Received: 31 October 2022 | Revised: 17 March 2023 | Accepted: 22 March 2023

DOI: 10.1111/hel.12979

ORIGINAL ARTICLE

Helicobacter WILEY

Incidence of gastrointestinal malignancies increases in persons received eradication therapy for *Helicobacter pylori*: A cohort study

Timo U. Kosunen[1,†] | Anna A. Nieminen[2] | Arto Kokkola[2] | Perttu Arkkila[3] | Eero Pukkala[4,5] | Hilpi Rautelin[6]

[1]Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Helsinki, Finland

[2]Department of Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[3]Department of Gastroenterology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[4]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

[5]Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland

[6]Clinical Microbiology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Correspondence
Anna A. Nieminen, Department of Surgery, Helsinki University Hospital, Haartmaninkatu 4, 00290 Helsinki, Finland.
Email: anna.a.nieminen@hus.fi

Abstract

Background: Long-term *Helicobacter pylori* infection increases the risk of gastric malignancies. Since the symptoms for *H. pylori* gastritis, as well as for several malignancies, may be nonexisting or highly unspecific, even *H. pylori*-positive subjects with underlying malignancies may receive eradication therapy. The aim was to assess the incidence of gastrointestinal and various other malignancies in individuals after eradication therapy for *H. pylori* infection.

Materials and Methods: A cohort of 217,554 subjects (120,344 women and 97,210 men), who had purchased specific combinations of drugs for *H. pylori* eradication therapy in 1994–2004, was identified by the Finnish National Prescription Registry and followed for cancer incidence until the end of 2008 (1.89 million person-years at risk).

Results: A total of 22,398 malignancies were identified in the cohort. In both genders, for the first 6 months after drug prescription, the standardized incidence ratios (SIRs) were between 5 and 32 for gastric, colorectal, and pancreatic cancers, and 2 and 3 for several other malignancies. Although later on the SIRs of most malignancies fell rapidly, those of gastric noncardia and lung cancers remained elevated up to 5 years of follow-up. The only SIRs below unity were seen in men for gastric cancers (cardia 0.61, 95% CI: 0.37–0.95; intestinal noncardia 0.74, 95% CI: 0.56–0.97) during the post-therapy period covering years 5–15.

Conclusion: Incidence levels significantly above the population rates were detected for many malignancies. Although eradication of *H. pylori* may have a long-lasting protective effect against gastric cancer, *H. pylori* therapy may postpone the detection of malignancies possibly underlying unspecific gastrointestinal symptoms. Therefore, it should be emphasized that the diagnostic work-up for malignancies should not be stopped in case of detection and treatment of *H. pylori* infection.

KEYWORDS
cancer epidemiology, eradication therapy, gastric cancer, *Helicobacter pylori*, malignancy

†Deceased

1 | INTRODUCTION

Helicobacter pylori (*H. pylori*) causes chronic gastritis, which is the best-known risk factor for peptic ulcer disease[1] and gastric malignancies.[2–5] Some studies have suggested that *H. pylori* infection could even be a minor risk factor in colorectal, pancreatic, and lung cancer.[6–8] International Agency for Research on Cancer (IARC) has stated *H. pylori* as a Group 1 carcinogen in gastric cancer.[9] Smoking has been associated with *H. pylori* infection in some population-based studies.[10,11] In 2004, IARC monographs summed up the smoking-related malignancies to include, in addition to lung and tracheal cancers, several other malignancies of the upper respiratory, gastrointestinal, and urinary tract.[12]

Eradication of *H. pylori* is best achieved by giving a combination of 2–3 antimicrobial agents—most commonly amoxicillin, clarithromycin, and metronidazole—together with acid-suppressing drug.[13] Such combination therapies are rarely prescribed for other indications. Treatment of the infection and eradication of the bacterium have been shown to lead to permanent cure of active gastritis, as well as peptic ulcer disease[14] and, after several years, also to a significantly lower risk for gastric cancer.[15–18] The drugs used for eradication therapy are not specific for *H. pylori* and, due to the wide antimicrobial spectrum of the combination, may also affect many other bacteria and possible infections. Orally administered antimicrobial therapy and PPI for *H. pylori* eradication may also alter the composition of gut microbiota. Although the reduced bacterial alfa-diversity, detected after 1 week of therapy, seemed to have returned to normal a year later, the perturbed bacterial flora, including the macrolide resistance gene *erm*(B), remained altered in some subjects for up to 4 years.[19]

Dyspepsia, epigastric pain, and other gastrointestinal symptoms that typically lead to medical consultations are not merely associated with abdominal diseases.[20] In a population-based study in Finland, these symptoms were not more commonly reported by *H. pylori*-positive than -negative participants.[11] Thus, due to the lack of distinct and specific symptoms for *H. pylori* gastritis, it is likely that even *H. pylori*-positive subjects with symptoms associated with other diseases may receive *H. pylori* eradication therapy. These could include individuals with underlying cancers that typically give only vague and nonspecific symptoms.

In Finland, *H. pylori* has been actively tested and treated in patients with dyspeptic and other gastrointestinal symptoms. Antibiotics can be purchased by physicians' prescription only and therefore all the purchased *H. pylori* eradication treatments are registered. As all diagnosed malignant tumors are registered as well, and causes of death and emigrations are available, we had a unique possibility, using broad national registers, to evaluate whether malignancies were overrepresented among individuals treated for *H. pylori* infection.

2 | MATERIALS AND METHODS

The study cohort included 217,544 persons (120,344 women and 97,210 men) who had received reimbursement for the combination of drugs used in *H. pylori* eradication therapy in 1994–2004 in Finland. The cohort was identified from the prescription registry of the National Social Insurance Institution.

The drugs used in *H. pylori* therapy and included in the study were the following: Industry made combination packages Helipak A (Orion Pharma); amoxicillin (1000 mg) b.i.d., metronidazole (400 mg) t.i.d., and lansoprazole (30 mg) b.i.d. for 7 days, Helipak K (Orion Pharma); amoxicillin (1000 mg) b.i.d., clarithromycin (500 mg) b.i.d., and lansoprazole (30 mg) b.i.d. for 7 days, Helipak T (Orion Pharma); tetracycline (500 mg) q.i.d., metronidazole (400 mg) t.i.d., and lansoprazole (30 mg) b.i.d. for 7 days, and Losec Helira (AstraZeneca); amoxicillin (500 mg) t.i.d., metronidazole (400 mg) t.i.d., and omeprazole (40 mg) q.d. for 7 days. In addition, combinations of 2–4 of the following drugs intended to be used for 7–14 days and purchased at the same time were included: amoxicillin, clarithromycin, tetracycline, metronidazole, and levofloxacin.

The accumulation of the person-years at risk began on the date of the first reimbursement of drugs used in *H. pylori* therapy and ended on the date of emigration, death, or on the 31st of December 2008, whichever was first. Data on deaths and emigrations were achieved from the National Population Registry. Eleven-digit personal identity codes were used in all linkages. Information on cancer incidence were taken from the Finnish Cancer Registry.

Patients were enrolled only once, at the date of the first known eradication therapy purchase. Possible further *Helicobacter* eradication therapies were not counted. Previous cancer was not an exclusion criterion, but only cancers that were diagnosed after the treatment of *H. pylori* were included in the analysis.

The person-years at risk and observed numbers of cancers were stratified by sex, 5-year age groups, 5-year calendar periods, and time since drug purchase. In addition to the category of all malignancies combined, separate numbers were calculated for gastrointestinal and other most common malignancies presented in Table S1.

The expected numbers of malignancies were calculated by multiplying the number of person-years in each stratum by the respective cancer incidence rate in the Finnish population (derived from the Finnish Cancer Registry). The relative risks were expressed as standardized incidence ratios (SIRs), that is, as ratios of the observed and expected numbers of cases. For each SIR, the exact 95% confidence interval (CI) was defined assuming a Poisson distribution of the observed number of cases.

The study was approved by the Ethical Committee for Epidemiology and Public Health of the Helsinki University Hospital District. Permission to link the data from national registries was obtained from the Ministry of Social and Health Affairs.

3 | RESULTS

A total of 217,554 persons (120,344 women and 97,210 men) and 1,893,460 person-years at risk were included in the study. During the up to 15 years of follow-up, 22,398 malignancies were identified. The subjects treated for *H. pylori* had a higher overall risk for malignancy

than the general population of the same age (in men, SIR 1.20, 95% CI 1.18–1.22; in women SIR 1.13, 95% CI 1.11–1.15, Table S1).

Covering the total follow-up period in both genders, SIRs were significantly above 1.0 for all common gastrointestinal malignancies, except for cancers of the cardia and esophagus in men, as well as for lung cancer and lymphohaematopoietic malignancies. The SIR for lung cancer was 28% higher in women and 22% higher in men. The SIR for prostate cancer was modestly but statistically significantly elevated (SIR 1.14, 05% CI 1.11–1.17; Table S1).

For most malignancies, the highest SIRs were seen during the first 6 months after eradication therapy (Table S1). Especially high SIRs were seen for *H. pylori*-associated malignancies (Figures 1 and 2): gastric mucosa-associated lymphoid tissue lymphoma (MALT), the SIR in men was 31.7 (95% CI: 22.4–43.5) and in women 22.0 (95% CI: 14.4–32.2). The SIR for noncardia gastric cancer in men was 11.6 (95% CI: 9.9–13.5) and in women 13.3, (95% CI: 11.4–15.4). Out of all noncardia gastric cancers, 91% were either diffuse or intestinal by the histology type. The SIRs for the diffuse type of noncardia gastric cancers were clearly higher than those of the intestinal type in both genders (Figures 1 and 2). Further high SIRs (4.9–7.1) during the first 6 months were found for pancreatic and colorectal cancers in both genders (Figures 1 and 2).

After the first 6 months, the SIRs declined rapidly for most malignancies (Table S1). During both the latter half of the first year of follow-up and the 4-year period from the second year thereon, significantly elevated values were still found for gastric noncardia and lung cancers in both genders. In men, prostate malignancies showed SIR 1.59 (95% CI 1.38–1.79) during the first 6 months of follow-up and after that an excess of about 10% in all further follow-up periods (Table S1). The SIRs for lung cancer were significantly elevated in all follow-up periods in both sexes (Table S1).

In this study, the only SIRs significantly below 1.0 were seen in men during the follow-up period of 5+ years for the gastric cardia and intestinal types of noncardia cancers (Figure 2, Table S1).

4 | DISCUSSION

In this large registry-based cohort study, the only types of malignancy with significantly declining SIRs along with years elapsed after the *H. pylori* eradication therapy were *H. pylori*-associated cancers, that is, cancer of the gastric cardia and intestinal noncardia cancers. In general, the overall risk for malignancy was higher in individuals who had received eradication therapy for *H. pylori* than in the general population of the same age. The peak of cancer diagnoses was during the first 6 months after therapy. All types of gastrointestinal tumors were overrepresented, but the highest SIRs were seen in *H. pylori*-associated malignancies, such as gastric cancer and MALT lymphoma. The incidence of several nongastrointestinal cancers was elevated, too. However, *H. pylori* infection may not be the actual reason for cancer, but there may be only a temporal coincidence of *H. pylori* and cancer.

In Finland, patients usually seek for medical advice because of their symptoms, and the *H. pylori* test is easily achieved in a primary healthcare setting. Due to the unspecific nature of the gastrointestinal symptoms,[20] the discomfort experienced may be caused by both *H. pylori* infection and malignancy. The positive *H. pylori* test result may delay the diagnosis of malignancy if further diagnostic work-up is not considered. In an earlier Finnish study,[21] the eradication of *H. pylori* delayed the diagnosis of gastric cancer with a median of 7.5 months, even in patients with new or alarming symptoms.

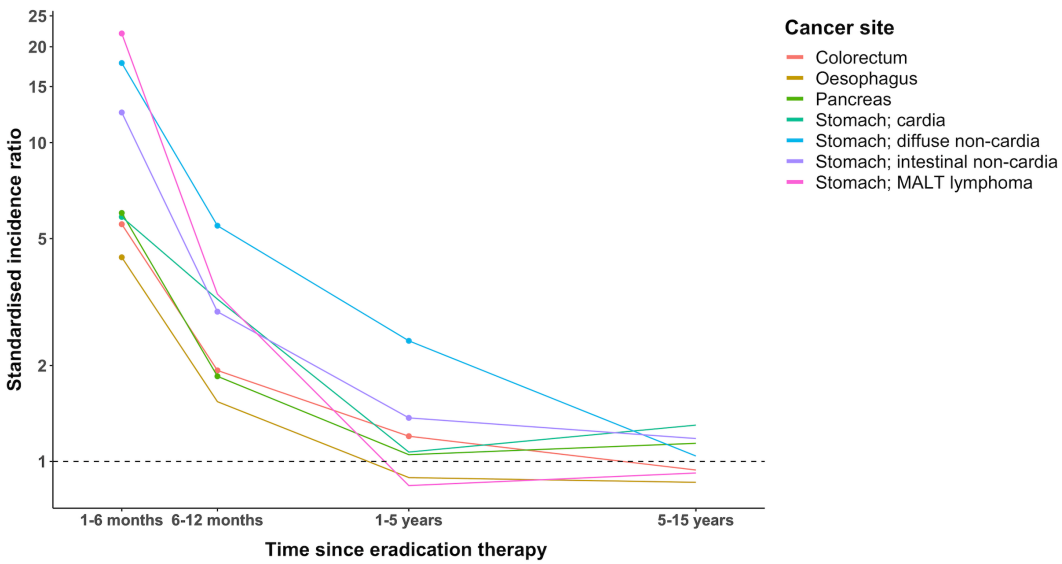

FIGURE 1 Standardised incidence ratios (SIR) of selected gastrointestinal malignancies for women, by follow-up period. Statistically significant SIRs are highlighted with dots in the curve.

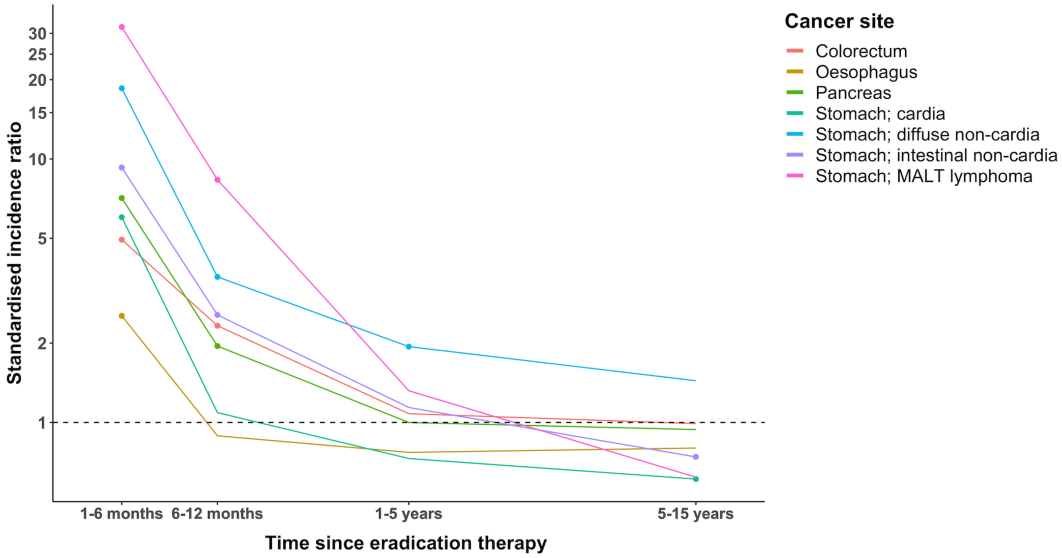

FIGURE 2 Standardised incidence ratios (SIR) of selected gastrointestinal malignancies for men, by follow-up period. Statistically significant SIRs are highlighted with dots in the curve.

Chronic inflammation in gastric mucosa for years or decades may progress to atrophic gastritis and lead to genetic damage in the epithelium. *H. pylori*, the causative pathogen, should be eradicated before precancerous changes develop.[22] Ford et al.[23] calculated in a recent Cochrane review that, the successful treatment of the infection lowered the risk ratio for gastric cancer to 0.54 (95% CI 0.40–0.72) in asymptomatic *H. pylori*-positive individuals. However, the eradication of *H. pylori* does not abolish the gastric cancer risk if "the point of no return" has been passed. In the present study, in men, the gastric cardia and intestinal noncardia cancers were the only cancer types the incidence of which was significantly declined 5–15 years after eradication therapy.

The association with *H. pylori* is opposite for cancers of the esophagus and cardia. Gastroesophageal reflux disease (GERD) predisposes Barrett's esophagus, a precursor of adenocarcinoma of the gastroesophageal junction and cardia. Due to long-lasting *H. pylori* infection and thereby reduced acidity, the incidence of esophageal adenocarcinoma decreases.[24] The gastric acidity does not predispose to squamous cell carcinoma of the esophagus. In our data, the esophageal cancer incidence was elevated in both genders for the first 6 months after the eradication but not in a longer follow-up. The risk of esophageal cancer was not analyzed by histological type. Similarly, the cardia cancer incidence was elevated for the first 6–12 months after the eradication, but in the follow-up of >5 years, SIR was only 0.61 (95% CI 0.37–0.95) in men. There is a risk that some of the gastric cancers are misdiagnosed as cardia cancers and therefore the benefit of *H. pylori* eradication is obtained.

The highest SIRs were observed in MALT lymphoma. Eradication therapy for *H. pylori* is the primary treatment for this malignancy, and rarely other treatment is required. The effect of the eradication is gained relatively rapidly.

It has been estimated that over half of the global population is infected by *H. pylori*, but the prevalence of *H. pylori* infection is rapidly declining in developed countries.[25] Likewise, in Finland, the prevalence of *H. pylori* infection has for a long time decreased towards the later birth cohorts.[26] Furthermore, in Finland, the incidence of gastric cancer, which is considered the most severe consequence of *H. pylori* infection, has strongly declined.[27]

Worldwide gastric cancer incidence is about twice as high in men than in women, and the lack of power in the present study might explain why a similar kind of reduction in long-term cancer incidence could not be observed in women.

Gastric cancer is not the only malignancy the diagnosis of which can be hidden by *H. pylori*. Here, in addition to gastrointestinal malignancies, the highest incidence rates of several nongastrointestinal cancers were detected during the first 6 (to 12) months after *H. pylori* therapy. This suggests that people seek for medical help due to nonspecific symptoms. Colorectal cancer is the most common gastrointestinal malignancy, representing in our study almost 20% of all cancers diagnosed during the first 6 months after *H. pylori* therapy. In another Finnish study,[28] the diagnosis of colorectal cancer was delayed in *H. pylori*-positive patients with functional dyspeptic symptoms, but not in those with alarming symptoms like blood in the stool or occlusion. In the present study, the incidence rates of cancers not causing vague abdominal symptoms, for example, breast, skin, and brain cancers, did not differ between individuals treated for *H. pylori* and those of general population.

Socioeconomic status has an impact on the risk of different cancers. In the Finnish population, subjects from lower social classes have been shown to have a higher incidence of noncardia gastric cancer than those presenting higher social classes.[29] Furthermore, smoking is associated with lower socioeconomical classes[30] and lung cancer.[29,31] In the present study, lung cancer was the only malignancy the incidence of which stayed elevated for all the 15 years of follow-up.

This study was based on a large cohort with a rather long follow-up. In Finland, the national registries are population-based

and reliable. Although the follow-up lasted for 15 years, it would have been interesting to continue the follow-up to the present time. However, limitations of the study include that no clinical data on either symptoms or indications for *H. pylori* eradication were available, the successful eradication rates were not known, and lifestyle habits, such as smoking, could not be elucidated either. The data on the cancer stages were not available to us. Such data would have added possibilities for understanding the aggressiveness of the cancers.

In conclusion, in this large registry-based cohort study, the risk for malignancy was more than doubled for the first 6 months after *H. pylori* eradication therapy. Awareness of possible underlying malignancy should be kept in mind, and simultaneous diagnostic work-up for malignancies should not be forgotten, even if *H. pylori* infection is detected and treated. Cardia and intestinal type of non-cardia gastric cancers in men were here the only types of malignancies, the incidence of which was below those detected in general population, implicating a benefit of *H. pylori* eradication therapy.

ACKNOWLEDGMENTS

This research project was originally led by the late Professor Timo U. Kosunen and we other authors would very much like to fulfill the process, which has been postponed for some years and now send the manuscript in honor of him. The family members of the late Professor Kosunen have been contacted and their approval has been obtained. We acknowledge PhD Sushmita Katuwal for her help with the graphics.

FUNDING INFORMATION

Anna A. Nieminen has received research grants from the Mary and Georg C. Ehrnrooth Foundation, The Finnish Cultural Foundation, and the Finnish Medical Foundation, which are not related to this study. Arto Kokkola, Perttu Arkkila, Eero Pukkala, and Hilpi Rautelin: nothing to declare.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study is available in the Supplementary material of this article.

ORCID

Anna A. Nieminen https://orcid.org/0000-0001-9486-4245

REFERENCES

1. Blaser MJ. *Helicobacter pylori* and the pathogenesis of gastroduodenal inflammation. *J Infect Dis*. 1990;161:626-633.
2. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut*. 2001;49:347-353.
3. Wotherspoon AC, Diss TC, Pan L, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. *Lancet*. 1993;342:575-577.
4. Hansen S, Vollset SE, Derakhshan MH, et al. Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and *Helicobacter pylori* status. *Gut*. 2007;56:918-925.
5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100 B. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum*. 2012;100(Pt B):1-441.
6. Zhuo W-L, Zhu B, Xiang Z-L, Zhuo XL, Cai L, Chen ZT. Assessment of the relationship between *Helicobacter pylori* and lung cancer: a meta-analysis. *Arch Med Res*. 2009;40:406-410.
7. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol*. 2015;44:186-198.
8. Zuo Y, Jing Z, Bie M, Xu C, Hao X, Wang B. Association between *Helicobacter pylori* infection and the risk of colorectal cancer. *Medicine*. 2020;99:e21832.
9. Schistosomes, liver flukes and *Helicobacter pylori*. IARC working Group on the evaluation of carcinogenic risks to humans. Lyon, 7–14 June 1994. *IARC Monogr Eval Carcinog Risks Hum*. 1994;61:1-241.
10. Murray L, McCrum E, Evans A, Bamford K. Epidemiology of *Helicobacter pylori* infection among 4742 randomly selected subjects from Northern Ireland. *Int J Epidemiol*. 1997;26:880-887.
11. Salomaa-Räsänen A, Kosunen TU, Aromaa ARJ, et al. A "screen-and-treat"; approach for *Helicobacter pylori* infection: a population-based study in Vammala, Finland. *Helicobacter*. 2010;15:28-37.
12. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Tobacco Smoke and Involuntary Smoking*. International Agency for Research on Cancer; 2004.
13. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence consensus report. *Gut*. 2017;66:6-30.
14. Graham DY. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. *Ann Intern Med*. 1992;116:705-708.
15. Wong BC-Y, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China. *JAMA*. 2004;291:187-194.
16. Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med*. 2009;151:121-128.
17. Kosunen TU, Pukkala E, Sarna S, et al. Gastric cancers in Finnish patients after cure of *Helicobacter pylori* infection: a cohort study. *Int J Cancer*. 2011;128:433-439.
18. Take S, Mizuno M, Ishiki K, et al. The long-term risk of gastric cancer after the successful eradication of *Helicobacter pylori*. *J Gastroenterol*. 2011;46:318-324.
19. Jakobsson HE, Jernberg C, Andersson AF, Sjölund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS ONE*. 2010;5:e9836.
20. Moayyedi P. Dyspepsia. *Curr Opin Gastroenterol*. 2012;28:602-607.
21. Kokkola A, Sipponen P, Arkkila P, Danielson H, Puolakkainen P. Does the eradication of *Helicobacter pylori* delay the diagnosis of gastric cancer? *Scand J Gastroenterol*. 2008;43:1456-1460.
22. Liou J-M, Malfertheiner P, Lee Y-C, et al. Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: the Taipei global consensus. *Gut*. 2020;69:2093-2112.
23. Ford AC, Yuan Y, Forman D, et al. *Helicobacter pylori* eradication for the prevention of gastric neoplasia. *Cochrane Database of Syst Rev*. 2020;7(7):CD005583.
24. Holleczek B, Schöttker B, Brenner H. *Helicobacter pylori* infection, chronic atrophic gastritis and risk of stomach and esophagus cancer: results from the prospective population-based ESTHER cohort study. *Int J Cancer*. 2020;146(10):2773-2783.
25. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology*. 2017;153(2):420-429.
26. Kosunen TU, Aromaa A, Knekt P, et al. *Helicobacter* antibodies in 1973 and 1994 in the adult population of Vammala, Finland. *Epidemiol Infect*. 1997;119(1):29-34.

27. Larønningen S, Ferlay J, Beydogan H, et al. *NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 9.2 (23.06.2022)*. Association of the Nordic Cancer Registries. Cancer Registry of Norway; 2022. Accessed January 24, 2023. https://nordcan.iarc.fr/
28. Soveri L-M, Österlund P, Ruotsalainen T, et al. *Helicobacter pylori* and gastrointestinal symptoms in diagnostics and adjuvant chemotherapy of colorectal cancer. *Oncol Lett*. 2014;7:553-559.
29. Pukkala E. Cancer risk by social class and occupation. A Survey of 109,000 cancer cases among Finns of working age. In: Wahrendorf J, ed. *Contributions to Epidemiology and Biostatistics*, Vol. 7. Karger; 1995:1-277.
30. Laaksonen M, Rahkonen O, Karvonen S, Lahelma E. Socioeconomic status and smoking. *Eur J Public Health*. 2005;15:262-269.
31. Schwartz AG, Cote ML. Epidemiology of lung cancer. *Adv Exp Med Biol*. 2016;893:21-41.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kosunen TU, Nieminen AA, Kokkola A, Arkkila P, Pukkala E, Rautelin H. Incidence of gastrointestinal malignancies increases in persons received eradication therapy for *Helicobacter pylori*: A cohort study. *Helicobacter*. 2023;28:e012979. doi:10.1111/hel.12979