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Association between *Helicobacter pylori* and its eradication and the development of cancer

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ABSTRACT

Background *Helicobacter pylori* (*H. pylori*) is a gram-negative gastrointestinal pathogen that colonises the human stomach and is considered a major risk factor for gastric cancer and mucosa-associated lymphoid tissue lymphoma. Furthermore, *H. pylori* is a potential trigger of a wide spectrum of extragastric cancer entities, extraintestinal chronic inflammatory processes and autoimmune diseases. In the present study, we evaluated the association between *H. pylori* infection and its eradication with the development of subsequent gastrointestinal and non-gastrointestinal cancer.

Methods We identified 25 317 individuals with and 25 317 matched individuals without a diagnosis of *H. pylori* from the Disease Analyzer database (IQVIA). A subsequent cancer diagnosis was analysed using Kaplan-Meier and conditional Cox-regression analysis as a function of *H. pylori* and its eradication.

Results After 10 years of follow-up, 12.8% of the *H. pylori* cohort and 11.8% of the non-*H. pylori* cohort were diagnosed with cancer (p=0.002). Results were confirmed in regression analysis (HR: 1.11; 95% CI 1.04 to 1.18). Moreover, a non-eradicated *H. pylori* status (HR: 1.18; 95% CI 1.07 to 1.30) but not an eradicated *H. pylori* status (HR: 1.06; 95% CI 0.97 to 1.15) was associated with a subsequent diagnosis of cancer. In subgroup analyses, *H. pylori* eradication was negatively associated with bronchus and lung cancer (HR: 0.60; 95% CI 0.44 to 0.83).

Conclusion Our data from a large outpatient cohort in Germany reveal a distinct association between *H. pylori* infection and the subsequent development of cancer. These data might help to identify patients at risk and support eradication strategies in the future.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While the role of *H. pylori* infection in gastric cancer and primarily intestinal diseases is obvious, extraintestinal diseases from *H. pylori*, for example, cancer, and the potential role of *H. pylori* eradication remain a matter of debate.

WHAT THIS STUDY ADDS

⇒ Our study reveals the impact of *H. pylori* infection on extraintestinal cancer prevalence as well as the role of *H. pylori* eradication for bronchus and lung cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study may help to identify patients at risk for extraintestinal cancer related to *H. pylori* infection as well as to identify patients who will benefit from *H. pylori* eradication therapy.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a common human-to-human transmitted (usually fecal-oral or oral-oral) gram-negative spiral-shaped bacterium that persists in the stomach, with approximately 50% of the world's population infected.[1] The individual risk for an *H. pylori* infection depends on numerous factors, above all on geographic and ethnic affiliation, socioeconomic status, higher age and lower hygiene conditions. Germany belongs worldwide and within Europe to the countries with comparatively low *H. pylori* prevalence rate of 20%–40%.[2 3] *H. pylori* plays a major role in the pathogenesis of chronic gastritis, peptic ulceration and malignant diseases, for example, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.[4 5] It has been classified as a class 1 carcinogen since 1994.[6–8] *H. pylori* risk is associated with a host-dependent genetic predisposition to carcinogenesis and intrinsic *H. pylori* virulence factors (eg, cytotoxin-associated gene A (CagA) antigen-producing strains).[9–13] On the other hand, the effect of *H. pylori* eradication in gastric cancer (GC), as well as the influence of *H. pylori* in the development of extra gastric non-malignant diseases (eg, autoimmune, cardiovascular) and malignant diseases (eg, cancer of the lungs, pancreas, and colon), are still controversial.[8 14] The long-term *H. pylori*-triggered immune and inflammatory responses are postulated as the main underlying mechanisms for extradigestive pathologies.[15]

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In the present study, we evaluated the association between *H. pylori* infection and its eradication with the development of subsequent gastrointestinal (GI) and non-GI cancer over a long observational period of 10 years for the individual cases in Germany, the most populous country in the European Union.

MATERIALS AND METHODS

Database

This retrospective cohort study was based on data from the Disease Analyzer database (IQVIA), which contains drug prescriptions, diagnoses and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists.[16] The database covers approximately 3% of all medical practices in Germany. The sampling method for the Disease Analyzer database is based on summary statistics from all doctors in Germany published yearly by the German Medical Association. IQVIA uses these statistics to determine the panel design according to the four strata, including specialist group, German federal state, community size category and age of physician. It has previously been shown that the panel of practices included in the Disease Analyzer database is representative of general and specialised practices in Germany.[16] Finally, this database has already been used in previous studies focusing on cancer.[17 18]

Study population

This study included adult patients (≥18 years) with an initial diagnosis of *H. pylori* infection in 1284 general practices in Germany between January 2005 and December 2021 (index date; figure 1). As physicians used different codes of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, Version 10) to code *H. pylori*, we used original diagnosis text to identify *H. pylori* patients. Further inclusion criteria were an observation time of at least 12 months before the index date and a follow-up time of at least 6 months after the index date. Patients with a diagnosis of cancer (ICD-10: C00–C97), in situ neoplasms (ICD-10: D00–D09) and neoplasms of uncertain or unknown behaviour diagnoses (ICD-10: D37–D48) before the index date, on the index date or within 3 months after the index date were excluded.

After applying similar inclusion criteria, individuals without *H. pylori* were matched to *H. pylori* patients based on age, sex, index year, average yearly consultation frequency during follow-up and Charlson Comorbidity Score using propensity score matching (1:1). The Charlson index is a weighted index that accounts for the number and severity of comorbidities in administrative database studies and includes a wide range of comorbidities (macrovascular diseases, pulmonary diseases, GI, liver, and renal diseases, diabetes, AIDS and others).[19] For the cohort without *H. pylori*, the index date was a randomly selected visit between January 2005 and December 2021 (figure 1).

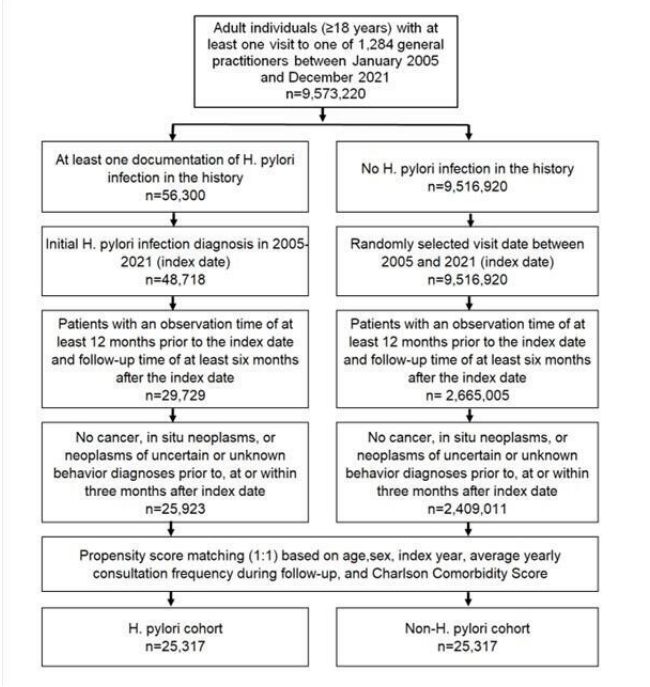

Figure 1 Selection of study patients.

Study outcomes

The outcomes of the study were the initial diagnoses of cancer in total (ICD-10: C00–C97) as well as GI cancers, including oesophagus (ICD-10: C15), stomach (ICD-10: C16), colorectal (ICD-10: C18, C20), liver (ICD-10: C22) and pancreatic (ICD-10: C25) cancer and respiratory cancers including the larynx (ICD.10: C32), bronchus and lung (ICD-10: C34) cancer within up to 10 years following the index date as a function of *H. pylori*. The *H. pylori* cohort was then divided into two subgroups depending on the prescription of an eradication therapy between the index date and 2 months after the index date to analyse both eradicated and non-eradicated *H. pylori* patients compared with patients without *H. pylori* in terms of a subsequent cancer diagnosis.

Statistical analyses

Differences in baseline characteristics and the prevalence of diagnosis between the cohorts with and without *H. pylori* were compared using the Wilcoxon signed-rank test for continuous variables, the McNemar test for categorical variables with two categories and the Stuart-Maxwell test for categorical variables with more than two categories. The 10-year cumulative incidence of cancer in the cohort with *H. pylori* with or without eradication versus the cohort without *H. pylori* was further studied with Kaplan-Meier curves. Curves were compared using the log-rank test. Patients were censored at the time of loss to follow-up (last visit to physician), last date in the database (31 January 2022), or cancer diagnosis, whichever occurred first. The average follow-up time was 5.9 (SD: 3.8) years. Finally, an univariable conditional Cox

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Table 1 Baseline characteristics of the study sample (after 1:1 matching)

Variable	Proportion among patients with *H. pylori* (N, %), n=25317	Proportion among patients without *H. pylori* (N, %), n=25317	P value
Age (mean, SD)	53.2 (15.8)	53.2 (15.8)	0.453
Age 18–30	5805 (22.9)	5814 (23.0)	1.000
Age 31–40	5115 (20.2)	5115 (20.2)	
Age 41–50	5839 (23.1)	5840 (23.1)	
Age 51–60	4492 (17.7)	4491 (17.7)	
Age >60	4065 (16.1)	4057 (16.0)	
Female	14741 (58.2)	14733 (58.2)	0.943
Male	10576 (41.8)	10584 (41.8)	
Number of physician visits per year during the follow-up (mean, SD)	7.5 (3.8)	7.5 (3.8)	0.969
Charlson Comorbidity Score (CCS)	2.0 (1.8)	2.0 (1.8)	0.992
CCS 0	5130 (20.3)	5130 (20.3)	1.000
CCS 1	6699 (26.5)	6701 (26.5)	
CCS 2	5322 (21.0)	5322 (21.0)	
CCS 3	3715 (14.7)	3713 (14.7)	
CCS>3	4451 (17.6)	4451 (17.6)	
Index year 2005–2008	3078 (12.2)	3081 (12.2)	1.000
Index year 2009–2012	4783 (18.9)	4777 (18.9)	
Index year 2013–2016	8414 (33.2)	8414 (33.2)	
Index year 2017–2021	9042 (35.7)	9045 (35.7)	

Proportions of patients given in N and % unless otherwise indicated.

regression analysis was performed to assess the association between *H. pylori* and its eradication and cancer in total, as well as GI and respiratory cancers. Results of the Cox regression model are displayed as HRs and 95% CIs. A p value of p<0.01 was considered statistically significant due to multiple comparisons. Analyses were conducted using SAS V.9.4 (SAS Institute).

Patient and public involvement

This study included adult patients (≥18 years) with an initial diagnosis of *H. pylori* infection in general practices in Germany between January 2005 and December 2021. The database used for this study analysis contains anonymised electronic patient records. Patient data were analysed in aggregated form without individual data being available. Participant consent was waived because this was a retrospective study, and data were anonymised entirely.

RESULTS

Baseline characteristics of the study cohort

The present study included 25317 *H. pylori*-positive individuals, and 25317 matched individuals without a diagnosis of *H. pylori*. Of those diagnosed with *H. pylori*, 13737 received eradication therapy from their general practitioner (GP) within 2 months of the index date. Baseline characteristics of the study patients are displayed in table 1. The mean age was 53.2 (SD: 15.8), and 58.2% were female. Patients had an average of 7.5 GP visits per year during follow-up. Baseline characteristics of *H. pylori* patients with and without eradication therapy are shown in the online supplemental table S1.

Association of *H. pylori* and a subsequent cancer diagnosis

After up to 10 years of follow-up, 12.8% of the *H. pylori* cohort and 11.8% of the non-*H. pylori* cohort were diagnosed with cancer (p=0.002, figure 2). Based on the power analysis, with absolute patient samples and event

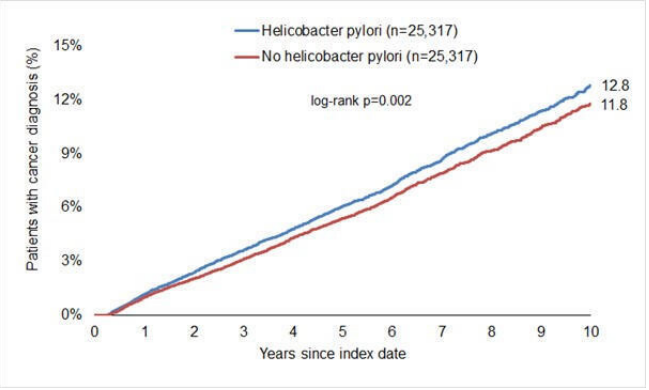

Figure 2 Cumulative incidence of cancer in patients with and without *H. pylori*.

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Table 2 Association between *H. pylori* and subsequent gastrointestinal and respiratory cancer diagnosis in patients followed in general practices in Germany (univariable Cox regression models)

	HR for *H. pylori* versus no *H. pylori*		HR for *H. pylori* with eradication versus no *H. pylori*		HR for *H. pylori* without eradication versus no *H. pylori*	
Outcome diagnosis	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cancer total	**1.11 (1.04 to 1.18)**	**0.002**	1.06 (0.97 to 1.15)	0.232	**1.18 (1.07 to 1.30)**	**<0.001**
Oesophagus	0.49 (0.26 to 0.89)	0.020	0.52 (0.22 to 1.23)	0.137	0.45 (0.19 to 1.07)	0.072
Stomach	1.59 (1.00 to 2.53)	0.049	1.48 (0.78 to 2.83)	0.224	1.70 (0.87 to 3.32)	0.118
Colon and rectum	0.99 (0.78 to 1.26)	0.941	0.98 (0.72 to 1.32)	0.877	1.02 (0.68 to 1.54)	0.910
Liver	0.75 (0.41 to 1.36)	0.339	0.69 (0.30 to 1.58)	0.380	0.82 (0.35 to 1.93)	0.649
Pancreas	1.46 (0.99 to 2.17)	0.058	1.77 (1.01 to 3.12)	0.048	1.21 (0.70 to 2.09)	0.498
Larynx	1.06 (0.51 to 2.20)	0.885	0.87 (0.28 to 2.70)	0.804	1.21 (0.46 to 3.18)	0.704
Bronchus and lung	0.88 (0.69 to 1.11)	0.278	**0.60 (0.44 to 0.83)**	**0.002**	1.51 (1.03 to 2.20)	0.035

rates, the estimated statistical power was 0.99. In the regression analysis, there was a small but significant association between *H. pylori* and a subsequent cancer diagnosis (HR: 1.11; 95% CI 1.04 to 1.18, p=0.002, table 2). In the stratified analyses by cancer type, there was a strong but not significant association between *H. pylori* and stomach cancer (HR: 1.59; 95% CI 1.00 to 2.53, p=0.049) and for pancreatic cancer (HR: 1.46; 95% CI 0.99 to 2.17, p=0.058, table 2).

The role of *H. pylori* eradication therapy

Figure 3 and online supplemental table S2 show the cumulative incidence of cancer in eradicated and non-eradicated patients with *H. pylori* compared with patients without *H. pylori*. There was a significant difference between non-eradicated patients with *H. pylori* and patients without *H. pylori* (13.2% vs 11.8%, p<0.001), but no significant difference between eradicated patients with *H. pylori* and patients without *H. pylori* (12.5% vs 11.8%, p=0.231). In regression analyses, a non-eradicated *H. pylori* status (HR: 1.18; 95% CI 1.07 to 1.30) but not an eradicated *H. pylori* status (HR: 1.06; 95% CI 0.97 to 1.15) was associated with a subsequent diagnosis of cancer (table 2). In subgroup analyses, the only cancer entity with a significant effect of *H. pylori* eradication was bronchus and lung cancer. Here, *H. pylori* eradication

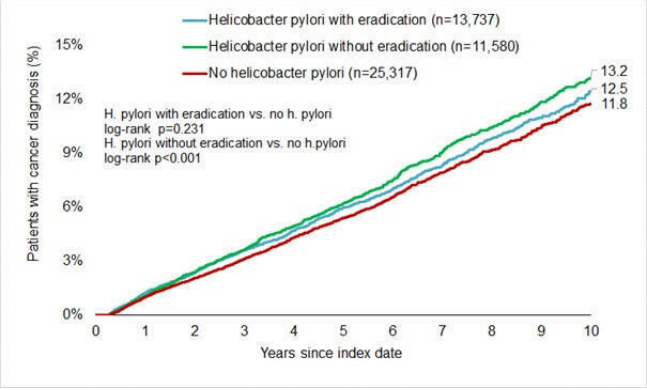

Figure 3 Cumulative incidence of cancer in patients with and without *H. pylori* depending on eradication therapy.

was negatively associated with cancer of the bronchus and lung (HR: 0.60; 95% CI 0.44 to 0.83), and there was a strong trend towards an association between non-eradicated *H. pylori* and subsequent cancer of the bronchus and lung (p=0.035, table 2).

DISCUSSION

H. pylori has been classified as a group 1 carcinogen since 1994, with an uncontroversial role in GC and MALT lymphoma.[6–8] On the other hand, the effect of *H. pylori* eradication in GC and the influence of *H. pylori* in the development of extra gastric non-malignant (eg, autoimmune, cardiovascular) and other malignant diseases (eg, cancer of the lungs, pancreas, and colon) is still a matter of debate.[8 14] In the present primary care study, we evaluated the association between *H. pylori* infection and its eradication with the development of subsequent GI and non-GI cancer over a long observational period in Germany.

Study cohort and *H. pylori* eradication

We included 25 317 *H. pylori*-positive individuals, and 25 317 matched individuals without a diagnosis of *H. pylori* (figure 1). The mean age in our study was 53.2 (SD: 15.8) years and 58.2% were female (table 1). Worldwide data suggest a slightly higher prevalence of *H. pylori* in males.[20] The higher rate of females in our study remains unclear. However, this may reflect the higher adherence of female patients to primary care and the higher number of females in the general population in Germany (50.7 vs 49.3%).[21] Patients had an average of 7.5 GP visits per year during follow-up, which is approximately in line with current data in the general German population (average of 10 visits/year).[22] Of those individuals diagnosed with *H. pylori*, 13 737 (54.3%) received eradication therapy from their GP within 2 months of the index date (figure 1). The proportion of the therapies carried out in our study is comparatively low, and it is important to mention that we were not able to evaluate which reasons led to the decision for (or against) eradication therapy in individual cases. For decades, the advice for *H. pylori*

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eradication therapy remained unchanged regarding peptic ulcer disease, low-grade gastric B-cell lymphoma (MALT lymphoma), atrophic gastritis and after gastric carcinoma resection. According to the 2022 updated German guideline, *H. pylori* infection is considered a bacterial disease of the stomach, regardless of symptoms or clinical appearance.[3] Therefore, a positive test for *H. pylori* in adulthood is always an indication for therapy, even if the patient has no clinical symptoms. At the same time, the indication for testing (and therefore, in the case of *H. pylori* detection consecutive eradication) has been extended in the German guideline, which will likely lead to an increasing number of eradication therapies in the following years and therefore possibly a decreased prevalence of *H. pylori* in the general German population.[3] On the other hand, other factors (eg, local preferences and experience, expertise of GPs) may contribute to the number of therapies carried out, and a future impact on the incidence of *H. pylori*-associated gastric and extragastric carcinoma remains unclear.

Association of *H. pylori* and a subsequent cancer diagnosis

After up to 10 years of follow-up, 12.8% of the *H. pylori* cohort were diagnosed with cancer (p=0.002, figure 2), and in the regression analysis, there was a small but significant association between *H. pylori* and a subsequent diagnosis of cancer (HR: 1.11; 95% CI 1.04 to 1.18). The role of *H. pylori* in gastric malignancies, particularly GC and gastric MALT lymphoma, is indisputable. *H. pylori* has been recognised as a class I carcinogen by the International Agency for Research on Cancer.[4 23–25] Despite a close causal link between *H. pylori* infection and the development of gastric malignancies, the precise mechanisms involved in this process are still a matter of debate. Specific virulence factors such as CagA, vacuolating cytotoxin A, the host genotype, environmental factors such as diet and alternations in stem cell populations, and the microbiome act in complex and only partially understood ways in the development of gastric malignancies.[26 27] Our data support a strong association between *H. pylori* and GC (HR: 1.59; 95% CI 1.00 to 2.53), but the results failed to reach statistical significance (p=0.049), table 2. It is important to mention that we could not record individual host or intrinsic *H. pylori* factors contributing to the risk of cancer (of any entity). However, due to the large cohort and matched CCS (table 1), these aspects are potentially less relevant. We have to state that a vast majority of *H. pylori* tests by GPs will probably have been carried out due to upper GI symptoms, reflecting a state of inflammation (eg, gastritis), but this remains speculative. Despite recording the timepoint of positive *H. pylori* testing, the time between the actual infection and the onset of cancer, like in most published studies, remains unclear (just as potentially subsequent infections) due to the usually long-term asymptomatic *H. pylori* infection. This is particularly relevant given the predominantly long-term effects of *H. pylori* infections and in long-term *H. pylori*-infected but asymptomatic individuals.

According to published data, *H. pylori* is associated with a decreased risk of oesophageal squamous cell carcinomas and oesophageal adenocarcinomas.[28] Our data support these findings: carcinoma of the oesophagus was negatively associated with *H. pylori* infection (HR: 0.49, 95% CI 0.26 to 0.89), but the results did not reach statistical significance (p=0.020).

During the late 1990s, the first reports showing that *H. pylori* is associated with extradigestive diseases (autoimmune diseases, cardiovascular diseases, colonic and pancreatic diseases, haematological and respiratory diseases) appeared. These observations were most likely linked to the immune and inflammatory responses triggered by *H. pylori* infection.[29–31] In this context, the role of *H. pylori* in triggering chronic respiratory disease (and lung cancer) is relatively well understood but still a matter of debate.[24 31] In our study, *H. pylori* infection was not associated with a higher incidence of cancer of bronchus and lungs (HR: 0.88, 95% CI 0.69 to 1.11, p=0.278). This finding is contrary to other data, including a meta-analysis.[32] The role of *H. pylori* in pancreatic cancer remains highly controversial.[33–36] In the stratified analyses by pancreatic cancer, our data showed a strong but not significant association between *H. pylori* and pancreatic cancer (HR: 1.46; 95% CI 0.99 to 2.17, table 2). Other tumour entities showed no relevant association with *H. pylori* infection: colon and rectum, liver and larynx (table 2).

The role of *H. pylori* eradication therapy

The cumulative incidence of cancer in eradicated and non-eradicated patients with *H. pylori* compared with patients without *H. pylori* in our study is shown in figure 3: there was a significant difference between non-eradicated patients with *H. pylori* and patients without *H. pylori* (13.2% vs 11.8%, p<0.001), reflecting the role of known but untreated *H. pylori* infection in carcinogenesis. As mentioned above, we could not evaluate which reasons led to the decision for (or against) eradication therapy in individual cases. In subgroup analyses, the only cancer entity with a significant effect of *H. pylori* eradication was bronchus and lung cancer. Here, *H. pylori* eradication was negatively associated with cancer of the bronchus and lung (HR: 0.60; 95% CI 0.44 to 0.83), and there was a strong trend towards an association between non-eradicated *H. pylori* and subsequent cancer of the bronchus and lung (p=0.035, table 2).

In GC, eradication of *H. pylori* led to a decreased HR (1.48, 95% CI 0.78 to 2.83) compared with the non-eradicated group (HR: 1.7, 95% CI 0.87 to 3.32), but the results failed to show statistical significance. Therefore, our data could not reveal the findings other data suggested: in a systematic review and meta-analysis, the eradication of *H. pylori* infection was associated with a generally reduced incidence of GC with variation regarding the baseline GC incidence, but applicable to all levels of baseline risk.[37] We have to state that we cannot rule out misclassifying some adenocarcinomas of

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the esophagogastric junction as oesophagus carcinomas in our study due to poor coding quality, and therefore, underestimate the role of eradication therapy in our study in the GC group. Furthermore, it is important to mention that we did not perform subgroup analyses regarding age and other individual factors influencing the risk for GC. Therefore, we did not record the effect of *H. pylori* eradication in the elderly and/or higher risk group, in which eradication should be most effective.

Overall, there was no significant difference between eradicated patients with *H. pylori* and patients without *H. pylori* (12.5% vs 11.8%, p=0.231) regarding cancer development. In regression analyses, a non-eradicated *H. pylori* status (HR: 1.18; 95% CI 1.07 to 1.30) but not an eradicated *H. pylori* status (HR: 1.06; 95% CI 0.97 to 1.15) was associated with a subsequent diagnosis of cancer (table 2). This is in line with previously published data revealing a reduced incidence for certain tumour entities, particularly GC, but is largely lacking for different other entities.[38 39] Other published data revealed elevated standardised incidence ratios up to 5 years of follow-up after *H. pylori* eradication in gastric and lung cancers.[40] The authors concluded that although eradicating *H. pylori* may have a long-lasting protective effect against GC, *H. pylori* therapy may postpone the detection of malignancies, possibly underlying unspecific GI symptoms. It is important that *H. pylori*-associated carcinogenesis is usually a long-term process and, therefore, can occur and/or become clinically apparent years after *H. pylori* eradication.

A main limitation of the study is that there was no detailed information on hospitalisations available because the database only includes data obtained by primary care physicians in their clinical practice. Diagnostic data from external specialists and hospitals are only recorded in the database if the primary care physician adds this information. Furthermore, no mortality data are available. Because of the potential for incomplete medical records, information bias may have been introduced in our database. Moreover, the database does not contain information about lifestyle-related factors (eg, smoking behaviour, physical mobility and alcohol use), socioeconomic factors (eg, marital status, profession and income) and genetic factors. Another important limitation is the lack of documentation about the *H. pylori* detection method, the used eradication regimen, length of therapy, eradication control and subsequent infections. It must be pointed out that due to the retrospective database evaluation, we are unable to draw any causal link between the reported proportions and cannot exclude pre-existing disorders or poor coding quality. Still, the reported frequencies are mostly in line with previously reported rates.

The strengths of the study are its use of a nationwide primary care database that is representative of diagnoses and the comparatively long observational period of 10 years.[16] Furthermore, recall bias was unlikely because of the use of original data collected in primary care.

CONCLUSION

Our study gives a detailed insight into the 10-year cancer prevalence of different entities regarding *H. pylori* infection and the effects of *H. pylori* eradication in a large GP cohort in Germany. We report higher cancer rates in the *H. pylori* cohort. Moreover, a non-eradicated *H. pylori* status but not an eradicated *H. pylori* status was associated with a subsequent diagnosis of cancer. In subgroup analyses, *H. pylori* eradication was negatively associated with bronchus and lung cancer.

Contributors SHL, KK, AM and CR designed the study. KK performed statistical analyses and generated figures and tables. SK, JK and CL contributed to the interpretation of the results. SHL, AM, IK and CR wrote the manuscript. TL provided intellectual input. CR and KK are joint last authors. AM is responsible for the overall content as the guarantor. All authors agreed to the final version of the manuscript.

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