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Review Article

Peptic Ulcer Disease and its Treatments and Risk of Pancreatic Cancer: a Meta–analysis

Nasser Alkhushaym[1], Goot Albuainain[2], Tuqa A AbuShaheen[3], Mohammed Y. Alshami[4], Ali S Almutairi[3], Ayman Ahmed Sakr[5], Ayat S Almuhayshi[3]

[1]Pharmaceutical Care Department, Royal Commission Health Services Program, Jubail, Saudi Arabia
[2]Pharmaceutical Care Department, King Abdulaziz Naval Base, Armed Forces Hospital, Jubail, Saudi Arabia
[3]Pharmaceutical Services Department, Mouwasat Medical Services, Eastern Province, Saudi Arabia
[4]Pharmaceutical Care Services, King Abdulaziz Hospital, Ministry of National Guard Health Affairs, Al–Ahsa, Saudi Arabia
[5]Assistant professor of Tropical Medicine–Faculty of Medicine–Menoufia University–Egypt

Background and objective: Pancreatic cancer (PC) is the seventh leading cause of death among cancers mortality. Pancreatic carcinogenesis remains poorly understood. There is still an urge to allocate other related risk factors that may help in better recognition of this pathogenesis. There is increasing evidence suggested that peptic ulcer disease (PUD), and its treatment might affect the development of PC however, studies findings reported conflicting results. Our meta–analysis aimed to study the association between PUD and its treatments (proton pump inhibitors [PPIs] and histamine–2 receptor antagonists [H2RAs]) and risk of PC.

Methods: We searched PubMed/MEDLINE, Embase, and Cochrane library databases from inception through January 2022. We included case–control studies, cohort, and randomized control trials which reported the association between PUD, PPIs, and H2RAs and the risk of PC. Odds ratio (OR) were used to calculate pooled estimates for PC risk. The association were evaluated using random–effects models, in two sided statistical tests.

Results: A total of 22 publications were retained for the meta–analysis. PUD was associated with a significant increase in PC risk (OR 1.26, 95% CI= 1.01–1.57, P= 0.038, I^2= 92%). The risk of developing PC were significant in patients receiving PPIs (OR 1.76, 95% CI= 1.26–2.46, P=0.001, I^2= 98%) and H2RAs (OR 1.25, 95% CI = 1.042–1.49, P= 0.016, I^2= 80%).

Conclusions: There is a 1.26–fold increase risk of PC in patients with PUD. The elevated PC is also attributable to 1.76–fold greater risk in PPIs group compared to 1.25–fold in H2RAs group.

Keywords: Peptic ulcer; proton pump inhibitors; histamin–2 receptor antagonist; pancreatic cancer

Introduction

Pancreatic cancer (PC) is the seventh leading cause of cancer related death and annually responsible for 496,000 new cases and 466,000 deaths worldwide. In UK, PC is the 10th most common cancer accounting for 3% of all new cancer cases every year[1]. Over the last decade, the incidence rate have increased by around 10% and considered as 5th most common cause of cancer death for around 9600 PC deaths in UK [1]. In United States, it stands as the third leading cause of cancer death with the lowest 5–year relative survival rate of 11% for all cancer[2,3]. It is suggested that PC will be the second leading cause of cancer–related death by 2030 in western countries[4]. The low survival rate of patients with PC signals the urgent need to identify the risk factors that lead to PC[5].

Pancreatic Carcinogenesis remains poorly understood however, many risk factors has been identified. Several personal and environmental factors have been reported to be associated with pancreatic carcinogenesis[6]. Numerous studies suggest that the factors associated with PC could be disease–related, such as diabetes, chronic pancreatitis, obesity and hepatitis B, C or Helicobacter pylori (H. pylori)

Corresponding Author: Nasser Alkhushaym, PharmD, BCPS,Pharmaceutical Care Department, Royal Commission Health Services Program, 31961 Jubail, Saudi Arabia
Email: **Nasser.alkhushaym@gmail.com**
Phone: +966544555618

infection or medication–related[5–10]. Furthermore, some factors related to a poor lifestyle such as cigarette smoking, alcohol, consumption of processed and smoked meat, as well as poor oral hygiene have also been revealed to be associated with PC[5,6,10].

Peptic ulcer disease (PUD) and the medications used to treat PUD by suppressing gastric acid secretion (proton pump inhibitors [PPIs] or histamine–2 receptor antagonists [H2RAs]) have been studied recently to investigate their association with PC [11–18]. PUD, PPIs and H2RAs are reported to have carcinogenic effects on the pancreas through different mechanisms. Several hypotheses have been suggested for the potential carcinogenic effect of PUD in PC, each of which relates to either the inflammatory response, increased production of nitrosamine and hyperacidity[13]. For the carcinogenic effect of gastric acid suppression medications, there are increasing concerns regarding their safety profile despite their established clinical efficacy, as evidence suggests an association of PC with the use of PPIs and H2RAs[14–18]. Therefore, our meta–analysis aimed to investigate the association between PUD, and its treatments (PPIs and H2RAs) and risk of PC.

Materials and Methods:

1–Data source and study selection:

In our meta–analysis, we followed the preferred reporting items for systematic reviews (PRISM) guidelines. We searched PubMed, Embase, and Cochrane library databases from their inception through January 2022. The search was conducted by five investigators (GB, ASM, TA, MS, AM) using a combination of text terms. Keyword and controlled vocabulary were used and included the terms 'peptic ulcer disease', 'proton pump inhibitors', 'histamine 2 receptor antagonists' for the exposure factor, and 'pancreatic cancer' for the outcome. Bibliographies of selected studies were checked manually to identify additional studies. Investigators independently evaluated all studies in the databases and any disagreement between investigators was adjudicated by sixth author (NK).

The included studies were case–control studies, cohort, and randomized control trials (RCTs) written in the English language which reported the association between either PUD, PPI, or H2RAs, and risk of PC in terms of odds ratio and corresponding 95% confidence interval (95% CI). The odds ratio calculated for studies that did not report odds ratio based on exposed and control groups. The following data were extracted from selected studies: author name, publication year, study design, country, type of exposure, participants, OR and 95% CI.

2– Statistical analysis:

The aim of the study was to investigate the association between PUD and its treatments, including PPIs and H2RAs and the risk of PC. We used Comprehensive Meta–Analysis (CMA) (Version 3.3; BioStat, Englewood, NJ, USA) software for the meta–analysis. Odds ratio was used to estimate the risk and I^2 was used to assess heterogeneity. Random effects model was considered when I^2 was greater than 50%, which is considered a significant heterogeneity.

Results:

Identification of relevant studies:

Our literature search yielded a total of 3,257 relevant studies, including from PubMed (1,602), Embase (1,564), and Cochrane library (91) (Figure 1). Additional records (529) were identified by reviewing the bibliography of the retrieved articles. After removing duplicates, 672 studies were screened. A total of 570 publications were excluded after reviewing the abstracts, leaving 102 publications for full text assessment. Of these, 80 were excluded and a total of 22 separate publications were retained for the meta–analysis (Table 1–3, Figure 1)[9,12–15,18–34].

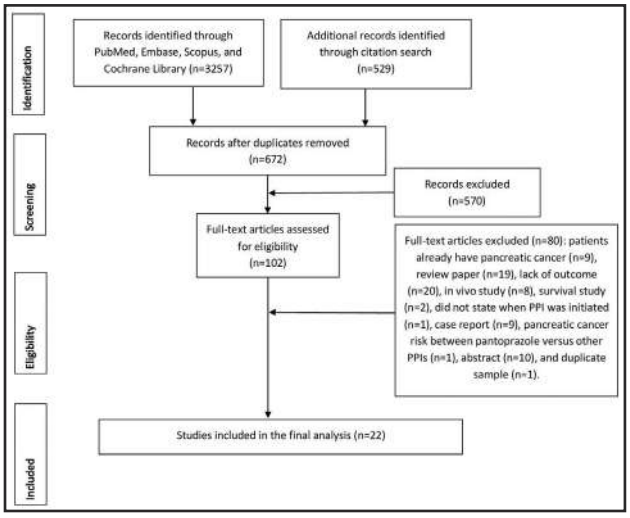

Figure 1. Preferred reporting items for systematic reviews and meta–analyses (PRISMA) flow diagram.

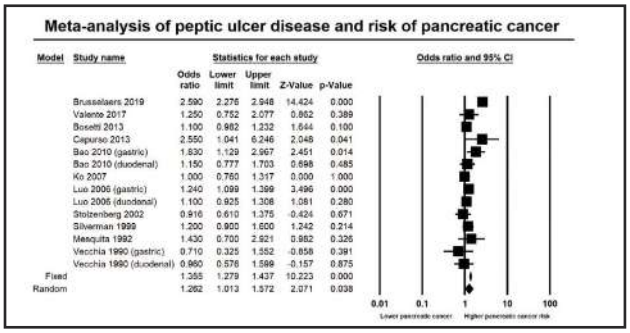

Figure 2. Forest plot for peptic ulcer disease and risk of pancreatic cancer.

Author	Design	Country	Ulcer type	Participants	Observed cases	Control	Observed cases	Adjustment	OR (95%CI)
Brusselaers, 2019	Cohort	Sweden	Peptic ulcer	359,158	234	3,828,553	1,733	Age, sex and indication	2.59 (2.27–2.94)
Valente, 2017	Case–control	Europe	Peptic ulcer	201	24	603	64	Sex, age and center of enrollment	1.25 (0.75–2.07)
Bosetti, 2013	Case–control	United States, zCanada, and Australia	Gastric or duodenal ulcer	1,183	673	8,146	3,976	Study center, age, sex, race/ethnicity, education, BMI, tobacco smoking, alcohol drinking, history of diabetes, and history of pancreatitis.	1.10 (0.98–1.23)
Capurso, 2013	Case–control	Italy	Peptic ulcer	390	28	390	16	–	2.55 (1 – 6)
Bao, 2010	Cohort	United States of America	Gastric ulcer	2,980	30	45,417	233	Age,smoking, diabetes, BMI and physical activity.	1.83 (1.13 – 2.97)
Bao, 2010	Cohort	United States of America	Duodenal ulcer	2,980	30	45,417	233	Age, smoking, diabetes, BMI and physical activity.	1.15 (0.78 – 1.71)
Ko, 2007	Case–control	United State of America	Gastric/ Duodenal ulcer	238	84	1,462	447	Race, education, BMI, smoking, and history of diabetes.	1.0(0.75, 1.3)
Luo, 2006	Retrospective cohort	Sweden	Gastric ulcer	81,379	403	444,971	182	–	1.2(1.1–1.4)
Luo, 2006	Retrospective cohort	Sweden	Duodenal ulcer	61,548	312	421,484	135	–	1.1(0.9–1.3)
Stolzenberg 2002	Prospective cohort	Finland	Peptic ulcer	48,045	27	229,521	145	Age, years smoked, self reported, diabetes, bronchial	0.91 (0.61–1.37)
Mesquita, 1992	Case–control	Netherlands	Ulcer	26	16	209	77	Age, gender, response status and lifetime smoking cigarettes	1.43 (0.7–2.92)
Vecchia, 1990	Case–control	Northern Italy	Gastric ulcer	45	8	1,089	247	Age and sex.	0.71 (0.32–1.53)
Vecchia, 1990	Case–control	Northern Italy	Duodenal ulcer	90	20	1,089	247	Age and sex.	0.96 (0.58–1.61)

Table 1. Summary of baseline characteristics of the peptic ulcer disease studies

BMI: body mass index, PPIs: proton pump inhibitors, COPD: chronic obstructive pulmonary disease, NSAIDs: non–steroidal anti–inflammatory drugs, NAFLD: non–alcoholic fatty liver disease, HBV: hepatitis B, HCV: hepatitis C, PUD: peptic ulcer disease, GERD: gastroesophageal reflux disease, H2RAs: histamine–2 receptor antagonist, HRT: hormone replacement therapy, OR: Odds ratio, CI: confidence interval.

Author	Design	Country	Drugs	Partici pants	Observed cases	Control	Observed cases	Adjustment	OR (95%CI)
Lee, 2020	Nested case–control	United States of America	Proton pump inhibitors	386	65	4,434	502	Long–term PPI Use, BMI,family history of pancreatic cancer, alcohol use, smoking, diabetes, chronic pancreatitis, and cystic fibrosis.	1.22, (0.89–1.67)
Brusselaers, 2019	Cohort	Sweden	Proton pump inhibitors	796, 492	3,127	20,210	25	Diabetes, alcohol–related disease, COPD, Chronic pancreatitis, gallstones, PUD, helicobacter pylori infection, HBV, HCV, use of lowdose aspirin, NSAIDs	2.22 (2.12–2.32)
Peng, 2018	Nested case–control	Taiwan	Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole	1,087	454	1,087	320	Age and chronic pancreatitis.	1.69 (1.42, 2.03)
Hwang, 2018	Cohort	South Korea	Proton pump inhibitors	49,785	374	403,826	2,712	–	1.12 (1.00–1.24)
Hicks, 2018	Casecontrol	Den mark	Omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole	8,796	1,923	25,809	4,998	Diabetes, alcohol–related disease, COPD, Chronic pancreatitis, gallstones, PUD, helicobacter pylori infection, HBV, HCV, use of lowdose aspirin, NSAIDs, statins, highest achieved education.	1.04 (0.971.11)
Boursi, 2017	Retrospective cohort	United Kingdom	Proton pump inhibitors	390	116	108,995	19,030	BMI, smoking, medication use (insulin, metformin and other oral hypoglycemic medications).	1.51 (1.20–1.90)
Kearns, 2017	Nested case–control	United Kingdom	Proton pump inhibitors	4,496	2,312	11,576	1,801	Diabetes, smoking, alcohol use and obesity.	3.613 (3.37–3.86)
Valente, 2017	Case–control	Europe	Proton pump inhibitors	201	78	603	239	Sex, age and center of enrollment	1.04 (0.74–1.45)
Chien, 2016	Nested case–control	Taiwan	Proton pump inhibitors	2,032	245	36,655	3,626	Choledochal cysts, cholangitis, cholelithiasis, cholecystitis, cirrhosis, alcoholic liver disease, NAFLD, HBV, HCV, diabetes, chronic pancreatitis, inflammatory bowel disease, PUD, GERD, cardiovascular disease, H2RAs, aspirin, NSAIDs, statins, metformin, insulins, other antidiabetic drugs and H. pylori eradication therapy.	1.20 (0.95–1.50)

Attwood, 2015	Randomised clinical trial	Belgium, Denmark, France, Germany, Austria, Iceland, Italy, Nor– way, Sweden, United Kingdom and Netherlands	Esomeprazole, Omeprazole	420	4	392	1	–	3.73 (0.42–33.55)
Risch, 2014	Case–control	United States of America	Proton pump inhibitors	194	193	582	260	Age, sex, Race, history of pancreatic cancer in first–degree relatives, seropositivity for Helicobacter pylori and cytotoxin–associated gene A	6.21 (1.68, 22.9)
Lai, 2014	Case–control	Taiwan	Proton pump inhibitors	977	619	3,908	521	Acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, and H2RAs, statins, non–statin lipid–lowering drugs, and both of aspirin and cyclooxygenase–2 inhibitors.	9.28 (7.77, 11.08)
Bosetti, 2013	Case–control	United States of America, Canada, and Australia	Proton pump inhibitors	4717	56	9374	51	Study center, age, sex, race/ethnicity, education, BMI, tobacco smoking, alcohol drinking, history of diabetes, and history of pancreatitis.	1.16 (0.72–1.88)
Bradley, 2011	Nested case–control	United Kingdom	Proton pump inhibitors	1,137	177	6,817	964	Smoking status, alcohol use, history of chronic pancreatitis, use of other drugs (NSAIDs, steroids and HRT), diabetes and prior cancer.	1.02 (0.85–1.22)

Table 2. Summary of baseline characteristics of the peptic ulcer disease studies proton pump inhibitors

BMI: body mass index, PPIs: proton pump inhibitors, COPD: chronic obstructive pulmonary disease, NSAIDs: non–steroidal anti–inflammatory drugs, NAFLD: non–alcoholic fatty liver disease, HBV: hepatitis B, HCV: hepatitis C, PUD: peptic ulcer disease, GERD: gastroesophageal reflux disease, H2RAs: histamine–2 receptor antagonist, HRT: hormone replacement therapy, OR: Odds ratio, CI: confidence interval.

Peptic ulcer disease and risk of pancreatic cancer

Eleven studies (seven case control studies, three cohort studies, and one retrospective cohort study) reported the association between PUD and risk of PC (Table 1, Figure 2). The results of the analysis revealed a significant increase in PC risk among patients with PUD versus patients without PUD (OR 1.26, 95% CI= 1.01–1.57, P= 0.038, I^2= 92%).

Proton pump inhibitors exposure and risk of pancreatic cancer

Fourteen studies (one RCT, three cohort studies, five case control studies, and five nested case–control studies) reported the association between PPIs and risk of PC (Table 2, Figure 3). The results of the analysis revealed a significant increase in PC risk among PPI users versus non–users (OR 1.76, 95% CI = 1.26–2.46, P= 0.001, I^2= 98%).

Histamine–2 receptor antagonists exposure and risk of pancreatic cancer

Seven studies (four case–control studies, two nested case–control studies, and one cohort study) reported the association between H2RAs and risk of PC (Table 3, Figure 4). The results of the analysis revealed a significant increase in PC risk among H2RAs users versus non–users (OR 1.25, 95% CI = 1.04–1.49, P= 0.016, I^2= 80%).

Author	Design	Country	Drugs	Participants	Observed cases	Control	Observed cases	Adjustment	OR (95%CI)
Brusselaers, 2019	Cohort	Sweden	Histamine–2 receptor antagonist	796,492	3,127	20,210	25	–	1.02 (0.66–1.51)
Hicks, 2018	Case–control	Denamark	Histamine–2 receptor antagonist	8,796	1,923	25,809	4,998	Diabetes, alcohol–related disease, COPD, chronic pancreatitis, gallstones, PUD, helicobacter pylori infection, HBV, HCV, low–dose aspirin, NSAIDs, statins and HRT, Charlson comorbidity Index (CCI) score, highest achieved education.	1.02 (0.94–1.11)
Peng, 2018	Nested case–control	Taiwan	Histamine–2 receptor antagonist	1,087	934	1,087	908	Age group and biliary tract disease.	1.20 (0.95–1.52)
Risch, 2014	Case–control	United States of America	Histamine–2 receptor antagonist	59	43	648	336	–	1.41 (0.93–2.13)
Lai, 2014	Case–control	Taiwan	Histamine–2 receptor antagonist	977	824	3,908	2,459	Acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, and H2RAs, statins, non–statin lipid–lowering drugs, and both of aspirin and cyclooxygenase–2 inhibitors.	1.90 (1.53,2.35)
Bosetti, 2013	Case–control	United States of America, Canada, and Australia	Histamine–2 receptor antagonist	312	140	645	310	Study center, age, sex, race/ethnicity, education, BMI, tobacco smoking, alcohol drinking, history of diabetes, and history of pancreatitis.	1.15 (0.92–1.43)
Bradley, 2011	Nested case–control	United Kingdom	Histamine–2 receptor antagonist	4,027	876	30,578	6,045	Smoking status, BMI, alcohol use, history of chronic pancreatitis, use of other drugs (NSAIDs, steroids and HRT), diabetes and prior cancer.	1.26 (1.03–1.52)

Table 3. Summary of baseline characteristics of the peptic ulcer disease studies histamine–2 receptor antagonist

BMI: body mass index, PPIs: proton pump inhibitors, COPD: chronic obstructive pulmonary disease, NSAIDs: non–steroidal anti–inflammatory drugs, NAFLD: non–alcoholic fatty liver disease, HBV: hepatitis B, HCV: hepatitis C, PUD: peptic ulcer disease, GERD: gastroesophageal reflux disease, H2RAs: histamine–2 receptor antagonist, HRT: hormone replacement therapy, OR: Odds ratio, CI: confidence interval.

Discussion:

To the best of our knowledge, the current meta–analysis is the first pooled meta–analysis investigating the association between PUD and risk of PC. This meta–analysis study revealed a significant association between PUD, PPIs and H2RAs and the risk of PC. The risk of PC elevation among patients with PUD increased by 1.26–fold while the use of PPIs and H2RAs increases risk by 1.76–fold and 1.25–fold respectively.

There are multiple modifiable and non–modifiable risk factors for PC currently under investigation. The most common modifiable factors include smoking, dietary factors, alcohol, obesity, and infection such as H. pylori. On the other hand, Age, sex ethnicity, family history of PC and diabetes are the common non modifiable risk factors[5,6]. Smoking is the most important identified risk factor for pancreatic carcinoma[35]. Because N–nitrosamines are the major tobacco carcinogens for the pancreas and responsible for the development of PC in smokers[36].

The mechanism by which PUD may cause PC is still unclear. Similar to smoking, the positive relation between PUD and risk of PC might be explained by excess formation of N–nitrosamine associated with gastric ulcer. Nitrosamines found to induces pancreatic tumors in animals[13,36]. This is consistent with the findings reported by Luo, which revealed that the corpus colonization of Helicobacter pylori, accompanying multifocal atrophic corpus gastritis with hypochlorhydria, bacterial overgrowth and intragastric formation of nitrosamines might contribute to pancreatic carcinogenesis[14]. Another evidence supporting nitrosamine hypothesis though the significant association between gastrectomy and PC risk. Patient who had undergone partial gastric resection have extremely high concentration of nitrosamines[37]. These individuals have increased risk of PC risk after 20 years of the surgery[38]. Alternative explanation for the association between gastric ulcer and PC risk might be the inflammation response related to H.pylori involves generation of pro–inflammatory cytokines which might contribute to pancreatic carcinogenesis[39]. Therefore, H. Pylori might promote the occurrence of other non–gastric tumors such as PC[40].

The use of PPIs is significantly associated with increased risk of PC, which is consistent with the findings reported in previous meta–analysis studies, which state that the use of PPIs is associated with 1.73–fold and 1.75–fold increase in PC risk, respectively [7,11]. Both studies suggested that this notable association is physiologically reasonable and might be interpreted by the PPIs mechanism of action. PPIs deactivate proton pumps on parietal cells in the stomach, which leads to a reduction of gastric acid secretion and thus gastrin production in G cells is increased. Increased gastrin production has a carcinogenic effect on PC pathophysiology,

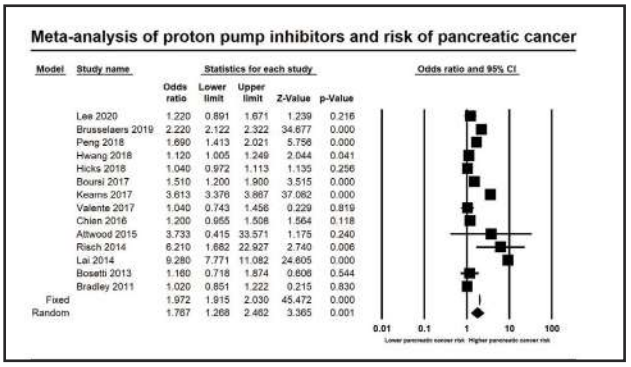

Figure 3. Forest plot for proton pump inhibitors exposure and risk of pancreatic cancer.

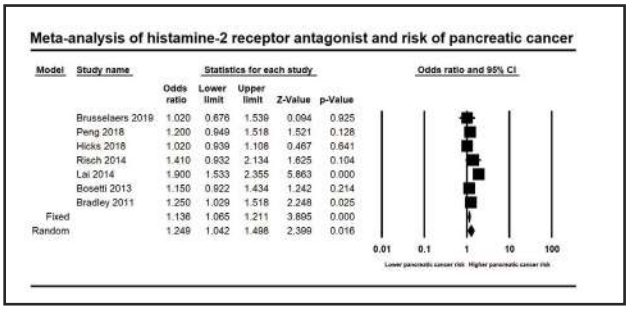

Figure 4. Forest plot for histamine–2 receptor antagonist exposure and risk of pancreatic cancer.

as gastrin binds to gastrin receptors that are expressed on human PC cells and stimulates cancer cells growth. Gastric acid suppression increases the growth of bacteria as well. Similarly in PUD, bacterial overgrowth induces the formation of N–nitrosamine, which has a carcinogenic effect by forming methyl and 2–hydroxypropyl adducts and in turn cause DNA damage [37,39]. On the other hand, our meta–analysis study revealed that the use of H2RAs is associated with increased risk of PC. This was parallel to what has been found in the Laoveeravat study in which there was a higher risk of PC in H2RAs users which could be explained by the same mechanism the PPIs perform, as both lead to decreased gastric acid secretion[7]. Compared to the previous meta–analysis used to assess the risk of PC among PPIs, and H2RAs, our meta–analysis included additional studies that reveal to similar significant risk of PC.

The current meta–analysis has some limitations and identifies issues for future research. First, this study could show the association, however a causal relationship remains speculative, as the included studies were case–control and cohort studies. Second, there was significant heterogeneity among studies, in terms of study design, clinical setting, type and duration of PUD and drug exposure before development of PC, and therefore compromise the robustness of our finding. Third, the sample size in most included studies related to PUD were relatively small, which would more likely cause overestimation of effect size. Consequently, well–conducted studies are warranted on PUD, PPIs, and H2RAs that consider other risk factors for PC.

Conclusion:

In conclusion, our meta–analysis shows significant association between PUD and risk of PC. Likewise, treatments of PUD which include PPIs and H2RAs show significant association with PC. These findings suggested that clinicians should pay more attention to the usage of PPIs and H2RAs. The occurrence of pancreatic cancer in patient with PUD or using PPIs or H2RAs should be considered during therapy. Further large, high quality prospective studies are required to confirm the association between PUD and its treatment and risk of PC.

Funding and Conflict of Interest

The authors have no affiliation or financial involvement with any organization with a financial conflict with a subject matter or material discussed in the manuscript.

References:

1. Pancreatic cancer statistics (2022) Cancer Research UK. Available at: https://www.cancerresearchuk.org/health–professional/cancer–statistics/statistics–by–cancer–type/pancreatic–cancer (Accessed: January 22, 2023).
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021;71:209–249.
3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: A Cancer Journal for Clinicians. 2022;72(1):7–33. doi:10.3322/caac.21708
4. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Research. 2014;74(11):2913–2921. doi:10.1158/0008–5472.can–14–0155
5. Tsai H, Chang JS. Environmental Risk Factors of Pancreatic Cancer. Journal of clinical medicine. 2019;8:1427.
6. Hassan MM, Bondy ML, Wolff RA, et al. Risk Factors for Pancreatic Cancer: Case–Control Study. The American journal of gastroenterology. 2007;102:2696–2707.
7. Laoveeravat P, Thavaraputta S, Vutthikraivit W, et al. Proton pump inhibitors and histamine–2 receptor antagonists on the risk of pancreatic cancer: a systematic review and meta–analysis. QJM: monthly journal of the Association of Physicians. 2020;2019;113:100–107.
8. McDowell R, Hughes C, Murchie P, et al. The effect of medications associated with drug–induced pancreatitis on pancreatic cancer risk: A nested case–control study of routine Scottish data. Cancer Epidemiology. 2021;71:101880.
9. Lai S, Liao K, Lai H, et al. Use of proton pump inhibitors correlates with increased risk of colorectal cancer in Taiwan. Asia–Pacific journal of clinical oncology. 2013;9:192–193.
10. Capasso M, Franceschi M, Rodriguez–Castro KI, et al. Epidemiology and risk factors of pancreatic cancer. Acta bio–medica : Atenei Parmensis. 2018;89:141.
11. Alkhushaym N, Almutairi AR, Althagafi A, et al. Exposure to proton pump inhibitors and risk of pancreatic cancer: a meta–analysis. Expert opinion on drug safety.2020;19:327.
12. Bradley MC, Murray LJ, Cantwell MM, et al. Proton pump inhibitors and histamine–2–receptor antagonists and pancreatic cancer risk: a nested casecontrol study. British journal of cancer. 2012;2011;106:233–239.
13. Bao Y, Spiegelman D, Li R, et al. History of Peptic Ulcer Disease and Pancreatic Cancer Risk in Men. Gastroenterology. 2010;138:541–549.
14. Luo J, Nordenvall C, Nyrén O, et al. The risk of pancreatic cancer in patients with gastric or duodenal ulcer disease. International Journal of Cancer. 2006;120:368–372.
15. Ko A, Wang F, Holly E. Pancreatic cancer and medical history in a population–based case–control study in the San Francisco Bay Area, California. Cancer Causes & Control. 2007;18:809–819.
16. Lundell L, Vieth M, Gibson F, et al. Systematic review: the effects of long–term proton pump inhibitor use on serum gastrin levels and gastric histology. Alimentary Pharmacology & Therapeutics. 2015;42:649–663.
17. Ahn J. Acid suppressive drugs and gastric cancer: A meta–analysis of observational studies. World Journal of Gastroenterology. 2013;19:2560.
18. Peng Y, Lin C, Hsu W, et al. Proton Pump Inhibitor Use is Associated With Risk of Pancreatic Cancer: A Nested Case–Control Study. Dose–Response. 2018;16:155932581880328.
19. Lee JK, Merchant SA, Schneider JL, et al. Proton Pump Inhibitor Use and Risk of Gastric, Colorectal, Liver, and Pancreatic Cancers in a Community–Based Population. The American journal of gastroenterology. 2020;115:706–715.
20. Brusselaers N, Sadr–Azodi O, Engstrand L. Long–term proton pump inhibitor usage and the association with pancreatic cancer in Sweden. Journal of gastroenterology. 2020;2019;55:453–461.
21. Hwang IC, Chang J, Park SM. Association between proton pump inhibitor use and the risk of pancreatic cancer: A Korean nationwide cohort study. PloS one. 2018;13:e0203918–e0203918.
22. Hicks B, Friis S, Pottegård A. Use of proton pump inhibitors and risk of pancreatic cancer. Pharmacoepidemiology and drug safety. 2018;27:926–930.

23. Boursi B, Finkelman B, Giantonio BJ, et al. A Clinical Prediction Model to Assess Risk for Pancreatic Cancer Among Patients With New–Onset Diabetes. Gastroenterology (New York, N.Y. 1943). 2017;152:840–850.e3.

24. Kearns MD, Boursi B, Yang Y. Proton pump inhibitors on pancreatic cancer risk and survival. Cancer epidemiology. 2016;2017;46:80–84.

25. Valente R, Hayes AJ, Haugvik S, et al. Risk and protective factors for the occurrence of sporadic pancreatic endocrine neoplasms. Endocrine–related cancer. 2017;24:405–414.

26. Chien L, Huang Y, Shao YJ, et al. Proton pump inhibitors and risk of periampullary cancers—A nested case–control study. International journal of cancer. 2016;138:1401–1409.

27. Attwood SE, Ell C, Galmiche JP, et al. Longterm safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. Alimentary pharmacology & therapeutics. 2015;41:1162–1174.

28. Risch HA, Yu H, Lu L, et al. Detectable Symptomatology Preceding the Diagnosis of Pancreatic Cancer and Absolute Risk of Pancreatic Cancer Diagnosis. American journal of epidemiology. 2015;182:26–34.

29. Bosetti C, Lucenteforte E, Bracci PM, et al. Ulcer, gastric surgery and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case–Control Consortium (PanC4). Annals of oncology. 2013;24:2903–2910.

30. SILVERMAN DT, SCHIFFMAN M, POTTERN LM, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. British Journal of Cancer. 1999;80:1830–1837.

31. De Mesquita H.B. Bueno, Maisonneuve P, Moerman CJ, et al. Aspects of medical history and exocrine carcinoma of the pancreas: A populationbased casecontrol study in The Netherlands. International journal of cancer. 1992;52:17–23.

32. Stolzenberg–Solomon RZ, Pietinen P, Taylor PR, et al. Prospective Study of Medical Conditions, Anthropometry, Physical Activity, and Pancreatic Cancer in Male Smokers (Finland). Cancer causes & control. 2002;13:417–426.

33. La Vecchia C, Negri E, D'Avanzo B, et al. Medical history, diet and pancreatic cancer. Oncology. 1990;47:463.

34. Capurso G, Boccia S, Salvia R, et al. Risk factors for intraductal papillary mucinous neoplasm (IPMN) of the pancreas: a multicentre case–control study. The American journal of gastroenterology. 2013;108:1003–1009.

35. Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: An analysis from the International Pancreatic Cancer Case–Control Consortium (PANC4). Annals of Oncology. 2012;23(7):1880–1888. doi:10.1093/annonc/mdr541

36. Rivenson A, Hoffmann D, Prokopczyk B, et al. Induction of lung and exocrine pancreas tumors in F344 rats by tobacco–specific and Areca–derived N–nitrosamines. Cancer Res. 1988;48(23):6912–6917.

37. Reed PI, Smith PL, Haines K, et al. Gastric juice N–nitrosamines in health and gastroduodenal disease. Lancet. 1981;2(8246):550–552. doi:10.1016/s0140–6736(81)90939–9

38. Caygill CP, Hill MJ, Hall CN, et al. Increased risk of cancer at multiple sites after gastric surgery for peptic ulcer. Gut. 1987;28(8):924–928. doi:10.1136/gut.28.8.924

39. Garcea G, Dennison AR, Steward WP, et al. Role of inflammation in pancreatic carcinogenesis and the implications for future therapy. Pancreatology. 2005;5(6):514–529. doi:10.1159/000087493

40. Butt J, Jenab M, Pawlita M, et al. Antibody Responses to Helicobacter pylori and Risk of Developing Colorectal Cancer in a European Cohort. Cancer Epidemiol Biomarkers Prev. 2020;29(7):1475–1481. doi:10.1158/1055–9965.EPI–19–1545