Helicobacter pylori eradication treatment and the risk of Barrett’s esophagus and esophageal adenocarcinoma

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Original Article

Abstract

Background: Helicobacter pylori (H. pylori) is associated with lower risks of Barrett’s esophagus and esophageal adenocarcinoma, but whether H. pylori eradication increases the risk of these conditions is unknown. This study aimed to test the hypothesis that H. pylori eradication leads to gradually increased risks of Barrett’s esophagus and esophageal adenocarcinoma over time, while esophageal squamous cell carcinoma was assessed for comparison reasons.

Material and Methods: This Swedish nationwide, population-based cohort study in 2005-2012 used data from the Swedish Prescribed Drug Registry to assess eradication treatment for H. pylori. Barrett’s esophagus was identified from the Swedish Patient Registry, and esophageal adenocarcinoma and squamous cell carcinoma from the Swedish Cancer Registry. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated by dividing the observed risk in the H. pylori eradication treatment cohort by the expected risk derived from the Swedish population of the same age, sex, and calendar period.

Results: The cohort included 81,919 patients having had eradication treatment. For Barrett’s esophagus (n = 178), the overall SIR was increased (SIR 3.67, 95% CI 3.15-4.25), but the SIRs slightly decreased over time after eradication treatment. For esophageal adenocarcinoma (n = 11), the overall SIR was 1.26 (95% CI 0.62-2.26), and the SIRs did not increase over time. The SIRs of esophageal squamous cell carcinoma (n = 10) were not influenced by eradication treatment.

Conclusions: This study did not provide any evidence of an increasing risk of Barrett’s esophagus or esophageal adenocarcinoma (or esophageal squamous cell carcinoma) over time after eradication treatment for H. pylori.

Keywords
antibiotics, Barrett’s esophagus, esophageal, Helicobacter pylori, Neoplasm, proton-pump inhibitors
INTRODUCTION

The incidence of esophageal adenocarcinoma has increased markedly in Western countries since the 1970s. In most Western countries (including Sweden), the incidence of esophageal adenocarcinoma has surpassed that of esophageal squamous cell carcinoma, which is the most common histologic type of esophageal cancer globally. For esophageal adenocarcinoma and its precursor lesion Barrett’s esophagus, the main risk factors are gastroesophageal reflux disease (GERD) and obesity, while presence of Helicobacter pylori (H. pylori) in the stomach is associated with a 32%-56% decreased risk of Barrett’s esophagus, and a 36%-44% decreased risk of esophageal adenocarcinoma. These inverse associations with H. pylori are thought to be the result of H. pylori-associated gastric atrophy, which leads to lower gastric acid production and thus lower prevalence of GERD. Yet, it is not studied if eradication treatment for H. pylori increases the risks of Barrett’s esophagus or esophageal adenocarcinoma. H. pylori infection is otherwise a well-established risk factor of noncardia gastric adenocarcinoma, and its eradication reduces the risk of this cancer by around 50%. For esophageal squamous cell carcinoma, the main risk factors are tobacco smoking and overconsumption of alcohol, and no association has been found with H. pylori.

To test the hypothesis that H. pylori eradication increases the risks of Barrett’s esophagus and esophageal adenocarcinoma, and does not influence the risk of esophageal squamous cell carcinoma, we conducted a nationwide Swedish cohort study.

MATERIAL AND METHODS

Design

This population-based and nationwide Swedish cohort study included patients aged 18 years and older who had eradication treatment for H. pylori during the study period July 1, 2005, to December 31, 2012. The source cohort has been described in detail previously. For the purpose of the present study, the risk of Barrett’s esophagus, esophageal adenocarcinoma, and esophageal squamous cell carcinoma among the cohort participants was compared to the risk in the corresponding Swedish background population. The data were retrieved from well-maintained nationwide Swedish registers that were linked for each study participant by their unique personal identity number assigned to all residents in Sweden at birth or immigration. The study was approved by the Regional Ethical Review Board in Stockholm (2014/1291-31/4), and the need for informed consent was waived.

Exposure

The study exposure was eradication treatment for H. pylori using a proton-pump inhibitor (PPI) in combination with at least two of the antibiotics clarithromycin, amoxicillin, or metronidazole, as described earlier. The data on eradication treatment were retrieved from the Swedish Prescribed Drug Registry, which started on July 1, 2005, and contains information on all prescribed and dispensed medications that are used outside in-hospital care for the whole Swedish population. The medications (with their Anatomical Therapeutic Chemical codes) representing H. pylori eradication were a combination package used for H. pylori eradication containing the PPI esomeprazole and the antibiotics clarithromycin and amoxicillin (A02BD06), and prescriptions of a PPI (A02BC) together with clarithromycin (J01FA09), amoxicillin (J01CA04), or metronidazole (J01XD01). The separate prescriptions had to include at least two antibiotics that were prescribed on the same date, and a PPI prescribed within a window of 60 days before to 5 days after the antibiotics. This was done in order to include individuals already using a PPI and to take nonavailability in the pharmacy into account.

Outcomes

The main outcome was Barrett’s esophagus, and the secondary outcome was esophageal adenocarcinoma. Esophageal squamous cell carcinoma was examined only for comparison reasons. New diagnoses of Barrett’s esophagus were assessed from the Swedish Patient Registry using the International Classification of Diseases 10 (ICD10) code K22.7 that was available from 2006 onwards. Newly detected esophageal cancers were assessed from the Swedish Cancer Registry using the ICD7 codes 150, 150.0, 150.8, and 150.9. The histologic code 096 from the C24 WHO classification of histology defined adenocarcinoma, and the code 146 defined squamous cell carcinoma. All outcomes occurring within 1 year of eradication treatment were excluded to avoid detection bias, that is, earlier detection of the outcomes due to examinations preceding the eradication treatment. Therefore, the start of follow-up was 1 year after H. pylori eradication treatment for all participants. In each individual, only the first ever cancer episode was considered. Thus, participants were eligible only if they had no history of cancer.

Statistical analysis

Standardized incidence ratios (SIRs) were calculated by dividing the observed number of cases in the H. pylori eradication cohort by the expected number of cases in the corresponding Swedish background population. Standardization was performed on the variables age group (18-59, 60-69, and ≥70 years), sex (men and women), and calendar period (2005-2006, 2007-2009, and 2010-2012). To calculate the number of person-years of follow-up in each stratum, Clayton’s algorithm was used, where follow-up started from 1 year after the date of the first dispensed prescription for eradication of H. pylori. An additional analysis instead counted person-years starting from the date of the last dispensed prescription for H. pylori eradication. Follow-up discontinued at the date of occurrence of any cancer, death, or end of the study period (December 31, 2012),
whichever came first. For the analysis of Barrett’s esophagus, the first date of Barrett’s diagnosis was added to the end of follow-up criteria. Barrett’s diagnoses in the first year after eradication treatment were removed from the analysis and the entire cohort started 1 year after eradication.

Subgroup analyses were performed to assess the risk of the outcomes over time after eradication treatment (categorized into 1-2, 3-4, or 5-7.5 years) and number of eradication treatments (1, 2, or ≥ 3). Multiple eradication treatments indicated that H. pylori was present for a prolonged amount of time.

The statistical software STATA (Stata Corp v. 13.0) was used for all data management and analyses.

3 | RESULTS

3.1 | Participants

The study cohort included 81 919 individuals with at least one dispensed prescription for H. pylori eradication treatment during the study period. Of these participants, 53.9% were women, 60.9% were 59 years of age or younger, and 74.8% resided in urban areas (Table 1). The study cohort for Barrett’s esophagus included slightly fewer cohort participants (n = 81 669) because individuals receiving Barrett’s esophagus diagnosis before the eradication treatment were excluded. During the follow-up (mean 3.2 years) from 1 year after eradication treatment, 178 (0.22%) participants had a new Barrett’s esophagus diagnosis, 11 (0.01%) developed esophageal adenocarcinoma, and 10 (0.01%) had an esophageal squamous cell carcinoma diagnosis.

3.2 | Helicobacter pylori eradication treatment and risk of Barrett’s esophagus

For Barrett’s esophagus, the overall SIR was increased (3.67, 95% CI 3.15-4.25), but the SIRs did not increase over time after eradication treatment, but rather decreased, from 4.32 (95% CI 3.53-5.23) at 1-2 years to 3.09 (95% CI 1.98-4.59) at 5-7.5 years after eradication (Table 2). Analysis from the date of last eradication treatment showed a similar trend apart from the analysis by number of eradication episodes (Table 3). There was no clear trend in risk depending on the number of eradication episodes (Table 2), and there were no clear differences in risk between the sexes (Table 4). Individuals aged 59 years or younger had a higher SIR of Barrett’s esophagus than the oldest age group at any follow-up time (Table 4).

3.3 | Helicobacter pylori eradication treatment and risk of esophageal adenocarcinoma

The overall SIR of esophageal adenocarcinoma was slightly increased after H. pylori eradication treatment although not statistically significant (SIR 1.26, 95% CI 0.62-2.26). The point estimates decreased after eradication treatment from 1.36 (95% CI 0.50-2.97) at 1-2 years to 0.73 (95% CI 0.01-4.08) at 5-7.5 years (Table 2). Ten out of 11 cases of esophageal adenocarcinoma were detected in participants with 1 prescribed eradication treatment (SIR 1.28, 95% CI 0.61-2.36). Analysis from the date of last eradication treatment showed similar findings (Table 3).

3.4 | Helicobacter pylori eradication treatment and risk of esophageal squamous cell carcinoma

The overall SIR of esophageal squamous cell carcinoma was slightly increased after H. pylori eradication treatment, but the result was not statistically significant, and the SIRs remained stable over time after eradication treatment (Table 2). Analysis from the date of last eradication treatment showed similar results (Table 3).

### Table 1 Characteristics of study participants at time of eradication treatment for Helicobacter pylori in Sweden in 2005-2012

| Characteristic | Participants number (%) |
|----------------|-------------------------|
| Total          | 81 919 (100.0)          |
| Sex            |                         |
| Men            | 37 726 (46.1)           |
| Women          | 44 193 (53.9)           |
| Age (years)    |                         |
| 18-59          | 49 866 (60.9)           |
| 60-69          | 15 479 (18.9)           |
| ≥70            | 16 574 (20.2)           |
| Calendar period at entry |         |
| 2005-2006      | 20 829 (25.4)           |
| 2007-2009      | 37 859 (46.2)           |
| 2010-2012      | 23 231 (28.4)           |
| Place of residence |                   |
| Rural          | 20 250 (24.7)           |
| Urban          | 61 246 (74.8)           |
| Missing        | 423 (0.5)               |
| Barrett’s esophagus (out of 81 669 individuals) | 178 (0.22) |
| Follow-up (years) for Barrett’s esophagus |          |
| Total          | 261 268                 |
| Mean           | 3.2                     |
| Esophageal cancer |                 |
| Esophageal adenocarcinoma | 11 (0.01) |
| Esophageal squamous cell carcinoma | 10 (0.01) |
| Follow-up (years) for esophageal cancer starting 1 y after eradication |          |
| Total          | 262 296                 |
| Mean           | 3.2                     |
4 | DISCUSSION

This study provided no support for the hypothesis of a gradually increased risk of Barrett’s esophagus or esophageal adenocarcinoma over time after eradication treatment for H. pylori, and no clear association was found with esophageal squamous cell carcinoma.

Strengths of this study were the population-based design which counteracts selection bias, the large cohort size with many person-years at risk, the data retrieved from well-maintained and national registers, and the complete follow-up. A major limitation was the low number of cases of esophageal adenocarcinoma (and esophageal squamous cell carcinoma), why the results for these cancers must be cautiously interpreted. There were however clearly more cases of Barrett’s esophagus, and these results may be representative of esophageal adenocarcinoma as well. A post hoc power analysis (alpha = 0.05; beta = 0.2) showed that 82 700 person-years would have been sufficient to obtain sufficient power to detect a doubled risk of Barrett’s esophagus, while over 261 000 person-years were included in this cohort. Yet, almost 400 000 years would have been needed for detecting a doubled risk for esophageal adenocarcinoma, while only 276 000 person-years were available.

Another weakness was the limited follow-up time (maximum of 7.5 years). Thus, longer-term associations could not be assessed. Although these results may be indicative for the risk of esophageal cancer after eradication, further research with longer follow-up times may clarify what happens years later. Yet, as indicated by the power-analyses, large groups are needed to detect any statistically significant differences.

Another limitation was exposure misclassification for various reasons. First, the registers did not have information on the success of the eradication treatment, which means that H. pylori might have remained after treatment in some participants. Second, the background population consists of both H. pylori-positive and H. pylori-negative individuals (H. pylori prevalence in Sweden is

| TABLE 2 | Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) of Barrett’s esophagus, esophageal adenocarcinoma and esophageal squamous cell carcinoma after Helicobacter pylori eradication treatment in Sweden in 2005-2012 |
|----------------------------------|------------------|------------------|------------------|
|                                  | Barrett’s esophagus | Esophageal adenocarcinoma | Esophageal squamous cell carcinoma |
|                                  | Number | SIR (95% CI) | Number | SIR (95% CI) | Number | SIR (95% CI) |
| Total                            | 178 | 3.67 (3.15-4.25) | 11 | 1.26 (0.62-2.26) | 10 | 1.63 (0.78-3.01) |
| Follow-up time, years            |        |                |        |              |        |                |
| 1-2                              | 104 | 4.32 (3.53-5.23) | 6 | 1.36 (0.50-2.97) | 5 | 1.59 (0.51-3.70) |
| 3-4                              | 50 | 3.00 (2.23-3.95) | 4 | 1.35 (0.36-3.47) | 5 | 2.45 (0.79-5.72) |
| 5-7.5                            | 24 | 3.09 (1.98-4.59) | 1 | 0.73 (0.01-4.08) | 0 | NA |
| Number of eradications           |        |                |        |              |        |                |
| 1                                | 141 | 3.27 (2.75-3.85) | 10 | 1.28 (0.61-2.36) | 9 | 1.15 (0.52-2.19) |
| 2                                | 30 | 7.31 (4.93-10.44) | 1 | 1.42 (0.02-7.92) | 0 | NA |
| ≥3                               | 7 | 5.44 (2.18-11.21) | 0 | NA | 1 | 4.71 (0.07-26.21) |

Abbreviation: NA, not applicable

| TABLE 3 | Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) of Barrett’s esophagus, esophageal adenocarcinoma, and esophageal squamous cell carcinoma after the last Helicobacter pylori eradication treatment in Sweden in 2005-2012 |
|----------------------------------|------------------|------------------|------------------|
|                                  | Barrett’s esophagus | Esophageal adenocarcinoma | Esophageal squamous cell carcinoma |
|                                  | Number | SIR (95% CI) | Number | SIR (95% CI) | Number | SIR (95% CI) |
| Total                            | 153 | 3.33 (2.82-3.90) | 11 | 1.28 (0.64-2.29) | 9 | 1.52 (0.62-2.88) |
| Follow-up time, years            |        |                |        |              |        |                |
| 1-2                              | 86 | 3.70 (2.96-4.57) | 6 | 1.41 (0.52-3.07) | 4 | 1.32 (0.35-3.40) |
| 3-4                              | 44 | 2.81 (2.04-3.77) | 4 | 1.44 (0.39-3.68) | 5 | 2.61 (0.84-6.09) |
| 5-7.5                            | 23 | 3.27 (2.07-4.91) | 1 | 0.81 (0.01-4.45) | 0 | NA |
| Number of eradications           |        |                |        |              |        |                |
| 1                                | 141 | 3.07 (2.58-3.62) | 10 | 1.28 (0.61-2.36) | 9 | 1.15 (0.52-2.19) |
| 2                                | 10 | 2.44 (1.17-14.48) | 1 | 2.45 (0.03-13.91) | 0 | NA |
| ≥3                               | 2 | 1.55 (0.18-5.61) | 0 | NA | 0 | NA |

Abbreviation: NA, not applicable
approximately 15%). Third, there was no information about eradication treatments before July 2005, meaning that there could have been previous eradication attempts that we could not capture, although less than 10% of the cohort received more than one eradication. These three potential sources of exposure misclassification could dilute the effect, but should not explain the trends over time after eradication treatment.12

To the best of our knowledge, this was the first study that examined the association between eradication treatment for H. pylori and the risk of Barrett’s esophagus, esophageal adenocarcinoma, and esophageal squamous cell carcinoma. The lack of increased risk estimates over time after eradication treatment during a period of 7.5 years argues against the hypothesis of an increased risk of Barrett’s esophagus and esophageal adenocarcinoma following eradication treatment. A possible explanation for these findings is that gastric atrophy caused by infection with H. pylori might not be reversible by means of eradication treatment. Gastric atrophy leads to reduced or absent secretion of gastric acid and thus a reduction in acidic gastroesophageal reflux, which is the main risk factor for Barrett’s esophagus and esophageal adenocarcinoma.

Although several studies suggested that H. pylori is protective against esophageal cancer, a recent meta-analysis did not provide strong and consistent evidence for this hypothesis.13 Although most sub-analyses in that meta-analysis suggested lower risks compared to the comparison groups in the individual studies, methodological heterogeneity was high and there were important variations based on study characteristics (including etno-geographical differences).13 Our study uses the entire Swedish population as a comparison group, and we have excluded the first year after eradication to reduce the risk of reverse causality (ie, individuals being diagnosed and treated for early signs of yet undiagnosed cancer). Yet, individuals who received eradication treatment may also be followed up more closely leading to earlier detection, and therefore creating a risk of detection bias; and residual confounding (beyond age, sex, time period) cannot be ruled out. These elements may contribute to the apparent higher risk of Barrett’s esophagus and esophageal adenocarcinoma compared to the Swedish background population, even in the time period closest to the eradication treatment when lower risks may have been expected.

The results of this study do not give any reason to hold back on eradication in individuals who have an indication to receive this treatment, despite being at an increased risk of developing esophageal adenocarcinoma. However, further and larger studies with longer follow-up are needed on this topic, including studies from different regions representing high and low prevalence areas of H. pylori and high and low incidence areas of esophageal adenocarcinoma.

### 5 | CONCLUSION

To conclude, this first study assessing the risk of Barrett’s esophagus and esophageal adenocarcinoma after eradication treatment for H. pylori did not show any gradually increased risk over time after treatment. These findings do not provide any strong evidence to refrain from H. pylori eradication whenever indicated, even in individuals at increased risk of esophageal adenocarcinoma.

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### CONFLICT OF INTEREST

The authors have nothing to disclose. The funding sources have not been involved in the design, conduct, or presentation of the study.

### AUTHORS’ CONTRIBUTIONS

All authors contributed to the study conception and design. Data collection and preparation for analyses by Nele Brusselaers and Eva Doorakkers; data analysis by Eva Doorakkers with support from Giola Santoni and Nele Brusselaers; data interpretation: all authors; writing of first draft: Eva Doorakkers, revised and approved by all authors.

### TABLE 4

Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) of Barrett’s esophagus after Helicobacter pylori eradication treatment in Sweden in 2005-2012

| Time after eradication | 1-2 y | 3-4 y | 5-7.5 y |
|------------------------|-------|-------|---------|
|                        | Patients (number) | SIR (95% CI) | Patients (number) | SIR (95% CI) | Patients (number) | SIR (95% CI) |
| Total                  | 104   | 4.32  (3.53-5.23) | 50     | 3.00  (2.23-3.95) | 24     | 3.09  (1.98-4.59) |
| Sex                    |       |       |         |       |       |         |
| Men                    | 63    | 3.93  (3.02-5.03) | 34     | 3.10  (2.14-4.33) | 14     | 2.76  (1.51-4.63) |
| Women                  | 41    | 5.08  (3.65-6.89) | 16     | 2.81  (1.61-4.56) | 10     | 3.71  (1.78-6.82) |
| Age, years             |       |       |         |       |       |         |
| 18-59                  | 38    | 7.62  (5.39-10.46) | 11     | 3.55  (1.77-6.36) | 6      | 4.60  (1.68-10.01) |
| 60-69                  | 33    | 3.76  (2.59-5.28) | 26     | 4.29  (2.80-6.28) | 8      | 2.81  (1.21-5.53) |
| ≥70                    | 33    | 3.20  (2.20-4.49) | 13     | 1.73  (0.92-2.96) | 10     | 2.76  (1.32-5.08) |
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