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Observational Study

Perceived risk of gastric cancer associated with long-term use of proton pump inhibitors: Bridging the gap

Ibrahim O Sawaied, Abraham O Samson, Efrat Golan

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Ibrahim O Sawaied, Abraham O Samson, Azrieli Faculty of Medicine, Bar Ilan University, Safed 21700000, Israel

Efrat Golan, Department of Pediatric Medicine, Haemek Hospital, Afula 2170000, Israel

Corresponding author: Ibrahim O Sawaied, Azrieli Faculty of Medicine, Bar Ilan University, Henrietta Szold St 8, Safed 21700000, Israel. ibomsa13@gmail.com

Abstract

BACKGROUND

Long-term use of proton pump inhibitors (PPIs) has been associated with potential adverse effects, including an increased risk of gastric cancer. Despite widespread use awareness of these risks among physicians varies considerably. Understanding physicians' perceptions and prescribing behaviors is critical to improving patient safety and promoting evidence-based practices. This study aimed to assess the level of awareness and risk perception among gastroenterologists and non-gastroenterologists regarding prolonged PPI use and its association with gastric malignancy.

AIM

To assess physicians' awareness of gastric cancer risk associated with long-term PPI use and compare perceptions between specialties.

METHODS

A cross-sectional observational study was conducted among 33 physicians (15 gastroenterologists and 18 non-gastroenterologists) in Israel. Participants completed a structured questionnaire evaluating knowledge, attitudes, and prescribing behaviors related to PPI use. Data were analyzed using descriptive statistics and nonparametric tests to assess differences between groups and correlation patterns. Ethical approval and informed consent were obtained.

RESULTS

Gastroenterologists demonstrated significantly higher awareness of the potential gastric cancer risks linked to prolonged PPI use (mean awareness score: 6.9 ± 1.2) compared with non-gastroenterologists (4.1 ± 1.3, $P < 0.01$). Despite their awareness 80% of gastroenterologists reported frequent long-term prescribing. Nonparametric correlation analysis revealed associations between specialty, knowledge level, and prescribing habits. Several misconceptions about cancer risk

mechanisms were identified across specialties.

CONCLUSION
Physician awareness regarding gastric cancer risk of long-term PPI use remains inconsistent, especially among non-specialists, emphasizing the need for targeted educational programs and clearer prescribing guidelines.

Key Words: Proton pump inhibitors; Gastric cancer; Family physicians; Gastroenterologists; Long-term use; Gastroesophageal reflux disease; Adverse effects; Clinical guidelines; Patient safety

Core Tip: This cross-sectional study highlighted a significant gap in physician awareness regarding the long-term risks of proton pump inhibitor use, particularly the association with gastric cancer. While gastroenterologists demonstrated higher awareness, they were also more likely to prescribe proton pump inhibitors long-term. These findings underscore the need for improved clinical guidelines, periodic medication reassessment, and targeted educational interventions to ensure safer prescribing practices and optimize patient care.

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INTRODUCTION

Proton pump inhibitors (PPIs) are one the most prescribed drugs worldwide. PPIs are used to manage acid-related gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), peptic ulcers, Zollinger-Ellison syndrome, and erosive esophagitis[1]. PPIs irreversibly bind H^+/K^+ ATPases, also known as proton pumps, and inhibit the final step of gastric acid production in parietal cells lining the stomach. PPIs effectively reduce gastric acid secretion and offer significant relief from symptoms including heartburn, acid reflux, and indigestion. Since their introduction in the late 1980s, PPIs have revolutionized gastroenterology and have become indispensable in clinical practice due to their efficacy, relative safety, and ability to promote mucosal healing[2].

PPIs are particularly effective in treating conditions associated with hyperacidity, including Barrett's esophagus, a precursor to esophageal cancer, and in preventing gastroduodenal ulcers in patients receiving nonsteroidal anti-inflammatory drugs, or antiplatelet therapy. PPIs are used extensively, and their popularity has increased with their availability over the counter for self-medication of heartburn and dyspepsia[3]. This availability has boosted short-term and long-term PPI use, raising concerns about their misuse, overuse, and abuse.

The first PPI, omeprazole, reached the market in 1988 and paved the way for other family members lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole[4]. Before PPI introduction histamine-2 receptor (H2R) antagonists, such as famotidine, ranitidine, and cimetidine, were the primary treatments for acid-related disorders. These antagonists bind reversibly to H2Rs and provide temporary acid-suppression only. The H2R antagonists are also associated with the development of tolerance over time unlike PPIs that provide sustained acid suppression[5].

The evolution of PPIs has led to better symptom control, faster mucosal healing, and improved clinical outcomes for conditions like erosive esophagitis and peptic ulcer disease. The emergence of PPIs is also paralleled with advances in understanding peptic ulcers and has solidified their role in combination therapies for eradicating *Helicobacter pylori* (*H. pylori*)[6]. Consequently, PPIs have become a cornerstone of modern gastroenterology, bringing about a paradigm shift from temporary symptomatic relief to long-term disease management.

PPIs are prodrugs that require activation in the acidic environment of the parietal cell canaliculi[7]. Upon ingestion PPIs are absorbed in the small intestine and undergo first-pass hepatic metabolism *via* the cytochrome P450 (CYP) enzymes, primarily CYP2C19 and CYP3A4. Then, they are distributed *via* systemic circulation throughout the organism until they reach the parietal cells. Once in the acidic canaliculi, PPIs are converted to their active sulfenic acid or sulfenamide form, which covalently bind to a cysteine residue on the proton pump, leading to irreversible inhibition. This mechanism explains their long duration of action despite the relatively short plasma half-life (1-2 h) of most PPIs.

Recent studies have highlighted the increased risk of gastric cancer with prolonged use of PPIs[8]. Other reports have shown a significantly increased risk of gastric cancer, particularly among patients with a history of *H. pylori* infection[9]. In addition, PPI use has been linked with chronic kidney disease[10]. Finally, PPIs have been associated with dementia and cognitive decline[11]. Despite increasing evidence of potential risks, several studies indicate a lack of awareness among healthcare professionals regarding the long-term adverse effects of PPIs[12]. This gap contributes to the overprescription and prolonged use of PPIs without adequate risk assessment.

Here we surveyed this gap and queried professional health practitioners, particularly gastroenterologists, about their prescription practices using a structured questionnaire. Our study uniquely investigated the perceived awareness gap between gastroenterologists and non-gastroenterologists regarding the gastric cancer risks associated with prolonged PPI use. We also integrated pharmacological risk rankings with physician perceptions, offering a novel angle that bridges clinical pharmacology and real-world clinical decisions.

MATERIALS AND METHODS

Study design

This cross-sectional study was designed to assess prescription practices, the awareness of risk, and the challenges in managing long-term PPI use among healthcare professionals. The study used a structured questionnaire, which included five sections: (1) Demographics and professional background; (2) Prescription practices; (3) Awareness of risks; (4) Risk mitigation strategies; and (5) Perceived challenges.

Sampling and recruitment

Physicians were recruited through social media platforms and by invitation to professional networks and medical and gastroenterology societies. The target population was gastroenterologists, but other specialties were also included.

Data collection

Data were collected anonymously through a secure online platform to ensure participant confidentiality. Ethical approval was secured from the Institutional Review Board, approval No. 06-2023 of the Faculty of Medicine, Bar Ilan University.

Statistical analysis

Data were analyzed using SPSS and R software. To summarize demographic information and response distributions, descriptive statistics were used. To examine relationships between demographic and other variables such as awareness and prescription practices. Binary variables were numericized using 1 and 0 for male and female, for aware and unaware, *etc.* Non-binary variables were also numericized using higher numerals. Finally, the numerical variables were analyzed using nonparametric methods, including χ^2 tests appropriate for categorical data. This study should be interpreted as a pilot study designed to identify trends and inform future, larger-scale studies.

RESULTS

Table 1 summarizes the demographic background of the surveyed physicians (n = 33). Altogether the participants included a wide variety of physicians. Both gastroenterologists and non-gastroenterologists were surveyed to examine the effect of discipline on the responses. Table 1 shows a balanced representation of gastroenterologists and others, ensuring a broad perspective on PPI prescribing practices. Likewise, the number of years of experience highlighted a varied mix of early-career (< 10 years), mid-career (10-20 years), and experienced practitioners (> 20 years). Finally, the gender distribution in Table 1 revealed a nearly equal representation of male and female participants, thus minimizing potential bias. Notably, gender, geographical location, and years of experience were uncorrelated with each other, as reflected by $P < 0.01$.

Notably, all physicians agreed that PPIs are effective in the treatment of peptic ulcers and GERD. Thus, the perceived effectiveness of PPIs contributes to their widespread and long-term use. When asked if they prescribe PPIs chronically for more than 3 months, 29 of 33 physicians (87%) responded yes, while 4 (13%) said no (Table 2). Thus, a vast majority of physicians perceive PPIs suitable for chronic long-term use of more than 3 months, and a small minority prefer avoiding chronic long-term prescription of PPI due to potential risks. Among the non-gastroenterologists 14 out of 18 respondents (74%) have prescribed long-term PPI. On the other hand all 15 gastroenterologists (100%) responded they prescribe PPIs chronically for more than 3 months. Notably, gastroenterologists are more likely to prescribe PPIs than any other medical specialty (P = 0.04). These findings are summarized in Table 2.

Table 2 also uncovers a significant knowledge gap, with 22 of 33 physicians (66%) aware of the long-term adverse effects and the increased risk of gastric cancer. From the open comments, many of those aware of the gastric cancer risk are generally also aware of other adverse effects linked to chronic PPI usage, such as nutrient deficiencies (*e.g.*, vitamin B12, iron, *etc.*). The awareness gap was even more pronounced between non-gastroenterologists and gastroenterologists, with all 15 gastroenterologists (100%) but only 7 of 18 non-gastroenterologists (38%), confirming the known associations between PPIs and gastric cancer. As such gastroenterologists demonstrated a higher awareness of long-term risks, as indicated by the correlation (P = 0.04) consistent with their higher awareness of potential risks. The gap between gastroenterologists and non-gastroenterologists advocates the need for specialized training among non-gastroenterologists and continued education in general practice settings (P = 0.0007) between the gastroenterology specialty and awareness of gastric cancer. In addition, gastroenterologists are more likely to prescribe long-term PPIs compared with non-gastroenterologists.

After reading information about the cancer risk associated with PPI, the physicians were asked again if they would prescribe PPIs chronically for more than 3 months: 25 of 33 physicians (75%) said yes; and only 8 (25%) responded no. The gap is even more pronounced between gastroenterologists and non-gastroenterologists, with 93% of gastroentero-

Table 1 Demographics of participants

Characteristics	*n* = 33
Medical specialty	
Gastroenterologist	15 (45.0)
Non-gastroenterologists	18 (55.0)
Years of experience	
< 10	24 (26.3)
10-20	34 (37.4)
> 20	33 (36.3)
Gender	
Male	42 (46.0)
Female	49 (54.0)
Geographical region	
North	48 (53.0)
Center	33 (36.0)
South	10 (11.0)

Data are presented as *n* (%).

Table 2 Responses of gastroenterologists *vs* non-gastroenterologists

Characteristic	Gastro (*n* = 15)	Non-gastro (*n* = 18)	*P* value	Together (*n* = 33)
Have prescribed long-term PPI	15 (100)	14 (74)	0.0400[a]	29 (87)
Aware of gastric cancer risk	15 (100)	7 (38)	0.0001[b]	22 (66)
Will prescribe long-term PPI	14 (93)	12 (66)	0.0800	25 (75)

[a]$P < 0.05$.
[b]$P < 0.01$.
PPI: Proton pump inhibitors; Gastro: Gastroenterologist; Non-gastro: Non-gastroenterologist.

logists and only 66% of non-gastroenterologists in favor of prescribing long-term PPIs in the future. The main reasons provided by physicians for continued use include variations of the following: (1) The risk for gastric cancer is unreal and confounded by various parameters; (2) The risk for gastric cancer is low and the likelihood small; and (3) The overall benefit of treatment outweighs the potential risk citing concerns over patients' pain. Interestingly, some physicians also noted that PPIs have been associated with a reduced risk of neoplastic progression of Barrett's esophagus[9] and could in fact benefit cancer therapy[10].

Our results also showed a correlation ($P = 0.07$) between physicians that prescribed long-term PPIs in the past and those that will in the future despite acknowledging the gastric-cancer risk. Likewise, the awareness of gastric cancer risk is slightly associated with long-term prescriptions ($r = 0.24$) among all physicians. This correlation was absent among non-gastroenterologists ($r = 0.01$), and we believe that awareness among gastroenterologists is an important factor for continued long-term prescription of PPI.

There is no correlation between the awareness of cancer risk and the years of experience ($r = -0.09$), with more experienced practitioners demonstrating the same awareness of long-term risks. Likewise, there was no association between awareness and gender ($r = 0.09$), and both male and female physicians exhibited a similar awareness to adverse effects. Also, there is no association between awareness and geographic location ($r = -0.03$). with physicians from different parts of the country showing similar awareness. These results underscore the need for continued education in particular for non-gastroenterologists and for both early-career and late-career physicians and males and females alike.

DISCUSSION

Here, we surveyed healthcare professionals on their awareness of gastric cancer risk associated with long-term use (>

3 months) of PPIs. We found that all gastroenterologists (100%) but only a few non-gastroenterologists (38%) were aware of the gastric cancer risk. This awareness did not prevent them from prescribing PPIs chronically for more than 3 months. In fact 93% of gastroenterologists and 66% of non-gastroenterologists responded that they would prescribe PPIs for more than 3 months in the future again. Generally, gastroenterologists are more aware of long-term PPI risks compared with non-gastroenterologists due to their specialized training. This did not prevent them from prescribing long-term use of PPI.

Gastroenterologists showed higher awareness than non-gastroenterologists, with a correlation of $r = 0.65$. Notably, there was no correlation between awareness, gender, years of experience, and geographical location. Likewise, similar risk management tendencies were noted for practitioners in different districts, gender, and years of experience. Interestingly, practitioners with awareness of gastric cancer risks were also more likely to continue with long-term prescriptions ($r = 0.24$). This correlation was absent among non-gastroenterologists ($r = 0.01$). As such we believe that awareness, particularly among gastroenterologists, is a key factor for the continued willingness to prescribe long-term PPI, emphasizing the importance of this study as well as the educational opportunity. Our analysis provided valuable insights into the interplay between awareness and prescribing practices of long-term PPI and informed the development of educational programs and clinical guidelines to optimize long-term PPI usage.

Perception gap

The perception gap is also reflected in guidelines of leading medical and gastroenterological societies. For example, the American Association of Family Physicians (2018) raised some concern about PPIs and gastric cancers and emphasized the importance of appropriate indication. The association writes that a small yet clinically significant increase in the risk of gastric cancer exists among PPI users. The number of doses needed to harm a user amount to 1191 over 10 years. Thus, practitioners initiating antacids should begin with an H2R antagonist and if prescribing a PPI should use the lowest dose and duration possible. The Royal Australian College of General Practitioners (2020) minimized the concern and reported that more PPI users died of heart disease (15 per 1000) and chronic kidney disease (4 per 1000) than of gastric cancer (and 2 per 1000). The Canadian Association of Gastroenterology (2021) questioned the evidence of gastric cancer risk[13] .The association disapproved of the adjustment for confounders and suggested that gastric cancer is less associated with PPI use than with age and other risk factors for gastric cancer, like smoking, alcohol, and obesity. Likewise, The American Association of Gastroenterology American College of Gastroenterology (2017) suggested that gastric cancers were associated with GERD and peptic ulcers, particularly if left untreated[14]. As such PPIs themselves do not cause cancer. Rather their use is associated with cancer. These discrepancies coincide with the awareness gap among physicians and results in different prescription practices.

To support evidence-based prescription and calculate risk assessment independently, there is a need to use different approaches and different PPI formulations. Usually, PPIs are orally administered, but this need not be the case. Transdermal administration of the prodrug through a skin-patch is bioavailable as suggested by the hydrophobic log *P* values of PPIs[15]. This alternative route of administration as well as intravenous administration avoids exposure of the gastric microbiome to PPIs. The alternative routes of administration do not interfere with the mechanism of action as the prodrug is absorbed into the circulatory system before reaching the secretory canaliculi of gastric parietal cells and before being metabolized into the active compound that exerts a therapeutic effect by irreversibly inhibiting the H^+/K^+ ATPase enzyme, also known as the proton pump. The pump is responsible for the final step in gastric acid secretion, exchanging hydrogen ions with potassium ions to maintain gastric acidity. By blocking this exchange PPIs effectively reduce both basal and stimulated gastric acid secretion, leading to increased intragastric pH and promoting healing of acid-related mucosal damage. By avoiding microbiome exposure to PPI, circumventing first pass-metabolism, and skipping absorption through the portal vein, PPI may exert a less toxic effect. In addition, evidence-based studies should use dose-dependent effects to corroborate or discredit causality.

Likewise, PPIs should be prescribed for evidence-based indications. These indications include a wide range of acid-related gastrointestinal disorders such as: (1) GERD as a standard first-line therapy for healing erosive esophagitis and maintaining symptomatic relief[16]; (2) Peptic ulcer disease for the treatment of both duodenal and gastric ulcers, including *H. pylori*-associated ulcers as part of combination therapy[17]; (3) Zollinger-Ellison syndrome where high-dose PPIs are the treatment of choice for this rare condition characterized by gastrin-secreting tumors leading to severe hyperacidity[18]; (4) Nonsteroidal anti-inflammatory drug-induced ulcers as a prophylactic measure in high-risk patients on antiplatelet therapy[19]; (5) Barrett's esophagus and esophageal strictures with long-term PPI therapy is recommended for reducing the risk of adenocarcinoma in patients with Barrett's esophagus[20]; and (6) Functional dyspepsia and stress ulcer prophylaxis in patients who are critically ill to prevent stress-related mucosal damage[21].

Periodic reassessment (automated and not)

Regular evaluation of the necessity for continued PPI therapy, particularly for long-term users, is needed. Our results underscore the need for educational interventions and unified clinical guidelines to enhance awareness and promote safer prescribing practices[22]. We believe that enhancing awareness of long-term risks leads to more cautious and informed PPI prescribing practices. Awareness and periodic reassessment ultimately improve patient safety and treatment outcomes. Our findings highlighted the importance of periodic reassessment of PPI and alternative management strategies. This may be achieved through clinical decision support systems integrated into electronic health records to prompt periodic reassessments and deprescribing alerts[23]. The clinical decision support systems could initiate interdisciplinary collaboration between gastroenterologists and primary care physicians to optimize patient management and follow-up.

Physician burnout and its impact on awareness

One interesting finding in this study was that more experienced physicians showed lower awareness of the gastric cancer risk associated with long-term PPI use. At first, this might seem surprising as experienced doctors are often expected to stay up to date with the latest research. However, a possible explanation is physician burnout, a common issue among doctors with many years in practice[24]. The heavy workload, time pressure, and growing administrative demands can make it harder to keep up with new guidelines, leading many to rely on well-established habits rather than constantly updating their knowledge[25].

Additionally, experienced physicians often develop strong clinical intuition based on years of practice, which sometimes takes priority over new research findings. Studies have shown that burnout can make it harder to adapt to changes, causing doctors to stick with familiar treatments instead of adjusting to evolving guidelines[26]. This pattern has been observed in several medical fields, including internal medicine and cardiology[27].

These findings highlight the importance of continued education and regular training sessions, not just for young doctors but also for experienced physicians. Keeping up with updated guidelines can help ensure safer prescribing practices while also making daily work more engaging and less routine. This could not only improve patient care but also help reduce burnout by giving doctors fresh perspectives and strategies in their practice[28].

PPIs are among the most widely prescribed medications globally, with estimates suggesting that up to 15% of the adult population in developed countries use PPIs regularly. In the United States approximately 15 million people are on long-term PPI therapy, with similar trends observed in Europe and Asia. The increasing prevalence is attributed mainly to over-the-counter availability, contributing to self-medication and extended use beyond recommended durations. Despite the widespread use and proven efficacy, concerns about overprescription, inappropriate long-term use, and potential adverse effects prompt calls for more stringent regulations[29].

Limitation

The number of respondents was 33, and it is possible that a larger number of respondents would provide a different result. To increase the likelihood of our results, more respondents are required. Moreover, the results reported herein may not reflects attitudes and prescription patterns of all Israel. Another potential limitation to this study was the self-reporting of the physicians' responses that is affected by a subjective bias. Participants may have chosen responses that align with their own perceptions. Finally, this study included a single time-point and without a second time point, future scenarios are taken at face value. The questionnaire used in this study was adapted from previously validated physician surveys assessing drug safety awareness. We acknowledge the presence of potential biases, such as recall bias and social desirability bias, and attempted to minimize them through anonymous and neutrally phrased items.

CONCLUSION

This study provided comprehensive insights into the awareness and management of long-term PPI usage among physicians, particularly gastroenterologists. The study highlighted a significant knowledge gap between gastroenterologists and non-gastroenterologists about the risk of gastric cancer. The study advocated periodic reassessments to promote safer long-term PPI usage.

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FOOTNOTES

Author contributions: Sawaied IO designed the study, drafted the manuscript, and coordinated data collection and statistical analysis; Samson AO provided biostatistical analysis, interpretation of data, and critical revision of the manuscript; Golan E contributed to the design of the questionnaire, supervised the research process, and reviewed the final manuscript; All authors read and approved the final manuscript.

Institutional review board statement: This study was approved by the Medical Ethics Committee of Azrieli Faculty of Medicine Bar Ilan University, approval No. 06-2023.

Informed consent statement: All participating physicians provided informed consent prior to inclusion in the study. The survey was anonymous and voluntary, and participants were informed about the purpose, procedures, and confidentiality of the data collected.

Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

Data sharing statement: The dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request. All data have been anonymized to protect participant confidentiality.

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ORCID number: Ibrahim O Sawaied 0009-0009-1312-9579.

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