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# Proton pump inhibitors and histamine-2-receptor antagonists and pancreatic cancer risk: a nested case–control study

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BACKGROUND: The relationship between use of proton pump inhibitors (PPIs) and histamine-2-receptor antagonists (H2RAs) and pancreatic cancer risk has yet to be examined. Data from a range of studies suggest biologically plausible mechanisms, whereby these drugs (or the conditions for which they are prescribed) may affect pancreatic cancer risk. The objective of this study was to investigate the relationship between use of PPIs/H2RAs and pancreatic cancer risk.
METHODS: A nested case–control study was conducted within the UK general practice research database (GPRD). Cases had a diagnosis of exocrine pancreatic cancer and controls were matched to cases on general practice site, sex and year of birth. Exposure to PPIs and to H2RAs since entry into GPRD until 2 years before the diagnosis date (corresponding date in controls) and in the 5 years before the diagnosis date were separately assessed. Conditional logistic regression analyses were used to generate odds ratios (ORs) and 95% confidence intervals (CIs) associated with PPI or H2RA use compared with nonuse.
RESULTS: Ever use of PPIs since entry into the GPRD (excluding the 2 years prior to diagnosis) was not associated with risk of pancreatic cancer; OR (95% CI) 1.02 (0.85–1.22). Neither the dose nor the duration of PPI or H2RA use was associated with pancreatic cancer risk. No consistent patterns of association were seen when cumulative exposure (dose and duration) to these drugs was examined separately or together.
CONCLUSION: PPI/H2RA use, in a UK population, was not associated with pancreatic cancer risk.

Pancreatic cancer is rapidly fatal and is the fifth leading cause of cancer mortality in the western world. Almost 50% of patients present with distant metastases and little progress has been made in recent decades in the diagnosis or treatment of this cancer, resulting in poor survival rates (Jemal *et al*, 2007).

Proton pump inhibitors (PPIs) are some of the most commonly prescribed medications in North America (IMS Health, 2008) and the United Kingdom (National Health Service Business Services Authority, 2009). They are used in the treatment of gastrointestinal disorders, such as gastro-oesophageal reflux disease (DeVault and Castell, 2005; BMJ group, 2009). PPIs are potent suppressors of gastric acid and recently they have been used with increased frequency and for prolonged durations (Naunton *et al*, 2000). The long-term gastric hypoacidity associated with PPI use results in raised serum gastrin levels (hypergastrinaemia) (Klinkenberg-Knol *et al*, 1994). Histamine-2-receptor antagonists (H2RAs) are also used for similar indications, have been in use since the 1970s, and may induce hypergastrinaemia and hypoacidity (Wynn *et al*, 2007).

There are a number of potential mechanisms, whereby use of PPIs/H2RAs may influence pancreatic cancer risk (Risch, 2003). Gastric hypoacidity favours the overgrowth of bacteria in the stomach (Fried *et al*, 1994; Thorens *et al*, 1996), which results in the production of N-nitrosamines (Yeomans *et al*, 1995), although there is some evidence to the contrary (Vermeer *et al*, 2001). Pancreatic ductal adenocarcinomas have been seen to develop in mice and human pancreatic cells exposed to nitrosamines (Parsa *et al*, 1981; Parsa, 1987). PPI-/H2RA-related hypergastrinaemia may also contribute to pancreatic cancer carcinogenesis. Gastrin appears to have a role in the development and progression of gastrointestinal malignancies (Chao and Hellmich, 2010). Gastrin receptors are expressed in human pancreatic cancer cells (Smith *et al*, 1994), and gastrin has been seen to stimulate the growth of human pancreatic cancer cells in culture and in tumours transplanted into nude mice (Smith *et al*, 1995). These effects were blocked by gastrin-receptor antagonists (Smith *et al*, 1995), such as gastrazole (Roberts *et al*, 2002), which in a small randomised controlled trial increased the survival time among pancreatic cancer patients (Chau *et al*, 2006) Other studies refute this theory (Chu *et al*, 1997).

PPI/H2RA use increases secretin levels, which may influence pancreatic cell growth (Sarfati *et al*, 1985; Howatson and Carter, 1987).

The relationship between use of PPI/H2RAs and pancreatic cancer risk has yet to be examined, despite widespread use of these drugs and data from a range of studies suggesting biologically plausible mechanisms, whereby these drugs (or the conditions for which they are prescribed) may affect pancreatic cancer risk. We examined this relationship in a large nested case–control study within the UK general practice research database (GPRD).

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## MATERIALS AND METHODS

We undertook a nested case–control study within the UK GPRD. The GPRD collects data from around 500 general practices in the United Kingdom, covers about 8% of the population and is broadly representative of the UK population. The data obtained are assessed in terms of completeness, continuity and plausibility, and general practices that meet predefined standards are registered as 'up to standard' (UTS) practices. The information recorded in GPRD includes demographic information, clinical diagnoses, referral information, specialty consultation notes, results of laboratory tests and hospital discharge information. The Read and Oxford Medical Information System codes are used to classify medical diagnoses. The GPRD also contains details of all prescriptions issued for patients registered with the participating practices (García Rodríguez and Pérez Gutthann, 1998). The high quality of GPRD prescription and diagnosis information has been documented (Jick et al, 1991, 1992). Ethical approval for all observational research using GPRD data has been obtained from a multicentre research ethics committee.

### Study population

The study included patients from UTS practices with diagnostic codes for primary malignant neoplasia of the exocrine pancreas, with a date of diagnosis/index date (first recorded occurrence of a pancreatic cancer code) between January 1995 and June 2006. Data were extracted from the GPRD in February 2007. Patients aged 85 or older were excluded as were cases without at least 5 years of UTS data collection prior to the index date. Controls with no GPRD record of pancreatic cancer were selected and matched to cases on year of birth, sex and general practice site. Controls also had at least 5 years of UTS data collection before their index date (date of pancreatic cancer diagnosis in their matched case). Up to seven controls were matched for each case.

### Review of cancer codes

Pancreatic cancer is difficult to conclusively diagnose without histological or cytological examination of relevant specimens and these specimens are often not available. Pancreatic cancer may therefore be confused with primary malignancies in anatomically related organs or with secondary tumours. In one UK cancer registry (unrelated to this study), only 57% of the patients had histological or cytological confirmation of their diagnosis (Kinnear et al, 2005). Data on histological or cytological confirmation of pancreatic cancer were not available from GPRD, at the time the data were obtained, as there was no routine linkage to cancer registries. In order to minimise misclassification of pancreatic cancer within this study, all cancer codes recorded in the medical records of potential cases were reviewed. Only cases with consistently recorded pancreatic cancer codes were included. All other cases, for example, patients with codes for both pancreatic cancer and cholangiocarcinoma, or carcinoma of bile duct, gallbladder and so on, and their matched controls were excluded from the dataset. Periampullary tumours were also excluded. Cases and controls with a prior history of cancer (at least one year before the index date) were also identified by review of cancer codes. These patients were flagged as having a previous cancer but were not excluded from the dataset.

### Exposure to PPIs/$H_2$RAs

The primary exposures of interest were PPI and $H_2$RA use since entry into the database until 2 years before the index date. PPIs/$H_2$RAs were defined as listed in the British National Formulary 2009 (British Medical association and Royal Pharmaceutical Society of Great Britain, 2009), a national reference source for information on drugs. A priori, we decided that a positive association between pancreatic cancer risk and use of antisecretory drugs, in the 2 years preceding the index date, may be observed as pancreatic cancer symptoms often present as non-specific abdominal symptoms and antisecretory drugs may have been used to alleviate these symptoms. As a result, PPI/$H_2$RA use in the 2 years before diagnosis was excluded from the analyses. PPI/$H_2$RA use individually in the 5 years before the index date (excluding the 2 years before) was also examined, as well as combined dose and duration of PPI/$H_2$RA use since entry into the database. The total exposure (dose and duration) to antisecretory drugs (PPIs and $H_2$RAs) was also examined. The drug history for subjects in the study population was reviewed and data were extracted on all PPIs/$H_2$RAs prescribed for cases and controls. PPI/$H_2$RA use was expressed in units of defined daily dose (DDD), a validated measure of drug consumption maintained by the World Health Organisation. It is the assumed average maintenance dose per day of a drug that is used for its main indication in adults (World Health Organisation Working Group, 2008), as the DDD of a drug may be assumed to be functionally equivalent to the DDD of any other drug used for a similar purpose.

The number of DDDs for each PPI/$H_2$RA prescription issued was calculated by multiplying the dose of the PPIs/$H_2$RAs prescribed by the quantity given and dividing this by the DDD value assigned to that drug. For each time period under study, the total number of DDDs, for each PPI/$H_2$RA prescribed, and for all PPIs/$H_2$RAs combined, were calculated for each case and control. Total dose of PPIs/$H_2$RAs (expressed in DDDs), in the periods under study, were categorized into approximate quartiles on the basis of total PPI/$H_2$RA use within the controls. Cumulative duration of any PPI/$H_2$RA use was calculated as the total number of intended treatment days. Total duration of any PPI/$H_2$RA use, in the periods under study, was also categorized into approximate quartiles, on the basis of duration of treatment within the controls.

Exposure to PPIs/$H_2$RAs at any time prior to the index date excluding the 2 years before the index date was further categorized according to both dose and duration of use. The median number of DDDs, per day, of PPI/$H_2$RA exposure in the controls during this period was 1 DDD per day, therefore low dose PPI/$H_2$RA exposure was classified as the use of < 1.0 DDD of PPIs/$H_2$RAs per day and high dose as > 1.0 DDDs per day. Categories for duration of low and high PPIs/$H_2$RAs use were subsequently created; no use or use for < 1 year, use for 1–3 years, use for 3–5 years and use for ⩾5 or more years (Yang et al, 2007). The total use of PPIs and $H_2$RAs was calculated by summing the total number of DDDs/days of use since entry into the database.

### Statistical analysis

Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between disease status and use of PPIs/$H_2$RAs. Models were constructed for ever/never use of all PPIs/$H_2$RAs separately. Dose and duration of PPI/$H_2$RA use was examined using continuous variables (output expressed per 100 DDDs and 100 days of use), approximate quartiles of dose and duration of PPIs/$H_2$RAs use and the combined dose and duration variable. A model detailing total exposure to antisecretory drugs (PPIs and $H_2$RAs) was also generated. For presentation purposes the output from the continuous variables was reported per 100 DDDs and 100 days. PPI/$H_2$RA use in the 2 years before diagnosis was excluded in all analyses and models were constructed relating to the period since entry into the GPRD and the 5 years before diagnosis/index date.

All analyses were adjusted for potential confounders, including smoking status (unknown, current smoker, non-smoker and ex-smoker), body mass index (unknown, underweight, normal, overweight and obese) according to the World Health Organisation

categories (World Health Organisation Working Group, 2009), alcohol use (unknown, current drinker, lifelong non-drinker and ex-drinker), history of pancreatitis, history of diabetes and history of cancer. For smoking, alcohol use and body mass index, the most recent record excluding those within the year prior to the index date was used and for history of diabetes, pancreatitis and cancer we also excluded events within the year prior to the index date. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin (ever/ never) was accounted for as users are increasingly likely to receive a PPI/$H_2$RA for prevention of NSAID-induced ulceration in the GI tract (National Institute for Health and Clinical Excellence, 2008). NSAID/aspirin use has been associated with a reduced risk of pancreatic cancer (Anderson *et al*, 2002). Use of systemic steroids (ever/never use) and hormone replacement therapy (ever/never use) was accounted for, as use of these drugs may confound the association between PPI/$H_2$RA and pancreatic cancer. Use of NSAIDs/aspirin, hormone replacement therapy and steroids, in the year before diagnosis, was excluded. Test for trends across categories of dose and duration, where appropriate, was performed. Data on the confounders were not available for all subjects and for those subjects for whom all data were available, a restriction analyses was carried out. All *P*-values were two sided. STATA Version 9 (Timberlake Consultants Ltd, London, UK) was used for all analyses.

## RESULTS

Within the UK GPRD, 1361 pancreatic cancer cases met our initial inclusion criteria and these were matched to 9487 controls. After review of cancer codes, 220 cases (16%) and their controls (1542) were excluded, leaving 1141 pancreatic cancer cases and 7954 matched controls. Each case had at least one matched control and >90% of cases had seven matched controls. The mean duration of UTS follow-up was 10.6 years (s.d., 3.4) for both cases and controls. The mean age at database enrolment was identical for cases and controls at 57.3 years (s.d., 9.8). Over 50% (53.7%) of all study subjects were male (Table 1). The risk of pancreatic cancer was elevated among smokers in our study population OR (95% CI) 1.92 (1.63–2.26) and the OR for pancreatic cancer among subjects with diabetes was 1.90 (95% CI: 1.53–2.35). Any use of a PPI since entry into the GPRD (excluding the 2 years prior to diagnosis) was not associated with the risk of pancreatic cancer, OR (95%CI) 1.02 (0.85–1.22). There was no overall association between pancreatic cancer risk and the total dose of PPI used since entry into the GPRD. The adjusted ORs (95% CI) for an increase in 100 DDDs of PPIs in this period was 0.99 (0.97–1.01). When the dose of PPIs was categorised according to use in controls (approximate quartiles), no association was seen between dose category and pancreatic cancer risk (Table 2). Similar results were observed in the period of 5 years before the index date (excluding the 2 years prior to diagnosis) (data not shown).

Duration of PPI use was examined in a similar manner to dose and no associations with pancreatic cancer risk were seen (Table 3).

Dose and duration of PPI use combined was not associated with pancreatic cancer risk, although there was a suggestion of a reduced risk of pancreatic cancer among those using lower doses of PPIs (Table 4).

No overall association was found between pancreatic cancer risk and the dose and duration of $H_2$RAs used since entry into the GPRD (Data not shown). Similar results were seen for use in the 5 years before the index date. The analysis that combined dose and duration of $H_2$RA use demonstrated an increased risk of pancreatic cancer, OR (95%CI) 1.25 (1.03–1.52), among short-term users (0–1 years) of high-dose $H_2$RAs. However, no increases in risk were seen among those using high-dose $H_2$RAs for longer durations of time and the number of these users was small (Table 4).

**Table I** Characteristics of cases and controls

| | Cases (n = 1141) | Controls (n = 7954) | *P*-value |
|---|---|---|---|
| Mean age at database enrolment (year) (s.d.) | 57.3 (9.8) | 57.3 (9.8) | >0.99 |
| Male sex (%) | 53.7 | 53.7 | >0.99 |
| Mean duration of follow-up before index date (year) (s.d.) | 10.6 (3.4) | 10.6 (3.4) | >0.99 |
| *Smoking status* | | | <0.01 |
|   Current smoker | 302 (26.5%) | 1372 (17.3%) | |
|   Non-smoker | 463 (40.6%) | 3961 (49.8%) | |
|   Ex-smoker | 235 (20.6%) | 1499 (18.9%) | |
|   Missing data | 141 (12.4%) | 1122 (14.1%) | |
| *BMI (kg m$^{-2}$)* | | | 0.1 |
|   <18.5 | 16 (1.4%) | 102 (1.3%) | |
|   ⩾18.5 and <25 | 353 (31.0%) | 2323 (29.2%) | |
|   ⩾25 and <30 | 343 (30.1%) | 2525 (31.8%) | |
|   ⩾30 | 187 (16.4%) | 1108 (13.9%) | |
|   Missing | 242 (21.21%) | 1896 (23.8%) | |
| *Current drinking status* | | | 0.4 |
|   Current drinker | 731 (64.1%) | 4992 (62.8%) | |
|   Non-drinker | 165 (14.5%) | 1107 (13.9%) | |
|   Ex-drinker | 7 (0.6%) | 77 (1.0%) | |
|   Missing data | 238 (20.9%) | 1778 (22.4%) | |
| *HRT use* | | | 0.3 |
|   Never | 1095 (95.9%) | 7574 (95.2%) | |
|   Ever | 46 (4.1%) | 380 (4.8%) | |
| *Steroid use* | | | 0.2 |
|   Never | 990 (86.8%) | 6999 (88.0%) | |
|   Ever | 151 (13.2%) | 955 (12.0%) | |
| *Pancreatitis* | | | <0.01 |
|   Never | 1085 (95.1%) | 7901 (99.3%) | |
|   Ever | 56 (4.9%) | 53 (0.7%) | |
| *PPI use* | | | 0.27 |
|   Never | 964 (84.5%) | 6817 (85.7%) | |
|   Ever | 177 (15.5%) | 1137 (14.3%) | |
| *$H_2$RA use* | | | <0.01 |
|   Never | 877 (76.9%) | 6423(80.8%) | |
|   Ever | 264 (23.1%) | 1531 (19.2%) | |
| *Diabetes* | | | <0.01 |
|   Never | 1006 (88.2%) | 7442 (93.56%) | |
|   Ever | 135 (11.8%) | 512 (6.44%) | |
| *Prior cancer* | | | 0.35 |
|   Never | 1049 (91.9%) | 7374 (92.7%) | |
|   Ever | 92 (8.1%) | 580 (7.3%) | |

Abbreviations: BMI = body mass index; $H_2$RA = histamine-2-receptor antagonist; HRT = hormone replacement therapy; PPI = proton pump inhibitor.

The total dose and duration of antisecretory drug use combined (PPI plus $H_2$RA use) was not associated with pancreatic cancer risk either in the period since entry into the GPRD (Table 5). The results from the restriction analysis completed for all subjects with complete data on confounders showed that the absence of data on some confounders, did not affect the overall estimates (data not shown).

## DISCUSSION

In this large population-based study, no association between risk of pancreatic cancer and antisecretory drug use was seen for ever

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**Table 2** Total dose of PPI, H2RA and risk of pancreatic cancer

| PPI use<br>Dose of PPI use (DDDs) | Entry into GPRD until 2 years before index date | | | | H2RA use<br>Dose of H2RA use (DDDs) | Entry into GPRD until 2 years before index date | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases (n) | Controls (n) | OR (95% CI) | Adjusted OR (95% CI)[a] | | Cases (n) | Controls (n) | OR (95% CI) | Adjusted OR (95% CI)[a] |
| Category 1 (no use) | 964 | 6817 | 1.0 | 1.0 | Category 1 (no use) | 877 | 6423 | 1.0 | 1.0 |
| Category 2 (0–28) | 52 | 311 | 1.19 (0.88–1.61) | 1.14 (0.84–1.55) | Category 2 (0–30) | 83 | 464 | 1.31 (1.03–1.69) | 1.30 (1.01–1.68) |
| Category 3 (28.5–112) | 31 | 257 | 0.86 (0.59–1.25) | 0.79 (0.54–1.17) | Category 3 (30.5–90) | 53 | 316 | 1.24 (0.92–1.68) | 1.15 (0.84–1.56) |
| Category 4 (112.5–476) | 51 | 288 | 1.26 (0.93–1.72) | 1.14 (0.83–1.56) | Category 4 (90.5–480) | 67 | 370 | 1.34 (1.02–1.76) | 1.20 (0.91–1.59) |
| Category 5 (>476) | 43 | 281 | 1.09 (0.78–1.52) | 0.96 (0.68–1.36) | Category 5 (>480) | 61 | 381 | 1.18 (0.89–1.57) | 1.05 (0.78–1.40) |

Abbreviations: BMI = body mass index; CI = confidence interval; DDD = defined daily dose; H$_2$RA = histamine-2-receptor antagonist; HRT = hormone replacement therapy; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PPI = proton pump inhibitor. [a]Adjusted for smoking status (current smoker, non-smoker, ex-smoker, missing data), BMI ($<18.5$, $\geqslant18.5$, $<25$, $\geqslant25$, $<30$ and $\geqslant30\,kg\,m^{-2}$, missing), alcohol use (current drinker, non-drinker, ex-drinker), history of chronic pancreatitis (ever/never), use of other drugs (NSAIDs, steroids and HRT (ever/never)), diabetes (ever/never) and prior cancer (ever/never).

**Table 3** Duration of PPI, H$_2$RA use and risk of pancreatic cancer

| PPI use<br>Duration of PPI use (days) | Entry into GPRD until 2 years before index date | | | | H2RA use<br>Duration of H$_2$RA use (Days) | Entry into GPRD until 2 years before index date | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases (n) | Controls (n) | OR (95% CI) | Adjusted OR (95%CI)[a] | | Cases (n) | Controls (n) | OR (95% CI) | Adjusted OR (95%CI)[a] |
| -Category 1 (no use) | 964 | 6817 | 1.0 | 1.0 | -Category 1 (no use) | 877 | 6424 | 1.0 | 1.0 |
| -Category 2 (0–28) | 51 | 308 | 1.18 (0.87–1.60) | 1.13 (0.83–1.55) | -Category 2 (0–30) | 80 | 449 | 1.31 (1.02–1.69) | 1.30 (1.01–1.69) |
| -Category 3 (28.5–106) | 37 | 264 | 1.0 (0.70–1.42) | 0.92 (0.64–1.32) | -Category 3 (30.5–90) | 57 | 320 | 1.32 (0.98–1.77) | 1.20 (0.89–1.63) |
| -Category 4 (106.5–552) | 47 | 281 | 1.20 (0.87–1.65) | 1.07 (0.77–1.48) | -Category 4 (90.5–520) | 71 | 379 | 1.39 (1.06–1.81) | 1.26 (0.96–1.65) |
| -Category 5 (>552) | 42 | 284 | 1.05 (0.75–1.47) | 0.93 (0.65–1.32) | -Category 5 (>520) | 56 | 382 | 1.08 (0.81–1.44) | 0.95 (0.71–1.29) |

Abbreviations: BMI = body mass index; CI = confidence interval; DDD = defined daily dose; H$_2$RA = Histamine-2-receptor antagonist; HRT = hormone replacement therapy; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PPI = proton pump inhibitor. [a]Adjusted for smoking status (current smoker, non-smoker, ex-smoker, missing data), BMI ($<18.5$, $\geqslant18.5$, $<25$, $\geqslant25$, $<30$ and $\geqslant30\,kg\,m^{-2}$, missing), alcohol use (current drinker, non-drinker, ex-drinker), history of chronic pancreatitis (ever/never), use of other drugs (NSAIDs, steroids and HRT (ever/never)), diabetes (ever/never) and prior cancer (ever/never).

**Table 4** Pancreatic cancer risk according to dose and duration of PPI, H$_2$RA use since entry into GP

| | <1.0 DDD per day | | | | ≥1.0 DDD per day | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases n | Controls n | OR (95% CI) | Adjusted OR (95%CI)[a] | Cases n | Controls n | OR (95% CI) | Adjusted OR (95%CI)[a] |
| *(a) PPI* | | | | | | | | |
| *Duration of PPI use* | | | | | | | | |
| Nonusers | 964 | 6817 | 1.0 | 1.0 | 964 | 6817 | 1.0 | 1.0 |
| 0–1 year | 20 | 195 | 0.70 (0.44–1.12) | 0.60 (0.37–0.98) | 107 | 592 | 1.27 (1.02–1.58) | 1.20 (0.95–1.50) |
| 1–4 years | 14 | 113 | 0.87 (0.50–1.54) | 0.70 (0.39–1.27) | 20 | 115 | 1.23 (0.76–1.99) | 1.08 (0.65–1.77) |
| >4 years | 5 | 61 | 0.61 (0.24–1.53) | 0.54 (0.20–1.42) | 11 | 61 | 1.32 (0.69–2.55) | 1.32 (0.67–2.60) |
| *(b) H$_2$RA* | | | | | | | | |
| *Duration of H$_2$RA use* | | | | | | | | |
| Nonusers | 877 | 6424 | 1.0 | 1.0 | 877 | 6424 | 1.0 | 1.0 |
| 0–1 years | 29 | 193 | 1.09 (0.72–1.63) | 0.98 (0.65–1.49) | 163 | 887 | 1.34 (1.12–1.61) | 1.25 (1.03–1.52) |
| 1–4 years | 13 | 109 | 0.91 (0.5–1.63) | 0.92 (0.51–1.68) | 36 | 190 | 1.40 (0.97–2.01) | 1.24 (0.84–1.81) |
| >4 years | 9 | 80 | 0.96 (0.47–1.96) | 0.82 (0.39–1.72) | 14 | 71 | 1.54 (0.86–2.77) | 1.35 (0.73–2.48) |

Abbreviations: BMI = body mass index; CI = confidence interval; DDD = defined daily dose; H$_2$RA = histamine-2-receptor antagonist; HRT = hormone replacement therapy; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PPI = proton pump inhibitor. [a]Adjusted for smoking status (current smoker, non-smoker, ex-smoker, missing data), BMI ($<18.5$, $\geqslant18.5$, $<25$, $\geqslant25$, $<30$ and $\geqslant30\,kg\,m^{-2}$, missing), alcohol use (current drinker, non-drinker, ex-drinker), history of chronic pancreatitis (ever/never), use of other drugs (NSAIDs, steroids and HRT (ever/never)), diabetes (ever/never) and prior cancer (ever/never).

compared with non-use of PPIs or H$_2$RAs. There was also no overall association between pancreatic cancer risk and the total dose or duration of PPIs or H$_2$RAs used and no increases in risk were seen among subjects who used these drugs at the highest doses or for the longest durations. No consistent patterns of association were seen when cumulative exposure (dose and duration) to these drugs were examined separately or together (total antisecretory drug use, i.e., PPI plus H$_2$RA), although there was some evidence of a decrease in risk among low-dose PPI users and an increase in risk among short-term low-dose H$_2$RA users.

Overall, this study does not provide consistent evidence for either an increased or decreased risk of pancreatic cancer associated with

the use of PPIs or H$_2$RAs. However, few study subjects had long-term exposure to PPIs. Just 16 cases and 122 controls used PPIs (at low or high doses) for longer than 4 years. More profound suppression of acid and subsequent hypergastrinaemia, which occurs with higher doses of PPIs, is biologically more likely to affect pancreatic cancer risk. However, in this study no increased risk of pancreatic cancer was observed among long-term (>4 years) high-dose PPI users, but the number of long-term high-dose PPI users (11 cases, 61 controls) was too small to adequately assess the effect of high doses of these drugs on pancreatic cancer risk.

Certain PPIs were not available in the United Kingdom until 2000 (UK Medicines Information Pharmacist groups, 2001) and

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**Table 5** Pancreatic risk according to total dose and duration of acidsuppressive therapy (PPIs and H$_2$RAs) since entry into the GPRD

| PPIs and H$_2$Ras Dose (DDDs) | Entry into GPRD until 2 years before index date | | | PPIs and H2RAs Duration (Days) | Entry into GPRD until 2 years before index date | | |
|---|---|---|---|---|---|---|---|
| | Cases | Controls | Adjusted OR (95% CI)[a] | | Cases | Controls | Adjusted OR (95% CI)[a] |
| No use | 818 | 5966 | 1.0 | -No use | 818 | 5968 | 10 |
| Category 2 (0–30) | 77 | 500 | 1.12 (0.86–1.45) | -Category 2 (0–37) | 78 | 502 | 1.15 (0.89–1.49) |
| Category 3 (31–144) | 81 | 496 | 1.12 (0.87–1.44) | -Category 3 (37–144) | 84 | 492 | 1.14 (0.89–1.47) |
| Category 4 (145–776) | 89 | 495 | 1.21 (0.95–1.55) | -Category 4 (145–849) | 84 | 496 | 1.16 (0.90–1.49) |
| Category 5 (>776) | 76 | 497 | 0.97 (0.74–1.27) | -Category 5 (>849) | 77 | 496 | 1.03 (0.79–1.35) |

Abbreviations: BMI = body mass index; CI = confidence interval; DDD = defined daily dose; H$_2$RA = Histamine-2-receptor antagonist; HRT = hormone replacement therapy; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PPI = proton pump inhibitor. [a]Adjusted for smoking status (current smoker, non-smoker, ex-smoker, missing data), BMI ($<$18.5, $\geqslant$18.5, $<$25, $\geqslant$25, $<$30 and $\geqslant$30 kg m$^{-2}$, missing), alcohol use (current drinker, non-drinker, ex-drinker), history of chronic pancreatitis (ever/never), use of other drugs (NSAIDs, steroids and HRT (ever/never)), diabetes (ever/never) and prior cancer (ever/never).

the dates of data capture in this study appear to have preceded the rapid increase in use of PPIs in recent years. Pancreatic carcinogenesis has a long latency period (Brat et al, 1998), therefore it may be too early to see a relationship between use of PPIs and pancreatic cancer development due to their relatively recent introduction to the UK market.

Since the introduction of PPIs, use of H$_2$RAs has declined (National Health Service Business Services Authority, 2009), however, it was deemed possible that some users may have been exposed to H$_2$RAs for prolonged periods of time and this may be important for cancer risk. Despite the earlier introduction of H$_2$RAs to the UK market (in the mid 1970s), there were very few long-term ($>$4 years) H$_2$RA users (23 cases and 151controls) compared with short-term users (192 cases, 1080 controls) in this study. As PPIs provide a more rapid and sustained increase in gastric pH (Brett, 2005), long-term H$_2$RA users may have switched to PPI therapy in recent years, resulting in the reduced number of long-term H$_2$RA users.

Epidemiological studies have shown an increased risk of gastric cancer among PPI users (Bateman et al, 2003; García Rodríguez et al, 2006; Poulsen et al, 2009), however, any effect may have been due to reverse causality or confounding by indication. The increasing use of PPIs, in the last decade, was thought to have been related to the sharp rise in oesophageal cancer incidence (Lepage et al, 2008; Rosch, 2010). However, increased incidence, along with the higher mortality rates for oesophageal cancer, was attributed to the underlying disease and not to treatment with PPIs (Bateman et al, 2003; García Rodríguez et al, 2006); Robertson et al, 2007). No association between PPI use and colorectal cancer has been observed in large case–control studies (Yang et al, 2007; Van soest et al, 2008).

Assessment of the relationship between PPI/H$_2$RA use and pancreatic cancer risk is likely to be complicated by the underlying indications for use of these drugs. Epidemiological studies have found an increased risk of pancreatic cancer among individuals with duodenal ulcers, gastric ulcers or peptic ulcers (indications for which these drugs are used) (Farrow and Davis, 1990; Luo et al, 2007), whereas others have failed to show an association (La Vecchia et al, 1990; Silverman et al, 1999). Helicobacter pylori infection is a leading cause of peptic ulcers and has been shown to be associated with pancreatic cancer risk (Stolzenberg-Solomon et al, 2001) as was partial gastrectomy and truncal vagotomy, which are surgical procedures used in the treatment of peptic ulcer disease (Tersmette et al, 1990; van Rees et al, 1999; Tascilar et al, 2002). However, conflicting results have been reported (Caygill et al, 1987; La Vecchia et al, 1990; Silverman et al, 1999).

This investigation has several key strengths. It is the only study to date to assess the association of PPI/H$_2$RA exposure and pancreatic cancer. A detailed analysis was possible by stratifying the analyses based on dose, duration, and dose and duration of PPI/ H$_2$RA use. The use of prospectively collected prescription data avoids errors of recall and potential recall bias. All subjects in our study had at least 5 years of data available prior to pancreatic cancer diagnosis and data were available prior to diagnosis for a mean of over 10 years. We also adjusted for all major confounders and, although data were not available for all subjects, the results of restriction analyses, including only those patients who had data on these confounders, were not different from the main analyses. The results for the association between pancreatic cancer and smoking and diabetes reported in this study are similar to those obtained in some larger international studies (Heinen et al, 2010; Bertuccio et al, 2011; Lipworth et al, 2011), which supports the validity of our study.

However, the study has some limitations. A low prevalence of long-term PPI/H$_2$RA use in the study population meant that we were unable to examine the effects of exposure to these agents for long periods of time. Data on prescriptions issued may not reflect actual use of PPIs/H$_2$RAs, but there is no reason to believe that noncompliance with prescription medication would be systematically different between cases and controls. No information was available on over-the-counter PPI/H$_2$RA use and misclassification of over-the-counter users as nonusers based on prescription information would have biased the estimates towards the null. However, at the time of this study there was only one PPI-available over-the-counter from pharmacies in the United Kingdom and uptake has been low (Stewart et al, 2007), although H$_2$RAs are more readily available. Pancreatic cancer diagnoses were not validated in this study and any misclassification of diagnosis is likely to bias the estimate towards the null. However, we excluded very elderly subjects, in whom diagnostic accuracy may be a particular problem, and all cancer codes were reviewed and cases with inconsistent coding were excluded. Furthermore, cancer diagnoses in GPRD appear to be a reliable record of incident cancer diagnoses and have been shown to concord with original medical records in 95% of cases (Jick et al, 1997).

In summary, despite biologically plausible mechanisms, whereby use of PPIs or H$_2$RAs may increase the risk of pancreatic cancer, we did not observe any consistent associations between use of these drugs and pancreatic cancer risk in a large study involving a representative UK population.

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