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WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, etc. The current columns of *WJGO* include editorial, frontier, field of vision, review, original articles, case report.

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Observational Study

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

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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),

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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

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Core tip: There are many risk factors well demonstrated in cholangiocarcinoma, but the impacts of advanced biliary interventions, like endoscopic sphincterotomy (ES), endoscopic papillary balloon dilatation (EPBD) and cholecystectomy, are inconsistency in previous literature. We tried to evaluate the subsequent cholangiocarcinoma risk in cholelithiasis patients who underwent ES, EPBD and cholecystectomy. Cholecystectomy can reduce the incidence of subsequent cholangiocarcinoma, while cholelithiasis patients underwent ES/EPBD are in a huge risk of subsequent cholangiocarcinoma in our database study.

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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^[1]. At the same time, previous studies have shown that the incidence of ICC has been rising, while the incidence of extra-hepatic cholangiocarcinoma (ECC) has declined internationally^[2-5] 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^[7-9], choledochal cyst disease^[10,11], specific parasite infection^[12], 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 choledocholithiasis, rather than biliary or pancreatic neoplasms, or the need to manage postoperative biliary complications^[21-23]. 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^[24-26]. 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^[27], and previous data have indicated that therapeutic ERCP can increase the subsequent cholangiocarcinoma rate^[28]. At the same time, many recent larger population-based studies have demonstrated that ES does not increase the incidence of cholangiocarcinoma^[29-31]. 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^[32] and ECC^[33], but some studies have shown that cholecystectomy decreases the subsequent cholangiocarcinoma rate in cholelithiasis patients^[34].

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^[35]. The study methods of NHIRD have been described in detail in previous studies^[36,37]. 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. The

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 χ^2 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 <i>n</i> = 7938		Control group <i>n</i> = 23814		<i>P</i> value
	<i>N</i>	SD, %	<i>N</i>	SD, %	
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					1
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					
Number (rate)	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, 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

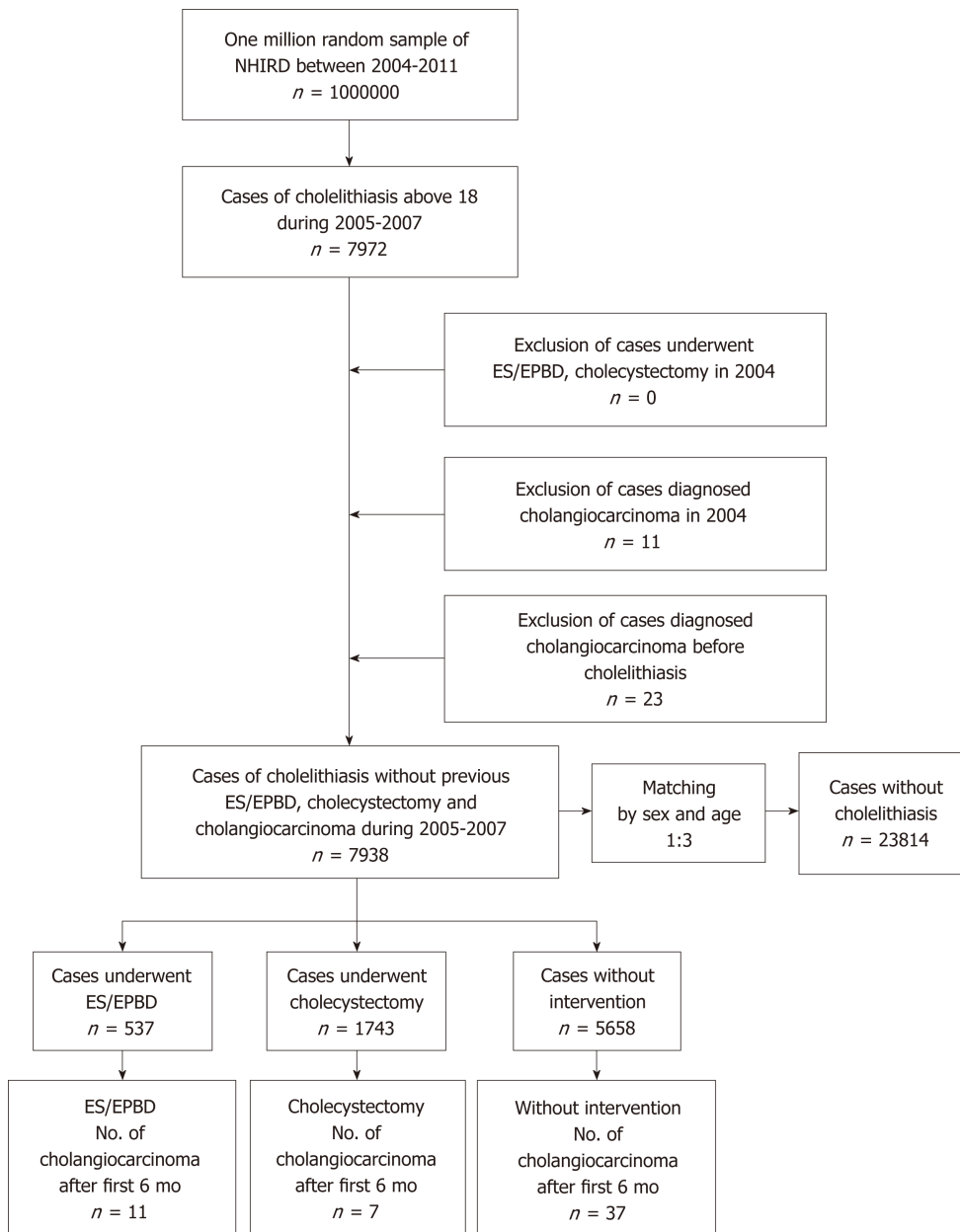


Figure 1 Case selection flow chart of one million nationwide representative data base. ES/EPBD: Endoscopic sphincterotomy/endoscopic papillary balloon dilatation; NHIRD: National Health Insurance Research Database.

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

Table 2 The comparisons of cholelithiasis patients underwent therapeutic endoscopic retrograde cholangiopancreatography, cholecystectomy or no intervention

	ES/EPBD <i>n</i> = 537		Cholecystectomy <i>n</i> = 1743		Without intervention <i>n</i> = 5658		<i>P</i> value
	<i>N</i>	SD, %	<i>N</i>	SD, %	<i>N</i>	SD, %	
Age, mean (SD)	64.33	16.33	56.95	16.53	59.34	16.43	0.941
Age, yr							
18-49	39.29	7.59	38.26	7.6	39.09	7.27	0.391
50-69	60	5.2	59.3	5.56	58.99	5.53	0.559
> 70	79.11	5.73	78.01	5.54	78.78	6.08	0.002
Gender							0.692
Male	264	49.16	843	48.36	2691	47.56	
Female	273	50.84	900	51.64	2967	52.44	
Follow up time (mo), mean (SD)	56.3	22.24	61.38	18.4	56.88	22.27	< 0.001
Economic status							0.16
MBS	319	59.4	1137	65.23	3590	63.45	
1-3 times MBS	209	38.92	574	32.93	1964	34.71	
Above 3 times MBS	9	1.68	28	1.61	94	1.66	
Place of residence							0.009
City	296	55.12	854	49	2813	49.72	
Countryside	205	38.18	681	39.07	2250	39.77	
Remote village	36	6.7	204	11.7	585	10.34	
Comorbidity							
CHB	50	9.31	137	7.86	567	10.02	0.026
CHC	22	4.1	73	4.19	447	7.9	< 0.001
HP	11	2.05	23	1.32	94	1.66	0.433
DM	167	31.1	478	27.42	1674	29.59	0.135
ESRD	12	2.23	37	2.12	137	2.42	0.76
CCDL	13	2.42	12	0.69	26	0.46	< 0.001
CO	0	0	0	0	0	0	NA
IBD	6	1.12	23	1.32	90	1.59	0.54
Cholangiocarcinoma							
Number of cholangiocarcinoma	27	5.03	15	0.86	105	1.86	< 0.001
Number of cholangiocarcinoma after first 6 mo	11	2.05	7	0.4	37	0.65	< 0.001
Odds ratio	3.13		0.61		1		
Number of cholangiocarcinoma after first 12 mo	10	1.86	6	0.34	35	0.62	< 0.001
Odds ratio	3.01		0.56		1		
Time to diagnosis of cholangiocarcinoma (excluding case in initial 6 mo), month	41.17	22.51	33.7	23.35	35.46	19.08	0.698

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.

In our study, the intervention rate was higher than that reported previously^[39], 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^[40], while the latter can be explained by diets high in cholesterol, saturated fat, and excess carbohydrates^[41]. The same conditions explained the higher portion of cholelithiasis patients among residents of remote villages than in the normal population. Because primary sclerosing cholangitis^[7-9], CCDL^[10,11], CO^[12], cholelithiasis^[13,14], CHB and CHC^[15,16], DM^[17,18] and HP infection^[19,20] 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

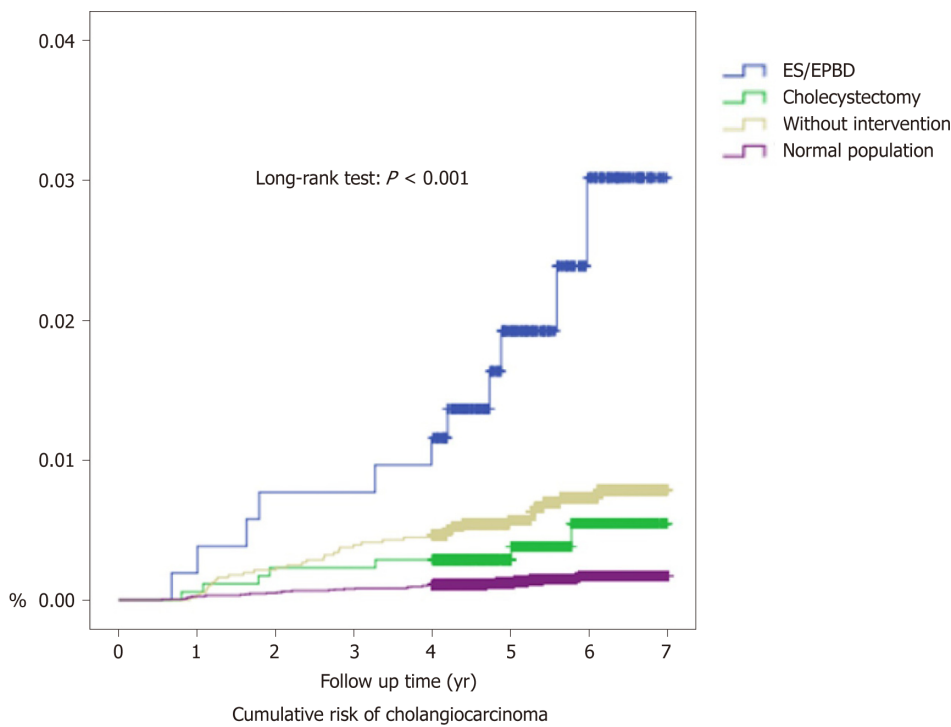


Figure 2 Cumulative risk of cholangiocarcinoma. The cases of cholangiocarcinoma within 6 mo after the therapeutic procedure or the diagnosis of cholelithiasis were excluded. ES/EPBD: Endoscopic sphincterotomy/endoscopic papillary balloon dilatation.

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	66162.61	8	15	6.31 (2.93-11.99)	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	66162.61	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	66162.61	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 inconsistent 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 no intervention for cholelithiasis. 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 choledocholithiasis patients, who underwent therapeutic endoscopic retrograde cholangiopancreatography with or without further 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.

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