Editorial Commentary

Proton pump inhibitors and an increased risk of gastric cancer: how much more evidence is needed?

Nele Brusselaers[1,2,3], Johanna Simin[1]

[1]Centre for Translational Microbiome Research, Karolinska Institutet, Stockholm, Sweden; [2]Global Health Institute, Antwerp University, Antwerp, Belgium; [3]Department of Head and Skin, Ghent University, Ghent, Belgium

Correspondence to: Nele Brusselaers, MD, PhD, MSc. Centre for Translational Microbiome Research, Karolinska Institutet, Solnavägen 9, 17165 Stockholm, Sweden. Email: Nele.Brusselaers@ki.se.

Comment on: Abrahami D, McDonald EG, Schnitzer ME, *et al.* Proton pump inhibitors and risk of gastric cancer: population-based cohort study. Gut 2022;71:16-24.

Received: 09 August 2022; Accepted: 20 August 2022; Published: 30 December 2022.

doi: 10.21037/dmr-22-57

View this article at: https://dx.doi.org/10.21037/dmr-22-57

The paper of Abrahami *et al.* in *Gut* is one of the most recent additions to the steadily expanding body of evidence supporting an association between long-term proton-pump inhibitor (PPIs) use and gastric cancer (1). In this study, the United Kingdom Clinical Practice Datalink data are used [1990–2018], including 973,281 new users of PPIs and 193,306 new users of H2-receptor antagonists (H2RAs), comparing the risk of gastric cancer head-to-head in an "active-comparator design" taking into account demographics and lifestyle (1). All users were older than 40 years, followed up from 1 year after cohort entry (median 5 years follow-up), and considered continuously exposed (1). Although the risk of gastric cancer was 45% higher among PPI users compared to H2RA users, the absolute risk was reported to be low, with a number-needed-to harm of 2,121 (5 years) or 1,191 (10 years) (1). Yet, considering the high number of (long-term) PPI users worldwide, with annual prevalences up to 10–30% of all adults, this associated risk is far from negligible (2-5).

Several meta-analyses have been published during the recent years regarding the same question, with similar conclusions, that PPI use is associated with an increased risk of gastric cancer (6-11). Additionally, increased risks have been suggested for many more diseases including gastro-intestinal cancers, osteoporosis, fractures, kidney disease and gastro-intestinal infections including *Clostridioides* infections, and even overall survival (7,12,13). The list of papers suggesting long-term harmful effects of PPI use is growing steadily.

While the majority of the previous papers investigating the gastric-carcinogenic potential of long-term PPIs used non-exposed individuals as comparator, this paper uses H2RA users as reference group (1). This comparator is used to tackle confounding by indication, a common problem in pharmaco-epidemiology studies. Is it the drug or is it the treatment which "causes" the increased risk? The problem with these gastro-intestinal indications for PPI, is that there is basically no one with lasting indications not being treated in the Western world—and that the alternative treatment, H2RA are clearly less popular—with almost a monopoly position of PPIs. Another approach to confounding by indication regarding this question, is looking at specific indications separately (2) or restrict to one or a few indications like those treated for *Helicobacter pylori* (14,15). Comparing PPI to H2RA head-to-head like in this UK study would not be feasible in Sweden, with 40 times more PPI maintenance users than H2RA users (2).

The reported absolute risk, with a number-needed-to-harm of 2,121 (5 years) or 1,191 (10 years), was described by the authors as low (1). Yet, we did some back-to-envelope calculations, which actually do show worrisome results. Measures of impact do depend on the prevalence of a certain risk or protective factor. In the presented paper, these numbers-needed-to-harm are based on a population of 40 years and older, and including any new (incident) users of PPIs with a follow-up of at least 1 year (maximal 29 years)—yet everyone was considered to remain exposed. Although no sub-analyses based on age were reported, we

Table 1 A quick estimate of how many cases of gastric cancer would be caused by PPIs, based on the Abrahami *et al.*'s results, United Nation population statistics and Globocan cancer numbers in a handful selected countries

Country	N_{adults} (thousands) (United Nations, 2021)	Gastric cancer incidence, crude* (Globocan/WHO 2020)	Annual $N_{gastric\ cancer}$ (Globocan/ WHO 2020)	N_{PPI} (assuming 10% prevalence)	Based on 5 y NNT/5 = (N_{PPI}/2,121)/5	Based on 10 y NNT/10 = (N_{PPI}/1,191)/10	% "caused" by PPI (based on 5 y NNH)	% "caused" by PPI (based on 10 y NNH)
United States	262,263	7.9	26,259	26,226,300	2,473	2,202	9.4	8.4
United Kingdom	53,112	9.7	6,568	5,311,200	501	446	7.6	6.8
Belgium	9,283	13.7	1,593	928,300	88	78	5.5	4.9
Sweden	8,252	7.8	787	825,200	78	69	9.9	8.8
France	50,964	10.9	7,140	5,096,400	481	428	6.7	6.0
Germany	69,573	18.3	15,322	6,957,300	656	584	4.3	3.8

Sources: Globocan Cancer Statistics/WHO (2020 estimates): https://gco.iarc.fr/today/online-analysis-table; United Nations-World Population Prospects 2022 (2021 estimates): https://population.un.org/wpp/Download/Standard/Population/. *, crude rate per 100,000. PPI, proton-pump inhibitor; WHO, World Health Organization; NNT, number-needed-to-treat; NNH, number-needed-to-harm [as reported by Abrahami *et al.*: 2,121 (5 years) and 1,191 (10 years)].

previously showed large differences in relative risk based on age, with the highest risks in those younger than 40 years [standardised incidence ratio (SIR) =22.8 versus SIR =2.8 among those older than 70 years] (2). But let us assume the risk is equal in all age groups above 18 years.

PPIs are used by up to 10–30% of adults, with approximately 11% maintenance use (accumulated 6 months) in our nationwide studies in Sweden (2-5). According to another paper by Abrahami *et al.*, PPI prevalence in the UK was 14.2% in 2018 (16). To obtain more conservative estimates, let us assume a prevalence of 10% among adults (18 years or older) and that all gastric cancer cases occur in adults. The Abrahami study was based on incident use, yet one prescription during the follow-up period of maximal 29 years was apparently sufficient (implying their incident use was most likely far above this assumed prevalence).

Table 1 shows the proportion of gastric cancer cases estimated to have been "caused" by PPI use, assuming the abovementioned numbers-needed-to-harm, also reporting the incidence in a few selected countries. This shows that approximately 5–10% of all gastric cancers would be caused by PPIs, assuming a causal relationship. We know that several factors are linked to gastric cancer, including *Helicobacter pylori*, smoking, diet, alcohol, obesity, etc., of which some are also linked to PPI use. According to US data, 1/3 of cardia adenocarcinoma would be caused by smoking and 1/3 by obesity; and 1/10 of non-cardia cancer by smoking—but drug intake was not considered (17). A recent review on environmental risk factors and gastric cancer did not mention drug intake either (18). With the growing body of evidence showing an association between PPI use and gastric cancer—it is essential to assess what this actually means. For the individual patient, it will remain challenging to pinpoint if PPIs were the causal factor, and we should assume a multi-causal origin in most cases. Yet, if we look at the population-level, PPI use should not be ignored in the evaluation of risk factors for gastric cancer—especially since it is a modifiable risk factor.

To conclude, even if the overall balance between short and long-term harms and benefits pleads in favour of PPI for the individual, it may be important to reconsider how we use PPIs, and particularly avoid long-term use if possible (19). A treatment of up to 4–8 weeks should be sufficient for most common indications of PPIs including gastro-oesophageal reflux, yet deprescribing is challenging (20). It is not known if there is a safe dose and duration for PPI use considering the risk of gastric cancer use since this may depend on the individual characteristics of the patient. Previous studies have used different definitions of PPI-use, like the Abrahami paper considering incident use of one prescription or more during the study period (1); while we used 6 months accumulated use in our Swedish studies (2). It can however be presumed that longer durations would lead to a higher risk of cancer, as continued exposure will also hinder a restoration to healthier gastrointestinal exposure (21,22).

We should also acknowledge our lack of knowledge and understanding on long-term side-effects of any maintenance therapy, not only PPIs. It has been reported that 25% to 70% of long-term PPI use lacks a clear medical indication, so over-prescription of PPIs does occur (23,24). The costs

of inappropriate use of PPIs are also alarmingly high, for the patient and society (25).

Acknowledgments

Funding: This work was supported by the Swedish Research Council (No. 2020-01058 to NB).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-57/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Abrahami D, McDonald EG, Schnitzer ME, et al. Proton pump inhibitors and risk of gastric cancer: population-based cohort study. Gut 2022;71:16-24.
2. Brusselaers N, Wahlin K, Engstrand L, et al. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open 2017;7:e017739.
3. Lassalle M, Le Tri T, Bardou M, et al. Use of proton pump inhibitors in adults in France: a nationwide drug utilization study. Eur J Clin Pharmacol 2020;76:449-57.
4. Hálfdánarson ÓÖ, Pottegård A, Björnsson ES, et al. Proton-pump inhibitors among adults: a nationwide drug-utilization study. Therap Adv Gastroenterol 2018;11:1756284818777943.
5. Tosetti C, Nanni I. Use of proton pump inhibitors in general practice. World J Gastrointest Pharmacol Ther 2017;8:180-5.
6. Song HJ, Jeon N, Squires P. The association between acid-suppressive agent use and the risk of cancer: a systematic review and meta-analysis. Eur J Clin Pharmacol 2020;76:1437-56.
7. Salvo EM, Ferko NC, Cash SB, et al. Umbrella review of 42 systematic reviews with meta-analyses: the safety of proton pump inhibitors. Aliment Pharmacol Ther 2021;54:129-43.
8. Zeng R, Cheng Y, Luo D, et al. Comprehensive analysis of proton pump inhibitors and risk of digestive tract cancers. Eur J Cancer 2021;156:190-201.
9. Tran-Duy A, Spaetgens B, Hoes AW, et al. Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2016;14:1706-1719.e5.
10. Islam MM, Poly TN, Walther BA, et al. Adverse outcomes of long-term use of proton pump inhibitors: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2018;30:1395-405.
11. Jiang K, Jiang X, Wen Y, et al. Relationship between long-term use of proton pump inhibitors and risk of gastric cancer: A systematic analysis. J Gastroenterol Hepatol 2019;34:1898-905.
12. Veettil SK, Sadoyu S, Bald EM, et al. Association of proton-pump inhibitor use with adverse health outcomes: A systematic umbrella review of meta-analyses of cohort studies and randomised controlled trials. Br J Clin Pharmacol 2022;88:1551-66.
13. Ben-Eltriki M, Green CJ, Maclure M, et al. Do proton pump inhibitors increase mortality? A systematic review and in-depth analysis of the evidence. Pharmacol Res Perspect 2020;8:e00651.
14. Cheung KS, Chan EW, Wong AYS, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018;67:28-35.
15. Niikura R, Hayakawa Y, Hirata Y, et al. Long-term proton pump inhibitor use is a risk factor of gastric cancer after treatment for Helicobacter pylori: a retrospective cohort analysis. Gut 2018;67:1908-10.
16. Abrahami D, McDonald EG, Schnitzer M, et al. Trends in acid suppressant drug prescriptions in primary care in the UK: a population-based cross-sectional study. BMJ Open

2020;10:e041529.
17. Wang SM, Katki HA, Graubard BI, et al. Population Attributable Risks of Subtypes of Esophageal and Gastric Cancers in the United States. Am J Gastroenterol 2021;116:1844-52.
18. Kayamba V, Kelly P. Environmental factors associated with gastric carcinogenesis. Curr Opin Gastroenterol 2022;38:156-61.
19. Waldum HL, Sørdal Ø, Fossmark R. Proton pump inhibitors (PPIs) may cause gastric cancer - clinical consequences. Scand J Gastroenterol 2018;53:639-42.
20. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. Can Fam Physician 2017;63:354-64.
21. Imhann F, Vich Vila A, Bonder MJ, et al. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microbes 2017;8:351-8.
22. Brawner KM, Morrow CD, Smith PD. Gastric microbiome and gastric cancer. Cancer J 2014;20:211-6.
23. Boghossian TA, Rashid FJ, Thompson W, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Syst Rev 2017;3:CD011969.
24. Kim J, Blackett JW, Jodorkovsky D. Strategies for Effective Discontinuation of Proton Pump Inhibitors. Curr Gastroenterol Rep 2018;20:27.
25. Ladd AM, Panagopoulos G, Cohen J, et al. Potential costs of inappropriate use of proton pump inhibitors. Am J Med Sci 2014;347:446-51.

doi: 10.21037/dmr-22-57
Cite this article as: Brusselaers N, Simin J. Proton pump inhibitors and an increased risk of gastric cancer: how much more evidence is needed? Dig Med Res 2022;5:52.