Observational Study

Risk of cholangiocarcinoma in patients undergoing therapeutic endoscopic retrograde cholangiopancre-atography or cholecystectomy: A population based study

Chi-Chih Wang, Ming-Chang Tsai, Wen-Wei Sung, Tzu-Wei Yang, Hsuan-Yi Chen, Yao-Tung Wang, Chang-Cheng Su, Ming-Hseng Tseng, Chun-Che Lin

ORCID number: Chi-Chih Wang (0000-0002-8222-0500); Ming-Chang Tsai (0000-0002-5770-9358); Wen-Wei Sung (0000-0002-2375-0029); Tzu-Wei Yang (0000-0002-1522-8177); Hsuan-Yi Chen (0000-0003-1001-7968); Yao-Tung Wang (0000-0002-0306-0896); Chang-Cheng Su (0000-0002-7211-4192); Ming-Hseng Tseng (0000-0001-8868-1610); Chun-Che Lin (0000-0002-2474-6734).

Author contributions: Tseng MH and Lin CC contributed equally to this manuscript; Wang CC, Tseng MH and Sung WW contributed to conception and design; Tseng MH contributed to acquisition of data; Tsai MC, Wang CC, Wang YT and Chen HY contributed to analysis and interpretation of data; Wang CC, Yang TW and Chen HY contributed to drafting of the manuscript; Yang TW, Sung WW and Lin CC contributed to critical revision of the manuscript; Tsai MC, Sung WW and Su CC contributed to statistical analysis; Tseng MH and Lin CC contributed to supervision.

Supported by Chung Shan Medical University Hospital research program, Taichung, Taiwan, No. CSH-2013-C-032.

Institutional review board statement: This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital.

Chi-Chih Wang, Ming-Chang Tsai, Wen-Wei Sung, Yao-Tung Wang, Chun-Che Lin, Institute of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan

Chi-Chih Wang, Ming-Chang Tsai, Wen-Wei Sung, Tzu-Wei Yang, Hsuan-Yi Chen, Yao-Tung Wang, Chun-Che Lin, School of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan

Chi-Chih Wang, Ming-Chang Tsai, Tzu-Wei Yang, Hsuan-Yi Chen, Chang-Cheng Su, Chun-Che Lin, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung 40201, Taiwan

Wen-Wei Sung, Department of Urology, Chung Shan Medical University Hospital, Taichung 40201, Taiwan

Tzu-Wei Yang, Institute and Department of Biological Science and Technology, National Chiao Tung University, Hsinchu 30010, Taiwan

Yao-Tung Wang, Division of Pulmonary Medicine, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung 40201, Taiwan

Ming-Hseng Tseng, Department of Medical Informatics, Chung Shan Medical University, Taichung 40201, Taiwan

Ming-Hseng Tseng, Information Technology Office, Chung Shan Medical University Hospital, Taichung 40201, Taiwan

Corresponding author: Chun-Che Lin, MD, PhD, Attending Doctor, Chief Doctor, Doctor, Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chung Shan Medical University Hospital, No.110, Sec.1, Jiantou N.Rd., Taichung 40201, Taiwan. cshy333@csuh.org.tw

Telephone: +886-424730022-11603
Fax: +886-423248130

Abstract

BACKGROUND
Cholangiocarcinoma is a highly lethal disease that had been underestimated in the past two decades. Many risk factors are well documented for in cholangiocarcinoma, but the impacts of advanced biliary interventions, like endoscopic sphincterotomy (ES), endoscopic papillary balloon dilatation (EPBD),
and cholecystectomy, are inconsistent in the previous literature.

**AIM**
To clarify the risks of cholangiocarcinoma after ES/EPBD, cholecystectomy or no intervention for cholelithiasis using the National Health Insurance Research Database (NHIRD).

**METHODS**
From data of NHIRD 2004-2011 in Taiwan, we selected 7938 cholelithiasis cases as well as 23814 control group cases (matched by sex and age in a 1:3 ratio). We compared the previous risk factors of cholangiocarcinoma and cholangiocarcinoma rate in the cholelithiasis and control groups. The incidences of total and subsequent cholangiocarcinoma were calculated in ES/EPBD patients, cholecystectomy patients, cholelithiasis patients without intervention, and groups from the normal population.

**RESULTS**
In total, 537 cases underwent ES/EPBD, 1743 cases underwent cholecystectomy, and 5658 cholelithiasis cases had no intervention. Eleven (2.05%), 37 (0.65%), and 7 (0.40%) subsequent cholangiocarcinoma cases were diagnosed in the ES/EPBD, no intervention, and cholecystectomy groups, respectively, and the odds ratio for subsequent cholangiocarcinoma was 3.13 in the ES/EPBD group and 0.61 in the cholecystectomy group when compared with the no intervention group.

**CONCLUSION**
In conclusion, symptomatic cholelithiasis patients who undergo cholecystectomy can reduce the incidence of subsequent cholangiocarcinoma, while cholelithiasis patients who undergo ES/EPBD are at a great risk of subsequent cholangiocarcinoma according to our findings.

**Key words:** Cholangiocarcinoma; Endoscopic sphincterotomy; Endoscopic papillary balloon dilatation; Cholecystectomy

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**INTRODUCTION**
Cholangiocarcinoma, which arises from the epithelial cells of the intrahepatic or extrahepatic bile ducts, is a highly lethal disease that has been underestimated in the past two decades. Unlike the decline in mortality due to primary liver cancer, the mortality of intra-hepatic cholangiocarcinoma (ICC) has increased in both sexes in Europe[6]. The incidence of extra-hepatic cholangiocarcinoma (ECC) has declined internationally[6] in the past thirty years, except in Denmark[6]. Unfortunately, the global incidence data may be inaccurate because of ICC registered as...
part of primary liver cancer and ECC mixed with gallbladder cancers in the databases of many countries.

The previous literature has listed many well known risk factors for cholangiocarcinoma, such as primary sclerosing cholangitis [12-19], choledochal cyst disease [20,21], specific parasite infection [22], cholelithiasis [13,14], chronic hepatitis B and C (CHB and CHC) infection [15,16], diabetes mellitus (DM) [17,18], and *Helicobacter* infection (HP) [19,20]. However, the true etiology of cholangiocarcinoma is still a mystery, although several hypotheses have been proposed, including destruction of the integrity of the bile duct through procedures like therapeutic endoscopic retrograde cholangiopancreatography (ERCP) or cholecystectomy. The major indications for ERCP are cholelithiasis, rather than biliary or pancreatic neoplasms, or the need to manage postoperative biliary complications [21,22]. Therapeutic ERCP, including endoscopic sphincterotomy (ES) and endoscopic papillary balloon dilatation (EPBD), has been considered to have increased future cholangiocarcinoma incidence for over a decade [23-25]. Because cholelithiasis itself is one of the risk factors of cholangiocarcinoma, the impact of the incidence of a subsequent cholangiocarcinoma for advanced bile duct management is hard to evaluate.

ES had been shown to increase biliary epithelial atypia [26], and previous data have indicated that therapeutic ERCP can increase the subsequent cholangiocarcinoma rate [27]. At the same time, many recent larger population-based studies have demonstrated that ES does not increase the incidence of cholangiocarcinoma [28-30]. Even some evidence has suggested that ES does not increase the subsequent cholangiocarcinoma rate over that seen with EPBD [29]. At the same time, cholelithiasis and cholecystectomy had been of concern due to the increase in ICC [30] and ECC [31], but some studies have shown that cholecystectomy decreases the subsequent cholangiocarcinoma rate in cholelithiasis patients [32].

The inconsistency of the previous evidence led us to conduct this study using the National Health Insurance Research Database (NHIRD) 2004-2011 in Taiwan. Our goal was to re-confirm the old risk factors in modern society and to clarify the risk of cholangiocarcinoma in the medium time period following therapeutic ERCP or cholecystectomy in cholelithiasis patients.

**MATERIALS AND METHODS**

This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital, Taiwan. The IRB waved the need for informed consent in this study as it is a retrospective study based on the NHIRD. All authors declare no any conflicts of interest.

**Study design**

This study is a population-based retrospective cohort study based on Taiwan’s NHIRD, which covers more than 99% of the Taiwanese population [33]. The study methods of NHIRD have been described in detail in previous studies [32,36]. Symptomatic cholelithiasis cases with above 18 years of age were included from one million random samples of NHIRD data obtained between January 2005 and December 2007 using Codes of International Statistical Classification of Diseases and Related Health Problems-9th Edition (ICD-9), which were registered once in admission or three times in outpatient clinics to avoid bias from possible classification errors. After study group selection, we built the control group with propensity score matching by sex and age in a 1:3 ratio. The control group cases were defined as individuals who had neither been diagnosed with cholelithiasis nor undergone a related medical procedure, such as cholecystectomy or ERCP, in the previous year. Cholelithiasis patients who had undergone ES, EPBD, or cholecystectomy in the previous year or who were diagnosed after cholangiocarcinoma were excluded from further analysis. We then excluded patients, who diagnosed with cholangiocarcinoma from January to December 2004 in both the control and study groups. The cholangiocarcinoma patients in Taiwan have catastrophic illness cards that waive their medical expenses by ICD-9 registration; therefore, we considered that a one year time period for exclusion was adequate. The variables such as economic status, place of residence, follow-up time, and cholangiocarcinoma rate, as well as the historical common risk factors, such as CHB, CHC, HP, DM, end-stage renal disease (ESRD) on dialysis, congenital cystic disease of liver (CCDL), Clonorchis Opisthorchis (CO), and inflammatory bowel disease (IBD), were compared in cholelithiasis and control group.

The cases of cholelithiasis were divided into three groups of patients who underwent ES or EPBD, patients who underwent cholecystectomy, and patients without any therapeutic intervention between January 2005 to December 2011.
patients who underwent both ES/EPBD and cholecystectomy were registered in the ES/EPBD group in our settings. The details of study design are shown in Figure 1. The ICD-9 codes for the listed diseases and procedure codes are listed in Supplementary Table 1. The stratification of age, gender, economic status, place of residence, follow-up time, cholangiocarcinoma rate, and historical common risk factors were compared in each group. Patients who experienced cholangiocarcinoma in the first 6 mo after ES, EPBD, or cholecystectomy were excluded from further analysis, because these cases should be considered as misdiagnoses or concurrent malignancies rather than subsequent cholangiocarcinoma. The time cumulative risk of cholangiocarcinoma in the different groups was calculated.

Data processing and statistical analysis
The NHIRD, which includes one a representative population of one million persons residing in Taiwan between 2004 and 2011 was managed using Microsoft SQL Server 2008 R2 (Microsoft Corporation, Redmond, WA, United States) and the SQL programming language for the data query and data processing jobs. Statistical analysis was done using OpenEpi: Open source epidemiologic statistics for public health, version 3.01[38]. Kaplan-Meier survival analyses were conducted using SPSS version 19. Person time analyses were done using OpenEpi version 3.01.

Data obtained from the study were compared with the use of the χ² test for categorical variables, the t-test, or one-way ANOVA (Analysis of Variance) for continuous variables, and the Log Rank (Mantel-Cox) test for survival curves. A two-tailed P-value of 0.05 was considered statistically significant in this study.

RESULTS
Because we used age and sex to find three times as many normal population subjects without cholelithiasis to be our control group, we could not evaluate age and sex as risk stratification in our comparisons of the cholelithiasis and control groups.

Cholelithiasis cases and their matched controls
In total, 7938 adult cholelithiasis cases were selected from one million random samples of NHIRD data obtained between January 2005 and December 2007. The control group consisted of 23814 cases without cholelithiasis and matched by age and sex. The mean age of both groups was 59.15 ± 16.53 and the proportion of female patients was 52.15% in both groups. The mean follow up time was 57.96 ± 21.48 mo in cholelithiasis group and 63.12 ± 15.6 mo in the normal population in our analysis. Demographic data revealed that the cholelithiasis patients had a minimum basic salary (49.92%) and residence in a lived in remote villages (1.65%) and the differences were statistically significant when compared to the control group. The proportion of historical risk factors for cholangiocarcinoma, like CHB, CHC, HP, DM, ESRD, CCDL, and IBD, were 9.50% vs 2.80%, 6.83% vs 1.99%, 1.61% vs 0.55%, 29.21% vs 18.17%, 2.34% vs 1.50%, 0.64% vs 0.03% and 1.5% vs 0.77% in the cholelithiasis group versus the normal population, respectively. All the proportions of comorbidity were significantly high (P < 0.001) in the cholelithiasis group, except for CO infection because neither group showed CO infection. In total,147 cholelithiasis cases and 39 normal population cases experienced cholangiocarcinoma during the follow-up period. After exclusion of cases with cholangiocarcinoma in the initial 6 mo in both groups, 55 cholelithiasis cases and 35 normal population cases developed cholangiocarcinoma, with a mean follow up of 36.73 ± 20.57 mo and 35.27 ± 19.94 mo, respectively. The subsequent cholangiocarcinoma rate was higher in the cholelithiasis group than in the control group (0.69% vs 0.15%, P < 0.001). The detailed information is shown in Table 1.

Cholelithiasis cases that underwent ES/EPBD, cholecystectomy, and no intervention
There were 537 cases that underwent ES/EPBD, 1743 cases that underwent cholecystectomy, and 5658 cases that received no intervention, and we observed no significant difference in the mean age. However, the mean age after age stratification of patients above 70 years old was higher in the ES/EPBD group (79.11 ± 5.13), followed by the no intervention group (78.78 ± 6.08) and the cholecystectomy group (78.01 ± 5.54). Other demographic data in our analysis showed some differences: Follow-up time, place of residence, proportion of CHB, proportion of CHC, and proportion of CCDL. The details are shown in Table 2.

In total, 27 patients (5.03%) were diagnosed with cholangiocarcinoma in the ES/EPBD group, while 105 (1.86%) were diagnosed with cholangiocarcinoma in the no intervention group, and 15 (0.86%) were diagnosed in the cholecystectomy group.
### Table 1 Demographic data of study and normal population

|                          | Cholelithiasis group n = 7938 | Control group n = 23814 | P value |
|--------------------------|-------------------------------|------------------------|---------|
| Age, mean (SD)           | 59.15 ± 16.53                | 59.15 ± 16.53          | 1       |
| Age, yr                  |                               |                        |         |
| 18-49                    | 38.89 ± 7.38                 | 38.94 ± 7.38           |         |
| 50-69                    | 59.13 ± 5.52                 | 59.13 ± 5.52           |         |
| > 70                     | 78.67 ± 5.95                 | 78.67 ± 5.95           |         |
| Gender                   |                               |                        |         |
| Male                     | 3798 47.85%                  | 11394 47.85%           |         |
| Female                   | 4140 52.15%                  | 12420 52.15%           |         |
| Follow up time (mo), mean (SD) | 57.96 ± 21.48       | 63.12 ± 15.6 < 0.001  |         |
| Economic status          |                               |                        | < 0.001 |
| MBS                      | 3963 49.92%                  | 11216 47.1             |         |
| 1-3 times MBS            | 3136 39.51%                  | 10217 42.9             |         |
| Above 3 times MBS        | 825 10.39%                   | 2336 9.81              |         |
| Place of residence       |                               |                        | 0.007   |
| City                     | 5046 63.57%                  | 15078 63.32            |         |
| Countryside              | 2747 34.61%                  | 8403 35.29             |         |
| Remote village           | 131 1.65%                    | 287 1.21               |         |
| Comorbidity              |                               |                        |         |
| CHB                      | 754 9.5%                     | 667 2.8 < 0.001        |         |
| CHC                      | 542 6.83%                    | 474 1.99 < 0.001       |         |
| HP                       | 128 1.61%                    | 131 0.55 < 0.001       |         |
| DM                       | 2319 29.21%                  | 4327 18.17 < 0.001     |         |
| ESRD                     | 186 2.34%                    | 357 1.5 < 0.001        |         |
| CCDL                     | 51 0.64%                     | 7 0.03 < 0.001         |         |
| CO                       | 0 0                          | 0 0                   | NA      |
| IBD                      | 119 1.5%                     | 184 0.77 < 0.001       |         |
| Cholangiocarcinoma       |                               |                        |         |
| Number (rate)            | 147 1.85%                    | 39 0.16 < 0.001        |         |
| Follow up time (mo), mean (SD) | 13.92 ± 21.96    | 31.8 21.48 < 0.001    |         |
| Cholangiocarcinoma after first 6 mo | 55 0.69%              | 35 0.15 < 0.001       |         |
| Follow up time (mo), mean (SD) | 36.73 ± 20.57   | 35.27 19.94 0.86     |         |

SD: Standard deviation; MBS: Minimum basic salary; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; HP: Helicobacter infection; DM: Diabetes mellitus; ESRD: End-stage renal disease; CCDL: Congenital cystic disease of liver; CO: Clonorchis Opisthorchis; IBD: Inflammatory bowel disease.

during the follow-up period. After exclusion of possible misdiagnoses and concurrent cholangiocarcinoma, by excluding cholangiocarcinoma diagnosed within 6 mo after the procedure, 11 (2.05%), 37 (0.65%), and 7 (0.40%) cholangiocarcinoma cases were diagnosed in the ES/EPBD, no intervention, and cholecystectomy groups, respectively. The time to diagnosis for subsequent cholangiocarcinoma was 41.17 ± 22.51 mo in the ES/EPBD group, no intervention, and cholecystectomy groups, respectively. The time to diagnosis for subsequent cholangiocarcinoma was 41.17 ± 22.51 mo in the ES/EPBD group, 35.46 ± 19.08 mo in the no intervention group, and 33.70 ± 23.35 mo in the cholecystectomy group. The odds ratio for subsequent cholangiocarcinoma was 3.13 in the ES/EPBD group and 0.61 in cholecystectomy group when compared with the no intervention group. The results were similar if we excluded the cholangiocarcinoma cases within one year after the procedure or the diagnosis of cholelithiasis. The cumulative cholangiocarcinoma rates in the three groups in the 7-year follow-up period are demonstrated in Figure 2.

**The incidence of cholangiocarcinoma**

The incidence of cholangiocarcinoma after the initial 6 mo was compared using incidence rate/1000 person-years. In the ES/EPBD group, the incidence of
cholangiocarcinoma was 4.37 (2.30-7.59) per 1000 person-years, which is more than 15 times of the incidence of the normal population. The incidence of cholangiocarcinoma in ES/EPBD was especially high in females (6.31/1000 person-years) and patients older than 70 years (7.53/1000 person-years).

In the cholecystectomy group, the incidence of cholangiocarcinoma was 0.79 (0.34-1.55) per 1000 person-years, which is still higher than the cholangiocarcinoma incidence in the normal population. The highest incidence of cholangiocarcinoma was found in patients older than 70 years (2.15/1000 person-years).

The cholelithiasis patients without advanced intervention had an incidence of cholangiocarcinoma of 1.38 (0.99-1.88) per 1000 person-years. The highest incidence of cholangiocarcinoma in this subgroup was observed in men (1.72/1000 person-years) and in elderly patients (2.80/1000 person-years). The incidence comparisons are shown in Table 3. For the recurrent biliary events, the comparisons between cholangiocarcinoma patients and non-cholangiocarcinoma patients in ES/EPBD group were listed in the Supplementary Table 2.

**DISCUSSION**

...
In our study, the intervention rate was higher than that reported previously, because this was a hospital-based cohort database, which meant that nearly all cholelithiasis cases were regarded as symptomatic patients. We found a higher incidence of cholelithiasis in people with a minimum basic salary and the highest economic status. The former seems connected with a poor health environment, as shown in previous literature, while the latter can be explained by diets high in cholesterol, saturated fat, and excess carbohydrates. The same conditions explained the higher portion of cholelithiasis patients among residents of remote villages than in the normal population. Because primary sclerosing cholangitis, CCDL, CO, cholelithiasis, CHB, and CHC are important risk factors for cholangiocarcinoma, we subjected these factors to further evaluation to compare cholelithiasis patients and a normal population. In our analysis, CHB, CHC, DM, HP infection, ESRD, CCDL, and IBD were more common in cholelithiasis patients and some of these factors logically increased the rate of cholangiocarcinoma.
by increasing the incidence of cholelithiasis[42]. Because CO infection is extremely rare in modern Taiwanese society, no CO-infected patient was found in our study in either group. The cholangiocarcinoma rate was higher in cholelithiasis patients than in the normal population (0.69% vs 0.15%), thereby confirming the previous concept of cholelithiasis as an important risk factor for cholangiocarcinoma.

The rate of total cholangiocarcinoma and subsequent cholangiocarcinoma (diagnosed 6 mo after procedure) are highest in ES/EPBD patients, followed by cholelithiasis patients without intervention, and the lowest cholangiocarcinoma rate was found in cholecystectomy patients. The odds ratio of ES/EPBD patients for cholangiocarcinoma was 3.13 when compared with no intervention, indicating that the subsequent cholangiocarcinoma rate was high after ES/EPBD in cholelithiasis patients. Cholecystectomy decreased the cholangiocarcinoma rate in cholelithiasis patients in our study and this effect was compatible with previous literature reports[34].

Another interesting finding of our study was the high incidence of cholangiocarcinoma in the medium time period for cholelithiasis patients who had undergone ES/EPBD, especially in women and in patients older than 70 years. However, current guidelines do not suggest close follow-up in these patients.

This study has two major limitations. First, this is a retrospective database cohort study that showed an increase in the further incidence of cholangiocarcinoma after EST/EPBD in cholelithiasis patients, but the true consequence of cholangiocarcinoma and ES/EPBD is unclear. Second, even though this is a one million representative database, the incidence of cholangiocarcinoma is so low that we only found 11 cases, 7 cases, and 37 cases in the ES/EPBD, cholecystectomy, and without intervention group, respectively, but the power of our results is still credible. We will try to initiate a prospective hospital-based cohort study in cholelithiasis patients, who underwent therapeutic intervention to clarify the consequence of cholangiocarcinoma in ES/EPBD and cholecystectomy patients.

In conclusion, symptomatic cholelithiasis did increase the cholangiocarcinoma rate in our analysis, and patients with cholelithiasis who underwent cholecystectomy could reduce the incidence of subsequent cholangiocarcinoma, but the incidence is still significantly higher than the incidence in the normal population. Meanwhile, the patients with cholelithiasis who undergo ES/EPBD are at high risk of subsequent cholangiocarcinoma.
Table 3 Incidence of cholangiocarcinoma amount patient with cholelithiasis underwent therapeutic endoscopic retrograde cholangiopancreatography, cholecystectomy or no intervention compared with normal population (excluding cholangiocarcinoma in the initial 6 mo)

| Variables                  | Person-years at risk in study cohort | Person-years at risk in control cohort | No. of observed cases of cholangiocarcinoma in study cohort | No. of observed cases of cholangiocarcinoma in control cohort | Incidence rate/1000 person-years (95%CI) in study cohort | Incidence rate/1000 person-years (95%CI) in control cohort |
|----------------------------|--------------------------------------|----------------------------------------|------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| ES/EPBD                    |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| Total                      | 2519.33                              | 125339.21                             | 11                                                         | 35                                                            | 4.37 (2.30-7.59)                                          | 0.28 (0.20-0.38)                                          |
| Gender                     |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| Male                       | 1252.12                              | 59176.6                               | 3                                                         | 20                                                            | 2.40 (0.61-6.52)                                          | 0.34 (0.21-0.51)                                          |
| Female                     | 1267.21                              | 66162.6                               | 8                                                         | 15                                                            | 6.31 (2.90-11.99)                                         | 0.23 (0.13-0.37)                                          |
| Age, yr                    |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| 18-49                      | 561.74                               | 37789.95                              | 1                                                         | 5                                                             | 1.78 (0.09-8.78)                                          | 0.13 (0.05-0.29)                                          |
| 50-69                      | 895.32                               | 48272.57                              | 2                                                         | 14                                                            | 2.23 (0.38-7.38)                                          | 0.29 (0.17-0.48)                                          |
| > 70                       | 1062.27                              | 39276.69                              | 8                                                         | 16                                                            | 7.53 (3.50-14.30)                                         | 0.41 (0.24-0.65)                                          |
| Cholecystectomy            |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| Total                      | 8911.32                              | 125339.21                             | 7                                                         | 35                                                            | 0.79 (0.34-1.55)                                          | 0.28 (0.20-0.38)                                          |
| Gender                     |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| Male                       | 4187.56                              | 59176.6                               | 3                                                         | 20                                                            | 0.72 (0.18-1.95)                                          | 0.34 (0.21-0.51)                                          |
| Female                     | 4723.76                              | 66162.6                               | 4                                                         | 15                                                            | 0.85 (0.27-2.04)                                          | 0.23 (0.13-0.37)                                          |
| Age, yr                    |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| 18-49                      | 3173.23                              | 37789.95                              | 1                                                         | 5                                                             | 0.32 (0.02-1.55)                                          | 0.13 (0.05-0.29)                                          |
| 50-69                      | 3413.76                              | 48272.57                              | 1                                                         | 14                                                            | 0.29 (0.01-1.45)                                          | 0.29 (0.17-0.48)                                          |
| > 70                       | 2324.33                              | 39276.69                              | 5                                                         | 16                                                            | 2.15 (0.79-4.77)                                          | 0.41 (0.24-0.65)                                          |
| Cholelithiasis without intervention |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| Total                      | 26820.41                             | 125339.21                             | 37                                                        | 35                                                            | 1.38 (0.99-1.88)                                          | 0.28 (0.20-0.38)                                          |
| Gender                     |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| Male                       | 12201.3                              | 59176.6                               | 21                                                       | 20                                                            | 1.72 (1.09-2.59)                                          | 0.34 (0.21-0.51)                                          |
| Female                     | 14619.11                             | 66162.6                               | 16                                                       | 15                                                            | 1.09 (0.65-1.74)                                          | 0.23 (0.13-0.37)                                          |
| Age, yr                    |                                      |                                        |                                                            |                                                               |                                                          |                                                          |
| 18-49                      | 8423.77                              | 37789.95                              | 4                                                         | 5                                                             | 0.48 (0.15-1.15)                                          | 0.13 (0.05-0.29)                                          |
| 50-69                      | 10889.04                             | 48272.57                              | 12                                                       | 14                                                            | 1.10 (0.60-1.87)                                          | 0.29 (0.17-0.48)                                          |
| > 70                       | 7507.6                               | 39276.69                              | 21                                                       | 16                                                            | 2.80 (1.78-4.20)                                          | 0.41 (0.24-0.65)                                          |

ES/EPBD: Endoscopic sphincterotomy/endoscopic papillary balloon dilatation.

ARTICLE HIGHLIGHTS

Research background
Cholangiocarcinoma is a highly lethal disease. There are many well known risk factors of cholangiocarcinoma, most of them result from chronic biliary system inflammation, such as primary sclerosing cholangitis, choledochal cyst disease, specific parasite infection, cholelithiasis, chronic hepatitis B and C infection, diabetes mellitus and Helicobacter infection, but the impacts of advanced biliary interventions, like endoscopic sphincterotomy (ES), endoscopic papillary balloon dilatation (EPBD) and cholecystectomy, are inconsistence in previous literature. It is important to understand the major hypothesis result in cholangiocarcinoma.

Research motivation
We focused on the most common disease, cholelithiasis, which can result in cholangiocarcinoma. We conducted this study using the National Health Insurance Research Database to clarify the risks of cholangiocarcinoma after ES/EPBD, cholecystectomy or no intervention for cholelithiasis.

Research objectives
We try to evaluate hospital base cholelithiasis retrospective cohort and analyzed further
cholangiocarcinoma risk in patients underwent ES/EPBD, cholecystectomy or without further therapeutic management. Further studies, to clarify whether the inflammation location or the different methods of therapeutic managements affect the incidence of cholangiocarcinoma, are needed in this field.

Research methods
Because of cholangiocarcinoma is still a disease with very low incidence in normal population, we collect data of NHIRD 2004-2011 in Taiwan using one million random samples. We selected 7938 cholelithiasis cases as well as 23814 control group cases (matched by sex and age in 1:3 ratio). The incidences of total and subsequent cholangiocarcinoma were calculated in ES/EPBD patients, cholecystectomy patients, cholelithiasis patients without intervention and normal population. This topic is hard to be analyzed because subsequent cholangiocarcinoma incidence is low and both cholelithiasis and the managements for cholelithiasis maybe influence the cholangiocarcinoma rate.

Research results
There are 537 cases underwent ES/EPBD, 1743 cases underwent cholecystectomy and 5658 cases without intervention in our cholelithiasis cohort. Eleven (2.05%), 37 (0.65%) and 7 (0.40%) subsequent cholangiocarcinoma cases diagnosed in ES/EPBD, no intervention and cholecystectomy group respectively and the odds ratio for subsequent cholangiocarcinoma is 3.13 in ES/EPBD group and 0.61 in cholecystectomy group comparing with no intervention group.

Research conclusions
Symptomatic cholelithiasis patients underwent cholecystectomy had the lowest incidence of subsequent cholangiocarcinoma, but the incidence is still higher than normal population. Patients underwent ES/EPBD are in a high risk of subsequent cholangiocarcinoma and a follow-up plane should be needed in these kinds of patients. The hypotheses of these results can be explained by both inflammation at bile ducts increases incidence of cholangiocarcinoma than inflammation at gallbladder, or cholecystectomy reduce recurrent biliary events in cholelithiasis patients and decrease future cholangiocarcinoma rates. We need a series studies to clarify this mystery we left today.

Research perspectives
The future direction of research is to evaluate choledochohliasis patients, who underwent therapeutic endoscopic retrograde cholangiopancreatography with or without cholecystectomy, and their subsequent cholangiocarcinoma incidence. Because we think the procedure related cholangiocarcinoma need longer time period to take place, the influences of subsequent cholangiocarcinoma between ES and EPBD may be clarified in whole population based cohort study.

REFERENCES
1 Bertuccio P, Bosetti C, Levi F, Decarli A, Negri E, La Vecchia C. A comparison of trends in mortality from primary liver cancer and intrahepatic cholangiocarcinoma in Europe. Ann Oncol 2013; 24: 1667-1674 [PMID: 23378539 DOI: 10.1093/annonc/mds652]
2 Welzel TM, McGlynn KA, Hsing AW, O’Brien TR, Pfeiffer RM. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. J Natl Cancer Inst 2006; 98: 873-875 [PMID: 16708161 DOI: 10.1093/jnci/dji234]
3 Patel T. Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2002; 2: 10 [PMID: 11991810 DOI: 10.1186/1471-2407-2-10]
4 West J, Wood H, Logan RF, Quinn M, Astral GP. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971-2001. Br J Cancer 2006; 94: 1751-1758 [PMID: 16736026 DOI: 10.1038/sj.bjc.6603127]
5 Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001; 33: 1353-1357 [PMID: 11391537 DOI: 10.1053/jhep.2001.25087]
6 Jepsen P, Vilstrup H, Tarone RE, Friis S, Sørensen HT. Incidence rates of intra- and extrahepatic cholangiocarcinomas in Denmark from 1978 through 2002. J Natl Cancer Inst 2007; 99: 895-897 [PMID: 17551150 DOI: 10.1093/jnci/djk201]
7 Bergquist A, Eksson A, Olsson R, Kornfeld D, Lööf L, Danielsson A, Hultcrantz R, Lindgren S, Prytz H, Sandberg-Gertzén H, Almer S, Granath F, Broomé U. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol 2002; 36: 321-327 [PMID: 11867174 DOI: 10.1053/jhep.2002.0488-827801.00284-x]
8 Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol 2004; 99: 523-526 [PMID: 15056096 DOI: 10.1111/j.1572-0241.2004.04067.x]
9 Chapman MH, Webster GJ, Bannoo S, Johnson GJ, Wittmann J, Pereira SP. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience. Eur J Gastroenterol Hepatol 2012; 24: 1051-1058 [PMID: 22653260 DOI: 10.1097/MEG.0b013e3283548bb]
10 Scott J, Shoussah S, Thomas HC, Sherlock S. Bile duct carcinoma: a late complication of congenital hepatic fibrosis. Case report and review of literature. Am J Gastroenterol 1980; 73: 113-119 [PMID: 6249110]
11 Lipsett PA, Pitt HA, Colombani PM, Boitnott JK, Cameron JL. Choleodochal cyst disease. A changing pattern of presentation. Ann Surg 1994; 220: 644-652 [PMID: 7979612 DOI: 10.1097/00000658-199411000-00007]
12 Watanapa P, Watanapa WB. Liver fluke-associated cholangiocarcinoma. Br J Surg 2002; 89: 962-970
Wang CC et al. Risk of cholangiocarcinoma in patients undergoing therapeutic bile duct management

[PMID: 12153620 DOI: 10.1046/j.1365-2168.2002.01245.x]

Welzel TM, Mellemkjær L, Gloria G, Sakoda LC, Hisag AW, El Ghomri L, Olsen JH, McGlynn KA. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. *Int J Cancer* 2007; 120: 638-641 [PMID: 17109384 DOI: 10.1002/ijc.22283]

Hsing AW, Gao YT, Han TQ, Rashid A, Sakoda LC, Wang BS, Shen MC, Zhang BH, Niwa S, Chen J, Fraumeni JF. Gallstones and the risk of biliary tract cancer: a population-based study in China. *Br J Cancer* 2007; 97: 1577-1582 [PMID: 18000589 DOI: 10.1038/sj.bjc.6600447]

Shin HH, Lee CU, Park HJ, Seol SY, Chung JM, Choi HC, Ahn YO, Shimamura T. Hepatitis B and C virus, Clonorchis sinensis for the risk of liver cancer: a case-control study in Pusan, Korea. *Int J Epidemiol* 1996; 25: 933-940 [PMID: 8922477 DOI: 10.1093/ije/25.5.933]

Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology* 2005; 128: 620-626 [PMID: 15765398 DOI: 10.1053/j.gastro.2004.12.048]

Jing W, Jin G, Zhou X, Zhou Y, Zhang Y, Shao C, Liu R, Hu X. Diabetes mellitus and increased risk of cholangiocarcinoma: a meta-analysis. *Eur J Cancer Prev* 2012; 21: 24-31 [PMID: 21857525 DOI: 10.1097/CEJ.0b013e3283481d89]

Zhang LF, Zhao BX. Diabetes mellitus and increased risk of extraperitoneal cholangiocarcinoma: a meta-analysis. *Hepatogastroenterology* 2013; 60: 684-687 [PMID: 23252013]

Chang JS, Tsai CR, Chen LT. Medical risk factors associated with cholangiocarcinoma in Taiwan: a population-based case-control study. *PLoS One* 2013; 8: e69981 [PMID: 23894567 DOI: 10.1371/journal.pone.0069981]

Murphy G, Michel A, Taylor PR, Albanis D, Weinsten SJ, Tortamano M, Parisi D, Snyder K, Butt J, McGlynn KA, Koshiel J, Powell L, Lai GY, Abou EM, Freedman ND. Association of seropositivity to Helicobacter species and biliary tract cancer in the ATBC study. *Gastroenterology* 2003; 60: 1963-1971 [PMID: 14595292 DOI: 10.1016/S0016-5107(03)01994-1]

Costamagna G, Shah SK, Tringali A. Current management of postoperative complications and benign biliary strictures. *Gastrointest Endosc Clin N Am* 2003; 13: 635-648, ix [PMID: 14986791 DOI: 10.1016/S1052-5157(03)00103-X]

Seth SG, Howell DA. What are the really the true late complications of endoscopic biliary sphincterotomy? *Am J Gastroenterol* 2002; 97: 2699-2701 [PMID: 12425534 DOI: 10.1111/j.1572-0241.2002.07051.x]

Bergman JJ, van Berkel AM, Groen AK, Schoeman MN, Offerhaus J, Tytgat GN, Huibregtse K. Biliary manometry, bacterial characteristics, bile composition, and histologic changes fifteen to seventeen years after endoscopic sphincterotomy. *Gastrointest Endosc* 1997; 45: 400-405 [PMID: 9165322 DOI: 10.1016/S0016-5107(97)70151-2]

Kurumado K, Naga T, Kondo Y, Abe H. Long-term observations on morphological changes of cholecdochal epithelium after cholecdochoenterostomy in rats. *Dig Dis Sci* 1994; 39: 809-820 [PMID: 8149847 DOI: 10.1007/BF02087428]

Kalaitzis J, Vezakis A, Fragalidis G, Aragostopolou I, Rizos S, Papalambros E, Polydorou A. Effects of endoscopic sphincterotomy on bile duct epithelium: a case-control study. *World J Gastroenterol* 2002; 18: 799-809 [PMID: 12371639 DOI: 10.3748/wjg.v18.i8.794]

Oliva-Cunha M, Dennis AR, Garcia G. Late Complications After Endoscopic Sphincterotomy. *Surg Laparosc Endosc Percut Tech* 2016; 26: 1-5 [PMID: 26679684 DOI: 10.1097/SLE.0000000000000226]

Peng YC, Lin CL, Hsu WY, Chow WK, Lee SW, Yeh HZ, Chang CS, Kao CH. Association of Endoscopic Sphincterotomy or Papillary Balloon Dilatation and Biliary Cancer: A Population-Based Cohort Study. *Medicine (Baltimore)* 2015; 94: e926 [PMID: 26663135 DOI: 10.1097/MD.0000000000000926]

Langerth A, Sandblom G, Karlsson BM. Long-term risk for acute pancreatitis, cholangitis, and malignancy more than 15 years after endoscopic sphincterotomy: a population-based study. *Endoscopy* 2015; 47: 1132-1136 [PMID: 26165737 DOI: 10.1055/s-0034-1392482]

Strömberg C, Böckelman C, Song H, Ye W, Pukkala E, Haglund C, Nilsson M. Endoscopic sphincterotomy and risk of cholangiocarcinoma: a population-based cohort study in Finland and Sweden. *Endosc Int Open* 2016; 4: E1096-E1100 [PMID: 27742825 DOI: 10.1002/eoi.414982]

Guo L, Mao J, Li Y, Jiao Z, Guo J, Zhang J, Zhao J. Cholecistitis, cholecystectomy and risk of hepatocellular carcinoma: a meta-analysis. *J Cancer Res Ther* 2014; 10: 834-838 [PMID: 25579515 DOI: 10.4103/0973-1482.135992]

Tao LY, He XD, Qu Q, Cai L, Liu W, Zhou L, Zhang SM. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a case-control study in China. *Liver Int* 2010; 30: 215-221 [PMID: 19540244 DOI: 10.1111/j.1478-3231.2009.01249.x]

Nordenstedt H, Mattsson F, El-Serag H, Lagergren J. Gallstones and cholecystectomy in relation to risk of intra- and extrahepatic cholangiocarcinoma. *Br J Cancer* 2012; 106: 1011-1015 [PMID: 22240785 DOI: 10.1038/bjc.2011.607]

Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. *Health Aff (Millwood)* 2005; 22: 61-78 [PMID: 15757273 DOI: 10.1377/hlthaff.22.3.61]

Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* 2009; 137: 1641-8.e1-2 [PMID: 19664631 DOI: 10.1053/j.gastro.2009.07.060]

Wu CY, Chan FK, Wu MS, Kuo KN, Wang CB, Tao CR, Lin JT. Histamine2-receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel. *Gastroenterology* 2010; 139: 1165-1171 [PMID: 20060012 DOI: 10.1053/j.gastro.2010.06.067]

Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01, updated Apr 6, 2013, accessed Jan 6, 2018. Available from: URL: http://www.openepi.com/Menu/03E_Menu.htm

Lirussi F, Nassauto G, Passera D, Toso S, Zalmuaro B, Monica F, Virgilio C, Frasson F, Okolicsanyi L.
Gallstone disease in an elderly population: the Silea study. *Eur J Gastroenterol Hepatol* 1999; **11**: 485-491 [PMID: 10755250 DOI: 10.1097/00042737-199905000-00004]

40 Naeem M, Rahimnajjad NA, Rahimnajjad MK, Khurshid M, Shahid SM, Khawar F, Najjar MM. Assessment of characteristics of patients with cholelithiasis from economically deprived rural Karachi, Pakistan. *BMC Res Notes* **2012**; **5**: 334 [PMID: 22741543 DOI: 10.1186/1756-0500-5-334]

41 Gaby AR. Nutritional approaches to prevention and treatment of gallstones. *Altern Med Rev* **2009**; **14**: 258-267 [PMID: 19803550 DOI: 10.1136/aim.2009.001172]

42 Acalovschi M, Buzas C, Radu C, Grigorescu M. Hepatitis C virus infection is a risk factor for gallstone disease: a prospective hospital-based study of patients with chronic viral C hepatitis. *J Viral Hepat* **2009**; **16**: 860-866 [PMID: 19486279 DOI: 10.1111/j.1365-2893.2009.01141.x]

P- Reviewer: Lan C

S- Editor: Ji FF  L- Editor: A  E- Editor: Song H
