International Journal of Family Medicine and Primary Care

Research Article
Published: 05 Aug, 2022

Association between Proton Pump Inhibitor and Risk of Stomach Cancer: A Meta-Analysis of Epidemiologic Studies

Eunbi Oh, Byung Sung Kim, Sunyoung Kim, Jihyun Kim and Changwon Won*

Department of Family Medicine, Kyung Hee University Hospital, Seoul, South Korea

Abstract

Background: Proton Pump Inhibitor (PPI) is one of the most widely used drugs in the world. Some studies have suggested that using PPI increases the risk of stomach cancer, but the conclusion is still controversial. Therefore, this study conducted a meta-analysis investigating the relationship between PPI use and stomach cancer.

Materials and Methods: Through PubMed, EMBASE, and Cochrane Library databases, papers on PPI and gastric cancer risk were searched using 'proton pump inhibitor OR PPI' AND 'stomach OR gastric' and 'canner OR tumor OR malignancy' as search terms. The period was limited to placebo-control studies and cohort studies for papers published from 2006 to 2021, and two researchers conducted a qualitative evaluation. For statistical analysis, a meta-analysis was performed using STATA version 17.

Results: The Odds Ratio (OR) for the incidence of gastric cancer and PPI was 2.46 (95% CI, 2.36~2.56), which was associated stomach cancer. Through subgroup analysis by quality, the odds ratio of the high-quality group was 1.37 (95% CI 1.22~2.53), and the odds ratio of the low-quality group was 3.32 (95% CI, 3.18~3.46), which still showed the relationship between the high-quality group.

Conclusion: As a result of analyzing the relationship between PPI and gastric cancer, PPI significantly increased the incidence of gastric cancer.

Keywords: Stomach cancer; Proton pump inhibitors; Meta-analysis; Odds ratio

OPEN ACCESS

Correspondence:
Byung Sung Kim, Department of Family Medicine, College of Medicine, Kyung Hee University Hospital, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, South Korea, Tel: +82-2-958-8700; Fax: + 82-2-958-8699; E-mail: byungskim@naver.com

Received Date: *12 Jul 2022*
Accepted Date: *01 Aug 2022*
Published Date: *05 Aug 2022*

Citation:
Oh E, Kim BS, Kim S, Kim J, Won C. Association between Proton Pump Inhibitor and Risk of Stomach Cancer: A Meta-Analysis of Epidemiologic Studies. Int J Fam Med Prim Care. 2022; 3(3): 1066.

Introduction

Since its introduction in the 1980s, PPI has been one of the world's most widely used drugs. PPI is a potent gastric acid secretion inhibitor, which irreversibly inhibits H+/K+ATPase, at the last stage of gastric acid secretion, preventing Hydrogen ions (H+) from coming out into the gastric lumen, thereby lowering the acidity of the stomach [1]. PPI is also used to treat peptic ulcers such as gastroesophageal reflux disease and gastroduodenal ulcers, treat Helicobacter eradication, and prevent peptic ulcers caused by Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). In addition, as it is used to avoid bleeding due to the use of anticoagulants, more and more patients are taking PPI for a long time [2,3].

In addition to PPI, studies have shown that drugs such as histamine-2 receptor antagonists, which are gastric acid inhibitors, can cause gastric cancer [4]. However, the PPI administration duration differed for each patient, so the side effects were not explicitly identified.

Previously, there were meta-analysis studies examining the relationship between gastric acid inhibitors and gastric cancer, but sub-analysis studies such as qualitative evaluation were rare. In addition to the association with *H. pylori* infection eradication or gastric cancer, studies focused on examining the overall incidence rate such as esophageal and colon cancer [5-9]. In addition, there is no consensus on meta-analysis studies dealing with the use of PPI and the incidence of gastric cancer, so no clear conclusion has been reached on the association with PPI.

Therefore the authors conducted a meta-analysis using the latest data to confirm the relationship between stomach cancer and PPI more clearly.

Materials and Methods

Literature search

PubMed, EMBASE, and Cochrane Library were used as the database, and studies on PPI and

gastric cancer risk were searched using 'Proton pump inhibitor OR PPI' AND 'Stomach OR gastric' and 'cancer OR tumor OR malignancy' as keywords. The study's design was selected by limiting it to a randomized controlled trial-oriented case-control study and a cohort study. The publication year period was searched for studies published from 2006 to 2021.

Literature selection and quality assessment

Among the studies entering the keyword in the online database, a paper published from 2006 to 2021 was selected. Among them, duplicate studies were excluded, and studies with unsuitable research designs or unsuitable forms of results were also excluded. In addition, the study with precise data or methods was selected in the case of studies with similar designs by the same author.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the selected studies [10]. The case-control studies were independently assessed with a score of 10 and the cohort studies with a score of 12. Then, the average value was obtained, and sub-group analysis was conducted by dividing them into high quality and low quality. Based on the average score of the two reviewers, the case-control studies were defined as high quality with more than 9 points, and the cohort studies were defined as high quality with more than 9.5 points, and low quality with less than 9 points and 9.5 points, respectively.

Statistical analysis

Meta-analysis statistics were analyzed through STATA version 17. Higgins I^2 statistics were used in the heterogeneity analysis of the Forest plot, and the equation is as follows.

$$I^2 = 100\% \times (Q\text{-}df)/Q$$

In the above equation, Cochran's Q is an indicator of heterogeneity, and df in the equation is an indicator of freedom. I^2 (%) ranges from 0 to 100, suggesting that 30% to 60% is moderate and over 60% is heterogeneous. In addition, the following items were extracted for the paper selected for meta-analysis.

In each article, the author, year of publication, country, the number of cancer cases in the treatment and control group, the number of non-cancer patients in the treatment and control group, odds ratio, lower confidence interval, and upper confidence interval were extracted, and a forest plot was completed.

Results

Identified papers

Among the studies published from 2006 to 2021, the selection process for papers for meta-analysis is shown in Figure 1. A total of 1,270 initial papers were obtained through three databases, with 78 for PubMed, 928 for EMBASE, and 264 for Cochrane. Among them, 168 articles searched in duplicate were excluded, and nine papers were finally selected as appropriate, excluding inappropriate research designs (n=634), result variables (n=435), and other meta-analysis papers (n=24). Among them, a total of 8 studies were finally selected, excluding one article with a similar research design by the same author. Of these, 4 were case-control studies, and 4 were cohort studies. Table 1 shows the characteristics of the selected paper.

For the eight selected papers, two researchers conducted a qualitative evaluation. The Newcastle-Ottawa scale was used for evaluation, and the qualitative assessment was conducted by scoring 0 to 10 for the case-control study and 0 to 12 for the cohort study [10].

Meta-analysis: Overall & subgroup analysis

The number of cancer occurrences in the treatment and control group, the number of non-cancer occurrences in the treatment and control group, the Lower Confidence Interval (LCI), Odds Ratio (OR), and the Upper Confidence Interval (UCI) were extracted. Figure 2 shows a forest plot statistically analyzing the extracted value through the STATA program. As a result, when interpreting all eight papers, the odds ratio for PPI dose and gastric cancer was 2.46 (95% Confidence Interval [CI], 2.36~2.56), but I^2 which indicates the heterogeneity, was quite heterogeneous at 98.1%.

Accordingly, the sub-group analysis was divided into high-quality and low-quality, and the results are shown in Figure 3. There were three papers corresponding to low quality, and as a result of statistical analysis of the three papers, the Odds Ratio (OR) was 3.32 (95% Confidence Interval [CI], 3.18~3.46). However, I^2 is 88.9%, which is more than 60%, indicating that this is also a heterogeneous result. There are five papers of high-quality, and statistical analysis shows that the Odds Ratio (OR) is 1.37 (95%) Confidence Interval [CI], 1.22~1.53), and I^2 is 53.5%, falling into the category of moderate heterogeneity in the range of 30%~60%.

When meta-analysis was conducted on all eight papers, heterogeneous results were shown. However, when the sub-analysis was performed according to quality, low-quality papers also showed heterogeneous results, but high-quality articles showed moderate heterogeneity and an odds ratio of 1.37. Therefore, when a meta-analysis was conducted on high-quality papers, it can be considered that there is a significant correlation between PPI and gastric cancer risk. In addition, some of the documents belonging to high quality concluded that the correlation between PPI and gastric cancer was

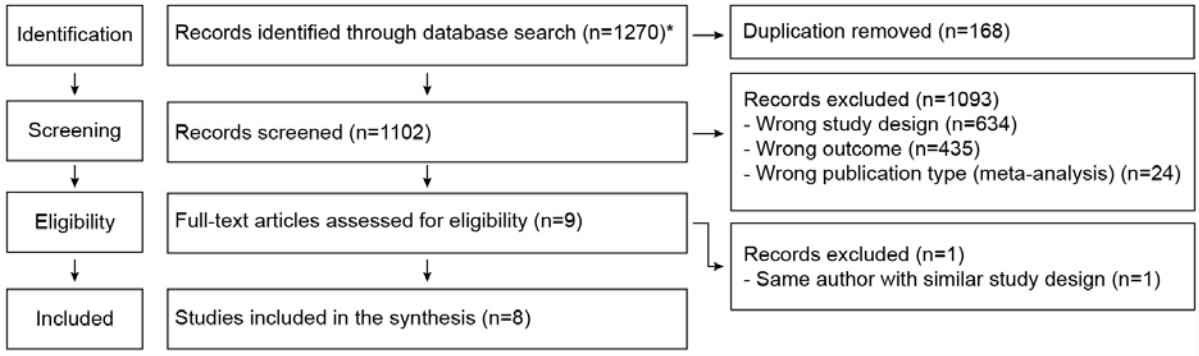

Figure 1: Literature search and screening process.

Table 1: Characteristics of the included trials and participants.

Author	Year	Study design	Country	Sample size	Period	OR	95% CI		Definition of PPI use
Rodregue [8]	2006	Case-control	UK	1,950	1994-2001	1.75	1.1	2.79	Longer than one year before the index date.
Tamin [5]	2008	Case-control	Canada	8,229	1995-2003	1.46	1.22	1.74	At least one dispensed prescription of the medication of interest during the study period
Lee [9]	2020	Case-control	US	11,776	1996-2016	1.07	0.81	1.42	Exposed patients had a ≥ 2-year cumulative PPI supply before the index date.
Liu [6]	2020	Case-control	UK	PICCU: 6,513 UK_Biobank: 471,779	PICCU: 1999-2011 UK_Biobank: 2006-2010	1.49	1.24	1.8	NA
Poulsen [10]	2009	Cohort	Denmark	18,790	1990-2003	1.2	0.8	2	Use of PPI was defined as filing ≥ 2 PPI prescriptions during the study period
Brusselaers [3]	2017	Cohort	Sweden	7,97,067	2005-2012	3.38	3.25	3.53	At least 6 months (≥ 180 days) during the study period
Cheung [7]	2018	Cohort	Hong Kong	63,397	2003-2012	2.14	1.27	3.58	At least weekly use
Seo [2]	2021	Cohort	Korea	23,482	2002-2013	2.37	1.56	3.68	For more than 30 consecutive days

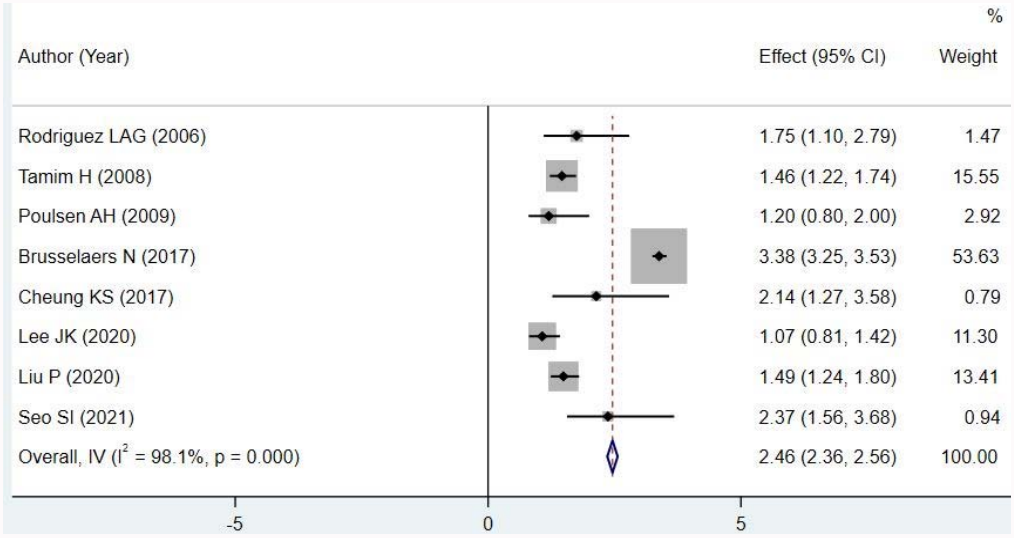

Figure 2: Forest plot for overall studies.

insignificant. Still, it is also noteworthy that the correlation between PPI use and gastric cancer was significant when the data were extracted. Meta-analysis was performed with the remaining high-quality papers.

Discussion

In this study, a total of eight papers, four case-control studies and four cohort studies, were selected, and a meta-analysis was conducted. Looking at the risk of PPI and gastric cancer, the forest plot, which analyzed all eight papers, showed 2.46 (95% Confidence Interval [CI], 2.36~2.56). In the subgroup analysis according to quality, for the three papers defined as low quality, am odds ratio of 3.32 (95% CI, 3.18-3.46) was found. The odds ratio for the five high-quality papers was 1.37 (95% CI, 1.22-1.53). Here, it can be seen that the odds ratio is not ambiguous and has meaningful results in low-quality papers and sub-group analysis that analyzed only high-quality articles. Therefore, combining the five documents classified as high quality, it was concluded that PPI and gastric cancer were related.

Previous studies have shown that PPI acts as an excessive acid inhibitor, resulting in atrophic gastritis. PPI stimulates gastrin production, which can lead to hypergastrinemia and lead to hyperplasia of enterochromaffin-like cells, increasing the risk of gastric cancer [11,12]. Therefore, it is suggested that PPI can act as a risk factor for gastric cancer, and various studies and meta-analysis studies are in progress. Still, no agreement has been reached on the current opinion. In this state, this paper can support the opinion that PPI acts as a risk factor for gastric cancer.

Several previous meta-analysis studies analyzed the correlation between PPI and gastric cancer. However, since most of them conducted a meta-analysis by setting only case-control or randomized-control design, it is different from this paper, which selected both cohort study and randomized-control design. In addition, most meta-analysis studies are limited to one country, but this paper covers results from several countries, which can be seen as representative of the result values. Also, existing studies show a variety of ranges, such as limiting the incidence of adenocarcinoma among gastric cancers, or covering all cancers that occur in the gastrointestinal tract. On the contrary, this paper was limited to the incidence of gastric cancer, and included all types of gastric cancer.

Therefore it focused only on the incidence of PPI and gastric cancer. In addition, many papers included both PPI and histamine-2 receptor antagonists, but this paper was conducted including only PPI which is relatively more commonly used.

As a disadvantage of this paper, it can be limited in that the dose and duration of PPI were not subdivided, and underlying diseases that could be risk factors for gastric cancer such as *H. pylori* infection were not identified. However, the strength is that the total number

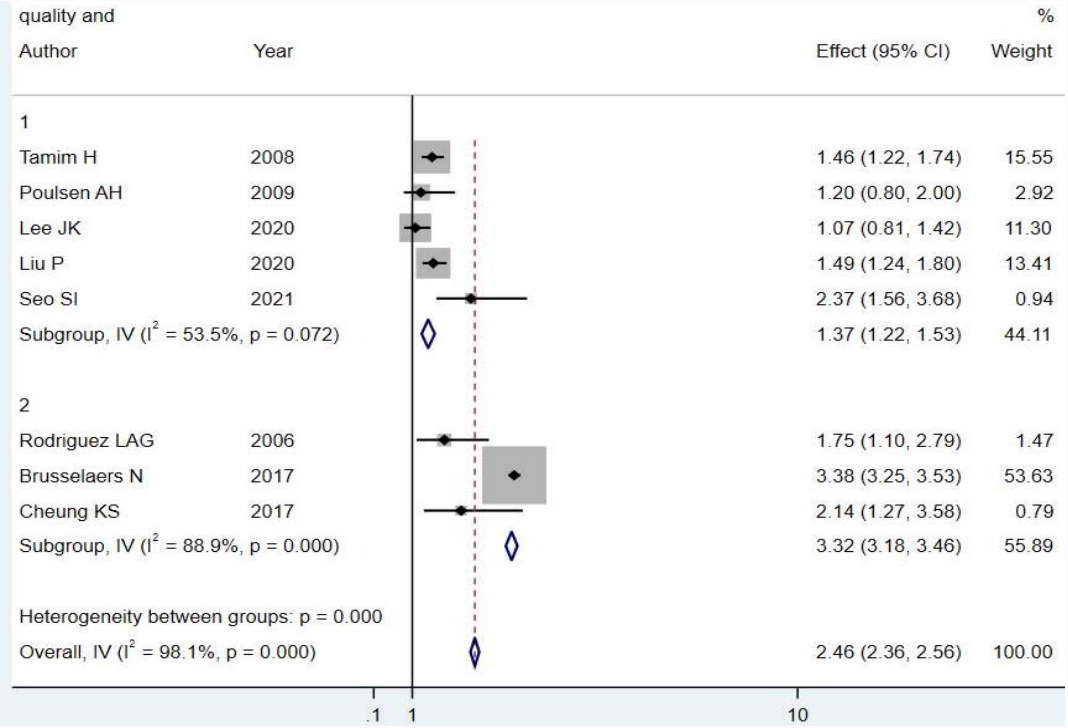

Figure 3: Forest plot according to qualitative classification.
*Number 1 stands for high quality, and number 2 stands for low quality group

of populations of the eight selected papers is about 1.5 million, so it can be representative of the result value. Also, this paper's strength is that the cancer incidence period was included as much as possible by selecting a combination of cohort studies and random control test studies. Furthermore, this paper differs from other papers in that studies were classified for each quality and a meta-analysis was conducted.

Through this paper, it was possible to derive that there is a correlation between PPI and gastric cancer. But additionally, in the future, it seems that a study to confirm the difference according to the period of taking PPI and a study on the mechanism in which PPI causes gastric cancer should be conducted.

References

1. Lin JL, Lin JX, Zheng CH, Huang CM, Xie JW, Lu J, et al. Long-term proton pump inhibitor use and the incidence of gastric cancer: A systematic review and meta-analysis. J Gastric Surg. 2020;2(1):1-11.
2. Seo SI, Park CH, You SC, Kim JY, Lee KJ, Kim J, et al. Association between proton pump inhibitor use and gastric cancer: A population-based cohort study using two different types of nationwide databases in Korea. Gut. 2021;70(11):2066-75.
3. Brusselaers N, Wahlin K, Engstrand L, Lagergren J. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: A nationwide population-based cohort study in Sweden. BMJ Open. 2017;7:e017739.
4. La Vecchia C, Negri E, Franceschi S, D'Avanzo B. Histamine-2-receptor antagonists and gastric cancer: Update and note on latency and covariates. Nutrition. 1992;8(3):177-81.
5. Tamim H, Duranceau A, Chen LQ, Lelorier J. Association between use of acid-suppressive drugs and risk of gastric cancer. A nested case-control study. Drug Saf. 2008;31(8):675-84.
6. Liu P, McMenamin ÚC, Johnston BT, Murchie P, Iversen L, Lee AJ, et al. Use of proton pump inhibitors and histamine-2 receptor antagonists and risk of gastric cancer in two population-based studies. Br J Cancer. 2020;123(2):307-15.
7. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: A population-based study. Gut. 2018;67(1):28-35.
8. García Rodríguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: A nested case control study in the UK. Gut. 2006;55(11):1538-44.
9. Lee JK, Merchant SA, Schneider JL, Jensen CD, Firemen GH, Corley DA, et al. Proton pump inhibitor use and risk of gastric, colorectal, liver, and pancreatic cancers in a community-based population. Am J Gastroenterol. 2020;115(5):706-15.
10. Qumseya BJ. Quality assessment for systematic reviews and meta-analyses of cohort studies. Gastrointest Endosc. 2021;93(2):486-94.
11. Poulsen AH, Christensen S, McLaughlin JK, Thomsen RW, Sorensen HT, Olsen JH, et al. Proton pump inhibitors and risk of gastric cancer: A population-based cohort study. Br J Cancer. 2009;100(9):1503-7.
12. Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: A review of the current evidence. Therap Adv Gastroenterol. 2019;12:1756284819834511.