# Table of Contents

## Original Articles

**Identification of the Physiological Dimension and SelfConcept among Husbands of Iranian Women with Mastectomy; a Directed Content Analysis**
Marzieh Beigom Bigdeli Shamloo, Nasrin Elahi, Marziyeh Asadi Zaker, Kourosh Zarea, Armin Zareiyan

**Tumor–Stroma Ratio in ER+/HER2− Breast Cancer: Is it a Tool for Treatment Decision?**
Choukri ELMHADI, Mohammed Allaoui, Meryem Zerrik, Mohammed Oukabli, Rachid Tanz, Mohammed Ichou

**Prevalence of BRCA1 and BRCA2 Mutations Among High–risk Bahraini Patients with Breast Cancer**
Zain Bukamal, Amal AlRayes

**Survival Outcomes of Post–mastectomy Breast Cancer Patients Treated with Hypofractionated Radiation Treatment Compared to Conventional Fractionation—a Retrospective Cohort Study**
Ciniraj Raveendran, Suma Susan Meloot, I Yadev

**Variants of Human Mucin Genes in Clear Cell Renal Cell Carcinoma and their Potential Prognostic and Predictive Values**
Jamal Zekri, Mohammed A. Baghdadi, Abdelrazak Meliti, Turki M. Sobahy, Saba Imtiaz

**Study of Efficacy and Toxicity of Capecitabine Maintenance After Response to Docetaxel, Cisplatin, and 5−Fluracil−Based Chemotherapy in Advanced Carcinoma Stomach**
Udip Maheshwari, Pankaj Goyal, Varun Goel, Nivedita Patnaik, Venkata Pradeep babu koyyala, Krishna Chaudhari, DC Doval, Vineet Talwar

**EGFR Expression in Gallbladder Carcinoma in North Indian Population**
Vikash, Vikas Kailashya, Mohan Kumar, Puneet

**Does the Nightmare of Distressing Complications of Groin Dissection Over with “River Flow” Incision? – Experience of 240 Dissections from Tertiary Referral Oncology Centre,India**
M D Ray, J R Jeena Josephin, Premanand N

## Review Article

**Peptic Ulcer Disease and its Treatments and Risk of Pancreatic Cancer: a Meta−analysis**
Nasser Alkhashaym, Goot Albuainain, Tuqa A AbuShaheen, Mohammed Y. Alshami, Ali S Almutairi, Ayman Ahmed Sakr, Ayat S Almuhayshi

## Case Reports

**Treatment Process of Primary Prostate Leiomyosarcoma: A Rare Case Report**
Denis Cetin, Mustafa Murat Mıdük, Mustafa Mustafayev, Burçak Karaca

**Metastatic Small Cell Carcinoma of a Male Breast: A Case Report and Review of the Literature**
Nadin Shawar Al Tamimi, Yousra Bennouna, Mohammed El Fadli, Rhizlane Belbaraka

**A Rare Tumor in Adulthood: Extrapancreatic Pancreatoblastoma**
Uğur Topal, Begüm Çalış Gürbüz, Hasan Bektas

## Conference Highlights/Scientific Contributions

**News Notes**

**Advertisements**

**Scientific events in the GCC and the Arab World for 2023**
Review Article

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

Nasser Alkhushaym¹, Goot Albuainain², Tuqa A AbuShaheen³, Mohammed Y. Alshami⁴, Ali S Almutairi³, Ayman Ahmed Sakr⁵, Ayat S Almuhayshi³

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²Pharmaceutical Care Department, King Abdulaziz Naval Base, Armed Forces Hospital, Jubail, Saudi Arabia
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⁵Assistant 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, I²= 92%). The risk of developing PC were significant in patients receiving PPIs (OR 1.76, 95% CI= 1.26–2.46, P=0.001, I²= 98%) and H2RAs (OR 1.25, 95% CI = 1.042–1.49, P=0.016, I²= 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; histamine–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)
Peptic ulcer and its treatments and risk of pancreatic cancer, Nasser Alkhushaym, et. al.

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 nitrosoamine 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 I² was used to assess heterogeneity. Random effects model was considered when I² 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.
<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Country</th>
<th>Ulcer type</th>
<th>Participants</th>
<th>Observed cases</th>
<th>Control</th>
<th>Observed cases</th>
<th>Adjustment</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brusselaers, 2019</td>
<td>Cohort</td>
<td>Sweden</td>
<td>Peptic ulcer</td>
<td>359,158</td>
<td>234</td>
<td>3,828,553</td>
<td>1,733</td>
<td>Age, sex and indication</td>
<td>2.59 (2.27–2.94)</td>
</tr>
<tr>
<td>Valente, 2017</td>
<td>Case–control</td>
<td>Europe</td>
<td>Peptic ulcer</td>
<td>201</td>
<td>24</td>
<td>603</td>
<td>64</td>
<td>Sex, age and center of enrollment</td>
<td>1.25 (0.75–2.07)</td>
</tr>
<tr>
<td>Bosetti, 2013</td>
<td>Case–control</td>
<td>United States, zCanada, and Australia</td>
<td>Gastric or duodenal ulcer</td>
<td>1,183</td>
<td>673</td>
<td>8,146</td>
<td>3,976</td>
<td>Study center, age, sex, race/ethnicity, education, BMI, tobacco smoking, alcohol drinking, history of diabetes, and history of pancreatitis.</td>
<td>1.10 (0.98–1.23)</td>
</tr>
<tr>
<td>Capurso, 2013</td>
<td>Case–control</td>
<td>Italy</td>
<td>Peptic ulcer</td>
<td>390</td>
<td>28</td>
<td>390</td>
<td>16</td>
<td>–</td>
<td>2.55 (1–6)</td>
</tr>
<tr>
<td>Bao, 2010</td>
<td>Cohort</td>
<td>United States of America</td>
<td>Gastric ulcer</td>
<td>2,980</td>
<td>30</td>
<td>45,417</td>
<td>233</td>
<td>Age, smoking, diabetes, BMI and physical activity.</td>
<td>1.83 (1.13–2.97)</td>
</tr>
<tr>
<td>Bao, 2010</td>
<td>Cohort</td>
<td>United States of America</td>
<td>Duodenal ulcer</td>
<td>2,980</td>
<td>30</td>
<td>45,417</td>
<td>233</td>
<td>Age, smoking, diabetes, BMI and physical activity.</td>
<td>1.15 (0.78–1.71)</td>
</tr>
<tr>
<td>Ko, 2007</td>
<td>Case–control</td>
<td>United States of America</td>
<td>Gastric/ Duodenal ulcer</td>
<td>238</td>
<td>84</td>
<td>1,462</td>
<td>447</td>
<td>Race, education, BMI, smoking, and history of diabetes.</td>
<td>1.0 (0.75, 1.3)</td>
</tr>
<tr>
<td>Luo, 2006</td>
<td>Retrospective cohort</td>
<td>Sweden</td>
<td>Gastric ulcer</td>
<td>81,379</td>
<td>403</td>
<td>444,971</td>
<td>182</td>
<td>–</td>
<td>1.2 (1.1–1.4)</td>
</tr>
<tr>
<td>Luo, 2006</td>
<td>Retrospective cohort</td>
<td>Sweden</td>
<td>Duodenal ulcer</td>
<td>61,548</td>
<td>312</td>
<td>421,484</td>
<td>135</td>
<td>–</td>
<td>1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>Stolzenberg 2002</td>
<td>Prospective cohort</td>
<td>Finland</td>
<td>Peptic ulcer</td>
<td>48,045</td>
<td>27</td>
<td>229,521</td>
<td>145</td>
<td>Age, years smoked, self reported, diabetes, bronchial</td>
<td>0.91 (0.61–1.37)</td>
</tr>
<tr>
<td>Mesquita, 1992</td>
<td>Case–control</td>
<td>Netherlands</td>
<td>Ulcer</td>
<td>26</td>
<td>16</td>
<td>209</td>
<td>77</td>
<td>Age, gender, response status and lifetime smoking cigarettes</td>
<td>1.43 (0.7–2.92)</td>
</tr>
<tr>
<td>Vecchia, 1990</td>
<td>Case–control</td>
<td>Northern Italy</td>
<td>Gastric ulcer</td>
<td>45</td>
<td>8</td>
<td>1,089</td>
<td>247</td>
<td>Age and sex.</td>
<td>0.71 (0.32–1.53)</td>
</tr>
<tr>
<td>Vecchia, 1990</td>
<td>Case–control</td>
<td>Northern Italy</td>
<td>Duodenal ulcer</td>
<td>90</td>
<td>20</td>
<td>1,089</td>
<td>247</td>
<td>Age and sex.</td>
<td>0.96 (0.58–1.61)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Country</th>
<th>Drugs</th>
<th>Participants</th>
<th>Observed cases</th>
<th>Control</th>
<th>Observed cases</th>
<th>Adjustment</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee, 2020</td>
<td>Nested case–control</td>
<td>United States of America</td>
<td>Proton pump inhibitors</td>
<td>386</td>
<td>65</td>
<td>4,434</td>
<td>502</td>
<td>Long–term PPI Use, BMI, family history of pancreatic cancer, alcohol use, smoking, diabetes, chronic pancreatitis, and cystic fibrosis.</td>
<td>1.22</td>
</tr>
<tr>
<td>Brusselaers, 2019</td>
<td>Cohort</td>
<td>Sweden</td>
<td>Proton pump inhibitors</td>
<td>796, 492</td>
<td>3,127</td>
<td>20,210</td>
<td>25</td>
<td>Diabetes, alcohol–related disease, COPD, Chronic pancreatitis, gallstones, PUD, helicobacter pylori infection, HBV, HCV use of lowdose aspirin, NSAIDs</td>
<td>2.22</td>
</tr>
<tr>
<td>Peng, 2018</td>
<td>Nested case–control</td>
<td>Taiwan</td>
<td>Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole</td>
<td>1,087</td>
<td>454</td>
<td>1,087</td>
<td>320</td>
<td>Age and chronic pancreatitis.</td>
<td>1.69</td>
</tr>
<tr>
<td>Hwang, 2018</td>
<td>Cohort</td>
<td>South Korea</td>
<td>Proton pump inhibitors</td>
<td>49,785</td>
<td>374</td>
<td>403,826</td>
<td>2,712</td>
<td>--</td>
<td>1.12</td>
</tr>
<tr>
<td>Hicks, 2018</td>
<td>Case control</td>
<td>Denmark</td>
<td>Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole</td>
<td>8,796</td>
<td>1,923</td>
<td>25,809</td>
<td>4,998</td>
<td>Diabetes, alcohol–related disease, COPD, Chronic pancreatitis, gallstones, PUD, helicobacter pylori infection, HBV, HCV use of lowdose aspirin, NSAIDs</td>
<td>1.04</td>
</tr>
<tr>
<td>Boursi, 2017</td>
<td>Retrospective cohort</td>
<td>United Kingdom</td>
<td>Proton pump inhibitors</td>
<td>390</td>
<td>116</td>
<td>108,995</td>
<td>19,030</td>
<td>BMI, smoking, medication use (insulin, metformin and other oral hypoglycemic medications).</td>
<td>1.51</td>
</tr>
<tr>
<td>Kearns, 2017</td>
<td>Nested case–control</td>
<td>United Kingdom</td>
<td>Proton pump inhibitors</td>
<td>4,496</td>
<td>2,312</td>
<td>11,576</td>
<td>1,801</td>
<td>Diabetes, smoking, alcohol use and obesity.</td>
<td>3.613</td>
</tr>
<tr>
<td>Valente, 2017</td>
<td>Case–control</td>
<td>Europe</td>
<td>Proton pump inhibitors</td>
<td>201</td>
<td>78</td>
<td>603</td>
<td>239</td>
<td>Sex, age and center of enrollment</td>
<td>1.04</td>
</tr>
<tr>
<td>Chien, 2016</td>
<td>Nested case–control</td>
<td>Taiwan</td>
<td>Proton pump inhibitors</td>
<td>2,032</td>
<td>245</td>
<td>36,655</td>
<td>3,626</td>
<td>Choleodochal 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, insulin, other anti diabetic drugs and H. pylori eradication therapy.</td>
<td>1.20</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Location</td>
<td>Proton Pump Inhibitors</td>
<td>Cases</td>
<td>Controls</td>
<td>OR (95% CI)</td>
<td>I² (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
<td>------------------------</td>
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<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attwood, 2015</td>
<td>Randomised clinical trial</td>
<td>Belgium, Denmark, France, Germany, Austria, Iceland, Italy, Norway, Sweden, United Kingdom and Netherlands</td>
<td>Esomeprazole, Omeprazole</td>
<td>420</td>
<td>193</td>
<td>4.392 (0.42–33.55)</td>
<td>3.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risch, 2014</td>
<td>Case-control</td>
<td>United States of America</td>
<td>Proton pump inhibitors</td>
<td>194</td>
<td>582</td>
<td>2.61 (1.68, 22.9)</td>
<td>6.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lai, 2014</td>
<td>Case-control</td>
<td>Taiwan</td>
<td>Proton pump inhibitors</td>
<td>977</td>
<td>3,908</td>
<td>2.61 (1.68, 22.9)</td>
<td>9.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosetti, 2013</td>
<td>Case-control</td>
<td>United States of America, Canada, and Australia</td>
<td>Proton pump inhibitors</td>
<td>4717</td>
<td>9374</td>
<td>1.16 (0.72–1.88)</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley, 2011</td>
<td>Nested case-control</td>
<td>United Kingdom</td>
<td>Proton pump inhibitors</td>
<td>1,137</td>
<td>6,817</td>
<td>1.16 (0.72–1.88)</td>
<td>1.16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 agents, **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, I² = 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, I² = 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, I² = 80%).
<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Country</th>
<th>Drugs</th>
<th>Participants</th>
<th>Control</th>
<th>Observed cases</th>
<th>OR (95% CI)</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brusselaers, 2019</td>
<td>Cohort</td>
<td>Sweden</td>
<td>Histamine–2 receptor antagonist</td>
<td>796,492</td>
<td>3,127</td>
<td>20,210</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>Hicks, 2018</td>
<td>Case–control</td>
<td>Denamark</td>
<td>Histamine–2 receptor antagonist</td>
<td>8,796</td>
<td>1,923</td>
<td>25,809</td>
<td>4,998</td>
<td>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.</td>
</tr>
<tr>
<td>Peng, 2018</td>
<td>Nested case–control</td>
<td>Taiwan</td>
<td>Histamine–2 receptor antagonist</td>
<td>1,087</td>
<td>934</td>
<td>1,087</td>
<td>908</td>
<td>Age group and biliary tract disease.</td>
</tr>
<tr>
<td>Risch, 2014</td>
<td>Case–control</td>
<td>United States of America</td>
<td>Histamine–2 receptor antagonist</td>
<td>59</td>
<td>43</td>
<td>648</td>
<td>336</td>
<td>–</td>
</tr>
<tr>
<td>Lai, 2014</td>
<td>Case–control</td>
<td>Taiwan</td>
<td>Histamine–2 receptor antagonist</td>
<td>977</td>
<td>824</td>
<td>3,908</td>
<td>2,459</td>
<td>Acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, and H2RAs, statins, non–statin lipid–lowering drugs, and both of aspirin and cyclooxygenase–2 inhibitors.</td>
</tr>
<tr>
<td>Bosetti, 2013</td>
<td>Case–control</td>
<td>United States of America, Canada, and Australia</td>
<td>Histamine–2 receptor antagonist</td>
<td>312</td>
<td>140</td>
<td>645</td>
<td>310</td>
<td>Study center, age, sex, race/ethnicity, education, BMI, tobacco smoking, alcohol drinking, history of diabetes, and history of pancreatitis.</td>
</tr>
<tr>
<td>Bradley, 2011</td>
<td>Nested case–control</td>
<td>United Kingdom</td>
<td>Histamine–2 receptor antagonist</td>
<td>4,027</td>
<td>876</td>
<td>30,578</td>
<td>6,045</td>
<td>Smoking status, BMI, alcohol use, history of chronic pancreatitis, use of other drugs (NSAIDs, steroids and HRT), diabetes and prior cancer.</td>
</tr>
</tbody>
</table>

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

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\[33\]. 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\[13,39\]. 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 intra gastric 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 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.

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.
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.

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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:


