Microb Health Dis 2024; 6: e1029

GASTRIC CANCER – CLINICAL ASPECTS

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Abstract – In the year of the 40th anniversary of the official discovery of *H. pylori*, the association between the infection and gastric cancer has been further investigated and thoroughly reviewed. Articles on PubMed, published between April 2023 and March 2024 were reviewed and studies with a clear clinical focus were included in this review. Several authors presented an excellent overview of the trends of gastric cancer incidence and mortality over the last four decades. These include details on different subtypes of gastric cancer, the respective impact of *H. pylori* infection as well as factors that modulate regional differences of gastric cancer epidemiology. In line with the general decline of *H. pylori* prevalence, there is now also more focus on the features of *H. pylori* negative gastric cancer. Clinically, there was a shift of attention towards early detection and screening to allow diagnosis at a stage when curative, most often endoscopic, treatment is feasible. Similarly, with the proportion of early gastric cancers increasing, a precise assessment of the individual risk for meta-chronous lesions after endoscopic resection is of high importance to allow appropriate surveillance regimens. This includes studies on the impact of modifiable risk factors as well as the relevance of preneoplastic conditions at the time of treatment. While there are some new data on blood-based biomarkers, the field is somewhat stagnating. New interest has been sparked in the influence of the gastric microbiota on the effect of immunotherapy in the palliative setting, but the results are not yet conclusive.

Keywords: Gastric cancer, *Helicobacter pylori*, Metachronous cancer, Screening, Methylation.

INTRODUCTION

In the wake of last year's 40th anniversary of the official discovery of *Helicobacter pylori* (*H. pylori*) some fantastic data have been published summarizing the association of *H. pylori* with different subtypes of gastric cancer over several decades. This was put in context to distinct clinical settings, in particular early detection and screening as well as prevention of meta-chronous lesions after treatment of early gastric cancer and impact of the infection in palliative settings.

METHODS

I screened articles published on PubMed between April 1, 2023, and March 31, 2024. Entering the search terms 'gastric cancer' and '*Helicobacter pylori*' revealed 669 publications. All titles were assessed with a clinical focus on the link between *H. pylori* and gastric cancer, and 112 articles remained. Further, 76 articles were excluded as they represented letters, editorials, narrative reviews, or case reports, or these were studies with a focus on preneoplastic conditions or basic science in general. Finally, 36 articles were included in this review.

Epidemiological Aspects

Sharma et al[1] analyzed the epidemiological trends for gastric cancer between 1990 and 2019, retrieving data from 204 countries included in the 'Global Burden of Disease Study'. While the absolute number of gastric cancer cases and related deaths were increasing, the actual age-standardized incidence rate decreased by 30% (from 22.4 per 100,000 to 15.6 per 100,000), and the age-standardized mortality rate by 41% (from 20.5 per 100,000 to 11.9 per 100,000). The largest decline was seen between 2004 and 2016. The highest case numbers were recorded for China, India, and Japan, accounting for 61.5% of all cases worldwide, as well as 58.6% of deaths[1]. Chen et al[2] focused on the *H. pylori* prevalence and respective link to the gastric cancer incidence, analyzing 1748 articles on data from 111 countries in the period from 1980 to 2022. The crude *H. pylori* prevalence in adults declined from 52.6% (95%CI: 49.6%-55.6%) before 1990 to 43.6% (95%CI: 42.3%-45.5%) in 2015-2022. The prevalence in children and adolescents did not show a similarly declining trend and remained reasonably high at 35.1% (95%CI: 30.5%-40.1%). In regions where a decline in *H. pylori* prevalence was seen, this matched a reduction in gastric cancer incidence[2]. A Korean study looked into the association of *H. pylori* infection and gastric cancer incidence per birth cohort in the Korean national screening data[3]. Stratifying a cohort of n=2002 individuals in those naïve for *H. pylori*, those after treatment of the infection and those currently infected revealed the highest rate of naïve individuals in the group with a more recent year of birth. There were no gastric cancers in naïve individuals, but 1.9% in those after treatment and 2.5% in those infected[3]. A recent meta-analysis on the prevalence of gastric cancer in *H. pylori* positive people showed significant regional differences, with the highest rate occurring in Japan and the lowest in Sweden[4]. The above-mentioned effect of age and the respective birth cohort on the individual gastric cancer risk is further influenced by regional or national healthcare management pathways. In 2013, Japan introduced a scheme for general *H. pylori* eradication under the national health insurance system following the Kyoto consensus recommendations. This led to a decrease in gastric cancer deaths in the country but does not seem to affect individuals at the age of 80 years or older, in whom the gastric cancer incidence is still on the rise[5]. The respective age group represents 9% of the total population but comprises about half of all gastric cancer related deaths. There is an ongoing debate about the criteria to define an age cut-off for any screening or surveillance programs.

Several articles addressed the distribution of different subtypes of *H. pylori*-associated gastric cancer comparing populations form East and West. With regards to location of the tumor, most studies still refer to the terms 'cardia' and 'non-cardia gastric cancer'. Hence, these terms are also used in this article. A meta-analysis including 108 articles reported an odds ratio (OR) of 4.36 (95% CI: 3.54-5.37) for non-cardia gastric cancer in East Asia and or 4.03 (95% CI: 2.59-6.27) in the West[6]. Figures were even higher if a follow-up of affected patients for more than 10 years was recorded. There was a clear discrepancy for cardia cancer with a link confirmed in East Asia (OR 2.68; 95% CI: 2.26-3.63) but not in the West (OR 0.80; 95% CI: 0.61-1.05). Similar data was reported in a separate meta-analysis by Gu et al[7]. The authors confirmed once again that not only the follow-up period, i.e., the interval between the diagnosis of *H. pylori* and the detection of gastric cancer, but also the method of *H. pylori* testing has an impact on the outcome. It is stated that 79% of non-cardia gastric cancers in Asia and 87% in Europe and North America are attributable to *H. pylori*, as well as 62% of cardia cancers in Asia[7]. The retrospective analysis of a Californian population of 716,567 individuals who underwent *H. pylori* testing between 1997 and 2015 compared patients with successful treatment of the infection with those in which eradication was not complete[8]. The hazard ratio (HR) for non-cardia gastric cancer in those without successful treatment was 6.07 (95% CI: 4.20-8.76) compared to those who tested negative. However, even after successful treatment, the risk was increased (HR 2.68; 95% CI: 1.86-3.86). The HR decreased for those after successful eradication in correlation with the length of follow-up, with the highest effect seen after 10 years or more (HR 0.51; 95% CI: 0.38-0.68). On the other side, *H. pylori* eradication does not seem to have an effect on the stage of gastric cancer when detected in a screening population[9]. However, risk features of the gastric mucosa in patients with early gastric cancer are less pronounced in individuals after *H. pylori* eradication, including the local microbiota composition[10,11].

In line with the decline of *H. pylori* prevalence, there are also more studies focusing on the features of *H. pylori*-negative gastric cancer[12]. A Japanese multicenter cohort of n=966 consecutive patients with either dysplasia or gastric cancer demonstrated that those with *H. pylori* negative lesions were younger (59.5 years vs 71.8 years; $p<0.05$), more likely to be female (40.0% vs 26.5%;

$p<0.05$), and the tumors of more proximal location, of smaller size and less invasive[13]. He et al[14] made predictions on the impact of other modifiable risk factors on the gastric cancer incidence towards 2050. While the authors predict an overall decrease of the gastric cancer incidence by 10.57% due to a decline of not only the *H. pylori* prevalence but also the use and intake of tobacco smoking[15], alcohol and pickled vegetables, more than 70% of gastric cancers will still remain attributable to modifiable risk factors. Among these, *H. pylori* infection will remain the key factor for 62.1% of non-cardia and 40.7% of cardia gastric cancers[14]. Metabolic diseases will be more of a dominating factor in the future[14,16].

Considerations Regarding Screening and Early Detection

While population-based screening for gastric cancer is not cost-effective and hence not feasible in low- to moderate-risk populations, surveillance of individuals with preneoplastic risk conditions is now more established also in the West. Kobayashi et al[17] presented retrospective data on a surveillance cohort of patients after *H. pylori* eradication, comparing those with gastric cancer within ten years after eradication to those in whom the cancer was diagnosed more than ten years after treatment. The prevalence of gastric glandular atrophy was similar between both groups, with about 50% of the patients presenting with severe atrophy. Patients with a cancer diagnosed later presented with more advanced stage and more often with tumors of the less differentiated type. In line with these data, an American group reported that there is a significantly lower likelihood of death from gastric cancer in those patients who were tested for *H. pylori* prior to any diagnosis (HR 0.22; 95% CI: 0.22-0.96)[18].

When it comes to screening and early detection, there is ongoing debate on the best strategy and test modality applied to the respective local population. Kusano et al[19] compared annual radiography by barium scan followed by targeted endoscopy in those with positive scan results versus endoscopic screening of individuals testing positive by serology (applying the ABC method testing for serum pepsinogens and *H. pylori* serology). A total of 1,206 individuals were randomized to either barium scan or different endoscopy screening regimens. Within five years of follow-up, 24 gastric cancers were found, 2.0% of the barium scan cohort and 1.8% of the serology plus endoscopy cohort. While the gastric cancer detection rates were similar, the proportion of early cancers that were curable by endoscopic resection was significantly higher in the endoscopy group (90.9% *vs.* 41.6%)[19]. Unfortunately, the cost-effectiveness study linked to this project focused on costs per cancer detected, which were significantly higher for the endoscopy group, so further extension of this trial to substantiate the data was rejected by the funders[20]. Huang et al[21] published data from a single-center case-control cohort in China assessing risk factors for early gastric cancer in a surveillance setting. A history of *H. pylori* infection, as well as a positive family history of gastric cancer, were confirmed as independent risk factors. With regards to the assessment of preneoplastic conditions, OLGIM staging performed more consistently than OLGA staging, but for both options, a clear risk association was already documented for stage II (OLGA: OR 2.52; OLGIM; OR 4.11)[21]. A study from Spain demonstrated that *H. pylori* remains an independent risk factor even in a cohort of familial intestinal gastric cancer (OR 6.4; 95% CI: 1.36-30.6)[22].

Follow-up After Endoscopic Resection of Early Gastric Cancer

Most of the data on the prognostic impact of *H. pylori* eradication in patients who underwent endoscopic resection for early gastric cancer or dysplasia originates from the East. A meta-analysis on the data from 9 cohort studies (n=2755 patients) did not conclude that there is an effect on the incidence of meta-chronous lesions by *H. pylori* eradication[23]. Interestingly, the authors report data confirming a risk increase in this setting for patients with atrophy or intestinal metaplasia (IM) in the gastric antrum only (Atrophy: RR 2.0, 95% CI: 1.35-2.98; IM: RR 7.08, 95% CI: 3.63-13.80), which is usually considered to be of negligible risk[23]. In contrast, data from the Korean National Insurance database suggest a lower risk for meta-chronous gastric cancer for patients treated endoscopically for gastric dysplasia (n=69,722; 2010-2020) who received treatment for *H. pylori* infection (49.5%)[24]. The adjusted HR for meta-chronous neoplasia was 0.76 (95% CI: 0.70-0.82) during a median follow-up period of 5.6 years. Lee et al[25] demonstrated that the cumulative incidence of meta-chronous gastric cancer increased with the age of the patient at the time of eradication (<50 years old: 2.1%, 50-59 years

old: 7.0%, 60-69 years old: 8.7%, >70 years old: 16.7%; $p<0.001$). The HR for meta-chronous gastric cancer was significantly raised for patients older than 60 years and highest for the oldest age group (HR 10.75; 95% CI: 2.45-47.12). The effect remained when the results were adjusted for the presence of IM, with age >60 years representing an independent risk factor[25]. A multicenter prospective cohort study from Japan on patients undergoing ESD for early gastric cancer (n=850; 2016-2019) reported that a positive smoking history (OR 1.93) and severe atrophic gastritis (as assessed by serology; OR 1.92) are significant risk factors for prevalent synchronous gastric cancer in a multivariate analysis[26]. Interestingly, as assessed by serum pepsinogen levels, atrophy remains a risk factor in patients who did not receive any *H. pylori* treatment but not in those who underwent eradication. Gong et al[27] used again data from the Korean National Insurance database to analyze the impact of PPI use on those who had received *H. pylori* treatment and endoscopic resection of early gastric neoplasia. The study included data from 1,836 PPI users and 12,218 non-users treated between 2009 and 2014, with a median follow-up period of 7.3 years. The risk for meta-chronous gastric cancer was more than five-fold higher in PPI users (adjusted HR 5.51; 95% CI: 5.12-5.92).

Independent from the prognostic impact, early *H. pylori* eradication can also yield further beneficial clinical effects. In a small prospective, randomized, investigator-blinded trial, Yan et al[28] demonstrated that precise delineation of neoplastic lesions for endoscopic resection is significantly more feasible in patients who underwent *H. pylori* eradication (40.0% *vs.* 7.4%; RR 5.4, 95% CI: 1.31-22.28).

Additional Risk Factors and Further Oncological Aspects

The body of literature on genetic and epigenetic risk factors continues to increase. A comprehensive study of 10,426 gastric cancer patients and 38,153 controls from the Biobank Japan analyzed the association of germline variants of 27 cancer-predisposing genes with the individual gastric cancer risk[29]. A relevant risk increase was confirmed for 9 key genes, including *APC, ATM, BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2*. Some studies investigated the association of the methylation status of genes reported to be associated with *H. pylori* infection and gastric cancer risk and specific clinical factors, as well as factors that mainly affect *H. pylori* negative patients[30,31]. The general methylation status of the gastric mucosa, as assessed on biopsies, was shown to be associated with a higher risk for gastric neoplasia and a shorter duration to develop these changes[32]. This was positively associated with the *H. pylori* status. Another interesting study revealed promising diagnostic properties of the methylation profile of circulating free DNA molecules in combination with *H. pylori* serology as a blood-based biomarker[33]. In addition to this, there are also new data on polymorphisms in genes related to the individual immune response[34].

There is an increasing interest in the effect of the gastrointestinal microbiota on the efficacy of immunotherapy of cancers. A study from the United States included 215 gastric cancer patients retrospectively that have been treated with immunotherapy between 2013-2021[35]. Of these, 49 patients were documented as *H. pylori* positive[35]. In this cohort, *H. pylori* infection represented an independent negative predictor with shorter progression-free survival (PFS: 3.2 *vs.* 6.8 months; HR 1.96; $p<0.01$) and overall survival (OS: 9.8 *vs.* 17.9 months; HR 1.54; $p=0.02$). Another study from China revealed different results. Jia et al[36] included patients undergoing immunotherapy for gastrointestinal cancers that also underwent a ^{13}C-urea breath test to confirm *H. pylori* status. While patients with colorectal and esophageal cancer showed similar results to the US study, mainly with shorter PFS, this was not the case for patients with gastric cancer in this cohort. *H. pylori* positive gastric cancer patients showed a longer PFS on immunotherapy (6.97 *vs.* 5.03 months; HR 0.76, 95% CI: 0.62-0.95; $p<0.001$) and a trend towards longer OS. It was stated that this might be attributable to *H. pylori* positive patients presenting with higher densities of PD-L1 positive cells and non-exhausted T-cell populations resulting in a hot tumor microenvironment[36].

CONCLUSIONS

The general decline of the global *H. pylori* prevalence during the past 4 decades is now also reflected in a decrease in gastric cancer incidence, although the effect is less pronounced than expected. There are multiple additional modifiable risk factors that need to be considered in the multifactorial

etiology of the disease, and a strong focus is still needed on early detection as well as prevention. There is also a better understanding of *H. pylori* negative gastric cancers and how the population at risk needs to be targeted. For both primary and tertiary prevention, i.e., tackling the problem of meta-chronous neoplasia after curative treatment, timing of preventive measures (mainly *H. pylori* eradication) has been highlighted as a key issue. The question at which time-point the intervention results in the greatest impact has not been conclusively elucidating but it seems to come back to the simple rule of thumb 'the earlier the better'. In the meantime, the search for reliable non-invasive as well as tissue-based diagnostic and prognostic biomarkers remains a task that has yet to be resolved.

Conflict of Interest

JB has no conflict of interest with regard to the content of this manuscript.

Authors' Contribution

JB is the sole author of this manuscript.

Funding

JB is supported by the UK Medical Research Council in context of the Clinical Academic Research Partnership (MRC CARP) scheme (Grant ref.: MR/W029960/1).

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Ethics Statement

Not applicable due to the type of study.

AI Statement

No artificial intelligence has been used for this article.

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