Cancer Epidemiology 62 (2019) 101585

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Duration of use of proton pump inhibitors and the risk of gastric and oesophageal cancer

Nele Brusselaers[a,b,c,*], Jesper Lagergren[d,e], Lars Engstrand[a,b]

[a] Centre for Translational Microbiome Research, Department of Microbiology, Tumour and Cell Biology, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden
[b] Science for Life Laboratory (SciLifeLab), Stockholm, Sweden
[c] Department of Head and Skin, Faculty of Medicine, Ghent University, Ghent, Belgium
[d] Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[e] School of Cancer and Pharmaceutical Sciences, King's College London, United Kingdom

ARTICLE INFO

Keywords:
Stomach neoplasms
Esophageal neoplasms
Neoplasms
Proton pump inhibitors
Adenocarcinoma
Carcinoma
Squamous cell

ABSTRACT

Background: There is increasing interest in the potential association between proton pump inhibitors (PPIs) and the risk of gastric and oesophageal cancer, yet the effect of duration of treatment needs clarification.
Methods: This Swedish population-based cohort study assessed the influence of time since initiation of PPI treatment on the risk of gastric and oesophageal cancer, presented as standardised incidence ratios and 95% confidence intervals.
Results: The risk of gastric and oesophageal cancer during the first year was 7–10 times higher than the background population, and remained 24–202% increased without any decrease over time after the first year.
Conclusion: PPI use was associated with an increased risk of gastric and oesophageal cancer and the risk remained increased over follow-up. These results support our original hypothesis that use of PPIs may be a risk factor for gastric and oesophageal cancer in the general population of maintenance users, independent of underlying indications.

1. Introduction

The interest in the potential risks related to long-term use of proton-pump-inhibitors (PPIs) has increased during the last few years, partly due to studies indicating increased risks of cancer and increased overall and cancer-related mortality [1–10]. A recent meta-analyses summarised the risk for gastric cancer, included 7 original studies, and showed a potential 2.5 increased relative risk of gastric cancer among long-term users, in particular among individuals exposed for 3 years or longer [11].

One of the included studies was our population-based study from Sweden assessing maintenance use [12], as defined as an estimated accumulated dosage of 6 months or more, a cohort which was also used to assess the risk of oesophageal cancer [13,14]. In our original nationwide and population-based studies we assessed the risk of gastric and oesophageal cancer overall, by indications of use and by the estimated duration of use [12,13]. The duration analyses were based on the exposure accumulated during the study period, estimated by adding the number of days as defined by the defined daily dose [DDD] for each prescribed and dispensed package. We only included individuals who accumulated at least 6 months of treatment, which is longer than the standard recommended duration of use [15], and was therefore considered maintenance use.

Yet, there are limitations related to the previously used method used to assess duration of use. Individuals who only contributed a few years into the cohort (because of death, cancer or enrolment towards the end of the study period) could never have accumulated 5 years of exposure. We also grouped them in mutually exclusive groups, so each individual could only contribute person-time to one of the 4 categories of duration of treatment; since the estimated duration did not necessarily correspond to the actual duration of exposure (for which reliable data are not available in the Prescribed Drug Registry). This may have led to an immortal time bias, implying that individuals in the category exposed to more than 5 years of treatment could not have developed cancer during the first 5 years. As a result, selection and survival bias occurred, which makes it difficult to assess the true effect related to duration of PPI exposure based on the presented findings. This may have been reflected in the unexpected downward trend of the risk estimates over

* Corresponding author at: Centre for Translational Microbiome Research, Department of Microbiology, Tumour and Cell Biology, Karolinska Institutet, Karolinska Hospital, NKS-Bioclinicum, Visionsgatan 4, 171 64 Stockholm, Sweden.
E-mail address: Nele.Brusselaers@ki.se (N. Brusselaers).

https://doi.org/10.1016/j.canep.2019.101585
Received 25 June 2019; Received in revised form 13 August 2019; Accepted 14 August 2019
Available online 21 August 2019
1877-7821/

time, which did not support our hypothesis of an effect of PPIs on gastric or oesophageal cancer development independent of the underlying indications.

Therefore, the aim of the present study was to assess the risk of gastric and oesophageal cancer based on the same cohort, but instead analysing the time since start of the treatment which should be a closer approximation to any true effect.

2. Material and methods

This nationwide Swedish population-based cohort, described previously in detail [12–14], was used to examine the association between duration of PPI use and the risk of gastric and oesophageal cancer [12–14]. The risk was compared to the Swedish background population, and only individuals without a history of any cancer were included [12,13]. Only adults (≥18 years) without a history of any cancer were included. Individuals who were exposed to maintenance use of both a PPI and a histamine-2-receptor antagonist (the most common alternative treatment for most of the PPI indications) during the study period were excluded. The study was approved by the Regional Ethical Review Board in Stockholm (2014/1291-31/4).

2.1. Exposure

PPI use was defined by the A02BC code of the Anatomical Therapeutic Chemical classification system (ATC). Maintenance use of any PPI was defined as at least 180 days of accumulated use during the study period (before onset of any cancer), estimated based on the Defined Daily Dosage (DDD) per package as registered in the Swedish Prescribed Drug Registry [12,13]. The DDD is the average daily maintenance dose for a drug when used for its main indication in adults, and therefore "DDD per package" is an approximation of the actual use [16]. PPIs are also available over-the-counter in Sweden, but only in smaller and more expensive packages for temporary use, thus making it unlikely to be used for longer term purposes [17].

Duration of use was now defined in relation to time since start of treatment, which was categorised as first year, ≥1–3 years, ≥3–5 years and ≥5 years since the first prescribed and dispensed PPI during the study period (from July 2005 to December 2012).

2.2. Outcomes

The main outcome was a first episode of gastric adenocarcinoma (including gastric cardia), oesophageal adenocarcinoma or oesophageal squamous cell carcinoma according to the Swedish Cancer Registry. The anatomical locations of respectively gastric and oesophageal cancer were defined by the C16 and C15 diagnostic codes of the International Classification of Diseases (ICD), 10th version. Adenocarcinoma and squamous cell carcinoma were defined by the histology codes 096 and 146, respectively.

3. Calculation

The risk of gastric and oesophageal cancer among maintenance PPI users was compared to the risk in the entire Swedish background population of the same sex (male or female), age group (categorised as < 40, 40–49, 50–59, 60–69, or ≥70 years), and calendar period (categorised as 2005–2006, 2007–2009, or 2010–2012). Follow-up time was calculated from the dispense date of the first prescription of PPIs within the study period until death, any cancer, or end of study period (31st December 2012), whichever occurred first. There were no missing data on the exposure, outcome, age, sex, or calendar period.

Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated by dividing the observed number of cases with the expected number, while accounting for changes in age and calendar categories [18]. The expected numbers were derived from the Swedish Cancer Registry and population statistics from Statistics Sweden [19]. The risk of cancer was assessed per time period, so all individuals have contributed person time to first group (first year after start PPI treatment), yet earlier person-time was not included in the analyses of the other time periods (which would have inflated person-time for those exposed to PPIs). Therefore, an individual who was followed-up for more than 5 years, contributed time to all 4 time-period analyses.

Table 1
Descriptive characteristics of all adults exposed to maintenance therapy with proton pump inhibitors in Sweden during 2005–2012.

	Total *Number (%)*
Total	796,492 (100)
Sex	
Men	330,652 (41.5)
Women	465,840 (58.5)
Age	
< 40 years	88,775 (11.2)
40–49 years	103,784 (13.0)
50–59 years	155,625 (19.5)
60–69 years	177,610 (22.3)
≥70 years	270,698 (34.0)
Calendar period	
2005–2006	437,230 (54.9)
2007–2009	227,141 (28.5)
2010–2012	132,121 (16.6)
Gastric adenocarcinoma	1929 (0.24)
Osophageal adenocarcinoma	649 (0.08)
Oesophageal squamous cell carcinoma	353 (0.04)

4. Results

In total, 796,425 adults were exposed to maintenance PPI use during the study period, of whom 59% were female, and 34% were 70 years or older (Table 1). Half of the cohort (53.5%) was followed up for ≥5 years. Overall, 2931 individuals developed gastric or oesophageal cancer, including 1929 gastric adenocarcinoma, 649 oesophageal adenocarcinoma and 353 oesophageal squamous cell carcinoma. During the first year after PPI treatment initiation, the risk of these cancers was strongly increased, with SIRs between 6.91 and 9.90, which was to be expected due to reverse causality (PPIs prescribed because of symptoms because of yet undiagnosed cancer in part of the cohort) (Table 2). Yet, the SIRs for gastric and oesophageal adenocarcinoma remained increased even after the first year of treatment, without any decreasing trend over time, and a 1.31 (95% 1.12–1.53) and 1.91 (1.48–2.43) increased risk 5 years or more after the start of the treatment. For squamous cell carcinoma, the risk appeared to increase over time since start of treatment (excluding the first year), although the 95% CI did not reach statistical significance for the periods ≥1-3 years and ≥3-5 years after start of the treatment, with a SIRs of 1.48 (1.04–2.04) ≥5 years after treatment initiation.

5. Discussion

This nationwide population-based study supports the hypothesis that long-term PPI may be an independent risk factor for gastric and oesophageal cancer, irrespective of underlying indications of use and confounding by indication. As shown previously, the risk of these cancer types was increased even in patients without apparent risk factors for these cancer types, e.g. those exposed to maintenance therapy with aspirin or non-steroidal anti-inflammatory drugs, respectively 35% and 30% of the cohort [12,13]. Only 25% of the total cohort had recorded gastro-oesophageal reflux, one of main known risk factors for oesophageal adenocarcinoma [13]. Several pathophysiological mechanisms have been postulated to explain the potential risks related to long-term PPI use, yet few clinical studies exist and most current

Table 2
Time since start of maintenance treatment with proton pump inhibitors and the risk of oesophageal adenocarcinoma and squamous cell carcinoma, expressed as standardised incidence ratios (SIRs) and 95% confidence intervals.

	Total		*Gastric adenocarcinoma*		*Oesophageal adenocarcinoma*		*Oesophageal squamous cell carcinoma*	
	N (%)	Person years	N (%)	SIRs	N (%)	SIRs	N (%)	SIRs
First year	796,492 (100)	979,007	1,074 (55.6)	**7.22 (6.79–7.66)**	345 (53.2)	**9.90 (8.88–11.00)**	195 (55.2)	**6.91 (5.97–7.95)**
1 year–3 years	729,482 (91.6)	2,340,030	417 (21.6)	**1.48 (1.34–1.63)**	127 (19.6)	**1.81 (1.51–2.16)**	68 (19.3)	**1.19 (0.93–1.51)**
3 years–5 years	580816 (72.9)	1,159,914	273 (14.2)	**1.24 (1.09–1.39)**	110 (16.9)	**2.02 (1.66–2.44)**	53 (15.0)	**1.25 (0.94–1.63)**
> 5 years	426190 (53.5)	747,495	165 (8.6)	**1.31 (1.12–1.53)**	67 (10.3)	**1.91 (1.48–2.43)**	37 (10.5)	**1.48 (1.04–2.04)**
Total	796,492 (100)	979,007	1929 (100)	2.97 (2.83–3.10)	649 (100)	3.93 (3.63–4.24)	353 (100)	2.77 (2.49–3.07)

evidence is based on cross-sectional data or mechanistic animal studies [20]. We hypothesise that the PPI-related changes in microbiome composition, structure and function may be associated with the apparently persistent increased risk of gastric and oesophageal cancer. Previous microbiome studies have suggested that PPIs are the drug group changing the lower-gut microbiome composition most drastically based on cross-sectional population-based data, so even more than antibiotics [21,22]. There is less clinical evidence available to date how PPIs affect the gastric and oesophageal microbiota composition in humans, beyond the unfavourable effects for Helicobacter pylori [23–25]. Yet, PPI-induced dysbiosis may result in chronic inflammation and/or genotoxicity, consequently promoting carcinogenesis [26–28].

By assessing the risk of cancer per time period since initiation of treatment, this study also shows that the risk does not decrease over time since initiation of PPI treatment, which would be expected if the treatment was initiated because of cancer-related symptoms, or if treatment of risk factors for cancer was entirely successful.

H2-receptor antagonists are used for relatively similar indications as PPIs and therefore a good comparator to evaluate potential confounding by indication. Yet, H2-receptor antagonists are clearly less popular, and in Sweden only 20,177 long-term users of H2-receptor antagonists were identified during the study period (who did not use long-term PPIs in parallel) [12,13]. Our previous studies showed a 43% reduced risk of gastric cancer compared to the background population, and 50–60% (non-significant) decrease of oesophageal adenocarcinoma and squamous cell carcinoma [12,13], with the numbers too low to further stratify by time since start of treatment (10 cases of gastric adenocarcinoma, 2 oesophageal adenocarcinoma and 2 squamous cell carcinoma of the oesophagus).

This cohort is the largest cohort described so far assessing the risk of gastric and oesophageal cancer among PPI users, and includes all individuals in Sweden exposed to large quantities of prescribed PPIs during the study period. Although no information was available on PPI use before the study period, this study only includes individuals on maintenance use, who are therefore expected to be “long-term” users. Nevertheless, some of the individuals may have taken PPIs because of yet undiagnosed cancer-related symptoms, which may also have delayed diagnosis.

6. Conclusions

These findings support the hypothesis that long-term PPI use is an independent risk factor for both gastric and oesophageal cancer, irrespective of the underlying indications of use.

Authorship contribution

NB is the guarantor of the article. Literature search: NB; Design of the study: all authors (NB, JL, LE); Data collection and preparation for analyses: NB; Data analysis: NB; Data interpretation: all authors (NB, JL, LE); Writing of first draft: NB, revised and approved by all authors (NB, JL, LE). The final version of the article is approved by all authors (NB, JL, LE).

Funding

This work was supported by Svenska Lakaresallskapet (2018, SLS-788751), Bengt Ihres foundation (2018, SLS-788731), Gastrologisk forskningsfond (2018, SLS-783091).

Declaration of Competing Interest

None.

Acknowledgement

None.

References

[1] H.L. Waldum, R. Fossmark, Proton pump inhibitors and gastric cancer: a long expected side effect finally reported also in man, Gut 67 (1) (2018) 199–200.
[2] K.S. Cheung, E.W. Chan, A.Y.S. Wong, L. Chen, I.C.K. Wong, W.K. Leung, Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study, Gut 67 (1) (2018) 28–35.
[3] R. Niikura, Y. Hayakawa, Y. Hirata, A. Yamada, M. Fujishiro, K. Koike, Long-term proton pump inhibitor use is a risk factor of gastric cancer after treatment for Helicobacter pylori: a retrospective cohort analysis, Gut (2017).
[4] L. Laterza, F. Scaldaferri, A. Gasbarrini, Risk factors for gastric cancer: is it time to discard PPIs? Gut 68 (1) (2019) 176-+.
[5] E. Akriviadis, C. Liava, Proton pump inhibitors and risk for gastric cancer: is it real? Turk. J. Gastroenterol. 30 (3) (2019) 309–310.
[6] H.L. Waldum, O. Sordal, R. Fossmark, Proton pump inhibitors (PPIs) may cause gastric cancer - clinical consequences, Scand. J. Gastroenterol. 53 (6) (2018) 639–642.
[7] C. Liatsos, T. Rokkas, The effect of chronic use of proton pump inhibitors on gastric cancer: should we be aware of It? Dig. Dis. 36 (6) (2018) 395–396.
[8] P.F. Haastrup, W. Thompson, J. Sondergaard, D.E. Jarbol, Side effects of long-term proton pump inhibitor use: a review, Basic Clin. Pharmacol. Toxicol. 123 (2) (2018) 114–121.
[9] J.J.S. Domingo, Proton pump inhibitors and gastric carcinogenesis, Med. Clin. 151 (10) (2018) 400–401.
[10] G.N.J. Tytgat, Gastro update Europe 2018, Dig. Dis. 37 (3) (2019) 175–187.
[11] K. Jiang, X. Jiang, Y. Wen, L. Liao, F. Liu, Relationship between long-term use of proton pump inhibitors and risk of gastric cancer: a systematic analysis, J. Gastroenterol. Hepatol. (2019).
[12] N. Brusselaers, K. Wahlin, L. Engstrand, J. Lagergren, Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden, BMJ Open 7 (10) (2017) e017739.
[13] N. Brusselaers, L. Engstrand, J. Lagergren, Maintenance proton pump inhibition therapy and risk of oesophageal cancer, Cancer Epidemiol. 53 (2018) 172–177.
[14] N. Brusselaers, L. Engstrand, J. Lagergren, PPI use and oesophageal cancer: what if the results are true? Cancer Epidemiol. 54 (2018) 139–140.
[15] B. Farrell, K. Pottie, W. Thompson, T. Boghossian, L. Pizzola, F.J. Rashid, C. Rojas-Fernandez, K. Walsh, V. Welch, P. Moayyedi, Deprescribing proton pump inhibitors: evidence-based clinical practice guideline, Can. Fam. Phys. 63 (5) (2017) 354–364.
[16] ATC/DDD-Index, The Anatomical Therapeutic Chemical (ATC)/ Defined Daily Dose (DDD) Index, (2014).
[17] FASS (Farmacevtiska specialiteter i Sverige/ Farmaceutical specialities in Sweden), (2015).
[18] N. Breslow, N. Day, Statistical Methods in Cancer research: The Design and Analysis of Cohort Studies, Lyon (1987).
[19] Statistics Sweden - Statistical Database Population Statistics (accessed 06 April 2016) http://www.statistikdatabasen.scb.se/http://www.statistikdatabasen.scb.se/.
[20] A. Corsonello, F. Lattanzio, S. Bustacchini, S. Garasto, A. Cozza, R. Schepisi, F. Lenci, F. Luciani, M.G. Maggio, A. Ticinesi, V. Butto, S. Tagliaferri, F. Corica, Adverse events of proton pump inhibitors: potential mechanisms, Curr. Drug Metab.

19 (2) (2018) 142–154.
[21] F. Imhann, A. Vich Vila, M.J. Bonder, A.G. Lopez Manosalva, D.P.Y. Koonen, J. Fu, C. Wijmenga, A. Zhernakova, R.K. Weersma, The influence of proton pump inhibitors and other commonly used medication on the gut microbiota, Gut Microbes 8 (4) (2017) 351–358.
[22] A. Zhernakova, A. Kurilshikov, M.J. Bonder, E.F. Tigchelaar, M. Schirmer, T. Vatanen, Z. Mujagic, A.V. Vila, G. Falony, S. Vieira-Silva, J. Wang, F. Imhann, E. Brandsma, S.A. Jankipersadsing, M. Joossens, M.C. Cenit, P. Deelen, M.A. Swertz, R.K. Weersma, E.J. Feskens, M.G. Netea, D. Gevers, D. Jonkers, L. Franke, Y.S. Aulchenko, C. Huttenhower, J. Raes, M.H. Hofker, R.J. Xavier, C. Wijmenga, J. Fu, Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity, Science 352 (6285) (2016) 565–569.
[23] G. Bruno, P. Zaccari, G. Rocco, G. Scalese, C. Panetta, B. Porowska, S. Pontone, C. Severi, Proton pump inhibitors and dysbiosis: current knowledge and aspects to be clarified, World J. Gastroenterol. 25 (22) (2019) 2706–2719.
[24] Y.C. Shi, S.T. Cai, Y.P. Tian, H.J. Zhao, Y.B. Zhang, J. Chen, R.R. Ren, X. Luo, L.H. Peng, G. Sun, Y.S. Yang, Effects of proton pump inhibitors on the gastrointestinal microbiota in gastroesophageal reflux disease, Genom. Proteom. Bioinf. 17 (1) (2019) 52–63.
[25] D.E. Freedberg, B. Lebwohl, J.A. Abrams, The impact of proton pump inhibitors on the human gastrointestinal microbiome, Clin. Lab. Med. 34 (4) (2014) 771–785.
[26] J. Pereira-Marques, R.M. Ferreira, I. Pinto-Ribeiro, C. Figueiredo, Helicobacter pylori infection, the gastric microbiome and gastric cancer, Adv. Exp. Med. Biol. (2019).
[27] O.O. Coker, Z. Dai, Y. Nie, G. Zhao, L. Cao, G. Nakatsu, W.K. Wu, S.H. Wong, Z. Chen, J.J.Y. Sung, J. Yu, Mucosal microbiome dysbiosis in gastric carcinogenesis, Gut 67 (6) (2018) 1024–1032.
[28] K. Vinasco, H.M. Mitchell, N.O. Kaakoush, N. Castano-Rodriguez, Microbial carcinogenesis: lactic acid bacteria in gastric cancer, Biochim. Biophys. Acta Rev. Cancer (2019).