic States still remains considerably higher than in Northern Europe.

Contrary to the adult population, the prevalence of *H. pylori* infection among children has significantly decreased in the Baltic States over the last two decades. In Estonia, the age-standardized *H. pylori* seroprevalence rate was 42.2% (95% CI 37.4–47.0%) for the children group investigated in 1991 and 28.1% (95% CI 23.1–33.6%) in 2002 (6). In 1997, in Lithuania, in various age groups the contamination was different and increased with age: in 10–11-year-olds, antibodies against *H. pylori* were detected in 25%, in 12–13-year-olds in 44%, and in 14–15-year-olds in 55% of children (7). In Latvia, the prevalence of *H. pylori* in children was 19% in 2001, and seropositivity was higher in children with a positive parent (8).

The cytotoxin-associated gene (cagA) and the vacuolating cytotoxin (vacA) are *H. pylori* virulence factors that have been linked with more severe outcomes in patients with persistent infection (9). Overall data suggest that the distribution of genotypes of *H. pylori* strains in the Baltic States resembles that in Western Europe (7). In Lithuania, cagA was identified in 59.3% of Lithuanian *H. pylori* strains investigated. The cagA/vacA combination was present in 93.8% of all strains carrying the cagA (10). The prevalence of antibodies to the cagA protein in subjects seroreactive to *H. pylori* was 62% in Estonia in 2007 (6). In Latvian children, the presence of both cagA-positive and cagA-negative genotypes was identified in 11 of the 31 culture-positive patients tested (11).

Although the incidence of *H. pylori* infection is gradually declining, gastroenterologists face the problem of increasing resistance of *H. pylori* to antibiotics. Boyanova et al. evaluated the resistance of *H. pylori* to five antimicrobial agents in 10 Eastern European countries, and isolates from Lithuania exhibited relatively low resistance rates (12). We have not observed any significant changes in the susceptibility of *H. pylori* to the most widely used antibiotics during the recent 10-year period in Lithuania (data not published).

Primary resistance rates in 1998, 2001 and 2007–2008 for metronidazole were 24.7%, 33.3%, and 35.6% and for clarithromycin 1.1%, 3.7%, and 3.3%, respectively. No cases of amoxicillin resistance have been detected. The current research suggests that in the Baltic States the primary *H. pylori* resistance to metronidazole is considerable and that to clarithromycin is low; therefore, clarithromycin-based triple regimes remain to be the first line therapy for *H. pylori* eradication in the region.

**H. Pylori Induced Premalignant Gastric Conditions**

Gastric carcinogenesis is thought to be a multistep process involving a complex interplay between *H. pylori* infection, environmental and host genetic factors (9). Correa et al. (1) has suggested that *H. pylori* infection induces chronic inflammation of the gastric mucosa, leading to atrophic gastritis, intestinal metaplasia, and gastric carcinoma. Atrophic gastritis and intestinal metaplasia are considered to be the mandatory predisposing factors in intestinal-type gastric cancer, but the accumulating evidence suggests that atrophic gastritis and intestinal metaplasia are also associated with diffuse-type gastric cancer (13).

The high incidence of gastric atrophy and intestinal metaplasia in Lithuanian, Latvian and Estonian populations is the outcome of the high prevalence of *H. pylori* infection among adults in the Baltic States. Jonaitis et al. (4) compared the prevalence and severity of gastric atrophy and intestinal metaplasia in Lithuanian and Latvian patients vs. Taiwanese patients. Among *H. pylori*-infected subjects, atrophic gastritis was detected in 60.5% of Taiwanese patients, in 35.7% of Latvian patients, and in 52.2% of Lithuanian patients. Intestinal metaplasia was detected in 51.2% of Taiwanese, 33.0% of Latvian and 44.9% of Lithuanian patients. The results of the study indicate that the prevalence of gastric atrophy and intestinal metaplasia in the Baltic countries is higher as compared with the Western countries and resembles the frequencies observed in Asian populations, where the incidence of gastric cancer is still very high.

Gastric atrophy is diagnosed by the histological examination of biopsies taken during endoscopy. This approach, however, is associated with discomfort for patients and is costly in populations with a high prevalence of *H. pylori* infection. A novel approach to diagnosing atrophy from a blood sample is becoming increasingly recognized. A joined Lithuanian, Latvian and Taiwanese study aimed to validate the biomarker method for indirect detection of stomach mucosa atrophy versus standard histopathology in Caucasian and Asian populations (14). The study showed that pepsinogen I/II ratio <3 correlated with gastric atrophy in the corpus of the stomach with an 83.3% sensitivity.
and 87.1% specificity. The results of the study suggest that a decreased pepsinogen I/II ratio is a reliable marker for atrophy in the corpus, and it may be recommended for the identification of individuals with this type of atrophy.

**GASTRIC CANCER IN THE BALTIC STATES**

Over the last two decades, gastric cancer mortality has declined in all European countries. The fall was more than 50% in the West and Northern European countries, 45% in the Baltic States and 40% in Russia. In the Baltic countries, gastric cancer incidence in 2008 ranged between 23.0–20.8 per 100 000 in males and 10.7–9.3 per 100 000 in females (15) (Table). The incidence of gastric cancer was lower than in the neighboring countries Russia and Belarus, being, however, significantly higher than in Northern European countries. The incidence of gastric cancer in the Baltic countries was approximately half as low as in the highest incidence areas worldwide; however, the mortality rate was similar to respective data of these countries.

Cancer patients’ survival is strongly dependent on socioeconomic factors, including access to and quality of medical care. Aareleid and Brenner (16) assessed the trends in Estonia of cancer patients’ survival before and after the collapse of the Soviet Union. Despite a moderate increase in 5- and 10-year relative survival over time, the prognosis for stomach cancer remained considerably worse than it was in more developed European countries many years ago.

Levi et al. (17) evaluated the overall trends in cancer mortality in the European Union and accession countries. For stomach cancer, female rates were substantially higher in central and eastern European accession countries as compared with the West. They have concluded that most of the unfavourable patterns and trends in cancer mortality in East European countries are due to recognized, and therefore potentially avoidable, causes of cancer, including tobacco, alcohol, dietary habits, as well as inadequate screening, diagnosis and treatment.

The incidence of gastric cancer may vary even within the countries, depending on life-style and living conditions. There is some evidence from an epidemiological study in Lithuania that males in rural populations show a higher mortality from gastric cancer than in the urban areas (18). Dietary habits have been linked with gastric carcinogenesis in different studies; however, the data are partially conflicting. An epidemiological study in Lithuania found a higher risk of gastric cancer in subjects that like salty food (19). They also suggested that a higher consumption of raw vegetables may decrease the risk of gastric cancer (20).

**ASSOCIATION BETWEEN *H. pylori* AND GASTRIC CANCER IN THE BALTIC STATES**

In 1994, *H. pylori* infection was classified as a class I carcinogen involved in the development of gastric carcinoma. A meta-analysis that included 19 studies reported an odds ratio of 1.92 for gastric cancer in *H. pylori* positive subjects as compared to controls (2). Another review including 12 papers reported even higher odds ratios of 3.0–5.9 for *H. pylori* induced gastric cancer (21). Results of case-control studies conducted in the Baltic States confirm *H. pylori* as a risk factor of gastric cancer.

In a Lithuanian study (2005), seroprevalence of *H. pylori* in gastric cancer patients was significantly higher as compared to controls (77% versus 57%, p < 0.05). A gender-related difference in *H. pylori* prevalence was revealed among gastric cancer patients. A significant difference in the prevalence of *H. pylori* infection between gastric cancer patients and controls was found only in females. In males, no significant difference was revealed. The study suggested that *H. pylori* could be more important for the development of gastric cancer in females than in males, or males may be exposed to more confounding risk factors for gastric cancer than females. This study also showed that a combination of vacA and cagA antibodies was sig-

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Table. Gastric cancer incidence and mortality per 100 000 inhabitants in the Baltic Sea Region and areas with highest gastric cancer rates worldwide (GLOBOCAN, 2008)

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<td>Lithuania</td>
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<td>Belarus</td>
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<td>Russia</td>
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<td>Northern Europe</td>
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<td>Japan</td>
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<td>Korea</td>
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<td>China</td>
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nificantly more frequent in gastric cancer patients (88%) than in the control group (71%) (22). The same group of researchers has also shown that detection of *H. pylori* antibodies to 94- and 30-kDa bands, together with cagA and vacA antibodies, may have a predictive value for the risk of gastric cancer (23).

A significantly higher *H. pylori* seroprevalence was found in patients in the early stages of tumour development compared with both advanced cancer patients and controls in Estonia; however, no significant difference in *H. pylori* seroprevalence between patients with the intestinal and diffuse types of tumour growth was observed (24). A higher frequency of cagA antibodies was found in patients with gastric cancer and gastric atrophy as compared with controls in an Estonian adult population (25).

**MOLECULAR ALTERATIONS RELATED TO *H. PYLORI* INDUCED PREMALIGNANT CONDITIONS AND GASTRIC CARCINOGENESIS**

Gastric cancer is rarely diagnosed in early stages due to the lack of clinical signs in the early course of the disease. Therefore, the search for molecular markers that could be used to identify individuals at an increased risk of gastric cancer has been a priority for many research groups. Different genetic and epigenetic alterations have been identified and linked with gastric cancer; however, none of them has been transferred to daily clinical practice due to the lack of association strength. The only molecular marker that is currently available for the screening of gastric cancer is E-cadherin gene mutation, but it is relevant only in hereditary diffuse-type gastric carcinomas (26). Researchers in the Baltic countries have also studied different molecular pathways involved in stomach carcinogenesis, which provide additional valuable knowledge to our understanding of this complex disease.

A Latvian study assessed the molecular mechanism of Ca²⁺ binding protein NUCB2, which has been implicated in calcium homeostasis and TNF receptor shedding. They proposed that NUCB2 may be implicated in gastric secretion via heterotrimeric Gα protein proteins and mediating the exocytosis of secretory granules (27). The study by the same researchers evaluated the role of transforming acidic coiled-coil (TACC) proteins that are essential for the mitotic spindle function. They have suggested that certain isoforms of these proteins may represent genetic markers for gastric cancer and that an inappropriate expression of the isoforms in gastric cancer cells might result in TACC1 dysfunction thus contributing to genetic instability (28).

An Estonian study compared oxidative phosphorylation in the atrophic and nonatrophic gastric corpus mucosa. They found that corpus-predominant atrophic gastritis is characterized by a decreased respiratory capacity and relative deficiency of the respiratory complex I of mitochondria in the mucosa, the latter defect probably limiting mitochondrial ATP production and the energetic support of the secretory function of zymogenic mucosal cells (29). Many investigators have demonstrated alterations of gastric mucins in *H. pylori*-infected individuals. In gastric cancer patients, the Estonian researchers found a higher level of anti-MUC1 IgG than in blood donors, irrespective of *H. pylori* status or cancer stage (30). They have suggested that *H. pylori* infection may stimulate immune response to the tumour-associated MUC1 peptide antigen, thus modulating tumour immunity.

Certain genetic polymorphisms have been linked with the development of gastric carcinoma (31). Contradictory results have been reported concerning the role of interleukin-1B (IL1B) polymorphisms in gastric carcinogenesis. In Lithuanian and Latvian studies, IL1B polymorphisms were analyzed as genotypes and haplotypes in relation to the presence of atrophic gastritis and intestinal metaplasia in the stomach (32). Overall data have shown that none of the major four IL1B polymorphisms, both individually or in haplotype configuration, was linked to the presence of premalignant lesions in Caucasians and had no predictive value for the stratification of subgroups with respect to gastric cancer risk.

Aberrant methylation has been implicated in the development of gastric adenocarcinomas. Our data suggest that methylation is present in the majority of gastric adenocarcinomas and in the surrounding tumour-free area, indicating that this epigenetic change may indicate a field effect in the gastric mucosa (33).

**CONCLUSIONS**

The current prevalence of *H. pylori* infection and gastric cancer in the Baltic States resembles those in the West and Northern European countries several decades ago. The decline in stomach cancer incidence and mortality as well as *H. pylori* prevalence in the Baltic States reflects the worldwide trends. The reasons for the generalized decrease in gastric cancer rates are complex and not completely understood. Data from the Baltic States show a clear link between *H. pylori* infection and the development of gastric cancer. The data suggest that *H. pylori* could be more important for the development of gastric cancer in females than in males, or males may have more confounding risk factors for gastric cancer, such as alcohol or tobacco, than females. Researchers from the region have conducted valuable fundamental research in the field that provides additional information to our understanding of this complex problem. The steady decline in *H. pylori* incidence and gastric cancer mortality in the Baltic countries are likely to persist; however, the further monitoring of these trends is required. Improving
References


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the socioeconomic conditions and the application of new knowledge on cancer prevention, diagnosis and treatment may substantially reduce the prevalence of H. pylori infection and gastric cancer mortality in Lithuania, Latvia and Estonia in the long run.


