Journal of Gastroenterology and Hepatology
JGHF
doi:10.1111/jgh.15234

GASTROENTEROLOGY

Symptomatic cholelithiasis patients have an increased risk of pancreatic cancer: A population-based study

Chi-Chih Wang,[*,†,‡] Ming-Hseng Tseng,[§] Sheng-Wen Wu,[*,†,¶] Tzu-Wei Yang,[*,†,‡] Hsuan-Yi Chen,[†,‡] Wen-Wei Sung,[*,†,**] Chang-Cheng Su,[‡] Yao-Tung Wang,[*,†,††] Wei-Liang Chen,[‡] Hsueh-Chou Lai,[‡‡,§§] Chun-Che Lin[‡‡,¶¶] and Ming-Chang Tsai[*,†,‡]

*Institute of Medicine, †School of Medicine, §Department of Medical Informatics, Chung Shan Medical University, ‡Division of Gastroenterology and Hepatology, ¶Division of Nephrology, **Department of Internal Medicine, Department of Urology, ††Division of Pulmonary Medicine, Chung Shan Medical University Hospital, ‡‡Digestive Medicine Center, §§School of Chinese Medicine, China Medical University Hospital and ¶¶School of Medicine, China Medical University, Taichung City, Taiwan

Key words
cholecystectomy, endoscopic papillary balloon dilatation, endoscopic sphincterotomy, pancreatic cancer.

Accepted for publication 25 August 2020.

Correspondence
Dr Ming-Chang Tsai, Division of Gastroenterology and Hepatology, Chung Shan Medical University Hospital, No. 110, Section 1, Jianguo North Road, South District, Taichung City 402, Taiwan.
Email: tsaimc1110@gmail.com

Declaration of conflict of interest: The authors declare that they have no conflict of interest.
Author contribution: C-C.W., M-H.T., and W-W.S. contributed to the conception and design of this study. M-H.T., S-W.W., and W-L.C. contributed to the acquisition of data. C-C.W., Y-T.W., and S-W.W. contributed to the analysis and interpretation of data. C-C.W., T-W.Y., and H-Y.C. drafted the manuscript. M-C.T., H-C.L., and C-C.L. contributed to the critical revision of the manuscript. M-C.T., W-W.S., and C-C.S. contributed to the statistical analysis: M-C.T. supervised the work. All authors have read and approved the manuscript.
Ethical approval: This database study was approved by the local Institutional Review Board of Chung Shan Medical University Hospital. Committee's reference number: CS18136. We received administrative ermission to access and use these data from the National Health Insurance Administration Ministry of Health and Welfare of Taiwan.

Abstract

Background and Aim: Pancreatic cancer is a fatal disease; currently, the risk factor survey is not suitable for sporadic pancreatic cancer, which has neither family history nor the genetic analysis data. The aim of the present study was to evaluate the roles of cholelithiasis and cholelithiasis treatments on pancreatic cancer risk.
Methods: Symptomatic adult patients with an index admission of cholelithiasis were selected from one million random samples obtained between January 2005 and December 2009. The control group was matched with a 1:1 ratio for sex, age, chronic pancreatitis, and pancreatic cystic disease. Subsequent pancreatic cancer, which we defined as pancreatic cancer that occurred ≥ 6 months later, and total pancreatic cancer events were calculated in the cholelithiasis and control groups. The cholelithiasis group was further divided into endoscopic sphincterotomy/endoscopic papillary balloon dilatation, cholecystectomy, endoscopic sphincterotomy/endoscopic papillary balloon dilatation and cholecystectomy, and no-intervention groups for evaluation.
Results: The cholelithiasis group and the matched control group included 8265 adults. The cholelithiasis group contained 86 cases of diagnosed pancreatic cancer, and the control group contained 8 cases ($P < 0.001$). The incidence rate ratio (IRR) of subsequent pancreatic cancer was significantly higher in the cholelithiasis group than in the control group (IRR: 5.28, $P < 0.001$). The IRR of subsequent pancreatic cancer was higher in the no-intervention group comparing with cholecystectomy group (IRR = 3.21, $P = 0.039$) but was similar in other management subgroups.
Conclusion: Symptomatic cholelithiasis is a risk factor for pancreatic cancer; the risk is similar regardless of the intervention chosen for cholelithiasis.

Informed Consent: The Institutional Review Board of Chung Shan Medical University Hospital waived the need for informed consent. There are no identifying images or other personal or clinical details of participants presented in this study. Because of the design of this de-linked database article, consent to publish is not applicable to this manuscript.

Financial support: This work was supported by a grant from the Chung Shan Medical University Hospital Research Program (CSH-2013-C-032). With this grant, Chun-Che Lin purchased the right to access representative samples from the National Health Insurance Research Database.

Background

Pancreatic cancer is a fatal disease, and surgical resection is possible only in a small portion of patients.[1] Even in patients who can undergo pancreaticoduodenectomy, the 5-year survival rate is < 30% for patients with T1 tumors and only 10% for those with other resectable pancreatic cancers.[2] Today, R0 resection remains the only curative treatment that guarantees that patients with pancreatic cancer will survive[2]; however, most symptomatic patients with pancreatic cancer have advanced, incurable disease at diagnosis. Therefore, an efficient screening policy is needed to ensure that R0 resection is possible.

Currently, the screening policy focuses on familial pancreatic cancer, the presence of Peutz–Jeghers syndrome,[3] and individuals with a family history of pancreatic cancer.[4] Many risk factors have already been recognized in the existing literature, including hereditary risk factors,[5] germline mutations,[6] non-O blood type,[7] diabetes mellitus (DM),[8–10] cigarette smoking,[11–14] obesity,[15,16] physical inactivity,[17,18] chronic hepatitis B (CHB),[19,20] chronic hepatitis C (CHC),[19,21] and *Helicobacter pylori* (HP) infection,[22–24] but the strongest risk factor is chronic pancreatitis (CP).[25,26] Moreover, pancreatic cystic diseases (PCDs) serve as pre-malignant lesions.[27,28] Unfortunately, there is currently no efficient screening policy; at this time, gene analysis is too expensive to use as a screening method.

In the past 5 years, some cohort[29] studies and one meta-analysis[30] have shown that gallstones and cholecystectomy (CCY) are robust risk factors for pancreatic cancer. However, some studies have found that gallstones and CCY do not appear to be significant risk factors for pancreatic cancer[31] in western countries. Currently, we know that cholelithiasis is a risk factor for cholangiocarcinoma[32]; we found this to be especially true in patients who underwent endoscopic sphincterotomy (ES) or endoscopic papillary balloon dilatation (EPBD) in our previous study.[33] We conducted this retrospective database study to examine whether symptomatic cholelithiasis or invasive interventions for cholelithiasis are risk factors for pancreatic cancer.

Methods

This population-based retrospective cohort study was based on the Taiwan National Health Insurance Research Database (NHIRD); the NHIRD study methods have been described in detail in our previous studies.[33,34] The dataset used in this study includes one million people who are nationally representative of the population of Taiwan between 2004 and 2011. This study was approved by the local Institutional Review Board; the Institutional Review Board waived the need for informed consent in this study. All authors have declared that they have no conflict of interest with this study.

Study design. Symptomatic patients (> 18 years old) with an index admission with a diagnosis of cholelithiasis were randomly selected from one million samples within the NHIRD dataset between January 2005 and December 2009 using the codes of International Statistical Classification of Diseases and Related Health Problems, 9th Edition (ICD-9). We excluded patients who had undergone ES/EPBD, CCY, and lithotripsy before January 2005. Patients with a diagnosis in 2004 of pancreatic cancer, benign neoplasm of the pancreas, or anomalies of the pancreas were also excluded. A control group was selected by matching (1:1 ratio) by sex, age, and the strong risk factors of pancreatic cancer (i.e. CP and PCD). The control group cases were defined as individuals who had neither been diagnosed with cholelithiasis nor undergone a related medical procedure before January 2005. Variables including follow-up length and known risk factors, such as CHB, CHC, HP infection, DM, end-stage renal disease (ESRD), CP, and PCD, which were identified by ICD-9 codes for at least three outpatient clinic visits or a one-time admission, were compared between the two groups. Subsequent pancreatic cancer is defined as pancreatic cancer that occurred 6 months after the measurement point. This is because the patients with pancreatic cancer who were diagnosed within 6 months after the index admission for cholelithiasis were more likely to have been misdiagnosed or to have a concurrent malignancy rather than a subsequent cancer process. We calculated the number, rates, and incidence rate ratios (IRRs) of pancreatic cancer and subsequent pancreatic cancer after index admission. The cumulative risks of pancreatic cancer and subsequent pancreatic cancer were compared in the cholelithiasis and control groups using the log-rank (Mantel–Cox) test. Detailed information about the study design is shown in Figure 1. The ICD-9 codes for the diseases listed previously and their procedure codes are provided in the Table S1.

We further divided the cholelithiasis group into cases who had undergone ES/EPBD, CCY, or ES/EPBD and CCY and cases who had not undergone any invasive intervention (the no-intervention group). The age, gender, previous known risk factors for pancreatic cancer, pancreatic cancer numbers, and IRR of subsequent pancreatic cancer after the procedure for these four subgroups are compared in Table 2. The incidence of subsequent pancreatic cancer in these subgroups was also compared with that in the control group, and the IRR of subsequent pancreatic cancer was calculated for each subgroup.

Data processing and statistical analysis. The NHIRD database was managed by employing a Microsoft SQL Server 2008 R2 (Microsoft Corporation, Redmond, WA, USA) and using the SQL programming language for data queries and data processing. Data obtained from the study were compared with either a χ^2 test for categorical variables, a *t*-test, or a one-way ANOVA for continuous variables; the log-rank (Mantel–Cox) test was used for survival curves. A two-tailed *P* value of 0.05 was considered statistically significant. The IRR was used to compare pancreatic cancer and subsequent pancreatic cancer risk (retrospective cohort study design); the follow-up times were heterogenous in different subgroups.

Statistical and person-time analyses were performed using Open Source Epidemiologic Statistics for Public Health (OpenEpi) version 3.01.[35] Kaplan–Meier survival analyses were conducted using SPSS version 19.

Results

In total, 8440 symptomatic adults who were admitted for cholelithiasis were selected from one million random samples of the NHIRD dataset between January 2005 and December 2009. Cases (n = 101) who had undergone ES/EPBD, CCY, or lithotripsy in

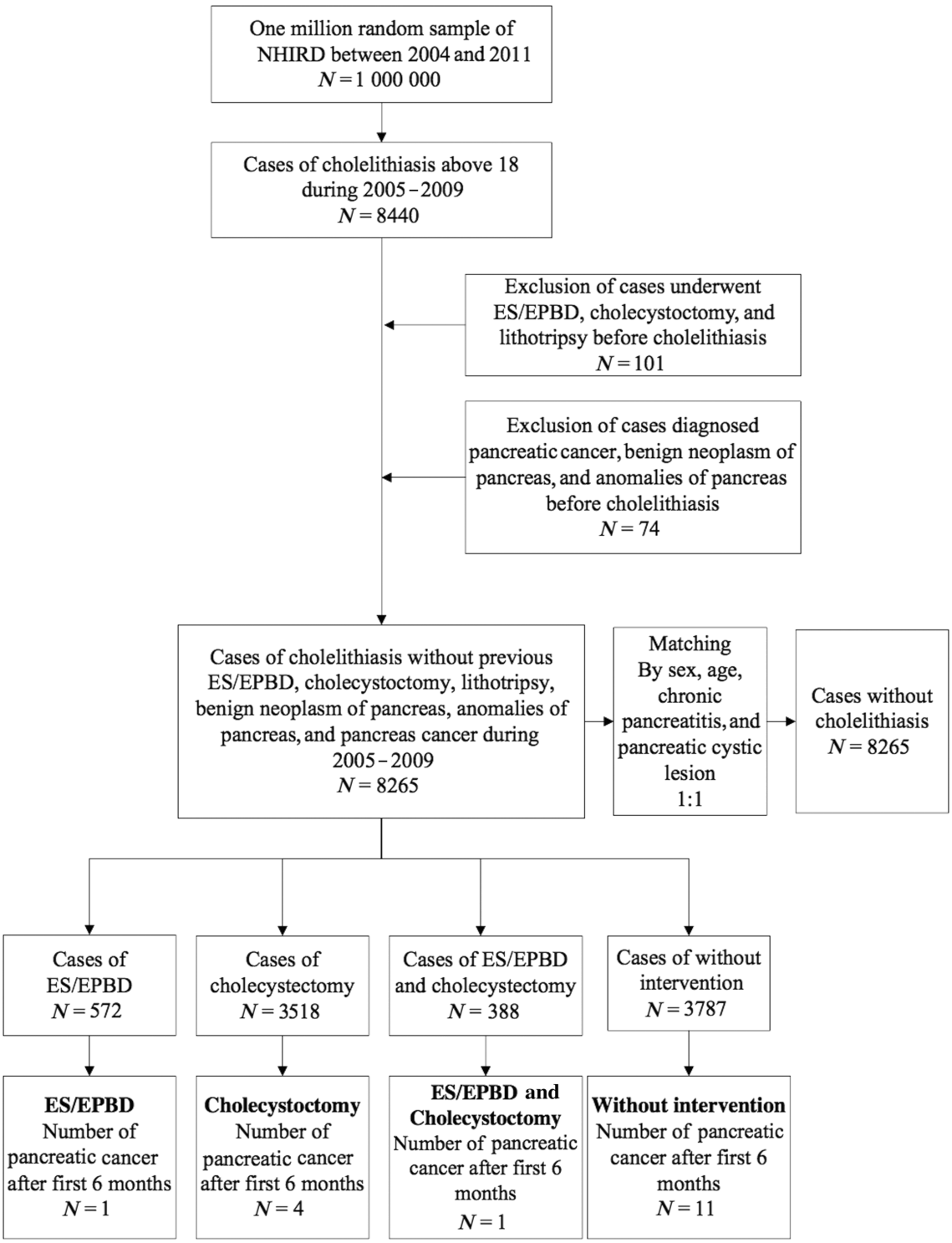

Figure 1 Flowchart of case selection from a nationally representative database of one million people in Taiwan. ES, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilatation; NHIRD, National Health Insurance Research Database.

2004 or before the diagnosis of cholelithiasis as well as cases (n = 74) diagnosed with pancreatic cancer, benign neoplasm of the pancreas, or anomalies of the pancreas before the index admission were excluded. We selected 8265 cholelithiasis patients from January 2005 to December 2009 as the study group. The control group was drawn (1:1 ratio) from cases without cholelithiasis

but who matched the study group in age, gender, and CP and PCD risk (Fig. 1). The 8265 patients in the cholelithiasis group had a mean age of 61 ± 16.98 years, and those in the control group had a mean age of 61 ± 17.29 years. Men accounted for 51.25% of the subjects in both the cholelithiasis and control groups.

Cholelithiasis group versus the control group. The age and gender distributions were similar in both groups. The cholelithiasis group had significantly higher pancreatic cancer risk factors, such as CHB (9.35% *vs*. 2.47%), CHC (7.48% *vs*. 2.06%), HP infection (1.58% *vs*. 0.59%), DM (32.56% *vs*. 17.29%), and ESRD (3.04% *vs*. 1.06%) compared with the control group. Some of these risk factors are difficult to adjust between cholelithiasis group and control group, because they are risk factors for cholelithiasis.[36]

The cholelithiasis group contained 86 (1.04%) cases diagnosed with pancreatic cancer, while the control group had 8 (0.10%) (IRR = 12.62, $P < 0.001$). The risk of subsequent pancreatic cancer revealed a 5.28 times higher IRR in the cholelithiasis group (0.22%) than in the control group (0.05%) ($P < 0.001$). These comparisons are shown in Table 1. The cumulative risks for the cholelithiasis and control groups for pancreatic cancer (panel [a]) and subsequent pancreatic cancer (panel [b]) are shown in Figure 2.

Cholelithiasis cases who underwent endoscopic sphincterotomy/endoscopic papillary balloon dilatation, cholecystectomy, endoscopic sphincterotomy/endoscopic papillary balloon dilatation and cholecystectomy, or no intervention. Of the 8265 patients with index cholelithiasis, 572 underwent ES/EPBD, 3518 underwent CCY, 388 underwent ES/EPBD and CCY, and 3787 received supportive care without further intervention. The average age was 67.00 ± 15.55 years in the ES/EPBD group, 56.00 ± 16.14 years in the CCY group, 60.00 ± 15.95 years in the ES/EPBD and CCY group, and 65.00 ± 16.69 years in the no-intervention group. Patients were significantly younger in the CCY and ES/EPBD and CCY groups, and these groups had a higher proportion of patients between the ages of 18 and 49 years. The CCY group had the highest proportion of women (52.73%); we believe that the higher prevalence of gallbladder stones in women can explain this result.

Evaluation of the subsequent risk of pancreatic cancer revealed 1 case of subsequent pancreatic cancer in the ES/EPBD group, 4 cases in the CCY group, 1 case in the ES/EPBD and CCY group, and 11 cases in the no-intervention group. Although the pancreatic cancer risk differed significantly among these groups, the subsequent pancreatic cancer rates were similar, at 0.17%, 0.11%, 0.26%, and 0.29% in the ES/EPBD, CCY, ES/EPBD and CCY, and no-intervention groups, respectively. After consideration of the follow-up time, we noticed that when using the incidence of

Table 1 Demographic data of the study and control group

	Cholelithiasis group *N* = 8265		Control group *N* = 8265		*P* value
	N	SD; %	*N*	SD; %	
Age, mean (SD)	61.00	16.98	61.00	17.29	1.000
Age, years					0.364
18–49	2118	25.63	2197	26.58	
50–69	3038	36.76	3013	36.45	
> 70	3109	37.62	3055	36.96	
Gender					1.000
Male	4236	51.25	4236	51.25	
Female	4029	48.75	4029	48.75	
Follow-up time (months), mean (SD)	43.69	22.75	51.30	18.63	< 0.001
Risk factors for pancreatic cancer					
CHB	773	9.35	204	2.47	< 0.001
CHC	618	7.48	170	2.06	< 0.001
HP	131	1.58	49	0.59	< 0.001
DM	2691	32.56	1429	17.29	< 0.001
ESRD	251	3.04	88	1.06	< 0.001
CP	141	1.71	141	1.71	1.000
PCD	32	0.39	32	0.39	1.000
Pancreatic cancer					
Number (rate)	86	1.04	8	0.10	
IRR (95% CI)	12.62	(6.39–27.95)	1	Ref.	< 0.001
Subsequent pancreatic cancer					
Number (rate)	18	0.22	4	0.05	
IRR (95% CI)	5.28	(1.90–18.21)	1	Ref.	< 0.001

CI, confidence interval; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CP, chronic pancreatitis; DM, diabetes mellitus; ESRD, end-stage renal disease; HP, *Helicobacter pylori* infection; IRR, incidence rate ratio; PCD, pancreatic cystic disease; SD, standard deviation.

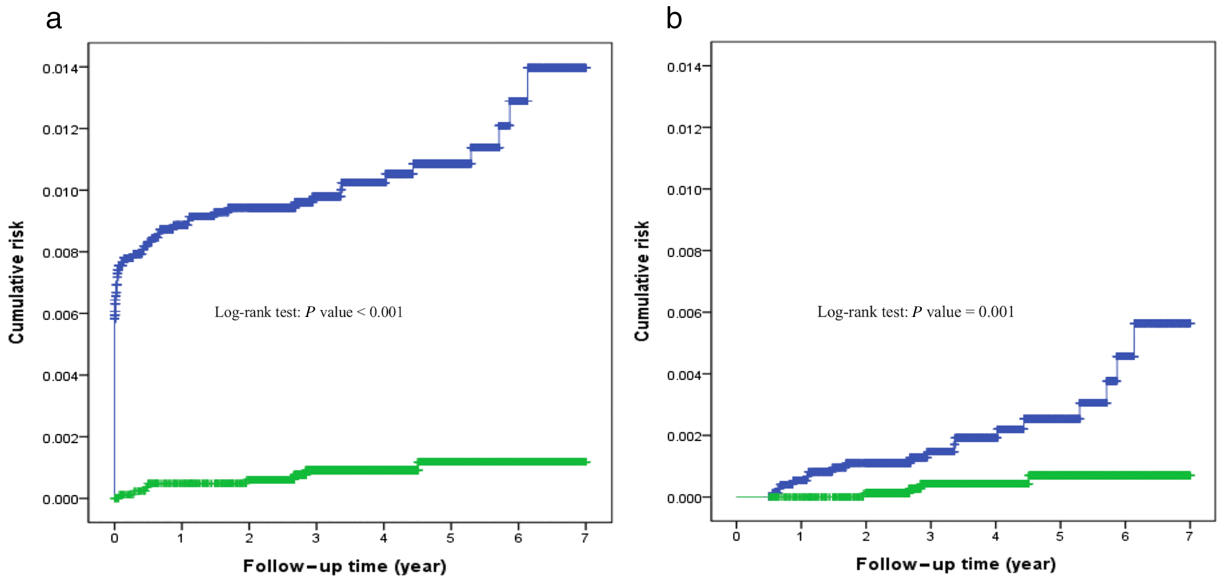

Figure 2 (a) Pancreatic cancer risk (, cholelithiasis group; , normal control group) and (b) subsequent pancreatic cancer risk (, cholelithiasis group; , normal control group) in the cholelithiasis and control groups.

subsequent pancreatic cancer in the CCY group as the reference, the IRR is significantly higher in the no-intervention group (IRR = 3.21, 95% confidence interval [CI]: 1.06–11.66, $P = 0.039$). The IRRs in the ES/EPBD, CCY, and ES/EPBD and CCY groups were similar (non-statistically significant; Table 2). The cumulative subsequent pancreatic cancer risks, shown in Figure 3, were similar in all four groups ($P = 0.207$).

Evaluation of previous pancreatic cancer risk factors indicated that CHB and HP infection were not statistically different in these subgroups. The no-intervention group had a higher proportion of patients with CHC, DM, and ESRD, whereas patients with CP and PCD were more frequently found in the ES/EPBD (2.80% and 0.70%, respectively) or ES/EPBD and CCY (3.09% and 0.77%, respectively) groups.

Incidence of subsequent pancreatic cancer. The risks of subsequent pancreatic cancer may be confounded by different follow-up times. Therefore, the incidences of subsequent pancreatic cancer in these four subgroups were compared using the incidence rate per 1000 person-years. The incidence of subsequent pancreatic cancer was 0.525 (0.007–2.921) per 1000 person-years in the ES/EPBD group, 0.285 (0.077–0.729) per 1000 person-years in the CCY group ($P = 0.214$), and 0.598 (0.030–2.950) per 1000 person-years in the ES/EPBD and CCY group ($P = 0.218$). The incidence of subsequent pancreatic cancer in the no-intervention group was 8.07-fold higher than in the control group; this was the only subgroup that had a subsequent pancreatic cancer incidence, at 0.915 (0.456–1.636) per 1000 person-years, that differed significantly from the incidence in the normal population, at 0.113 (0.030–0.290) per 1000 person-years (IRR: 8.07, 95% CI: 2.65–29.32, $P < 0.001$). These data are shown in Table 3.

Multivariate analysis of risk factors for pancreatic cancer. Because previous pancreatic cancer risk factors, such as CHB, CHC, HP, DM, and ESRD, are significantly higher in the cholelithiasis group compared with the control group, we performed a multivariate analysis to identify which one of them is the major risk factor. There were 86 patients with cholelithiasis, 10 patients with CHB, 4 patients with CHC, 3 patients with HP infection, 42 patients with DM, and 1 patient with ESRD, out of a total of 94 cases of patients with pancreatic cancer. When patients who were diagnosed with pancreatic cancer were compared with people who did not have pancreatic cancer, the following factors reached statistical significance, with odds ratios as follows: old age, 1.033 (1.019–1.048); cholelithiasis, 9.971 (4.793–20.744); and DM, 1.532 (1.010–2.325). A detailed summary of the results is shown in Table 4.

Discussion

In this study, we found that the risk of pancreatic cancer is significantly higher in the cholelithiasis group than in the control group after adjusting for CP and PCD (IRR: 12.62, $P < 0.001$). The subsequent pancreatic cancer risk evaluation showed similar results as IRR 5.28 in cholelithiasis group than control group. Because previous studies revealed inconsistent results regarding cholelithiasis as a risk factor for pancreatic cancer,[29–31,37] we performed this study to clarify whether cholelithiasis or the intervention for cholelithiasis is the factor that affects pancreatic cancer risk. Although many studies have aimed to identify the risk of pancreatic cancer in patients with cholelithiasis, most are case–control studies that did not measure exposure time,[38,39] and some cohort studies that had rigorous experimental designs were conducted more than 20 years ago.[31,40] Most of these studies had fewer cases of pancreatic cancer than our study; some adjusted for DM,[31,39] and others

Table 2 Comparison of patients with symptomatic cholelithiasis who underwent ES/EPBD, CCY, ES/EPBD and CCY, or no intervention

	ES/EPBD *N* = 572		CCY *N* = 3518		ES/EPBD and CCY *N* = 388		No intervention *N* = 3787		
	N	SD; %	*N*	SD; %	*N*	SD; %	*N*	SD; %	*P* value
Age, mean (SD)	67.00	15.55	56.00	16.14	60.00	15.95	65.00	16.69	< 0.001
Age, years									
18–49	89	15.56	1243	35.33	102	26.29	684	18.06	
50–69	191	33.39	1411	40.11	150	38.66	1286	33.96	
> 70	292	51.05	864	24.56	136	35.05	1817	47.98	
Gender									< 0.001
Male	314	54.90	1663	47.27	202	52.06	2057	54.32	
Female	258	45.10	1855	52.73	186	47.94	1730	45.68	
Total follow-up time (month), mean (SD)	42.42	22.12	48.87	19.55	51.70	19.58	38.25	24.50	< 0.001
Risk factors of pancreatic cancer									
CHB	58	10.14	305	8.67	28	7.22	382	10.09	0.077
CHC	32	5.59	186	5.29	16	4.12	384	10.14	< 0.001
HP	8	1.40	47	1.34	9	2.32	67	1.77	0.297
DM	198	34.62	951	27.03	112	28.87	1430	37.76	< 0.001
ESRD	19	3.32	71	2.02	2	0.52	159	4.20	< 0.001
CP	16	2.80	36	1.02	12	3.09	77	2.03	< 0.001
PCD	4	0.70	6	0.17	3	0.77	19	0.50	0.037
Pancreatic cancer									
Number	13	2.27	11	0.31	5	1.29	57	1.51	< 0.001
Subsequent pancreatic cancer after procedure	1	0.17	4	0.11	1	0.26	11	0.29	0.415
IRR (95% CI); *P* value	1.84(0.08–14.86)	0.582	Ref.	N/A	2.17 (0.09–17.29)	0.506	3.21 (1.06–11.66)	0.039	
Time to diagnosis of subsequent pancreatic cancer (month)	8.09	N/A	59.41	15.56	40.5	N/A	29.70	21.98	0.091

CCY, cholecystectomy; CI, confidence interval; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CP, chronic pancreatitis; DM, diabetes mellitus; ES, endoscopic sphincterotomy; ESRD, end-stage renal disease; EPBD, endoscopic papillary balloon dilatation; HP, *Helicobacter pylori* infection; IRR, incidence rate ratio; N/A, not applicable; PCD, pancreatic cystic disease; SD, standard deviation.

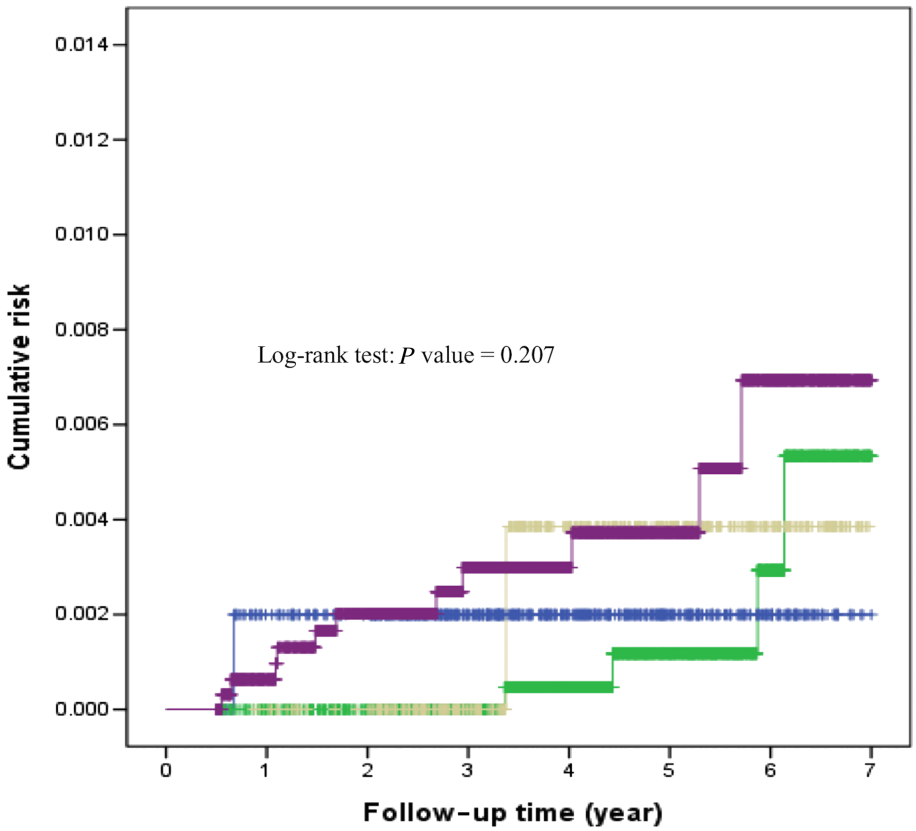

Figure 3 Cumulative risk of subsequent pancreatic cancer in the endoscopic sphincterotomy/endoscopic papillary balloon dilatation (ES/EPBD), cholecystectomy (CCY), ES/EPBD and CCY, and no-intervention groups (, cholelithiasis underwent ES/EPBD; , cholelithiasis underwent CCY; , cholelithiasis underwent ES/EPBD and CCY; , cholelithiasis underwent intervention).

did not.[40,41] Alcohol consumption, rather than more severe conditions such as CP, was adjusted in most of these studies; however, we choose to adjust for CP and PCD in our study design. Some recent studies (including our study) did not adjust for body mass index[42–44] due to the limitations of data or study design. Thus, we believe that our results can reflect the current condition in this topic.

Because previous known risk factors of pancreatic cancer, such as CHB, CHC, DM, and HP, are higher in the cholelithiasis group, the increased risk of pancreatic cancer may be confounded by these factors. We performed a multivariate analysis to compare these risk factors in order to identify the most important ones for pancreatic cancer, because we cannot adjust all the risk factors to establish control group initially. The results revealed that old age, symptomatic cholelithiasis (odds ratio 9.971 [4.793–20.744], $P < 0.001$), and DM were significant risk factors for pancreatic cancer after adjusting for CP and PCD. Symptomatic cholelithiasis was the most important risk factor for pancreatic cancer in both the cholelithiasis and control groups (details are shown in Table 4).

We defined pancreatic cancer diagnosed at least 6 months after the index admission or management procedure (ES/EPBD/CCY) date as subsequent pancreatic cancer to exclude the possibility of concurrent pancreatic cancer. Comparisons of the four subgroups in the cholelithiasis group revealed that the subsequent pancreatic cancer risk was only significantly higher in the no-intervention group compared with the risk in the CCY group (IRR 3.21, 95% CI: 1.06–11.66, $P = 0.039$). This is because the chronic inflammatory process in the bile ducts without adequate treatment, no matter reasons, may lead to increased subsequent pancreatic cancer risk. The different invasive procedures for cholelithiasis treatment therefore do not appear to affect the subsequent pancreatic cancer risk, according to our analysis. The effects of ES for cholelithiasis in subsequent pancreatic cancer risk was ever discussed in western society, which showed that the patients who accept ES had higher malignancy risk in the bile ducts, liver, and pancreas.[45] Patient who had further CCY decreased the malignancy risk. This evidence, combined with our findings, demonstrates that the true risk of malignancy in the pancreas in cholelithiasis patients comes from cholelithiasis itself rather than the relevant procedure.

The risk of subsequent pancreatic cancer in patients with cholelithiasis in the no-intervention group was significantly higher than the risk in the non-cholelithiasis control group, with an IRR of 8.07 (2.65–29.32). This is the only subgroup that had a significantly different risk of subsequent pancreatic cancer when compared with the control group with the IRR. This implies the importance of RBEs in the subsequent pancreatic cancer risk.

Our study has several limitations. First, because this was a retrospective, national cohort database study, no bodyweight, height, laboratory data results, smoking habits, alcohol use history, or clinical images could be tracked. Because of this, we were unable to

Table 3 Incidence of pancreatic cancer amount patient with cholelithiasis underwent ES/EPBD, cholecystectomy, ES/EPBD and cholecystectomy, or no intervention compared with normal population (excluding pancreatic cancer in the initial 6 months)

Variables	Person-years at risk in study cohort	Person-years at risk in control cohort	No. of observed cases of pancreatic cancer in study cohort	No. of observed cases of pancreatic cancer in control cohort	Incidence rate/1000 person-years (95% CI) in study cohort	Incidence rate/1000 person-years (95% CI) in control cohort	Incidence rate ratio (95% CI)	*P* value
ES/EPBD								
Total	1904.536	35 312.599	1	4	0.525 (0.007–2.921)	0.113 (0.030–0.290)	4.64 (0.19–36.90)	0.255
Gender								
Male	1041.741	17 977.378	0	3	0.000 (0.000–3.521)	0.167 (0.033–0.488)	0.00 (0.00–29.59)	0.845
Female	862.795	17 335.221	1	1	1.159 (0.015–6.448)	0.057 (0.000–0.321)	20.09 (0.52–783.6)	0.095
Cholecystectomy								
Total	14 046.555	35 312.599	4	4	0.285 (0.077–0.729)	0.113 (0.030–0.290)	2.51 (0.57–11.15)	0.214
Gender								
Male	6461.414	17 977.378	2	3	0.310 (0.035–1.117)	0.167 (0.033–0.488)	1.86 (0.22–12.47)	0.517
Female	7585.141	17 335.221	2	1	0.2637 (0.030–0.952)	0.057 (0.000–0.321)	4.57 (0.35–134.8)	0.250
ES/EPBD and cholecystectomy								
Total	1616.431	35 312.599	1	4	0.598 (0.030–2.950)	0.113 (0.030–0.290)	5.46 (0.22–43.48)	0.218
Gender								
Male	816.552	17 977.378	0	3	0.000 (0.000–0.000)	0.167 (0.033–0.488)	0.00 (0.00–37.74)	0.875
Female	799.879	17 335.221	1	1	1.250 (0.016–6.955)	0.057 (0.003–0.321)	21.67 (0.56–845.2)	0.088
No intervention								
Total	12 027.390	35 312.599	11	4	0.915 (0.456–1.636)	0.113 (0.030–0.290)	8.07 (2.65–29.32)	< 0.001
Gender								
Male	6285.307	17 977.378	4	3	0.636 (0.171–1.629)	0.167 (0.033–0.488)	3.81 (0.79–20.44)	0.094
Female	5742.083	17 335.221	7	1	1.219 (0.484–2.512)	0.057 (0.000–0.321)	21.13 (3.27–479.9)	< 0.001

CI, confidence interval; ES, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilatation.

Table 4 Multivariate analysis of risk factors for pancreatic cancer

	Pancreatic cancer		No pancreatic cancer		Univariate analysis		Multivariate analysis	
	N = 94		*N* = 16 436		OR (95% CI)	*P* value	OR (95% CI)	*P* value
	N	SD; %	*N*	SD; %				
Age, mean (SD)	70.09	15.02	61.48	17.14	1.033 (1.019–1.047)	< 0.001	1.033 (1.019–1.048)	< 0.001
Gender								
Male	44	46.81	8428	51.28	0.836 (0.557–1.255)	0.388	0.832 (0.553–1.253)	0.380
Cholelithiasis	86	91.49	8179	49.76	10.853 (5.256–22.410)	< 0.001	9.971 (4.793–20.744)	< 0.001
CHB	10	10.64	967	5.88	1.904 (0.985–3.680)	0.055	1.724 (0.876–3.394)	0.115
CHC	4	4.26	784	4.77	0.887 (0.325–2.422)	0.815	0.525 (0.190–1.450)	0.214
HP	3	3.19	177	1.08	3.028 (0.950–9.656)	0.061	2.465 (0.765–7.939)	0.131
DM	42	44.68	4078	24.81	2.448 (1.627–3.681)	< 0.001	1.532 (1.010–2.325)	0.045
ESRD	1	1.06	337	2.05	0.514 (0.071–3.696)	0.508	0.291 (0.040–2.109)	0.222

CI, confidence interval; CHB, chronic hepatitis B; CHC, chronic hepatitis C; DM, diabetes mellitus; ESRD, end-stage renal disease; HP, *Helicobacter pylori* infection; OR, odds ratio; SD, standard deviation.

include obesity, one of the known risk factors for pancreatic cancer, in the analysis. However, the innate characteristics of a national cohort database means that the selection avoids patient loss to follow-up and missed diagnoses of pancreatic cancer, even in patients who underwent treatment at different hospitals. In terms of the second limitation, the total number of patients with pancreatic cancer was 86 in the cholelithiasis group and 8 patients in the control group. However, subsequent pancreatic cancer only occurred in two patients (one in the ES/EPBD group and one in the ES/EPBD and CCY group), which makes statistically insignificance if we change the definition of subsequent pancreatic cancer from malignancy happened 6 months apart to 1 year apart in the no-intervention group. As a result, no-intervention group has higher subsequent pancreatic cancer risk than risk in CCY group, which is not a solid conclusion in our reports. In the future, prospective studies that are larger with longer observation periods are needed to evaluate the risks of procedure-related subsequent pancreatic cancer. A third limitation is that the cholelithiasis group had higher proportions of some pancreatic cancer risk factors, such as CHB, CHC, HP, and DM. Although CHC and ESRD[46] can be explained by common risk factors of cholelithiasis itself, CHB, HP, and DM may slightly affect the risk of pancreatic cancer between the cholelithiasis and control groups. For this reason, we have performed univariate and multivariate analyses on these risk factors of pancreatic cancer.

Conclusions

Symptomatic cholelithiasis patients were found to have an increased risk of pancreatic cancer compared with the control group. Risk of subsequent pancreatic cancer was similar between patients with cholelithiasis regardless of the intervention applied (ES/EPBD, CCY, and ES/EPBD and CCY).

Data availability statement. The datasets generated and analyzed during the current study are not publicly available as they were obtained from the National Health Insurance Research Database; however, data are partially available from the corresponding author on reasonable request.

References

1 Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS. National failure to operate on early stage pancreatic cancer. *Ann. Surg.* 2007; **246**: 173–80.
2 Allen PJ, Kuk D, Castillo CF *et al*. Multi-institutional validation study of the American Joint Commission on Cancer (8th edition) changes for T and N staging in patients with pancreatic adenocarcinoma. *Ann. Surg.* 2017; **265**: 185–91.
3 Canto MI, Harinck F, Hruban RH *et al*. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 2013; **62**: 339–47.
4 Schneider R, Slater EP, Sina M *et al*. German national case collection for familial pancreatic cancer (FaPaCa): ten years experience. *Fam. Cancer* 2011; **10**: 323–30.
5 Klein AP, Hruban RH, Brune KA, Petersen GM, Goggins M. Familial pancreatic cancer. *Cancer J.* 2001; **7**: 266–73.
6 Shindo K, Yu J, Suenaga M *et al*. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. *J. Clin. Oncol.* 2017; **35**: 3382–90.
7 Wolpin BM, Chan AT, Hartge P *et al*. ABO blood group and the risk of pancreatic cancer. *J. Natl. Cancer Inst.* 2009; **101**: 424–31.
8 Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. *Ann. Surg. Oncol.* 2014; **21**: 2453–62.
9 Bosetti C, Rosato V, Li D *et al*. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann. Oncol.* 2014; **25**: 2065–72.
10 Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas* 2013; **42**: 198–201.
11 Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int. J. Cancer* 1990; **45**: 816–20.
12 Lynch SM, Vrieling A, Lubin JH *et al*. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Am. J. Epidemiol.* 2009; **170**: 403–13.

13 Bosetti C, Lucenteforte E, Silverman DT *et al*. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann. Oncol.* 2012; **23**: 1880–8.
14 Duell EJ, Holly EA, Bracci PM, Liu M, Wiencke JK, Kelsey KT. A population-based, case-control study of polymorphisms in carcinogen-metabolizing genes, smoking, and pancreatic adenocarcinoma risk. *J. Natl. Cancer Inst.* 2002; **94**: 297–306.
15 Carreras-Torres R, Johansson M, Gaborieau V *et al*. The role of obesity, type 2 diabetes, and metabolic factors in pancreatic cancer: a Mendelian randomization study. *J. Natl. Cancer Inst.* 2017; **109**.
16 Aune D, Greenwood DC, Chan DS *et al*. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann. Oncol.* 2012; **23**: 843–52.
17 Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* 2001; **286**: 921–9.
18 Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer–viewpoint of the IARC working group. *N. Engl. J. Med.* 2016; **375**: 794–8.
19 Hassan MM, Li D, El-Deeb AS *et al*. Association between hepatitis B virus and pancreatic cancer. *J. Clin. Oncol.* 2008; **26**: 4557–62.
20 Huang J, Magnusson M, Torner A, Ye W, Duberg AS. Risk of pancreatic cancer among individuals with hepatitis C or hepatitis B virus infection: a nationwide study in Sweden. *Br. J. Cancer* 2013; **109**: 2917–23.
21 Mahale P, Torres HA, Kramer JR *et al*. Hepatitis C virus infection and the risk of cancer among elderly US adults: a registry-based case–control study. *Cancer* 2017; **123**: 1202–11.
22 Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ *et al*. *Helicobacter pylori* seropositivity as a risk factor for pancreatic cancer. *J. Natl. Cancer Inst.* 2001; **93**: 937–41.
23 Raderer M, Wrba F, Kornek G *et al*. Association between *Helicobacter pylori* infection and pancreatic cancer. *Oncology* 1998; **55**: 16–9.
24 Trikudanathan G, Philip A, Dasanu CA, Baker WL. Association between *Helicobacter pylori* infection and pancreatic cancer. A cumulative meta-analysis. *JOP* 2011; **12**: 26–31.
25 Duell EJ, Lucenteforte E, Olson SH *et al*. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann. Oncol.* 2012; **23**: 2964–70.
26 Bang UC, Benfield T, Hyldstrup L, Bendtsen F, Beck Jensen JE. Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study. *Gastroenterology* 2014; **146**: 989–94.
27 Pergolini I, Sahora K, Ferrone CR *et al*. Long-term risk of pancreatic malignancy in patients with branch duct intraductal papillary mucinous neoplasm in a referral center. *Gastroenterology* 2017; **153**: 1284–94 e1.
28 Tanaka M. Controversies in the management of pancreatic IPMN. *Nat. Rev. Gastroenterol. Hepatol.* 2011; **8**: 56–60.
29 Fan Y, Hu J, Feng B *et al*. Increased risk of pancreatic cancer related to gallstones and cholecystectomy: a systematic review and meta-analysis. *Pancreas* 2016; **45**: 503–9.
30 Gong Y, Li S, Tang Y *et al*. Cholelithiasis and risk of pancreatic cancer: systematic review and meta-analysis of 21 observational studies. *Cancer Causes Control* 2014; **25**: 1543–51.
31 Schernhammer ES, Michaud DS, Leitzmann MF, Giovannucci E, Colditz GA, Fuchs CS. Gallstones, cholecystectomy, and the risk for developing pancreatic cancer. *Br. J. Cancer* 2002; **86**: 1081–4.
32 Cai H, Kong WT, Chen CB *et al*. Cholelithiasis and the risk of intrahepatic cholangiocarcinoma: a meta-analysis of observational studies. *BMC Cancer* 2015; **15**: 831.
33 Wang CC, Tsai MC, Sung WW *et al*. Risk of cholangiocarcinoma in patients undergoing therapeutic endoscopic retrograde cholangiopancreatography or cholecystectomy: a population based study. *World J. Gastrointest. Oncol.* 2019; **11**: 238–49.
34 Wang CC, Tsai MC, Wang YT *et al*. Role of cholecystectomy in choledocholithiasis patients underwent endoscopic retrograde cholangiopancreatography. *Sci. Rep.* 2019; **9**: 2168.
35 Dean AGSK, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. updated 2013/04/06, accessed 2018/01/06.
36 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**: 860–6.
37 Bansal P, Sonnenberg A. Comorbid occurrence of cholelithiasis and gastrointestinal cancer. *Eur. J. Gastroenterol. Hepatol.* 1996; **8**: 985–8.
38 Tavani A, Rosato V, Di Palma F *et al*. History of cholelithiasis and cancer risk in a network of case–control studies. *Ann. Oncol.* 2012; **23**: 2173–8.
39 Chen YK, Yeh JH, Lin CL *et al*. Cancer risk in patients with cholelithiasis and after cholecystectomy: a nationwide cohort study. *J. Gastroenterol.* 2014; **49**: 923–31.
40 Johansen C, Chow WH, Jorgensen T, Mellemkjaer L, Engholm G, Olsen JH. Risk of colorectal cancer and other cancers in patients with gall stones. *Gut* 1996; **39**: 439–43.
41 Lin Y, Tamakoshi A, Kawamura T *et al*. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. *Int. J. Cancer* 2002; **99**: 742–6.
42 Nogueira L, Freedman ND, Engels EA, Warren JL, Castro F, Koshiol J. Gallstones, cholecystectomy, and risk of digestive system cancers. *Am. J. Epidemiol.* 2014; **179**: 731–9.
43 Zhang J, Prizment AE, Dhakal IB, Anderson KE. Cholecystectomy, gallstones, tonsillectomy, and pancreatic cancer risk: a population-based case-control study in Minnesota. *Br. J. Cancer* 2014; **110**: 2348–53.
44 Lai HC, Tsai IJ, Chen PC *et al*. Gallstones, a cholecystectomy, chronic pancreatitis, and the risk of subsequent pancreatic cancer in diabetic patients: a population-based cohort study. *J. Gastroenterol.* 2013; **48**: 721–7.
45 Stromberg C, Luo J, Enochsson L, Arnelo U, Nilsson M. Endoscopic sphincterotomy and risk of malignancy in the bile ducts, liver, and pancreas. *Clin. Gastroenterol. Hepatol.* 2008; **6**: 1049–53.
46 Genctoy G, Ayidaga S, Ergun T, Lakadamyali H, Erbayrak M, Sezer S. Increased frequency of gallbladder stone and related parameters in hemodialysis patients. *Turk. J. Gastroenterol.* 2014; **25**: 54–8.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Supporting information.