LETTER

Proton pump inhibitors and the risk of gallbladder cancer: a hospital-based case–control study

We read with great interest the article by Chuang *et al*[1] confirming proton pump inhibitor (PPI) use is associated with increased risk of cholecystitis.[1] PPIs are a potent class of agents used to suppress gastric acid secretion and are among the most commonly prescribed medications globally.[2] Presently, PPIs are routinely recommended for several GI disorders, including GORD, and as prophylaxis against peptic ulcer disease and GI bleeding in susceptible populations, such as individuals on dual antiplatelet therapy for secondary prevention of cardiovascular disease.[3–5] In view of the large population of patients receiving PPI therapy, in many cases long-term therapy, ensuring the safety of PPI therapy is of considerable public health importance.[6] Recently, PPIs have been reported to be associated with cholecystitis and might possibly be carcinogenic.[1] However, no research has been conducted to investigate the association of PPIs with gallbladder cancer (GBC). Herein, a hospital-based case–control study was carried out in China to explore the association between PPIs and GBC risk.

A hospital-based case–control study was performed by enrolling 3030 subjects (606 subjects with pathologically diagnosed GBC as well as 2424 healthy controls) from the Beijing Friendship Hospital of the Capital Medical University, Beijing, China, from February 2002 to October 2018. Differences in PPI use were compared between the GBC and control groups. Cases were frequency-matched 1 to 4 with controls (without a history of GBC) in the Health Screening Center of Beijing Friendship Hospital from May 2012 through January 2019 for age, sex and history of gallstone. Both study groups excluded individuals receiving cholecystectomy prior to the index date.

In this case–control study, 44 of 606 (7.3%) patients with GBC and 109 of 2424 (4.5%) controls have been exposed to PPI 28 cumulative defined daily dose (cDDD) (table 1). When comparing ever users of PPI with non-PPI users, we found PPI use was associated with 1.56-fold elevated GBC risk (p<0.0001) (OR=1.56, 95% CI 1.07 to 2.19; p=0.005) (table 2). Next, we determined the impact of dose and duration of PPI use on GBC risk (table 2). The ORs were 1.42 (95% CI 0.80 to 2.41), 1.67 (95% CI 1.03 to 2.76) and 2.69 (95% CI 1.15 to 7.28) in the 28–90, 91–180 and 180+ cDDD groups, respectively, compared with the ≤27 cDDD group (table 2). In considering the use of PPI according to cDDD subgroups, the risk significantly increased, and the highest dose–response effect was found in patients with PPI exposure of 180+ cDDD groups (p for trend <0.0001) (table 2). When stratified by duration of

Table 1 Baseline characteristics of GBC cases and controls

Characteristics	GBC, n=606 (%)	Controls, n=2424 (%)	P value*
Age (years)			0.955
<60	226 (32.3)	907 (37.4)	
≥60	380 (62.7)	1517 (62.6)	
Sex			
Male	195 (32.1)	781 (32.2)	
Female	411 (67.9)	1643 (67.8)	0.984
Gallstones	119 (19.7)	480 (19.8)	0.927
Infectious diseases			
HBV	59 (9.7)	104 (4.3)	<0.001
HCV	27 (4.5)	41 (1.7)	<0.001
Fatty liver disease	75 (12.4)	191 (7.9)	<0.001
Alcohol intake	156 (25.8)	393 (16.2)	<0.001
Smoking	204 (33.6)	448 (18.5)	<0.001
Diabetes mellitus	123 (20.3)	187 (7.7)	0.002
Dyslipoproteinaemia	176 (29.0)	373 (15.4)	<0.001
Hypertension	78 (12.9)	347 (14.3)	0.36
Obesity	138 (22.7)	330 (13.6)	<0.001
Coronary artery disease	134 (22.1)	625 (25.8)	0.062
Aspirin use	142 (23.5)	926 (38.2)	<0.001
PPI use	44 (7.3)	109 (4.5)	0.005
Duration of use (years)			
≤3	19 (3.1)	43 (1.8)	0.034
<3	9 (1.5)	15 (0.6)	0.031
Dose (cDDD)			
0–27	562 (92.7)	2291 (95.5)	
28–90	15 (2.5)	45 (1.9)	0.219
91–180	23 (3.8)	55 (2.3)	0.036
>180	6 (1.0)	7 (0.3)	0.018

*P value for difference between total GBC cases and controls.
cDDD, cumulative defined daily dose; GBC, gallbladder cancer; PPI, proton pump inhibitor.

Table 2 OR and 95% CI of GBC associated with PPI use and other covariates

Variables	OR (95% CI)	P value
Infectious diseases		
HBV	2.31 (1.72 to 3.25)*	<0.001
HCV	2.65 (1.44 to 4.36)*	<0.001
Fatty liver disease	1.63 (1.20 to 2.03)*	<0.001
Alcohol intake	1.68 (1.44 to 2.19)*	<0.001
Smoking	2.23 (1.84 to 2.73)*	<0.001
Diabetes mellitus	2.54 (1.87 to 3.41)*	0.002
Dyslipoproteinaemia	2.15 (1.72 to 2.66)*	<0.001
Hypertension	0.88 (0.67 to 1.15)	0.36
Obesity	2.12 (1.68 to 2.46)*	<0.001
Coronary artery disease	0.81 (0.56 to 1.15)	0.062
Aspirin use	0.49 (0.38 to 0.63)*	<0.001
PPI use	1.56 (1.07 to 2.19)*	0.005
Duration of use (years)		
≤3	1.79 (1.03 to 3.10)*	0.034
>3	2.41 (1.05 to 4.93)*	0.031
Dose (cDDD)		
0–27		
28–90	1.42 (0.80 to 2.41)	0.219
91–180	1.67 (1.03 to 2.76)*	0.036
>180	2.69 (1.15 to 7.28)*	0.018

*Adjusted OR was estimated using conditional logistic regression adjusted for other covariates listed in the table.
cDDD, cumulative defined daily dose; GBC, gallbladder cancer; PPI, proton pump inhibitor.

PPI use as >3 years or ≤3 years, the ORs were 1.79 (95% CI 1.03 to 3.10) and 2.41 (1.05 to 4.93) for PPI use of >3 years and ≤3 years, respectively (table 2).

This observation is biologically plausible as supported by preclinical studies of GBC and other cancers. It is hypothesised that hypochlorhydria induced by daily PPI use produces periods during the day in which the pH of the gastric juice is at or near neutral pH levels.[7 8] A study by Shindo *et al*[7] showed that hypochlorhydria can induce major changes in the gastric flora and affect the pH of small bowel fluid to allow bacterial overgrowth thereby increasing the risk of retrograding to the biliary system and thus elevating the incidence of biliary tract infection,[1] and biliary tract infection is a recognised risk factor for GBC.[9] Thus, our study may indirectly support the results of Chuang *et al*[1] that PPI use increased the incidence of cholecystitis.[1]

In conclusion, this hospital-based case–control study indicates PPI use as a significant risk factor for GBC progression, which seems to be dose-dependent.

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