

Association of Endoscopic Sphincterotomy or Papillary Balloon Dilatation and Biliary Cancer

A Population-Based Cohort Study

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Abstract: Endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilatation (EPBD) have become the main therapeutic procedures in the treatment of biliary and pancreas disease. The risk of cholangiocarcinoma (CCA) is not well investigated among post-EST/EPBD patients with benign diseases, particularly in Asia population.

A retrospective nationwide cohort study using data from Taiwan's National Health Insurance Research Database (from January 1, 1998 through December 31, 2010) was conducted. Among patients with history of biliary stone with cholangitis, there were 17,503 patients in the EST/EPBD cohort and 69,998 subjects in the comparison. The incidence rate ratio was calculated using the Poisson regression model. Multivariable Cox proportional hazard models, adjusted for potential confounding factors, were used to assess the risk of developing CCA associated with endoscopic EST/EPBD. The cumulative incidences of CCA in the 2 cohorts were calculated using Kaplan–Meier analyses,

and differences between the survival curves of the 2 cohorts were analyzed using a log-rank test.

The overall incidence of CCA in the EST/EPBD cohort was higher than in the controls (1.36 vs 7.37 per 1000 person-years, IRR = 5.40, 95% CI = 5.15–5.67), with an adjusted HR of 4.41 (95% CI = 3.86–5.04). There were no CCA occurrences among patients receiving EST over the follow-up period 3 year after EST performed. The cumulative incidence of extrahepatic CCA seemed to be little growing in patients receiving EPBD. The cumulative incidence of intrahepatic CCA was also steady increasing in patients treated with EPBD and was more than patients receiving EST 10 years after EPBD by Kaplan–Meier analysis.

In the population-based cohort study, EST is not associated with a long-term risk of intrahepatic and extrahepatic CCA. The risk of CCA for EPBD needs further investigation.

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Abbreviations: CCA = cholangiocarcinoma, CI = confidence interval, EPBD = endoscopic papillary balloon dilatation, EST = endoscopic sphincterotomy, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, IRR = incidence rate ratio, NHIRD = National Health Insurance Research Database, SD = standard deviation.

INTRODUCTION

The introduction of endoscopic exploration of biliary-pancreatic duct via the ampulla of Vater paved the way for the era of endoscopic retrograde cholangiopancreatography (ERCP).¹ Endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilatation (EPBD) has become one of the major standard diagnostic and therapeutic procedures in the treatment of biliary and pancreas disease.^{2–5} EST was developed earlier and is widely applied in the management of pancreas and biliary disease as a standard procedure.^{2,6} EPBD is also considered a mature procedure and has been developed in clinical practices for biliary and pancreas disease.^{7,8} Currently, EST and EPBD are considered equally effective in the endoscopic management of biliary disease.^{9–11} Both EPT and EPBD create a larger orifice for biliary access, which result in completely or partially loss of sphincter of Oddi function, and thus therapeutic instruments can be readily manipulated. The completely or partially removal of the biliary to intestine barrier by EST/EPBD allows the reflux of intestinal contents, food, or fluid to the biliary duct. Thus, reflux is possibly associated with chronic inflammation, and transformation of the biliary epithelium. However, whether reflux-related irritation of the biliary epithelium leads to transformation or carcinogenesis after EST/EPBD is unclear.

Following the introduction of ERCP and EST/EPBD for the treatment of biliary disease, concerns about the effect of bile reflux after EST/EPBD, particularly the association with biliary carcinogenesis, have been addressed. In 1997, an epidemiological study demonstrated that EST conducted for stones in the common bile duct does not appear to affect the risk of cancer in the pancreas, liver, or bile ducts, and long-term survival seems to be similarly unaffected.¹² Recent results from the same database also indicated that EST did not affect the risk of malignancy in the bile ducts, liver, or pancreas.¹³ A population-based Danish study suggested a lack of a causal association between EST and cholangiocarcinoma (CCA).¹⁴ Based on molecular mechanism, targeting p53 expression in biliary epithelium, Kalaitzis et al¹⁵ demonstrated EST was associated with biliary epithelial atypia change, and concluded that reactive epithelial changes occur rather than premalignant changes. The incidence of CCA varied geographically and limited risk factors account for CCA.¹⁶ Those known risk factors seem to be associated with chronic inflammation of the biliary epithelium and also linked with geographic differences.¹⁷ The above 3 epidemiological studies on EST and risk of CCA were conducted in Europe. More universal data are needed to confirm the incidence of EST/EPBD and risk of CCA. Currently, there is a lack of data on post-EST/EPBD-related risk of CCA among Asian populations.

More specifically, the issue as to whether EST/EPBD increases the risk of biliary cancer needs to be addressed, as does the optimal duration between CCA diagnosis and EST/EPBD. Furthermore, it remains unclear whether patients receiving EST/EPBD should be followed up routinely and what the follow-up strategy should entail. We conducted a nationwide population-based cohort study to analyze the risk of developing CCA among in a group of patients with benign biliary disease after EST/EPBD.

METHODS

Data Source

The National Health Insurance (NHI) program was initiated in 1995 in Taiwan to provide comprehensive health care for the nation's residents. Enrollment in this program is mandatory and the proportion of the insured population is greater than 99% (<http://www.nhi.gov.tw/english/index.aspx>). Taiwan's National Health Research Institutes (NHRI) established the National Health Insurance Research Database to record all inpatient and outpatient medical services of beneficiaries, including patients' demographics, primary and secondary diagnoses of diseases, procedures, prescriptions, and medical expenditures. All information that may potentially identify any individual patient is encrypted. In this study, we used scrambled patient identification numbers to link 3 files: the registry for beneficiaries, inpatient care claims, and the Catastrophic Illness Patients Database (CIPD). The confidentiality of the patients' data stored in the registry is guaranteed by the data regulations of the Bureau of NHI and the NHRI. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012).

Sampled Participants

All participants had a history of biliary stone with cholangitis; having a history of biliary stone with cholangitis was defined as having been hospitalized for biliary stone with cholangitis between 1998 and 2010. Biliary stone with

cholangitis was identified based on a diagnosis using the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) codes 574 and 576. Patients with EST or EPBD (ICD-9-CM procedure codes 518.4, and 518.5) were selected for the study cohort. Patients with a history of biliary cancer (ICD-9-CM 155.1 and 156), age less than 20 years, and those lacking complete information were excluded. The date of the endoscopic procedure of EST or EPBD was used as the index date. The comparison cohort was randomly selected from the rest of the biliary stone or cholangitis patients without procedure of EST/EPBD. For each patient in the study cohort, 4 comparisons were randomly selected, then frequency-matched by sex, age (every 5-year span), and the year of the index date. The same exclusion criteria were also applied to the comparison cohort.

Outcome and Comorbidities

All subjects were linked to the registry of the CIPD to identify participants diagnosed with CCA (ICD-9-CM 155.1 and 156) in the NHI program. The registration of a case of catastrophic illness requires the diagnosis to be made by a physician, with confirmatory pathological results or other supporting medical information; these documents are formally reviewed by the Bureau of NHI. The subjects of both study cohorts were followed up until a diagnosis of CCA was made, until the patient was lost to follow-up, until withdrawal from insurance, or until the end of 2011. For reducing the detection bias, the follow-up duration and frequency of medical visits/per year were estimated and compared between EST/EPBD groups and without EST/EPBD groups.

Patients with hospitalization records showing history of cirrhosis (ICD-9-CM 571), congenital cystic disease of liver (ICD-9-CM 555-556), parasitic infections, Clonorchis and Opisthorchis, (ICD-9-CM 121.1, 121.0), other anomalies of gallbladder, bile ducts and liver (ICD-9-CM 751.69, 751.62), and inflammatory bowel diseases (ICD-9-CM 555-556) identified at the baseline were considered to be comorbidities.

Statistical Analysis

The demographic and clinical characteristics of the biliary stone with cholangitis groups with and without EST/EPBD, including age (20-49, 50-64, 65-74, and ≥ 75 years), gender, and comorbidities, were compared by Chi-square test. We used a Student's *t* test for continuous variables. The incidence density rates by demographic status, comorbidity, and follow-up years were calculated for both cohorts. The incidence rate ratio (IRR) with 95% confidence interval (CI) was calculated using the Poisson regression model. Multivariable Cox proportional hazard models, adjusted for potential confounding factors, were used to assess the risk of developing CCA associated with endoscopic EST/EPBD. The cumulative incidence rates of CCA in the 2 cohorts were calculated using Kaplan-Meier analyses, and differences between the survival curves of the 2 cohorts were analyzed using a log-rank test. All analyses were executed using SAS statistical software (Version 9.3 for Windows; SAS Institute, Inc., Cary, NC). All statistical measurements were performed at a 2-tailed significance level of 0.05.

RESULTS

Demographics

Our study consisted of 17,503 patients in the EST/EPBD cohort and 69,998 subjects in the comparison cohort. The mean age in both cohorts was approximately 66 years, and there was

TABLE 1. Comparison of Demographic Characteristics and Comorbidities Among Biliary Stone with Cholangitis Patients With and Without EST/EPBD

	Endoscopic Sphincterotomy/Papillary Balloon Dilatation				P-Value
	No (n = 69,998)		Yes (n = 17,503)		
	n	%	n	%	
Age, mean (SD)*	66.3	15.3	66.5	15.2	0.13
Age, years					0.99
20–49	10,844	15.5	2711	15.5	
50–64	17,516	25.0	4379	25.0	
65–74	18,072	25.8	4518	25.8	
75+	23,566	33.7	5895	33.7	
Gender					0.99
Female	33,025	47.2	8258	47.2	
Male	36,973	52.8	9245	52.8	
Follow-up time, mean (SD)*	4.28	3.38	4.21	3.46	<0.001
Frequency of medical visits/per year	1.14	2.77	3.19	11.0	<0.001
Comorbidity					
Cirrhosis	12,836	18.3	4061	23.2	<0.001
Inflammatory bowel diseases	220	0.31	46	0.26	0.27
Congenital cystic disease of liver	55	0.08	33	0.19	<0.001
Parasitic infections	30	0.04	22	0.13	<0.001
Other anomalies of gallbladder, bile ducts, and liver	298	0.43	431	2.46	<0.001

Chi-square test.

* Student's *t* test.

no significant difference between the groups. The gender and age distributions were matched between the cohorts. Comorbidities including congenital cystic diseases of liver, parasitic infections, anomalies of gallbladder, bile ducts and liver, and cirrhosis were more prevalent in the EST/EPBD cohort than in the comparison cohort ($P < 0.001$) (Table 1).

Cumulative Incidence of Cholangiocarcinoma for EST/EPBD

The mean follow-up time in the EST/EPBD cohort and comparison cohort were 4.21 (standard deviation [SD] = 3.46) and 4.28 (SD = 3.38) years, respectively (Table 1). As shown in Figure 1A, significant differences between the patients with EST/EPBD and patients without EST/EPBD over the follow-up period after EST/EPBD ($P < 0.001$). There were no CCA occurrences among patients receiving EST over the follow-up period 3 year after EST performed.

For further analysis, we divided total CCA into extrahepatic CCA and intrahepatic CCA for evaluation the risk between extrahepatic/intrahepatic CCA and EST/EPBD. There were no CCA occurrences among patients receiving EST over the follow-up period 3 year after EST performed. The cumulative incidence of extrahepatic CCA seemed to be little growing in patients receiving EPBD (Figure 1B). The cumulative incidence of intrahepatic CCA was also steady growing in patients treated with EPBD. Then, the cumulative incidence of intrahepatic CCA in patients receiving EPBD is more than patients receiving EST about 10 years after procedure by Kaplan–Meier analysis (Figure 1C).

Risk of Cholangiocarcinoma for EST/EPBD

The overall incidence of CCA in the EST/EPBD cohort was higher than in the comparison cohort (1.36 vs 7.37 per 1000

person-years, IRR = 5.40, 95% CI = 5.15–5.67), with an adjusted hazard ratio (HR) of 4.41 (95% CI = 3.86–5.04) (Table 2). The sex-specific analysis showed that the adjusted HR of CCA for the EST/EPBD cohort compared with the comparison cohort was significant for females (adjusted HR = 5.21, 95% CI = 4.31–6.31). The age-specific EST/EPBD cohort to comparison cohort relative risk was the greatest for the elderly group. The comorbidity-specific EST/EPBD cohort to comparison cohort adjusted HR of CCA was significant for the without comorbidity subgroup (adjusted HR = 4.30, 95% CI = 3.65–5.06) and the with comorbidity subgroup (adjusted HR = 5.06, 95% CI = 4.01–6.37). Stratified by years of follow-up, in patients receiving EST/EPBD, highest risks were observed for developing CCA in the first 1 year of the follow-up period.

Incidence and Risk of Extrahepatic and Intrahepatic Cholangiocarcinoma of Endoscopic Sphincterotomy or Balloon Dilatation

Furthermore, both cohorts were recategorized according to EST or EPBD (Table 3). Among patients with EST, the EST cohort to comparison cohort adjusted HR of CCA, intrahepatic CCA, and extrahepatic CCA was higher (adjusted HR = 4.94, 95% CI = 3.56–6.88, adjusted HR = 6.22, 95% CI = 3.01–12.9 and adjusted HR = 13.4, 95% CI = 6.87–59.3). Compared with patients with EPBD, to the controls patients with EPBD had a significantly risk of CCA with higher adjusted HR of CCA, intrahepatic CCA, and extrahepatic CCA (adjusted HR = 4.11, 95% CI = 3.55–4.76, adjusted HR = 4.95, 95% CI = 3.63–6.76) and adjusted HR = 7.44, (95% CI = 4.33–12.8).

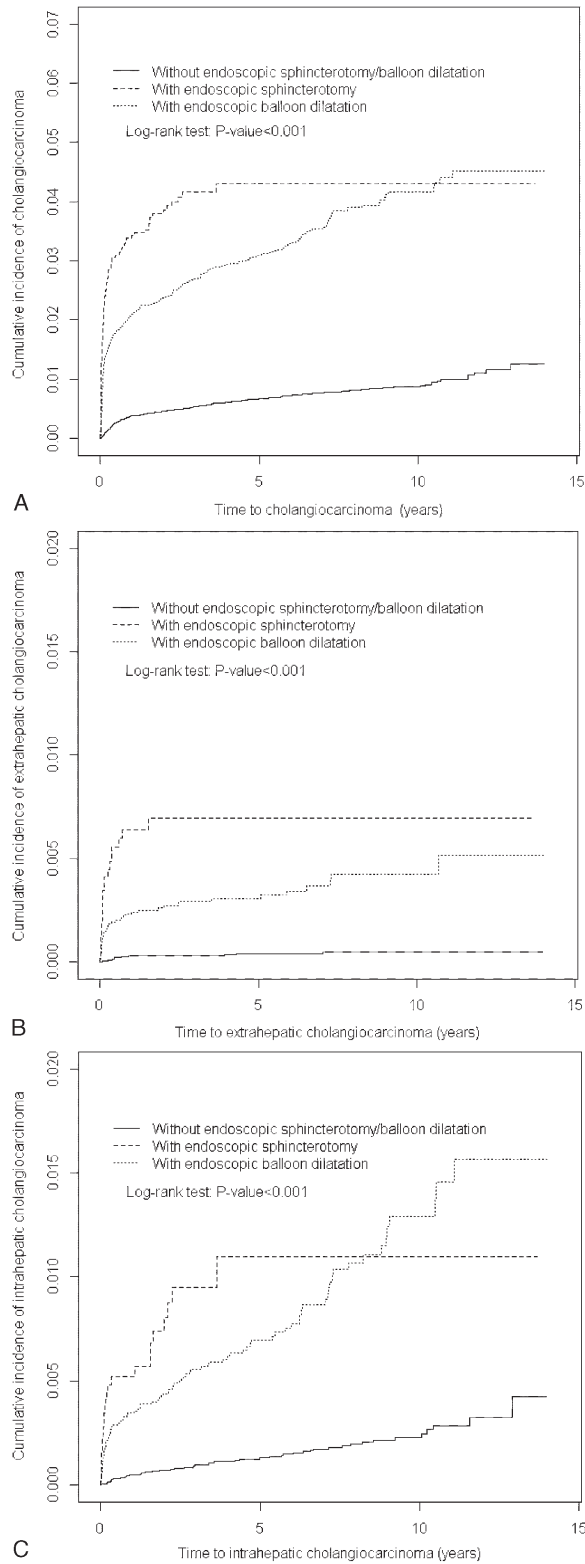


FIGURE 1. (A) Cumulative incidence of cholangiocarcinoma for patients with endoscopic sphincterotomy (rough dashed line), endoscopic balloon dilatation (fine dashed line), or without (solid line) both. (B) Cumulative incidence of extrahepatic cholangiocarcinoma for patients with endoscopic sphincterotomy (rough dashed line), endoscopic balloon dilatation (fine dashed line), or without (solid line) both. (C) Cumulative incidence of intrahepatic cholangiocarcinoma for patients with endoscopic sphincterotomy (rough dashed line), endoscopic balloon dilatation (fine dashed line), or without (solid line) both.

TABLE 2. Incidence and Adjusted Hazard Ratio of Cholangiocarcinoma Stratified by Sex, Age, and Comorbidity in Patients With and Without Endoscopic Sphincterotomy/Papillary Balloon Dilatation

	Endoscopic Sphincterotomy/Papillary Balloon Dilatation						IRR [‡] (95% CI)	Adjusted HR [§] (95% CI)
	No			Yes				
	Event	PY	Rate [†]	Event	PY	Rate [†]		
All	409	299,916	1.36	543	73,709	7.37	5.40 (5.15, 5.67) ^{***}	4.41 (3.86, 5.04) ^{***}
Gender								
Female	190	147,550	1.29	303	35,624	8.51	6.61 (6.15, 7.10) ^{***}	5.21 (4.31, 6.31) ^{***}
Male	219	152,366	1.44	240	38,085	6.30	4.38 (4.10, 4.69) ^{***}	3.83 (3.17, 4.62) ^{***}
Age, years								
20–49	24	55,728	0.43	32	13,726	2.33	5.41 (4.74, 6.18) ^{***}	3.62 (2.04, 6.45) ^{***}
50–64	93	86,573	1.07	154	20,746	7.42	6.91 (6.26, 7.63) ^{***}	4.35 (3.29, 5.76) ^{***}
65–74	133	83,004	1.60	167	20,002	8.35	5.21 (4.74, 5.72) ^{***}	3.43 (2.68, 4.39) ^{***}
75+	159	74,611	2.13	190	19,235	9.88	4.64 (4.27, 5.03) ^{***}	3.84 (3.08, 4.78) ^{***}
Comorbidity								
No	294	186,944	1.57	302	37,305	8.10	5.15 (4.83, 5.49) ^{***}	4.30 (3.65, 5.06) ^{***}
Yes	115	112,971	1.02	241	36,404	6.62	6.50 (6.01, 7.03) ^{***}	5.06 (4.02, 6.37) ^{***}
Follow-up years								
≤1	249	63,830	3.90	392	15,455	25.4	6.50 (6.19, 6.83) ^{***}	4.85 (4.10, 5.73) ^{***}
2–3	236	95,636	2.47	193	23,229	8.31	3.89 (3.70, 4.08) ^{***}	3.25 (2.68, 3.94) ^{***}
4–6	52	84,383	0.62	43	20,788	2.07	3.35 (3.13, 3.59) ^{***}	3.28 (2.19, 4.93) ^{***}
>6	30	56,167	0.53	33	14,237	2.32	4.34 (3.96, 4.75) ^{***}	4.03 (2.44, 6.65) ^{***}

*P < 0.05, **P < 0.01, ***P < 0.001.

† Incidence rate, per 1000 person-years.

‡ Incidence rate ratio.

§ Adjusted hazard ratio, adjusted for age, sex, frequency of medical visits, gastritis, gastric disease, gastric polyp, gastroesophageal reflux disease, cirrhosis, inflammatory bowel diseases, congenital cystic disease of liver, parasitic infections, and other anomalies of gallbladder, bile ducts, and liver.

DISCUSSION

ERCP with EST/EPBD removes a barrier, creating a permanent communication between the biliary tract and the intestines. Our results demonstrated that the overall incidence of CCA in the EST/EPBD cohort was 7.37 per 1000 person-years, IRR = 5.40, 95% CI = 5.15–5.67, with an adjusted HR of

IRR = 4.41, 95% CI = 3.86–5.04. There were no CCA occurrences among patients receiving EST over the follow-up period 3 year after EST performed. The cumulative incidence of extrahepatic CCA seemed to be little growing in patients receiving EPBD. The cumulative incidence of intrahepatic CCA was also steady growing in patients treated with EPBD

TABLE 3. Comparison of Incidence, and Hazard Ratios of Cholangiocarcinoma After Endoscopic sphincterotomy/Papillary Balloon Dilatation

Variables	Endoscopic sphincterotomy/Papillary Balloon Dilatation						IRR [‡] (95% CI)	Adjusted HR [§] (95% CI)
	No			Yes				
	Event	PY	Rate [†]	Event	PY	Rate [†]		
Endoscopic sphincterotomy (51.84)								
All	62	31,392	1.97	118	7101	16.6	8.41 (7.47, 9.47) ^{***}	4.94 (3.56, 6.88) ^{***}
IH CCA	12		0.38	24		3.38	8.84 (7.79, 10.0) ^{***}	6.22 (3.01, 12.9) ^{***}
EH CCA	4		0.13	20		2.82	22.1 (18.7, 26.2) ^{***}	13.4 (4.43, 40.5) ^{***}
Endoscopic papillary balloon dilatation (51.85)								
All	347	268,585	1.30	425	66,608	6.38	4.92 (4.67, 5.19) ^{***}	4.11 (3.55, 4.76) ^{***}
IH CCA	72		0.27	101		1.52	5.66 (5.35, 5.99) ^{***}	4.95 (3.63, 6.76) ^{***}
EH CCA	20		0.07	45		0.68	9.07 (8.48, 9.71) ^{***}	7.44 (4.33, 12.8) ^{***}

*P < 0.05, **P < 0.01, ***P < 0.001. CCA = cholangiocarcinoma, EH = extra-hepatic, IH = intrahepatic.

† Incidence rate, per 1000 person-years.

‡ Incidence rate ratio.

§ Adjusted for age, sex, frequency of medical visits, gastritis, gastric disease, gastric polyp, gastroesophageal reflux disease, cirrhosis, inflammatory bowel diseases, congenital cystic disease of liver, parasitic infections, and other anomalies of gallbladder, bile ducts, and liver.

and was more than patients receiving EST about 10 years after procedure by Kaplan–Meier analysis. EST and EPBD carried risk of CCA, but there are differences in the interaction of EST, EPBD, extrahepatic CCA, and intrahepatic CCA. It is interesting and worthy further discussions about these phenomenon.

Endoscopic management has become the mainstay of the treatment for biliary and pancreatic disease. EST and EPBD are considered equally effective and safe procedures for biliary access.⁹ With regard to the preservation of the function of the sphincter of Oddi, EPBD is considered to be comparable with EST.^{10,18} However, physicians as well as patients are becoming increasingly concerned about the changes of biliary, intestine, or both, in the era of post-EST/EPBD in patients with benign disease who have received ERCP. In the present study, we included both EST and EPBD in our analysis of patients with cholangitis or biliary stones. We determined the risk of CCA among cholangitis or biliary stone patients receiving EST/EPBD. However, there appear to be an increased risk of CCA after EST/EPBD in the first 6 months, and there was an almost equal risk in patients with or without EST/EPBD cohort after 3 years of follow-up. Our results are similar to those of a recent report that showed increased risk of CCA in the first 2 years after EST.¹⁴

The occurrence of CCA would be more likely considered an existing CCA rather than a post-EST/EPBD-associated CCA. These findings suggest that CCA diagnosed within a short duration after EST/EPBD in patients with a benign biliary disease should be monitored closely for possible occult biliary malignancy. Patients presenting as cholangitis or biliary stones may also have occult CCA which might have been missed on the cholangiogram. We suggest that cholangitis or biliary stone patients receiving EST/EPBD should be closely followed up in the first 1–3 years, based on the results of the present study.

Chronic liver and biliary diseases were considered to be risks for intrahepatic or extrahepatic CCA.^{16,17,19} As EST and EPBD are now main procedures for the management of biliary disease, the association of intestine reflux events after EST/EPBD and CCA is an important issue. Most of these studies on post-EST-associated CCA in benign diseases are conducted using epidemiological data, particularly from studies done in Europe. The risk of biliary cancer following EST was first studied by Karlson et al in 1997.¹² In the Swedish cancer registry data, EST performed for stones in the common bile duct did not appear to affect the risk of cancer in the liver, biliary tract, and pancreas, and the long-term survival was not affected. Ten years hence, EST still does not appear to affect the risk of liver, biliary, and pancreas cancer in the same Swedish data.¹³ In an epidemiological study conducted in Denmark, EST did not affect the risk of biliary and pancreatic cancer. However, the authors noted an important result: the incidence of CCA in EST patients was 404 per 100,000 person-years during the first 2 years postoperatively.¹⁴ Costamagna et al²⁰ reported that EST is found to be safe at long-term follow-up in choledocholithiasis patients and most recurrences occurred more than 2 years following EST. There is no bile duct cancer reported in this study. A hospital-based study that conducted a long-term follow-up of patients that received EST or EPBD in Japan revealed no new cases of CCA found, but 1 gallbladder cancer was found in 282 EST/EPBD patients (the incidence was about 0.35%).²¹ Due to the geographical variation in the incidence of CCA,^{16,22} there is a lack of epidemiological data on post-EST related risk of CCA in Asian populations.

Our results demonstrated similar findings to those of most previous studies, namely, that EST was not associated with

long-term risk of CCA. CCA in the first 3 year after EST may indicate CCA presenting as cholangitis or biliary stone that was not diagnosed at the time of EST/EPBD. However, cholangitis is a rare presentation for CCA.¹⁶ This may explain why possible CCA was missed after endoscopic management of cholangitis or biliary stones. Moreover, EPBD was also included in the present study and was not included in most previous studies. Our results about EPBD disclosed some interesting data, which is difference with EST and was not disclosed by previous studies. The cumulative incidence of intrahepatic CCA was also steady growing in patients treated with EPBD and was more than patients receiving EST about 10 years.

The distinction between relative and absolute effects is relevant in the study subject inequalities. In our study, the effect of characteristics such as ethnic background, geographical location, nature of stones, and decision of procedure (EST or EPBD) on health outcomes may be quantified about the absolute effect and relative effect. Our results disclosed both EST and EPBD carried risk of CCA, but there are different causes for CCA risk between EST and EPBD. Risk of CCA for EST is within 3 years after procedure. EPBD carried risk of intrahepatic CCA persistently in our study. There need more investigations for long-term risk of CCA for EPBD.

In the present study, there were some potential limitations. First, unmeasured confounding factors, which are possibly associated with CCA, such as body mass index, smoking, alcohol intake, and drug history, were not included in our database. Second, the performance and size of EST/EPBD may vary widely according to clinical conditions (stone size or anatomical variation) and the experience of the endoscopist. The size of EST/EPBD results in different degrees of intestinal reflux. Third, cholangitis or biliary stone that resolves clinically without EST/EPBD may indicate a minor disease status. Fourth, CCA is a less common cancer, so a relatively low number of patients was analyzed in this study. Fifth, there is likely a range of variance or error in the registration of diagnosis of disease and the procedure of EST and EPBD. Fifth, frequency of medical visits/per year was significant less in patients without EST/EPBD. This could result in more check about biliary disease on patients with EST/EPBD versus patients without EST/EPBD, leading to a potential higher detection for patients with EST/EPBD to be diagnosed with biliary cancer. Sixth, presenting CCA risk evidence for the effect of treatment procedures on biliary stone patients' outcomes in exclusively absolute or relative terms can have a different effect on its interpretation, which may lead to the procedures related risks of CCA for EST or EPBD.

In the population-based cohort study, EST is not associated with long-term risk of intrahepatic and extrahepatic CCA. Risk of CCA for EPBD need further investigation.

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