Association Between Acid-Suppressive Agents’ Use and Risk of Hepatocellular Carcinoma

Hsiu C. Lin¹,², Huan Y. Hsu³, Hsiu L. Lin⁴, Yow S. Uang³, Yi Ho³, and Li H. Wang³,⁵

Abstract

Background: Acid-suppressive agents (ASAs), which are mostly used in patients with upper gastrointestinal diseases (UGIDs), may influence the risk of hepatocellular carcinoma (HCC).

Methods: A population-based retrospective cohort study was conducted. Patients with UGID who used ASAs and those who did not receive ASAs were identified. Patients without UGIDs were randomly selected and matched (comparison group). All groups were followed up for 6 years. A Cox proportional hazard model was used to estimate the risk of HCC among the different groups.

Results: Patients with UGID who used ASAs had a significantly elevated HCC risk (adjusted hazard ratio [HR] 1.53; 95% confidence interval [CI], 1.32-1.76) compared to those who did not use ASAs. Patients with UGID who used more than 540 defined daily doses of ASAs had a significantly higher risk of HCC (adjusted HR 2.04; 95% CI, 1.62-2.58). Moreover, the dose effect on HCC risk exhibited a significant increasing trend (P < .01). Furthermore, patients with UGID who did not use ASAs had a significantly elevated HCC risk (adjusted HR 1.94; 95% CI, 1.59-2.36) compared to the comparison group.

Conclusion: The use of ASAs increased the risk of HCC in patients with UGIDs, and the effect of ASAs was dose dependent. In addition, UGIDs alone increased the risk of HCC.

Keywords
acid-suppressive agents, proton pump inhibitors, histamine 2 receptor antagonists, hepatocellular carcinoma, dose-dependent

Introduction

The most commonly used acid-suppressive agents (ASAs) to treat acid-related upper gastrointestinal (GI) diseases (UGIDs), such as gastroesophageal reflux disease and peptic ulcer disease (PUD), are proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs).¹² Both PPIs and H2RAs are generally known for their safety and efficacy for UGIDs.³ However, there is emerging evidence indicating that long-term use of PPIs and H2RAs is associated with concerns of bacterial overgrowth, hypergastrinemia, and malignancies.⁴⁻⁶

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer.⁷ In 2012, liver cancer was the seventh most frequently occurring cancer and the third leading cause of cancer-related deaths worldwide,⁸ whereas it was the third most common cancer and the second leading cause of cancer-related deaths in Taiwan.⁹,¹⁰

Currently, there are several potential mechanisms suggesting that PPIs and H2RAs might be related to HCC. Hypoacidity caused by PPIs and/or H2RAs may lead to bacterial overgrowth

¹ Department of Pediatrics, School of Medicine, College of Medicine, Taipei Medical University, Taipei
² Department of Clinical Pathology, Taipei Medical University Hospital, Taipei
³ School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei
⁴ Department of Neurology, General Cathay Hospital, Sijih Branch, New Taipei City
⁵ Department of Pharmacy, Taipei Medical University Hospital, Taipei

Received 19 July 2019; received revised 1 January 2020; accepted 16 January 2020

Corresponding Author:
Li H. Wang, School of Pharmacy, College of Pharmacy, Taipei Medical University, 250 Wu-Hsing St, Taipei 11031.
Email: shiuan@tmu.edu.tw
and facilitate formation of N-nitroso compounds, lipopolysaccharide (LPS), and deoxycholic acid (DCA).\textsuperscript{11-16} N-Nitroso compounds, LPS, and DCA were all shown to be associated with the development of HCC.\textsuperscript{15-24} In addition, hypergastrinemia induced by PPIs and/or H\textsubscript{2}RAs may be associated with HCC. Gastrin was found to be related to GI malignancies.\textsuperscript{4,14,25,26} Furthermore, gastrin receptors are expressed in tumor sections of patients with HCC, and gastrin was shown to stimulate the growth of liver cells.\textsuperscript{27,28} Moreover, the growth-stimulating effect is inhibited by the gastrin receptor antagonists such as the Parke-Davis compounds PD 135 and PD 138.\textsuperscript{29} However, very few studies have examined the influence of the use of ASAs, such as PPIs and/or H\textsubscript{2}RAs, on the risk of HCC, despite the common use of these medications in patients with UGID and the potential mechanism indicating the impact of these medications on the risk of HCC. Therefore, the aim of this study is to explore the impacts of ASAs on the risk of HCC in patients with UGID.

**Method**

**Data Sources**

The Longitudinal Health Insurance Database 2000 (LHID2000), one of the data subsets of the National Health Insurance (NHI) Research Database (NHIRD),\textsuperscript{29} was used to conduct a population-based retrospective nationwide cohort study. The NHIRD is a large computerized database derived from the nationwide NHI program in Taiwan and is maintained by the National Health Research Institutes (NHRI) for research purposes. There are approximately 23.75 million individuals in the NHIRD, which contains the original registration and claims data for reimbursement of the single-payer NHI program, and 1 million individuals randomly sampled from the 2000 Registry for Beneficiaries (ID) constitute the LHID2000. There was no significant difference in the number of birth per year, the age distribution, or the gender distribution between patients in the LHID2000 and the original NHIRD.

Data in the NHIRD were deidentified before being sent to the NHRI for database construction and further scrambled before being released to researchers. Researchers obtain no information that could potentially violate the privacy of patients and therefore informed consent was not required. This study was exempted from full review by the joint institutional review board of Taipei Medical University (TMU-JIRB: N201511002).

**Study Population**

Patients diagnosed with at least 2 episodes of UGIDs (International Classification of Diseases, ninth revision [ICD-9] codes 530-536) between January 1, 2001, and December 31, 2005, were included from the LHID2000, with an exclusion of those who were aged \( \leq 18 \) years. Patients with UGID receiving ASAs (PPIs and/or H\textsubscript{2}RAs) were identified, and those who had the first administration of ASAs after the UGID diagnosis date were recruited. Patients who had received PPIs and/or H\textsubscript{2}RAs for less than 90 days within 365 days after the index date (first administration of ASAs) or those with any cancers (ICD-9 codes 140-209) before the index date were excluded (study group I). In addition, patients with UGID who did not use PPIs or H\textsubscript{2}RAs were identified, and those with any cancers before the UGID diagnosis date were excluded as well (study group II). Patients without UGIDs between January 1, 2001, and December 31, 2005, were identified from the LHID2000, and those who had used PPIs and/or H\textsubscript{2}RAs were excluded. These patients were then randomly selected, matched (at a 1:1 ratio) to study group II patients by age, gender, and index year, and those with any cancers before the reference date (the first date of any records in the LHID2000) were excluded (comparison group). All groups were followed up for 6 years.

**Primary Outcomes**

The primary purpose of the study is to ascertain whether ASAs are associated with an increased risk of HCC (ICD codes 155.0 and 155.1) in patients with UGID. For the primary outcome, we evaluated the risk of occurrence of HCC during the follow-up period in the study groups compared to the comparison group.

**Secondary Outcomes**

We also endeavored to analyze the dose–response relationship between the risk of HCC and the use of ASAs. In order to calculate and compare the cumulative numbers of doses of different drugs, the concept of the defined daily dose (DDD) was applied. The anatomical therapeutic chemical (ATC)/DDD system, a universal drug measurement system, was used to measure the exposure to PPIs and/or H\textsubscript{2}RAs.\textsuperscript{30} The ATC system classifies drugs, and every medication with an ATC code is assigned a DDD as the unit of drug measurement. The DDD is defined as the assumed average daily maintenance dose for a medication used for its main indication in adults.\textsuperscript{30,31} The secondary outcome was an analysis of hazard ratios (HRs) of HCC in subgroups of patients only receiving PPIs or H\textsubscript{2}RAs during the follow-up period.

**Potential Risk Factors**

The potential risk factors included age, gender, viral hepatitis (ICD-9 codes 070.0-070.9, V02.61, and V02.62), chronic liver disease and cirrhosis (ICD-9 code 571), alcohol abuse (ICD-9 code 305.0), obesity (ICD-9 code 278.0), diabetes mellitus (ICD-9 code 250), schistosomiasis parasitic infection (ICD-9 code 120), tobacco use disorder (ICD-9 code 305.1), statin use, thiazolidinedione use, and metformin use.

**Statistical Analyses**

Pearson \( \chi^2 \) test and Student \( t \) test were used to evaluate differences in baseline characteristics of all groups. A Cox proportional hazard regression model was used to estimate the risk of HCC among different groups, after adjusting for potential risk
factors of HCC. The time of HCC occurrence and the cumulative incidence of HCC of the study group II and comparison group were assessed by the Kaplan-Meier method, and differences between the various groups were analyzed by a log-rank test. All significance tests were 2 sided, and \( P \) values of <.05 were considered significant. SAS version 9.1 software (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

**Results**

From the LHID2000 data subset of the NHIRD, 288 361 patients diagnosed with at least 2 episodes of UGIDs in 2001 to 2005 were included (Figure 1). After exclusion and matching, there were 55 793 patients with UGID who had used ASAs (study group I) and 54 187 patients with UGID who had not received ASAs (study group II). The comparison group consisted of 54 187 patients without UGIDs and who did not use
ASAs (comparison group). Baseline characteristics of these groups are presented in Table 1.

During the follow-up period, there were 600 (1.08%) new HCC cases in study group I, 299 (0.55%) in study group II, and 149 (0.27%) in comparison group, and the risks of HCC occurrence were compared among different groups (Table 2). After adjustment, patients with UGID who used ASAs (PPIs and/or H2RAs) had a significantly increased risk of HCC (adjusted HR 1.53; 95% CI, 1.32-1.76) compared to those who did not use them. Compared to patients without UGIDs and who did not use ASAs (comparison group), the risk of HCC was also significantly higher in patients with UGID who did not use ASAs (adjusted HR 1.94; 95% CI, 1.59-2.36).

For patients with UGID who only used PPIs, the risk of HCC was also significantly higher compared to those who used no PPIs or H2RAs (adjusted HR 2.73; 95% CI, 1.56-4.78, P < .001). However, for those who only used H2RAs, the adjusted HR was 0.77 (95% CI, 0.58-1.00), and the risk of HCC was not significantly higher compared to those who used neither PPIs nor H2RAs (Table 3).

When the exposure to ASAs was divided into 4 groups (<180 DDDs, 180-360 DDDs, 360-540 DDDs, and >540 DDDs), the risk of HCC was all significantly higher than that of study group 2, and P for trend was < .01 (Table 4). In addition, the result of Kaplan-Meier analysis, which patients with UGID who used no ASAs (study group II) had a higher cumulative incidence of HCC than patients without UGIDs and who used no ASAs (comparison group) is shown in Figure 2. The log-rank test of the Kaplan-Meier analysis was also significant (P < .001).

### Table 1. Baseline Characteristics of the Comparison and Study Groups.

| Variables | Study Group (Patients With UGID) | Comparison Group |
|-----------|----------------------------------|------------------|
|           | With PPI and/or H2RA Use (Study Group I), N = 55 793 | Without PPI or H2RA Use (Study Group II), N = 54 187 | Without UGIDs and H2RA Use, N = 54 187 |
| Age, years (mean ± SD) | 53.33 ± 15.27 | 45.90 ± 18.35 | 45.90 ± 18.35 | <.001 | 1 |
| Gender/male, n (%) | 25 558 (45.81) | 26 081 (48.13) | 26 081 (48.13) | <.001 | 1 |
| Viral hepatitis, n (%) | 7440 (13.35) | 3013 (5.56) | 2539 (4.69) | <.001 | <0.001 |
| Chronic liver disease and cirrhosis, n (%) | 17 427 (31.4) | 8316 (15.35) | 7221 (13.33) | <.001 | <0.001 |
| Alcohol abuse, n (%) | 564 (1.01) | 212 (0.39) | 205 (0.38) | <.01 | 0.73 |
| Obesity, n (%) | 1108 (1.99) | 710 (1.31) | 670 (1.24) | .07 | 0.28 |
| Diabetes mellitus, n (%) | 13 579 (24.34) | 6183 (11.41) | 6232 (11.50) | .32 | 0.64 |
| Parasite infection, schistosomiasis, n (%) | 2 (0.003) | 2 (0.003) | 0 | .86 | 0.16 |
| Tobacco use disorder, n (%) | 2014 (3.61) | 1010 (1.86) | 1001 (1.85) | .05 | 0.84 |
| Statin use, n (%) | 15 211 (27.26) | 6284 (11.61) | 6205 (11.45) | <.001 | 0.45 |
| Thiazolidinedione use, n (%) | 3632 (6.51) | 1573 (2.90) | 1399 (2.58) | .59 | <0.01 |
| Metformin use, n (%) | 7707 (13.81) | 3516 (6.49) | 3799 (7.01) | .72 | <0.01 |

Abbreviations: H2RA, histamine 2 receptor antagonist; PPI, proton pump inhibitor; SD, standard deviation; UGID, upper gastrointestinal disease.

*Study group I versus study group II patients with UGID.

bStudy group II patients with UGID versus comparison group.

### Table 2. Hepatocellular Carcinoma (HCC) Risk and Time of Occurrence Among the Comparison Group, Study Group II, and Study Group I (Patients With UGID with Proton Pump Inhibitor [PPI] and/or Histamine 2 Receptor Antagonist [H2RA] Use).

| Result | Study Group (Patients With UGID) | Comparison Group |
|--------|---------------------------------|------------------|
|        | With PPI and/or H2RA Use (Study Group I), N = 55 793 | Without PPI or H2RA Use (Study Group II), N = 54 187 | Without UGIDs and H2RA Use, N = 54 187 |
| HCC, n (%) | 600 (1.08) | 299 (0.55) | 149 (0.27) |
| Incidence rate (per 10 000 patients) (95% CI) | 107.57 (99.15-116.45) | 55.18 (49.12-61.78) | 27.50 (23.26-32.28) |
| Crude HR (95% CI) | 1.95 (1.71-2.24) | 1 |
| Adjusted HR* (95% CI) | 1.53 (1.32-1.76) | 1 |
| Crude HR (95% CI) | 2.01 (1.65-2.45) | 1 |
| Adjusted HR* (95% CI) | 1.94 (1.59-2.36) | 1 |

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation; UGID, upper gastrointestinal disease.

*P < .001.

bAdjusted for age, gender, viral hepatitis, chronic liver disease, cirrhosis, alcohol abuse, obesity, diabetes mellitus, parasite infection (schistosomiasis), tobacco use disorder, statin use, thiazolidinedione use, and metformin use.
Discussion

In this large population-based cohort study, the use of ASAs, that is, PPIs and/or H2RAs, significantly increased the risk of HCC in patients with UGID, and this increased HCC risk was dose dependent. To our best knowledge, very little research has studied the relationship between ASAs and HCC, and the mechanism is still unclear. It is possible that the hypoacidity resulting from ASAs might cause bacterial overgrowth and hypergastrinemia. Hypoacidity may lead to bacterial overgrowth and facilitate formation of N-nitroso compounds, LPS, and DCA.11-16 N-Nitroso compounds, LPS, and DCA are all known to be associated with the development of HCC.15-24 In addition, hypergastrinemia induced by ASAs may be associated with HCC. Gastrin receptors are expressed in tumor sections of patients with HCC, and gastrin was shown to stimulate the growth of liver cells.27,28 Moreover, bacterial overgrowth and hypergastrinemia could both be related to HCC, as mentioned above.

In this study, patients with UGID who used only PPIs had a bigger risk of HCC than those who used PPIs and/or H2RAs (study group I) compared to those who used neither PPIs nor H2RAs. In addition, patients with UGID who used only H2RAs were not associated with the risk of HCC compared to those who used neither PPIs nor H2RAs. This is possibly because PPIs are more potent in acid inhibition than H2RAs, so the extents of consequent bacterial overgrowth and hypergastrinemia were also greater.11,12,25 Besides, H2RAs were proposed to have an anticancer effect. In a hepatoma cell line study, it was demonstrated that histamine binding to H2 receptor can inhibit interleukin (IL)-6 binding to cancer cells, which leads to less

Table 3. Hepatocellular Carcinoma (HCC) Risk and Time of Occurrence Among the Comparison Group, Study Group II, and Patients With Upper Gastrointestinal Disease (UGID) Only With Proton Pump Inhibitor (PPI) Use or Only With Histamine 2 Receptor Antagonist (H2RA) Use.

| Result | Patients With UGID |
|--------|-------------------|
|        | Only With PPI Use, N = 700 | Only With H2RA Use, N = 13 776 | Without PPI or H2RA Use (II), N = 54 187 |
| HCC, n (%) | 13 (1.86) | 68 (0.49) | 299 (0.55) |
| Incidence rate (per 10 000 patients) (95% CI) | 185.71 (99.25-315.48) | 49.36 (38.35-62.54) | 55.18 (49.12-61.78) |
| Crude HR (95% CI) | 3.38 (1.94-5.89) | 0.89 (0.69-1.16) | 1 |
| Adjusted HRb (95% CI) | 2.73 (1.564.78) | 0.77 (0.581.00) | 1 |

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation.

Table 4. Effects of Proton Pump Inhibitor (PPI) and/or Histamine 2 Receptor Antagonist (H2RA) Exposure on the Hepatocellular Carcinoma (HCC) Risk and Time of Occurrence Among Patients With Upper Gastrointestinal Disease (UGID).

| Result | Patients With UGID |
|--------|-------------------|
|        | Without PPI and H2RA Use (Study Group II) | With PPI and/or H2RA Use (I) |
|        | N = 54 187 | N = 26 944 | N = 14 658 | N = 5986 | N = 8205 |
| HCC, n (%) | 299 (0.55) | 225 (0.84) | 166 (1.13) | 89 (1.49) | 120 (1.46) |
| Incidence rate (per 10 000 patients) (95% CI) | 55.18 (49.12-61.78) | 83.51 (72.99-95.10) | 113.25 (96.75-131.72) | 148.68 (119.57-182.65) | 146.25 (121.40-174.63) |
| Crude HR (95% CI) | 1 | 1.51 (1.27-1.81)c | 2.06 (1.70-2.48)c | 2.70 (2.13-3.43)c | 2.66 (2.15-3.28)c P for trend <.001 |
| Adjusted HRb (95% CI) | 1 | 1.26 (1.05-1.51)c | 1.55 (1.27-1.90)c | 1.98 (1.54-2.55)c | 2.04 (1.62-2.58)c P for trend <.01 |

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; SD, standard deviation.

aP < .001.
bAdjusted for age, gender, viral hepatitis, chronic liver disease, cirrhosis, alcohol abuse, obesity, diabetes mellitus, parasite infection (schistosomiasis), tobacco use disorder, statin use, thiazolidinedione use, and metformin use.

cP < .01.
IL-6 expression and reduces inhibition of cancer cell growth.\(^{31}\) Some clinical studies revealed that the use of the H\(_2\)RA, cimetidine, prolonged survival in patients with gastric cancer and colorectal cancer.\(^{32}\) A cohort study in Taiwan showed that exposure to a higher cumulative dose (≥360 DDD) of H\(_2\)RAs might be associated with a decreased risk of non-small cell lung cancer in type 2 diabetic patients.\(^{33}\) Moreover, it is plausible that patients with UGID who only use a higher cumulative dose of H\(_2\)RAs might have a significantly decreased risk of HCC. Tran et al\(^{34}\) found that the use of PPIs was associated with an increased liver cancer risk (adjusted OR 1.80, 95% CI, 1.34-2.41; adjusted HR 1.99, 95% CI, 1.34-2.94) and slight evidence of an association with H\(_2\)RA use (adjusted OR 1.21, 95% CI, 0.84-1.76; adjusted HR 1.70, 95% CI, 0.82-3.53). Their results are similar to our findings. However, our study patients all had a UGID diagnosis and long-term use of ASAs, that is, PPIs and/or H\(_2\)RAs. We could ensure patients’ ASA use was reasonable and show the cause–consequence relationship between ASAs and the risk of HCC. In addition, a case–control study explored the relationship between the use of PPIs and/or H\(_2\)RAs and the risk of HCC and reported no association between PPI use and HCC. Moreover, there was a significant positive association between H\(_2\)RA use and the risk of HCC.\(^{35}\) That result is opposite to the results of this study. However, PPI use and H\(_2\)RA use were only defined as “ever used” in that study, possibly underestimating the impact of PPI use and H\(_2\)RA use on the risk of HCC. Besides, it was a case–control study, and a logistic regression was used to analyze the risk of HCC. As a result, it is not likely to show cause–consequence relationships of PPIs and/or H\(_2\)RAs with the risk of HCC.

As mentioned above, the underlying indication for the use of PPIs and/or H\(_2\)RAs, that is, UGIDs, alone may increase the risk of HCC. In this study, UGIDs alone significantly increased the risk of HCC. The relationship between UGIDs and HCC has seldom been studied. Nevertheless, Helicobacter pylori (Hp) infection, the most common cause of PUP, was found to be related to HCC.\(^{36-41}\) Helicobacter pylori was detected in liver tissues of patients with HCC and found to be hepatotoxic.\(^{42-44}\) Helicobacter pylori can also produce LPS, which promotes adhesion and invasion of liver tumors and stimulates tumor growth.\(^{45,46}\) In addition, Hp infection in the oxyntic area, causing atrophy, leads to reduced gastric acid secretion and significant consequent hypergastrinemia.\(^{47,48}\) Partial reversion of hypergastrinemia and Enterochromaffin-like cells hyperplasia was found in patients with atrophic body gastritis after eradication of Hp.\(^{49}\) On the other hand, Hp infection in the antrum only results in slight hypergastrinemia, increased gastric acid secretion, and possibly subsequent bacterial overgrowth and hypergastrinemia.\(^{47,48}\) In a meta-analysis, Hp infection was positively associated with the risk of HCC (summary OR 13.63; 95% CI, 7.90-23.49).

In this study, the use of PPIs and/or H\(_2\)RAs increased the risk of HCC, and it was mainly caused by PPIs. Helicobacter pylori was shown to augment the acid-inhibiting effect of PPIs.\(^{50}\) In addition, in patients under long-term PPI therapy, the overgrowth of non-Hp bacteria was found to be more significant in patients with Hp infection compared to those without.

There are several strengths in this study. This is the first study to investigate the relationship between the use of ASAs and the risk of HCC in patients with UGIDs, the first study to explore the dose effect of ASAs on the risk of HCC, and the first study to analyze the cumulative incidence among patients with UGID with PPI and/or H\(_2\)RA use, without PPI and/or H\(_2\)RA use, and patients without UGIDs and who did not use PPIs and/or H\(_2\)RAs. In addition, the study population was selected from the NHIRD, so it is a large population-based cohort study with rather good generalizability. Moreover, the definitions of the use of ASAs and patients with UGID were very clear, thus reducing the classification bias. The potential confounders were deliberately selected, thereby decreasing interference by other factors. In addition, the follow-up period was rather long, reducing the possibility of underestimating or overestimating the occurrence of HCC.

There are some limitations of this study. The study information is restricted to recorded data of the NHIRD, but there is no evidence suggesting that there was a systematic difference among the various groups. The accuracy of the coding of diagnoses is not known; however, patients with UGID in this study were defined as having been diagnosed at least twice with UGIDs, so that possible bias was reduced. Information on compliance and the availability of over-the-counter PPIs and/or H\(_2\)RAs could not be collected; nevertheless, the definition of PPI and/or H\(_2\)RA use was the use of PPIs and/or
H2RAs for more than 90 days within 365 days after the first administration, and so all of these patients exhibited long-term use of PPIs and/or H2RAs to treat UGIDs. The cause–consequence relationship between ASAs and the risk of HCC was greatly increased.

In conclusion, the use of ASAs (PPIs and/or H2RAs) increased the risk of HCC in patients with UGIDs, and the impact was dose dependent. In addition, UGIDs alone were found to increase the risk of HCC. More clinical and/or animal studies are warranted to confirm these results.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Li H. Wang https://orcid.org/0000-0001-8047-5310

References
1. Mejia A, Kraft WK. Acid peptic diseases: pharmacological approach to treatment. Expert Rev Clin Pharmacol. 2009;2(4):295-314.

2. Kopic S, Geibel JP. Gastric acid, calcium absorption, and their impact on bone health. Physiol Rev. 2013;93(1):189-268.

3. McQuaid KR. Drugs used in the treatment of gastrointestinal diseases. In: Katzung BG, Trevor AJ, eds. Basic & Clinical Pharmacology. 13th ed. New York, NY: McGraw-Hill; 2015.

4. Sabesin SM. Safety issues relating to long-term treatment with histamine H2-receptor antagonists. Aliment Pharmacol Ther. 1993;7(suppl 2):35-40.

5. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci. 2011;56(2):931-950.

6. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol. 2012;5(4):219-232.

7. Goodman ZD. Neoplasms of the liver. Mod Pathol. 2007;20(suppl 1):S49-S60.

8. GLOBOCAN 2012 v1.0. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr/. Accessed March 9, 2016.

9. Health Promotion Administration, Ministry of Health and Welfare. 2015 Health Promotion Administration Annual Report. 2016. http://www.hpa.gov.tw/English/ClassShow.aspx?No =201601130001/. Accessed January 30, 2016.

10. Health Promotion Administration, Ministry of Health and Welfare. 2013 Health Promotion Administration Annual Report; 2014. http://www.hpa.gov.tw/English/ClassShow.aspx?No =201401170001/. Accessed January 30, 2016.

11. Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared to cimetidine: a prospective randomised double blind study. Gut. 1996;39(5):54-59.

12. Sanduleanu S, Jonkers D, De Bruine A, Hameeteman W, Stockbrügger RW. Non-Helicobacter pylori bacterial flora during acid-suppressive therapy: differential findings in gastric juice and gastric mucosa. Aliment Pharmacol Ther. 2001;15(3):379-388.

13. Sharma BK, Santana IA, Wood EC, et al. Intragastric bacterial activity and nitrosation before, during, and after treatment with omeprazole. Br Med J (Clin Res Ed). 1984;289(1):717-719.

14. Laine L, Ahnen D, McClain C, Solcia E, Walsh JH. Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. Aliment Pharmacol Ther. 2000;14(6):651-668.

15. Wilkinson J. The alimentary system. In: Naish J, Court DS, eds. Medical Sciences. 2nd ed. Oxford: Elsevier; 2015:699-748.

16. Tao X, Wang N, Qin W. Gut microbiota and hepatocellular carcinoma. Gastrointest Tumors. 2015;2(6):33-40.

17. Tannenbaum SR. N-nitroso compounds: a perspective on human exposure. Lancet. 1983;1(5):629-632.

18. Rowland JR. The toxicology of N-nitroso compounds. In: Hill MJ, ed. Nitrosamines—Toxicology and Microbiology. London: Ellis Horwood; 1988:117-141.

19. Andrade R, Reyes FG, Rath S. A method for the determination of volatile N-nitrosamines in food by HS-SPME-GC-TEA. Food Chem. 2005;91(8):173-179.

20. Mitacek EJ, Brunnenmann KD, Suttajit M, et al. Exposure to N-nitroso compounds in a population of high liver cancer regions in Thailand: volatile nitrosamine (VNA) levels in Thai food. Food Chem Toxicol. 1999;37(2):297-305.

21. Srivatanakul P, Parkin DM, Khlat M, et al. Liver cancer in Thailand. II. A case–control study of hepatocellular carcinoma. Int J Cancer. 1991;48(1):329-332.

22. Jirillo E, Caccavo D, Magrone T, et al. The role of the liver in the response to LPS: experimental and clinical findings. J Endotoxin Res. 2002;8(5):319-327.

23. Darnaud M, Faivre J, Moniaux N. Targeting gut flora to prevent progression of hepatocellular carcinoma. J Hepatol. 2013;58(6):385-387.

24. Roderburg C, Luedde T. The role of the gut microbiome in the development and progression of liver cirrhosis and hepatocellular carcinoma. Gut Microbes. 2014;5(1):441-445.

25. Orlando LA, Lenard L, Orlando RC. Chronic hypergastrinemia: causes and consequences. Dig Dis Sci. 2007;52(5):2482-2489.

26. Moore TC, Jepeal LI, Boylan MO, et al. Gastrin stimulates receptor-mediated proliferation of human esophageal adenocarcinoma cells. Regul Pept. 2004;120(1):195-203.

27. Caplin M, Khan K, Savage K, et al. Expression and processing of gastrin in hepatocellular carcinoma, fibrolamellar carcinoma and cholangiocarcinoma. J Hepatol. 1999;30(3):519-526.

28. Caplin M, Khan K, Grimes S, et al. Effect of gastrin and anti-gastrin antibodies on proliferation of hepatocyte cell lines. Dig Dis Sci. 2001;46(2):1356-1366.

29. National Health Insurance Research Database. National health research institutes. http://nhird.nhri.org.tw/en/index.htm/. Accessed January 30, 2016.

30. WHO Collaborating Centre for Drug Statistics Methodology. DDD—definition and general considerations. http://www.who
31. Meréty K, Falus A, Taga T, Kishimoto T. Histamine influences the expression of the interleukin-6 receptor on human lymphoid, monocytoid and hepatoma cell lines. *Agents Actions*. 1991;33(1):189-191.

32. Kubecova M, Kolostova K, Pinterova D, Kacprzak G, Bobek V. Cimetidine: an anticancer drug? *Eur J Pharm Sci*. 2011;42(6):439-444.

33. Hsu CL, Chang CH, Lin JW, Wu LC, Chuang LM, Lai MS. Histamine-2 receptor antagonists and risk of lung cancer in diabetic patients—an exploratory analysis. *Pharmacoepidemiol Drug Saf*. 2013;22(1):632-640.

34. Tran KT, McMenamin UC, Hicks B, et al. Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies. *Aliment Pharmacol Ther*. 2018;48(8):55-64.

35. Lai SW, Liao KF, Lai HC, Lin CL, Sung FC. Proton pump inhibitors and risk of hepatocellular carcinoma: a case–control study in Taiwan. *Acta Gastroenterol Beig*. 2013;76(1):348-350.

36. Chan FK, Lau JY. Peptic ulcer disease. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 10th ed. Philadelphia, PA: Elsevier; 2016:884-900.

37. Hagymási K, Tulassay Z. *Helicobacter pylori* infection: new pathogenetic and clinical aspects. *World J Gastroenterol*. 2014;20(2):6386-6399.

38. Ito K, Nakamura M, Toda G, Negishi M, Torii A, Ohno T. Potential role of *Helicobacter pylori* in hepatocarcinogenesis. *Int J Mol Med*. 2004;13(2):221-227.

39. Wu XZ, Chen D. *Helicobacter pylori* and hepatocellular carcinoma: correlated or uncorrelated? *J Gastroenterol Hepatol*. 2006;21(2):345-347.

40. Rabelo-Gonçalves EM, Roesler BM, Zeitune JM. Extragastric manifestations of *Helicobacter pylori* infection: possible role of bacterium in liver and pancreas diseases. *World J Hepatol*. 2015;7(2):2968-2979.

41. Venerito M, Selgrad M, Malfertheiner P. *Helicobacter pylori*: gastric cancer and extragastric malignancies—clinical aspects. *Helicobacter*. 2013;18(suppl 1):39-43.

42. Avenaud P, Marais A, Monteiro L, et al. Detection of *Helicobacter* species in the liver of patients with and without primary liver carcinoma. *Cancer*. 2000;89(1):1431-1439.

43. Xuan SY, Li N, Qiang X, Zhou RR, Shi YX, Jiang WJ. *Helicobacter* infection in hepatocellular carcinoma tissue. *World J Gastroenterol*. 2006;12(5):2335-2340.

44. Taylor NS, Fox JG, Yan L. In-vitro hepatotoxic factor in *Helicobacter hepaticus*, *H. pylori* and other *Helicobacter* species. *J Med Microbiol*. 1995;42(5):48-52.

45. Ito K, Yamaoka Y, Ota H, El Zimaity H, Graham DY. Adherence, internalization, and persistence of *Helicobacter pylori* in hepatocytes. *Dig Dis Sci*. 2008;53(1):2541-2549.

46. Liu X, Liang J, Li G. Lipopolysaccharide promotes adhesion and invasion of hepatoma cell lines HepG2 and HepG2.2.15. *Mol Biol Rep*. 2010;37(2):2235-2239.

47. Chao C, Hellmich MR. Gastrin, inflammation, and carcinogenesis. *Curr Opin Endocrinol Diabetes Obes*. 2010;17(6):33-39.

48. Waldum HL, Hauso O, Fossmark R. The regulation of gastric acid secretion—clinical perspectives. *Acta Physiol*. 2014;210(1):239-256.

49. Annibale B, Aprile MR, D’ambra G, Caruana P, Bordi C, Delle Fave G. Cure of *Helicobacter pylori* infection in atrophic body gastritis patients does not improve mucosal atrophy but reduces hypergastrinemia and its related effects on body ECL-cell hyperplasia. *Aliment Pharmacol Ther*. 2000;14:625-634.

50. Labenz J, Tillenburg B, Peitz U, et al. *Helicobacter pylori* augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. *Gastroenterology*. 1996;110(2):725-732.