Microb Health Dis 2025; 7: e1179

Microbiota in Health and Disease
A Journal of the European Helicobacter & Microbiota Study Group

European Helicobacter & Microbiota Study Group

HELICOBACTER SPP. IN GASTROINTESTINAL ONCOLOGY

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Abstract – The discovery of *Helicobacter pylori* and subsequent research efforts have led to a fundamental change in our understanding of several gastric and extra-gastric diseases, including cancer.
Chronic *Helicobacter pylori* infection is an etiological factor in non-cardia gastric cancer and most cases of low-grade mucosa-associated lymphoid tissue (MALT) lymphoma. However, there is an inverse association of *Helicobacter pylori* infection with other gastric malignancies, such as esophageal adenocarcinoma, cardia gastric cancer, and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). The possible role of *Helicobacter* spp. in pancreatic and colorectal cancers has been a subject of intensive research. Indication for the eradication of *Helicobacter pylori* must now be considered with caution on an individual basis of personalized medicine.
This paper provides a thorough review of the relevance of *Helicobacter* spp. in esophageal adenocarcinoma, gastric cancer and lymphoma, hepatobiliary malignant tumors, pancreatic ductal adenocarcinoma, and intestinal malignancies. Environmental factors, gastrointestinal niches, and possible perspectives are also discussed.
In the face of the continuously decreasing chronic *Helicobacter pylori* infection worldwide, it is necessary to accept that this phenomenon has not yet been fully clarified. There may be fundamental changes of "modern times" that could be responsible for the gradual disappearance of *Helicobacter* spp. from the human microbiome.

Keywords: Cancer, *Helicobacter* spp., *Helicobacter pylori*, Gastrointestinal oncology, Microbiome.

INTRODUCTION

Helicobacter spp. are spiral-shaped, microaerophilic Gram-negative bacteria. The genus *Helicobacter* includes more than 35 species[1]. *Helicobacter pylori* of all *Helicobacter* spp. has been investigated in humans best and for the longest time (since 1982). It can be cul-

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tured, making it accessible for various experimental research as well. *Helicobacter pylori* strains harbor several virulence factors to secure long-lasting gastric colonization and possess various mechanisms to escape intense human immune response[2,3] (Figure 1). The best-characterized virulence factors are Cytotoxin-associated gene A (*cagA*) and Vacuolating cytotoxin A (vacA), causing host tissue damage. *Helicobacter pylori* subgroup I, characterized by *cagA+ vacA+* strains, is associated with increased pathogenicity, while subgroup II consists of *cagA*-negative *vacA*-negative strains. Almost all *vac*-s1 strains also carry *cagA*, whereas almost all *cagA*-negative strains harbor the less virulent genotype *vacA*-s2/m[2]. A single human can be simultaneously infected by both *cagA*-positive and *cagA*-negative *Helicobacter pylori*[2]. *CagA*-positive strains occur closer to the gastric mucosa, tolerating better low gastric pH and comprising more interactions with a host, including the production of antigen mimicry Lewis^x and Lewis^{y}[4]. Several other bacterial virulence genes have been described with variable clinical significance, e.g., genes encoding outer membrane proteins (babA2, oipA, homB, sabA)[2]. There are various mutual associations of particular virulence factors, e.g., *cagA* is more commonly detected in *babA2* positive strains[2].

A whole range of guidelines and recommendations on *Helicobacter pylori* have been published, some of which are listed in Table 1. However, there is great variability in the different guidelines on *Helicobacter pylori* infection and their key recommendations[5].

Helicobacter pylori has been one of the most common human chronic bacterial infections worldwide[3], despite a global trend of declining prevalence, from 58% (1980-1990) to 43% (in the 2011-2022 period)[6]. There is still an important difference in *Helicobacter pylori* prevalence between developed and developing countries. Data on the epidemiology of non-*Helicobacter-pylori* human *Helicobacter* infection are rather heterogenous[7,8].

The recognition of *Helicobacter pylori* as a new species was accomplished in April 1982[9-11]. Subsequent intensive research has fundamentally changed our understanding of several

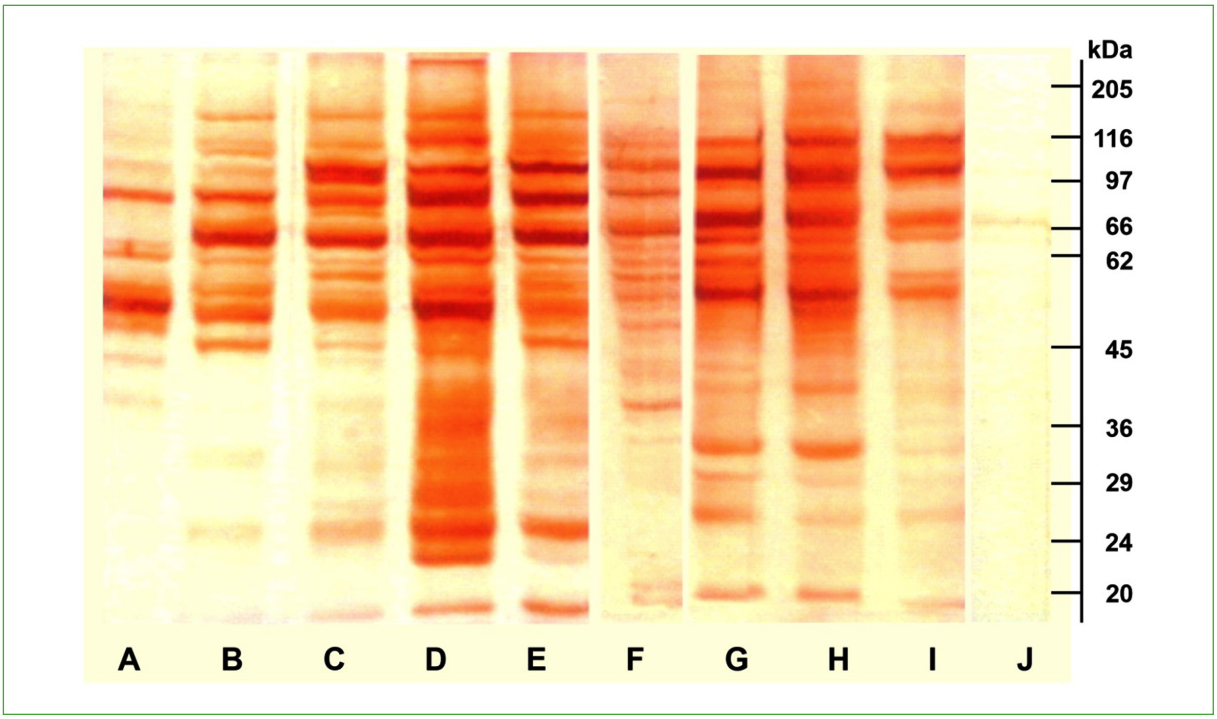

Figure 1. Serum Western blotting (immunoblot) analysis of IgG antibodies against *Helicobacter*-related proteins, e.g., CagA (120 kDa), VacA (87 kDa), BabA adhesin (78 kDa), heat-shock protein (66 kDa), UreaB (62 kDa) and UreaA (30 kDa). Samples taken from our own patients: A-C: *Helicobacter pylori* positive chronic active antral gastritis; D-E: *Helicobacter pylori* positive duodenal peptic ulcer; F: low-grade MALT-lymphoma of the stomach (with slightly increased serum ELISA IgG antibodies against *Helicobacter pylori*: 39.8 U/mL); G-H: previous Billroth II gastric resection for peptic ulcer disease; I: duodenal peptic ulcer with histologically proved *Helicobacter heilmanii*; J: negative control (subject without *Helicobacter pylori* infection). Courtesy of Jana Havlasova.

TABLE 1. GUIDELINES AND RECOMMENDATIONS ON *HELICOBACTER PYLORI*.

Global

- World Gastroenterology Organisation
  https://www.worldgastroenterology.org/guidelines/helicobacter-pylori
  https://pubmed.ncbi.nlm.nih.gov/36598803/
- European Society for paediatric Gastroenterology, Hepatology and Nutrition & North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
  https://www.naspghan.org/files/Joint_ESPGHAN_NASPGHAN_Guidelines_for_the.33.pdf
- Kyoto Global Consensus Conference
  https://pubmed.ncbi.nlm.nih.gov/26187502/

European

- Council of the European Union
  Improving Cancer Screening in the European Union. Science Advice for Policy by European Academies (SAPEA): Berlin, 2022. ISBN 978-3-9823562-0-4.
  https://scientificadvice.eu/advice/improving-cancer-screening-in-the-european-union/
- British Society of Gastroenterology
  https://www-ncbi-nlm-nih-gov.ezproxy.is.cuni.cz/pmc/articles/PMC6709778/pdf/gutjnl-2018-318126.pdf
- National Institute for Health and Care Excellence
  https://www.nice.org.uk/guidance/cg184
- The Maastricht / Florence Consensus Report
  https://pubmed.ncbi.nlm.nih.gov/35944925/
- German Society of Gastroenterology, Digestive and Metabolic Diseases
  https://register.awmf.org/assets/guidelines/021_D_Ges_fuer_Verdauungs-_und_Stoffwechselkrankheiten/021001eng_S2k_Helicobacter_pylori_and_gastroduodenal_ulcer_2023-09.pdf
- Italian Society of Gastroenterology & the Italian Society of Digestive Endoscopy
  https://pubmed.ncbi.nlm.nih.gov/35831212/
- Spanish Consensus Conference
  https://pubmed.ncbi.nlm.nih.gov/34629204/
- The Hellenic Society of Gastroenterology
  https://pubmed.ncbi.nlm.nih.gov/32127732/
- Belgian Consensus Report
  https://www.ageb.be/ageb-journal/ageb-volume/ageb-article/2081/
- Czech Gastroenterology Society
  https://www.cgs-cls.cz/wp-content/uploads/2015/04/guidelines-infekce-helicobacter-pylori.pdf
- Slovak Gastroenterology Society
  https://www.vpl.sk/files/file/hpfiles/SGSoptimiz_HP_II.pdf

US and Canadian

- American Gastroenterological Association
  https://gastro.org/clinical-guidance/management-of-refractory-helicobacter-pylori-infection/
- The Toronto Consensus
  https://www.cag-acg.org/images/publications/Hp_Toronto_Consensus_2016.pdf
- Houston Consensus Conference
  https://www.cghjournal.org/article/S1542-3565(18)30268-4/pdf

Asian

- The Japanese Society for Helicobacter Research
  https://onlinelibrary-wiley-com.ezproxy.is.cuni.cz/doi/full/10.1111/j.1523- 5378.2009.00738.x
- The Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition
  https://onlinelibrary-wiley-com.ezproxy.is.cuni.cz/doi/10.1111/ped.14388
- The Korean College of Helicobacter and Upper Gastrointestinal Research
  https://pubmed.ncbi.nlm.nih.gov/33468712/
- Chinese Society of Gastroenterology
  https://pubmed.ncbi.nlm.nih.gov/36579940/
- Indonesian Society of Gastroenterology
  https://www.actamedindones.org/index.php/ijim/article/view/594/261
- Vietnam Association of Gastroenterology
  https://pubmed.ncbi.nlm.nih.gov/36714104/
- Saudi Helicobacter pylori Working Group
  https://pubmed.ncbi.nlm.nih.gov/36204804/

CONTINUED

TABLE 1 *(CONTINUED)*. GUIDELINES AND RECOMMENDATIONS ON *HELICOBACTER PYLORI*.

Australian
• Royal Australian College of General Practitioners https://www.racgp.org.au/afp/2014/may/helicobacter-pylori-eradication
African
• Egyptian Association for Study of Gastrointestinal Diseases and Liver https://pubmed.ncbi.nlm.nih.gov/31564518/
South American
• Brazilian Consensus Conference https://pubmed.ncbi.nlm.nih.gov/30043876/

gastric and extragastric diseases, including cancer[12]. The first studies on the association between chronic *Helicobacter pylori* infection and gastric cancer were published in the early 1990s[13-16]. The World Health Organisation subsequently stated that *Helicobacter pylori* was a class I human carcinogen for gastric cancer in 1994[17]. An experimental model of *Helicobacter pylori*-induced gastric cancer was originally described in Mongolian gerbils[18]. This was followed by several murine models within the next two decades.

According to a PubMed search (accessed on 1 February 2025), there have been 17,494 records on "*Helicobacter* + cancer". Our goal was not to conduct meta-analyses given the considerable heterogeneity of the available studies. Instead, we aimed to offer a personal perspective while emphasizing and highlighting the current state of knowledge.

Microbiota in Gastrointestinal Malignancy

Gastrointestinal microbiota (not only bacteria but also archaea, viruses, protozoans, and fungi) and their dysbiosis play an important, wide-ranging role in the pathogenesis of gastrointestinal neoplasia[19-24]. These microbiota interact with a host in many aspects (especially immune and metabolic). Apart from others, there is also an important interplay between *Helicobacter* spp. and other gastrointestinal microbiota[20,23].

ESOPHAGUS

Esophageal Adenocarcinoma

The incidence of peptic ulcer disease and non-cardia gastric cancer has been decreasing in Western countries over decades, simultaneously with a decrease in *Helicobacter pylori* infection. In contrast, in the same countries, trends have been observed for increased incidence of gastresophageal reflux disease and adenocarcinoma of the esophagus[25].

In 1997, Labenz et al[26] suggested a hypothesis that *Helicobacter pylori* eradication can lead to gastroesophageal reflux disease. A subsequent meta-analysis of 24 studies showed a significant association between the absence of *Helicobacter pylori* infection and reflux symptoms and a positive association between anti-*Helicobacter pylori* therapy and the occurrence of both *de novo* and exacerbated gastroesophageal reflux disease[27]. These associations were supported by subsequent publications[28]. In a recent large prospective population-based cohort study including nearly 10 thousand subjects (with an average observation time of 14 years), the risk of esophageal adenocarcinoma was decreased by 35% in *Helicobacter pylori*-infected individuals[25].

Barrett's esophagus is a well-known complication of gastroesophageal reflux disease and a risk factor for esophageal adenocarcinoma[29]. Several studies (and subsequent meta-analy-

ses) clearly showed that patients with Barrett's esophagus had a significantly lower prevalence of *Helicobacter pylori* compared to those without this infection (odds ratio reduced overall up to 47%, decreased by 2/3 for dysplastic Barrett's esophagus and by 75% for a long-segment Barrett)[30,31].

While the incidence rates of many cancers have decreased in past decades, the incidence of esophageal adenocarcinoma continues to increase[32]. The only known precursor for esophageal adenocarcinoma is Barrett's esophagus[29]. The conducted studies have identified white race, male gender, gastroesophageal reflux disease, cigarette smoking, obesity, and the absence of *Helicobacter pylori* infection as risk factors for esophageal adenocarcinoma[33]. There was a significant inverse association between *Helicobacter pylori* infection and esophageal adenocarcinoma (pooled odds ratio 0.57). *CagA*-positive *Helicobacter pylori* strains were less likely to be associated with esophageal adenocarcinoma compared with *cagA*-negative strains (pooled odds ratio 0.64)[28]. According to a Swedish nationwide population-based cohort study (in 2005-2012; with 81,919 patients)[34], previous eradication of *Helicobacter pylori* infection was associated with an increased standardized incidence ratio for esophageal adenocarcinoma (OR 1.26). However, the standardized incidence ratio of esophageal spinocellular cancer was not influenced by eradication therapy[34]. A current study (Nordic *Helicobacter Pylori* Eradication Project) with more than 660 thousand participants (median follow-up 7.8 years) found no increased risk of esophageal adenocarcinoma after *Helicobacter pylori* eradication[35].

Spinocellular Cancer of the Esophagus

There is only sparse data on *Helicobacter pylori* in spinocellular (squamous cell) esophageal cancer[28]. Tobacco smoking and excessive alcohol use are the main risk factors for this type of cancer[33]. Chronic *Helicobacter pylori* infection does not substantially influence the risk and development of spinocellular esophageal cancer, either positively or negatively[35,36].

STOMACH

Sporadic Non-Cardia Gastric Cancer

According to the GLOBOCAN estimates, gastric cancer was the fifth most common malignant tumor in the world in 2022, with nearly 970 thousand new cases (two-fold higher in men than in women), causing 650,000 deaths a year[37]. The International Agency for Research on Cancer estimated that about one-third of all sporadic gastric cancers are solely attributed to chronic *Helicobacter pylori* infection, whereas non-cardia gastric cancer is associated with *Helicobacter pylo*ri in 70-90%[3,37].

Despite intensive research over decades, at least three major issues remain to be clarified: (a) detailed steps of the pathogenesis of gastric neoplasia; (b) the effect of early eradication of *Helicobacter pylori* on prevention of the subsequent development of gastric cancer ("point of no return" in tumor biology); and (c) the exact explanation of the negative association of *Helicobacter pylori* infection in duodenal peptic ulcer disease and cancer and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)[12].

The etiopathogenesis of sporadic non-cardia gastric adenocarcinoma is a complex, multistep process in which chronic *Helicobacter pylori* infection plays a crucial role, both in intestinal and diffuse types, as reviewed in our previous paper[12]. Various influences play a role, including bacterial virulence factors (particularly CagA, VacA), host response (cytokine polymorphism, neutrophil activation, epithelial responses, apoptotic pathways, cell-signaling), chronic atrophic gastritis, and environmental factors (including smoking and a diet high in salted, pickled, smoked, or poorly preserved foods)[12,38,39].

There has been a gradual decrease in the incidence of sporadic non-cardia gastric cancer in recent decades. This could be partly explained by the decreased prevalence of *Helicobacter pylori* infection, socioeconomic and dietary factors, decreased cigarette smoking, and environmental milieu[12]. For instance, based on two large cohort studies of unselected popu-

lations, the prevalence of *Helicobacter pylori* in adults in the Czech Republic decreased from 42% (2001) to 23.5% (2011)[40,41]. Within the same period, the incidence of gastric cancer in the Czech population decreased by 9%, from 17.9 (2001) to 15.6 per 100,000 population (2011), and the gross national product doubled[42]. It is important to highlight another interesting phenomenon: the decreased prevalence of *Helicobacter pylo*ri is represented by a prominent decline in *cagA*-positive *Helicobacter pylori* strains[43]. An explanation for this finding remains unclear.

It is still a matter of debate whether early eradication of *Helicobacter pylori* could prevent sporadic gastric cancer in the future[12,44,45]. Eradication of *Helicobacter pylori* can be followed by a complete reversal of chronic non-atrophic gastritis[39]. Prevention of further progression of superficial gastritis into atrophy can be associated with a decreased risk of development of premalignant lesions or even gastric cancer[12]. However, there is still an ongoing debate regarding the "point of no return," referring to the status of biological instability from which further progression of premalignant conditions into neoplasia cannot be prevented[12,39]. Cochrane Systematic Review[46] on *Helicobacter pylori* eradication of healthy asymptomatic subjects for the prevention of gastric neoplasia evaluated seven clinical trials (8,323 participants). The authors found moderate certainty evidence that searching for and eradicating *Helicobacter pylori* reduces the incidence of gastric cancer and death from gastric cancer in healthy asymptomatic infected Asian individuals, although data cannot necessarily be extrapolated to other populations[46]. However, non-cardia gastric cancer was described even after eradication. Early gastric cancer after *Helicobacter pylori* eradication was characterized by long-term use of proton pump inhibitors, moderate mucosal atrophy, mucosal map-like redness, a higher proportion of high-grade intraepithelial neoplasia, and lower levels of Ki-67[47].

One member of our group (SS) has been involved in a large prospective placebo-controlled study on *Helicobacter pylori* eradication to prevent gastric cancer in Linqu County (an underdeveloped rural region in Shandong Province, one of the areas with the highest incidence of gastric cancer in China)[48]. This Chinese-German-Czech Project started in 2011. A total of 180,284 eligible participants from 980 villages were enrolled over 12 years of follow-up, and a total of 1,035 cases of incident gastric cancer have been documented so far[48]. Final results on the possible change in gastric cancer incidence are expected by the end of 2026.

Patients with previous *Helicobacter pylori*-positive duodenal ulcers have a significantly lower subsequent risk of sporadic non-cardia gastric cancer (by 40%)[12]. This phenomenon can be explained, at least partly, by the genetic polymorphism of interleukin 1-b, polymorphism in HLA, TLR-4 (Toll-like receptor 4) signaling, and/or variations in a patient's age at the time of infection acquisition[49]. Diametrically opposed cytokine patterns were found in duodenal peptic ulcer disease (significantly higher gastric interleukin-12p70 and interferon-γ concentrations) compared to gastric cancer (with significantly higher interleukins IL-1β, IL-6, IL-17A, IL-23, and transforming growth factor β)[50]. A novel virulence factor *dupA* of *Helicobacter pylori* as an important risk determinant was proposed for duodenal ulcer development and reduced risk of gastric cancer[51].

In the early 1990's, Holcombe drew attention to the high prevalence of *Helicobacter pylori* infection in countries with low gastric cancer rates, which he called "The African Enigma"[52]. The so-called "African or Asian (Indian) Enigma" was explained merely by the high prevalence of helminth infections[52]. Subsequent prospective studies found that no such dissociation existed. The idea of these "Enigmas" is outdated based on more recent data[53]. Nevertheless, hygiene theories should be considered in the explanation of the gradual decline of *Helicobacter pylori* infection, at least in Western countries.

The possible role of non-*Helicobacter pylori* helicobacters in the pathogenesis of gastric cancer has been recently intensively investigated[54,55].

Cancer of the Gastric Cardia

The incidence of sporadic cardia gastric cancer has shown an alarming increase in recent decades. This subtype of adenocarcinoma differs biologically and epidemiologically from non-cardia gastric cancer, as well as adenocarcinoma involving the distal esophagus[56]. Smok-

ing, lifestyle, obesity, and environment are major risk factors[56]. Current evidence shows a heterogeneous distribution of etiologically distinct types of cardia cancer. Studies on Asian populations have revealed a higher positive association between *Helicobacter pylori* infection and gastric cardia adenocarcinoma, while some other studies of Western populations have reported no association or even an inverse association[56]. Meta-analysis of 12 studies (with 1,228 cases of gastric cancer) found that chronic *Helicobacter pylori* infection was not associated with an altered overall risk of cardia gastric cancer[57]. Another meta-analysis (of 34 articles) provided evidence for a positive association between cardia gastric cancer and *Helicobacter pylori* infection (RR 1.98 for high-risk subjects)[58].

Low-Grade MALT-Lymphoma of the Stomach

Lymphomas of the stomach are a rare (~3%) but important subgroup of gastric malignancies. Mucosa-associated lymphoid tissue (MALT) lymphoma is the most frequent (~2/3 of primary gastric lymphomas)[59]. Low-grade B-cell lymphomas of MALT are thought to arise within organized lymphoid tissue in the gastric mucosa and are most frequently acquired in response to acute or prior *Helicobacter pylori* infection (80-95%)[60]. This close association between this bacterium and lymphoma is further reflected by the demonstration that the proliferation of lymphoma cells can be driven by the presence of *Helicobacter pylori* through a complex path of cellular interactions involving specific T-cells[61].

The prevalence of *Helicobacter pylori* is indirectly proportional to the progression into the gastric wall. Mucosal and submucosal MALT lymphomas have a higher prevalence of these bacteria. However, genetic factors remain a risk factor, too, especially if eradication treatment fails. Based on a review of ten studies, it seems that infection with *cagA*-positive *Helicobacter pylori* strains does not have a meaningful effect on gastric MALT lymphoma formation, whereas translocated CagA antigen into the B-cells plays a crucial role in the development of diffuse large B-cell lymphoma[62].

Eradication therapy for this infection can be a highly effective treatment for these patients. Approximately 60-90% of cases with stage I/II disease achieve a complete histological response by successful *Helicobacter pylori* eradication[63]. The possible role of non-*Helicobacter pylori* gastric helicobacters in the pathogenesis of gastric MALT lymphoma has been intensively investigated in recent years[64]. Non-*Helicobacter pylori* cases of gastric MALT lymphomas may comprise 10-20%, including other *Helicobacter* spp. in 7%[65]. These cases are associated with a decreased alpha diversity of gastrointestinal microbiota. Host genetic factors are involved in the pathogenesis, and the clinical features are distinct[63]. Non-*Helicobacter pylori* helicobacters should be eradicated, regardless of the stage of disease[65].

Gastric MALT lymphoma is associated with a significantly increased risk of other synchronous or metachronous malignancies. The risk of gastric cancer is increased up to 16 times. A US population-based study, according to the SEER registry (1992-2012), reported 20/2,195 entries (1%)[66], and the PALGA registry from the Netherlands (1991-2006) noted 34/1,419 cases (2.5%)[67].

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a rare inherited disease with an autosomal dominant heredity (point mutation in promoter 1B of *APC* gene: c.-191 T>C)[68,69]. Worthley et al[68] described this new familial gastric polyposis syndrome in 2011 in three Caucasian families (American, Canadian, and Australian). Our group published the first family with GAPPS in Europe in 2016[69]. Only twelve papers with a total of 113 patients from 27 different families have been published worldwide so far[70].

Unlike in sporadic non-cardia gastric cancer, *Helicobacter pylori* is predominantly absent in GAPPS patients. We have reviewed an inverse association between GAPPS and *Helicobacter pylori* infection in our previous papers[69,71]. It is uncertain whether *Helicobacter pylori* could be a protective factor against progression to cancer in GAPPS or is just absent due to a disturbed intragastric milieu[68].

Liver and Biliary System

Helicobacter species may cause chronic inflammation of the biliary tract, but its causative relationship with hepato-biliary cancer is still controversial[72,73]. Both hepatocellular cancer (~85%) and intrahepatic cholangiocarcinoma (~15%) have multifactorial complex etiology, e.g., autoimmune and inherited diseases, hepatitis B and C (or other infections), lifestyle factors (alcohol, tobacco, diet), metabolic diseases (type 2 diabetes mellitus, obesity, non-alcoholic fatty liver disease) and others[74]. Numerous microbiological techniques for the detection of *Helicobacter* spp. in bile are available, such as polymerase chain reaction (PCR is the most sensitive, but perhaps not the most reliable due to possible positive false results), immunohistochemistry, ELISA (Enzyme-Linked ImmunoSorbent Assay), specific staining, and culture[73]. However, there is no gold standard, and these methods are not sufficiently comparable. The culture of most *Helicobacter* spp. is not feasible. PCR findings are neither proof of living bacteria nor do they clarify their place of origin (alternatively outside the biliary tract). ELISA lacks sufficient specificity due to a potential cross-reactivity between *Campylobacter* and *Helicobacter* species[73]. There is low-quality evidence from observational retrospective case-control studies, and some of them have been encumbered by bias and confoundings[73]. Nevertheless, a meta-analysis of 26 studies (4,083 subjects) showed patients with *Helicobacter* spp. infection had an increased risk of hepato-biliary tract malignancies (OR 3.6)[73].

Pancreas

Pancreatic cancer remains one of the most serious malignancies and a leading cause of cancer-related deaths worldwide[75]. According to the GLOBOCAN database, there were nearly 511 thousand new cases of pancreatic cancer worldwide in 2022 and 467,000 pancreatic cancer-related deaths a year[37]. According to the World Health Organization, the estimated number of new cases worldwide is predicted to rise by 70% between 2020 and 2040[75].

Apart from genetic factors (positive family history, underlying inherited diseases, genetic mutations) [75], major risk factors of pancreatic ductal adenocarcinoma comprise smoking, type 2 diabetes mellitus, obesity, dietary factors, alcohol abuse, higher age, ethnicity, non-O blood groups, chronic pancreatitis and some occupational factors (e.g., cadmium, arsenic)[76]. Long-term use of proton pump inhibitors, but not H2-receptor antagonists, is associated with a higher risk of pancreatic cancer, especially in younger subjects (< 40 years) with a history of *Helicobacter pylori* infection (standardized incidence ratio 2.99)[77].

The possible role of the microbiome in the development of pancreatic cancer has been intensively studied, too, including oral, duodenal, intrapancreatic, and fecal microbiota[78]. Gastric colonization with *Helicobacter pylori* is also associated with a greater risk of pancreatic cancer[76,79,80], with an estimated population attributable fraction of 4-25% (based on 117 meta-analytical or pooled reports, dealing with 37 etiological exposures)[79]. A population-based case-control study (373 pancreatic cancers and 690 controls) demonstrated an association between pancreatic cancer and *Helicobacter pylori*, particularly for individuals with non-O blood types[81]. Chronic *Helicobacter pylori* infection might enhance the pancreatic carcinogenic effect of *N*-nitrosamines conveyed by smoking or dietary sources. This effect is modulated by the host inflammatory response to bacteria, by various virulence properties of *Helicobacter pylori* itself, and by the host-bacteria interactions[76]. However, some other studies did not observe any correlation between chronic *Helicobacter pylori* infection and pancreatic cancer[82,83]. For instance, analysis of 9,506 subjects (Saarland Cancer Registry; average 10-year follow-up) found no association between *Helicobacter pylori* and pancreatic or colonic cancer, regardless of cagA seropositivity[82].

Other *Helicobacter* spp. (especially *Helicobacter bilis* and *Helicobacter hepaticus*) may also play a role in the etiology of pancreatic and biliary cancers[84].

Small Intestine

There are only sparse and inconsistent data on *Helicobacter* spp. in small intestinal lymphomas[85]. Non-ampullary duodenal adenocarcinoma can be associated with *Helicobacter* spp. infection[86].

Large Bowel

Colorectal cancer was the third most common malignant tumor in the world in 2022 (1,926-million incidence), with the second highest mortality (904 thousand deaths per year)[37]. Large intestinal microbiota and colonic dysbiosis play a causative role in the pathogenesis of sporadic colorectal neoplasia[19,87-90]. *Helicobacter pylori*-positive subjects have an increased risk for the development of colorectal adenoma (OR 1.3-2.3) and cancer (OR 1.5-1.7)[88-90], more expressed in women (40-80 years old)[88]. There are some geographic and ethnic differences: for instance, a higher risk in China was not observed in Korea[91].

Both experimental murine studies (APC mutant; germ-free animals) and human colonic tissue investigations showed a unique *Helicobacter pylori*-driven immune alteration signature characterized by a reduction in regulatory T-cells and pro-inflammatory T-lymphocytes[92]. *Helicobacter pylori* triggers pro-carcinogenic STAT3 signaling and a reduction in goblet cells. Combined with pro-inflammatory responses and mucus-degrading microbial signatures, these changes have been linked to tumor development. These changes were reversible by *Helicobacter pylori* eradication[92].

There is great debate about whether *Helicobacter pylori* eradication is indicated and effective in the prevention of colorectal neoplasia in clinical practice and how to overcome possible rigors[89,90]. A retrospective study of 615 patients (2006-2015) found that previous successful eradication of *Helicobacter pylori* significantly decreased the *de-novo* incidence of colorectal adenoma (52 cases/thousand per year) compared to subjects with persistent infection (161/thousand per year)[93]. A large Hong Kong population-based retrospective cohort study (96,572 subjects; 2003-2015; mean follow-up 10 years) observed a higher incidence of colorectal cancer in the first 5 years after eradication (SIR 1.47), but the incidence was lower compared to the general population after 11 years (SIR 0.85)[94]. There is as yet insufficient evidence to support a “test-and-treat” strategy for prevention of colorectal cancer. Based on current knowledge, eradication of *Helicobacter pylori* to prevent colorectal neoplasia should be reserved for clinical studies only.

Gastrointestinal Malignancies after *Helicobacter pylori* Eradication

Based on the Finnish National Prescription Registry, a cohort of 217,554 subjects with prescribed *Helicobacter pylori* eradication therapy (1994-2004) was analyzed[95]. In general, the overall risk for malignancy (including extragastrointestinal) was higher in individuals who had received eradication therapy for *Helicobacter pylori* compared to the general population of the same age. The peak of cancer diagnoses was during the first 6 months after eradication therapy. Awareness of possible underlying malignancies should be kept in mind, and simultaneous diagnostic work-up for malignancies should not be forgotten, even if *Helicobacter pylori* infection is detected and treated. *Helicobacter pylori* eradication therapy may delay the detection of malignancies possibly hidden by non-specific gastrointestinal symptoms[95].

Vaccines

Despite more than 40 years of research, no effective, feasible and safe vaccine against *Helicobacter pylori* has yet been developed[96,97]. Major vaccine issues are antigen selection, type of vaccines (whole bacteria, vector, subunit, nucleic acid or epitope vaccines), and suitable adjuvants[97]. The development of a safe and efficient vaccine would become an important measure to prevent *Helicobacter pylori* infection and *Helicobacter*-related cancer. A possible positive role for vaccines in the prevention of gastrointestinal malignancies remains unclear so far.

Shortcomings, Bias, and Confoundings

The possibility of bias and confoundings, which affect most clinical studies, must nevertheless be taken into account, especially for non-cardia gastric cancer: the absence of double-blind-

ed, placebo-controlled studies, bile reflux into the stomach (and/or the esophagus), age at the time of acquisition or eradication of *Helicobacter* infection, duration of subsequent follow-up, gender, different ethnicity, high-risk geographic areas and environmental factors, smoking, body weight, salt intake and other dietary factors, different socioeconomic status of particular classes of the population.

Different tests have been used for *Helicobacter* diagnostics, e.g., urea breath testing, serology, biopsy urease tests (at endoscopy), stool antigen assays, histology, bacterial culture, or methods of quantitative polymerase chain reaction (PCR)[98]. These methods are not fully comparable. Although the gold standard for *Helicobacter pylori* has been the ^{13}C-urea breath test, most population-based studies have used serology (anti-*Helicobacter* antibodies in sera or saliva). Serology does not reliably distinguish between active and past infection. Some subjects (~5-10%) remain seronegative despite actual chronic *Helicobacter* infection[98]. On the other hand, serological tests can overestimate the prevalence rate of *Helicobacter pylori* as some patients (up to 25%) do not return to seronegativity even years after successful eradication[40,98].

Perspectives

Niels Bohr, the Nobel Laureate in Physics in 1922, proclaimed “Prediction is very difficult, especially if it is about the future”[99].

It will be necessary to evaluate the possible negative role of *Helicobacter pylori* on the efficacy of oncology treatment. Current papers suggest that chronic *Helicobacter pylori* infection reduces the efficacy of cancer immunotherapy[100].

Further studies are needed to clarify in detail the mutual interaction of gastrointestinal microbiota, including *Helicobacter* spp., and host regulatory mechanisms in gastrointestinal oncology. By contrast, a possible beneficial role of *Helicobacter* spp. in a subgroup of the population should be addressed with respect to autoimmune diseases and the risk of associated malignancies.

Given the ongoing global decline in *Helicobacter pylori* prevalence, it is important to acknowledge with humility that the underlying reasons for this phenomenon remain unclear. Martin Blaser suggested years ago that there were fundamental determinants of “modern times” that could cause the gradual disappearance of *Helicobacter pylori* from the human microbiome[101].

CONCLUSIONS

There is a growing knowledge and awareness of the causative role of *Helicobacter* spp. in gastrointestinal oncology. Chronic *Helicobacter pylori* infection is an etiological factor in non-cardia gastric cancer and most cases of low-grade MALT lymphoma. However, there is an inverse association between *Helicobacter pylori* infection and other gastric malignancies. A possible role of *Helicobacter* spp. in pancreatic and colorectal cancers has been the subject of intensive research. Indication for the eradication of *Helicobacter pylori* must now be considered with caution on an individual basis of personalized medicine.

Conflict of Interest

The authors declare no competing interests.

Authors’ Contributions

J.B., D.K. and S.S. conceived the subject of the review. J.B., D.K. and S.S wrote the main manuscript text. J.B. designed the figure and the table. M.Z., B.V., O.N., R.P., O.M., P.U. and L.P. revised, edited and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by research projects DZVRO MO1012 and MH CZ - DRO (UHHK, 00179906).

Ethics Statement and Informed Consent

Not applicable.

AI Statement

No artificial intelligence has been used for this article.

Acknowledgments

The authors are grateful to Ian McColl, MD, PhD, for assistance with the manuscript.

Data availability

No datasets were generated or analyzed during the current study.

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