

Table S1. Association between exposure or outcome variable and comorbidities^a

	Comorbidity				
	Diabetes	Viral hepatitis	Liver cirrhosis	Fatty liver disease	Clonorchis sinensis
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Exposure variable					
Gallstone	2.33 (2.26-3.40)	2.05 (1.91-2.20)	4.65 (4.20-5.14)	2.40 (2.30-2.52)	0.83 (0.39-1.77)
Cholecystectomy	2.01 (1.91-2.12)	1.74 (1.53-1.97)	2.32 (1.88-2.88)	1.93 (1.78-2.10)	0.70 (0.17-2.81)
Outcome variable					
HBPC	1.39 (1.32-1.64)	3.64 (3.33-3.98)	13.17 (12.15-14.28)	2.34 (1.47-1.73)	1.59 (0.77-7.41)
Liver cancer	1.45 (1.36-1.54)	4.98 (4.53-5.48)	19.04 (17.48-20.74)	1.72 (1.56-1.89)	3.61 (1.17-11.16)
IBDC	1.20 (0.99-1.43)	1.38 (0.83-2.31)	1.23 (0.51-2.95)	1.97 (1.50-2.60)	11.34 (1.60-80.56)
Biliary tract cancer	1.12 (0.98-1.28)	1.37 (0.94-1.99)	2.57 (1.63-4.04)	1.22 (0.95-1.56)	-
EBDC	1.16 (0.91-1.47)	1.31 (0.65-2.65)	3.00 (1.52-6.35)	1.33 (0.86-2.05)	-
GBC	1.21 (1.03-1.50)	1.59 (0.95-2.65)	1.23 (0.46-3.28)	1.19 (0.83-1.72)	-
AOVC	0.93 (0.61-1.40)	1.68 (0.62-4.56)	1.11 (0.16-7.94)	0.91 (0.40-2.06)	-
Pancreatic cancer	1.45 (1.30-1.62)	0.98 (0.67-1.42)	2.44 (1.63-3.65)	1.45 (1.19-1.76)	-

HBPC, hepatobiliary and pancreatic cancer; IBDC, intrahepatic bile duct cancer; EBDC, extrahepatic bile duct cancer; GBC, gallbladder cancer, AOVC, ampulla of Vater cancer. ^aAdjusted for sex, age.

Table S2. HR of hepatobiliary and pancreatic cancer in the gallstone and cholecystectomy group by sex

Lag period	Person-years	Hepatobiliary and pancreatic cancer		Liver Cancer		Biliary tract cancer		Pancreatic cancer		
		Event	HR ^a (95% CI)	Event	HR ^a (95% CI)	Event	HR ^b (95% CI)	Event	HR ^c (95% CI)	
Gallstone										
Male										
No lag period	36,755	301	2.07 (1.79-2.39)	202	2.23 (1.89-2.63)	67	2.81 (1.97-3.99)	32	1.08 (0.67-1.75)	
1 year of lag	29,362	169	1.74 (1.47-2.06)	134	2.01 (1.66-2.43)	22	1.93 (1.22-3.06)	13	1.07 (0.36-1.34)	
3 year of lag	17,591	96	1.52 (1.22-1.90)	78	1.75 (1.36-2.25)	13	1.77 (0.97-3.22)	5	1.06 (0.26-1.48)	
5 year of lag	9,262	51	1.47 (1.09-1.98)	41	1.73 (1.24-2.41)	7	1.46 (0.60-3.52)	3	1.02 (0.22-2.07)	
Female										
No lag period	39,445	186	2.22 (1.84-2.68)	85	2.02 (1.57-2.61)	66	3.03 (2.08-4.41)	35	2.08 (1.38-3.13)	
1 year of lag	31,870	93	1.89 (1.51-2.35)	50	1.75 (1.30-2.35)	22	2.37 (1.50-3.75)	21	1.89 (1.18-3.01)	
3 year of lag	19,511	48	1.45 (1.07-1.97)	25	1.30 (0.86-1.97)	11	1.74 (0.90-3.37)	12	1.65 (0.88-3.08)	
5 year of lag	10,617	22	1.08 (0.61-1.59)	11	1.04 (0.43-1.61)	5	1.01 (0.33-3.15)	6	1.46 (0.61-3.53)	
Cholecystectomy										
Male										
No lag period	20,618	115	1.77 (1.44-2.18)	63	1.55 (1.18-2.03)	38	3.61 (2.40-5.44)	14	1.39 (0.79-2.46)	
1 year of lag	16,338	68	1.51 (1.17-1.93)	46	1.50 (1.11-2.03)	13	2.18 (1.23-3.87)	9	1.14 (0.57-2.28)	
3 year of lag	9,594	38	1.14 (0.80-1.63)	27	1.11 (0.72-1.73)	6	1.45 (0.60-3.51)	5	1.15 (0.48-2.78)	
5 year of lag	4,956	18	1.07 (0.66-1.76)	10	0.98 (0.53-1.82)	4	1.60 (0.51-4.98)	4	1.26 (0.41-3.91)	
Female										
No lag period	22,225	74	2.36 (1.81-3.08)	24	1.50 (0.95-2.36)	20	2.03 (1.08-3.78)	30	4.62 (3.14-6.78)	
1 year of lag	17,818	45	2.11 (1.55-2.87)	15	1.45 (0.87-2.42)	6	1.47 (0.66-3.29)	24	4.15 (2.66-6.48)	
3 year of lag	10,702	23	1.80 (1.18-2.74)	9	1.40 (0.73-2.70)	3	0.78 (0.19-3.11)	11	3.62 (1.99-6.57)	
5 year of lag	5,662	13	1.48 (0.80-2.77)	4	1.14 (0.43-3.04)	1	0.70 (0.10-4.96)	8	2.97 (1.23-7.16)	

HR, hazard ratio. ^aAdjusted diabetes, viral hepatitis, cirrhosis, fatty liver disease. ^bAjusted liver cirrhosis. ^cAdjusted diabetes, liver cirrhosis.

Table S3. HR of hepatobiliary and pancreatic cancer's subsite in the gallstone and cholecystectomy group by sex

Lag period	Person-years	Intrahepatic bile duct cancer		Gallbladder cancer		Extrahepatic bile duct cancer		Ampulla of Vater cancer	
		Event	HR ^a (95% CI)	Event	HR ^b (95% CI)	Event	HR ^c (95% CI)	Event	HR ^b (95% CI)
Gallstone									
Male									
No lag period	36,755	22	2.59 (1.61-4.17)	38	3.35 (2.01-5.58)	23	3.24 (1.84-5.71)	1	0.74 (0.10-5.29)
1 year of lag	29,362	17	2.80 (1.69-4.62)	10	1.98 (0.98-4.20)	9	2.70 (1.38-5.29)	1	0.91 (0.13-6.52)
3 year of lag	17,591	8	2.16 (0.97-3.37)	5	1.56 (0.58-4.20)	6	2.35 (0.96-5.72)	1	1.48 (0.21-10.66)
5 year of lag	9,262	6	2.93 (0.93-5.59)	2	0.71 (0.10-5.05)	3	1.67 (0.41-6.75)	1	1.70 (0.37-19.43)
Female									
No lag period	39,445	19	1.73 (0.86-3.51)	46	3.65 (2.26-5.88)	9	1.93 (0.79-4.72)	6	3.31 (1.03-10.58)
1 year of lag	31,870	8	1.84 (0.87-3.90)	15	3.41 (1.99-5.84)	2	0.46 (0.06-3.26)	2	2.65 (0.65-10.86)
3 year of lag	19,511	3	1.20 (0.39-3.76)	8	2.25 (0.99-5.04)	0	-	2	4.26 (1.04-17.46)
5 year of lag	10,617	3	2.12 (0.68-6.62)	3	1.31 (0.37-5.28)	0	-	1	3.34 (0.82-13.63)
Cholecystectomy									
Male									
No lag period	20,618	12	3.08 (1.73-5.49)	20	2.89 (1.43-5.86)	9	3.35 (1.69-6.62)	3	4.10 (0.29-13.04)
1 year of lag	16,338	11	3.14 (1.67-5.89)	4	1.76 (0.65-4.72)	6	2.18 (0.89-5.36)	2	3.34 (0.82-13.63)
3 year of lag	9,594	9	3.53 (1.67-7.47)	1	0.70 (0.10-4.99)	4	2.01 (0.63-6.37)	0	-
5 year of lag	4,956	5	4.61 (1.91-11.16)	0	-	3	2.29 (0.56-9.37)	0	-
Female									
No lag period	22,225	4	1.70 (0.63-4.55)	10	1.13 (0.36-3.53)	5	1.23 (0.30-5.01)	2	4.18 (0.02-17.12)
1 year of lag	17,818	4	2.06 (0.77-5.53)	3	1.38 (0.44-4.31)	0	-	2	5.11 (0.25-20.93)
3 year of lag	10,702	2	1.61 (0.40-6.47)	0	-	0	-	2	8.27 (0.02-33.90)
5 year of lag	5,662	2	2.88 (0.72-11.58)	0	-	0	-	1	7.32 (0.01-52.79)

HR, hazard ratio. ^aAdjusted fatty liver disease. ^bAdjusted diabetes. ^cAdjusted cirrhosis.

Table S4. Baseline characteristics according to history of cholelithiasis and cholecystectomy with medical check-up data

	Total	No-cholelithiasis	Cholelithiasis	<i>P</i> -value	Non-cholecystectomy	Cholecystectomy	<i>P</i> -value
Total	217,860 (30.9)	212,134 (97.4)	5,726 (2.6)		214,476 (98.5)	3,384 (1.6)	
Age (yr)	43.1 ± 13.7	43.0 ± 13.7	49.3 ± 13.6	0.1	43 ± 13.7	48 ± 13.7	< 0.01
Sex				0.61			0.6
Male	123,799 (56.8)	120,564 (56.8)	3,235 (56.5)		121,891 (56.8)	1,908 (56.4)	
Female	94,061 (43.2)	91,570 (43.2)	2,491 (43.5)		92,585 (43.2)	1,476 (43.6)	
Alcohol				< 0.01			< 0.01
Never	109,340 (50.2)	106,187 (50.9)	3,1543 (56.0)		107,465 (50.9)	1,875 (56.3)	
Current	105,012 (48.2)	102,531 (49.1)	2,481 (44.0)		103,556 (49.1)	1,456 (43.7)	
Smoking				< 0.01			< 0.01
Never	137,110 (62.9)	133,387 (64.3)	3,723 (66.4)		134,899 (64.3)	2,211 (66.8)	
Past	20,363 (9.4)	19,802 (9.5)	561 (10.0)		20,015 (9.5)	348 (10.5)	
Current	55,751 (25.6)	54,426 (26.2)	1,325 (23.6)		55,000 (26.2)	751 (22.7)	
BMI				0.02			< 0.01
≥ 25 kg/m ²	150,681 (69.2)	147,217 (69.4)	3,464 (60.5)		148,695 (69.4)	1,986 (58.7)	
< 25 kg/m ²	67,129 (30.8)	64,869 (30.6)	2,260 (39.5)		65,732 (30.7)	1,397 (41.3)	
Comorbidity							
Diabetes	24,319 (11.2)	23,176 (10.9)	1,143 (19.9)	< 0.01	23,676 (11.0)	645 (19.0)	< 0.01
Viral hepatitis	3,750 (1.7)	3,574 (1.7)	176 (3.1)	< 0.01	3,670 (1.7)	80 (2.4)	< 0.01
Cirrhosis	839 (0.4)	750 (0.4)	89 (1.6)	< 0.01	815 (0.4)	24 (0.7)	< 0.01
Fatty liver disease	9,026 (4.1)	8,586 (4.1)	440 (7.7)	< 0.01	8,779 (4.1)	247 (7.3)	< 0.01
Clonorchis sinensis	51 (0.0)	48 (0.0)	3 (0.1)	0.15	49 (0.0)	2 (0.1)	< 0.01

Values are presented as number (%) or mean ± SD. BMI, body mass index.

Table S5. HR of hepatobiliary and pancreatic cancer in the gallstone and cholecystectomy group with medical check-up data

Variable	Lag period	PY	Hepatobiliary and pancreatic cancer		Liver cancer		Biliary tract cancer		Pancreatic cancer	
			Event	HR ^a (95% CI)	Event	HR ^a (95% CI)	Event	HR ^b (95% CI)	Event	HR ^c (95% CI)
Gallstone										
	No lag period	26,273	157	1.97 (1.61-2.41)	82	1.86 (1.44-2.41)	49	3.04 (1.95-4.74)	26	1.71 (1.05-2.78)
	1 year of lag	21,253	86	1.67 (1.31-2.12)	54	1.61 (1.19-2.18)	18	2.61 (1.56-4.40)	14	1.33 (0.73-2.42)
	3 year of lag	13,008	49	1.54 (1.13-2.09)	31	1.63 (0.14-2.36)	12	2.42 (1.24-4.70)	6	0.76 (0.28-2.04)
	5 year of lag	7,027	24	1.43 (0.95-2.16)	16	1.51 (0.92-2.49)	5	1.89 (0.70-5.07)	3	1.01 (0.32-3.14)
Cholecystectomy										
	No lag period	14,805	55	1.52 (1.11-2.10)	23	1.19 (0.78-1.87)	22	3.01 (1.69-5.35)	10	1.49 (0.74-3.01)
	1 year of lag	11,808	28	1.19 (0.80-1.76)	16	1.07 (0.63-1.82)	7	2.12 (1.00-4.47)	5	0.91 (0.34-2.44)
	3 year of lag	7,015	15	0.82 (0.46-1.49)	11	0.96 (0.48-1.93)	4	1.45 (0.46-4.51)	0	-
	5 year of lag	3,668	4	0.53 (0.20-1.40)	3	0.63 (0.20-1.95)	1	0.88 (0.12-6.25)	0	-

HR, hazard ratio; PY, person-year. ^aAdjusted sex, alcohol consumption, cigarette smoking, body mass index (BMI), diabetes, viral hepatitis, cirrhosis, fatty liver disease. ^bAdjusted sex, alcohol consumption, cigarette smoking, BMI, diabetes, cirrhosis, fatty liver disease. ^cAdjusted sex, alcohol consumption, cigarette smoking, BMI, cirrhosis.

Table S6. HR of hepatobiliary and pancreatic cancer's subsite in the gallstone and cholecystectomy group with medical check-up data

Variable	Lag period	PY	Intrahepatic bile duct cancer		Gallbladder cancer		Extrahepatic bile duct cancer		Ampulla of Vater cancer	
			Event	HR ^a (95% CI)	Event	HR ^b (95% CI)	Event	HR ^c (95% CI)	Event	HR ^d (95% CI)
Gallstone										
	No lag period	26,273	9	1.60 (0.71-3.62)	30	3.72 (2.01-6.88)	12	2.24 (0.91-5.50)	4	3.45 (1.07-11.12)
	1 year of lag	21,253	5	1.29 (0.48-3.47)	10	3.28 (1.61-6.70)	3	1.60 (0.51-5.06)	3	4.16 (1.29-13.44)
	3 year of lag	13,008	2	1.00 (0.25-4.02)	5	1.89 (0.60-5.93)	3	1.67 (0.41-6.77)	3	6.55 (0.93-21.17)
	5 year of lag	7,027	2	1.74 (0.43-7.04)	1	1.13 (0.16-8.05)	1	1.48 (0.21-10.62)	2	3.94 (0.54-28.71)
Cholecystectomy										
	No lag period	14,805	5	2.49 (1.02-6.06)	13	2.82 (1.16-6.87)	5	3.31 (1.22-8.98)	1	2.00 (0.28-14.54)
	1 year of lag	11,808	4	2.43 (0.90-6.56)	3	2.04 (0.65-6.41)	3	3.01 (0.95-9.48)	1	2.45 (0.34-17.83)
	3 year of lag	7,015	4	1.93 (0.48-7.79)	1	1.09 (0.15-7.79)	2	1.59 (0.22-11.38)	1	4.02 (0.55-29.23)
	5 year of lag	3,668	2	3.49 (0.86-14.07)	0	-	1	2.93 (0.41-20.96)	0	-

HR, hazard ratio; PY person-year. ^aAdjusted sex, alcohol consumption, cigarette smoking, mass index (BMI), fatty liver disease. ^bAdjusted sex, alcohol consumption, cigarette smoking, BMI, diabetes. ^cAdjusted sex, alcohol consumption, cigarette smoking, BMI, cirrhosis. ^dAdjusted sex, alcohol consumption, cigarette smoking, BMI.

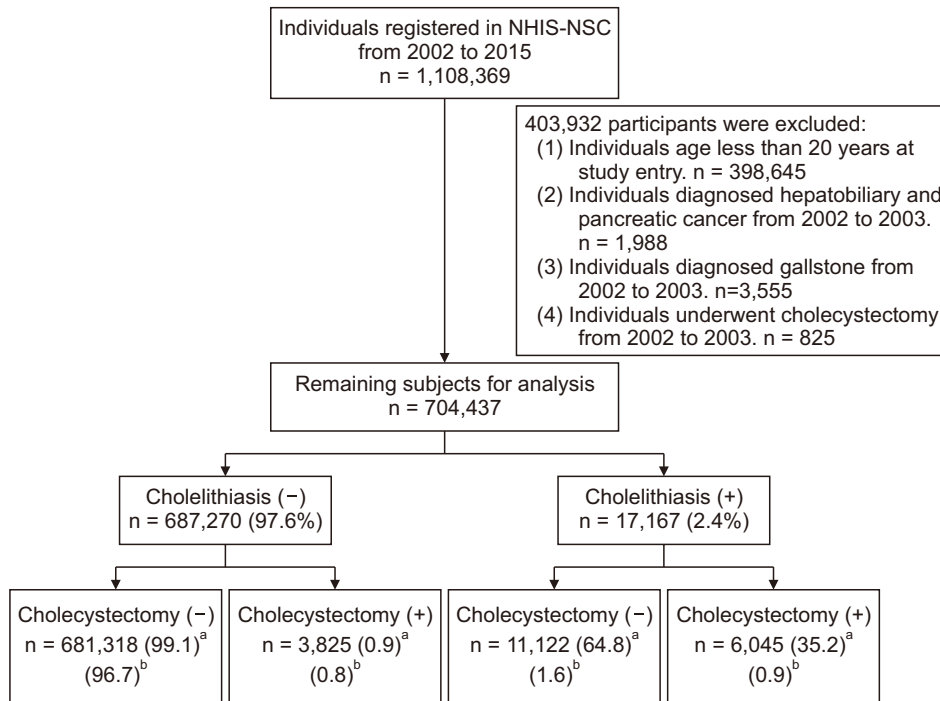
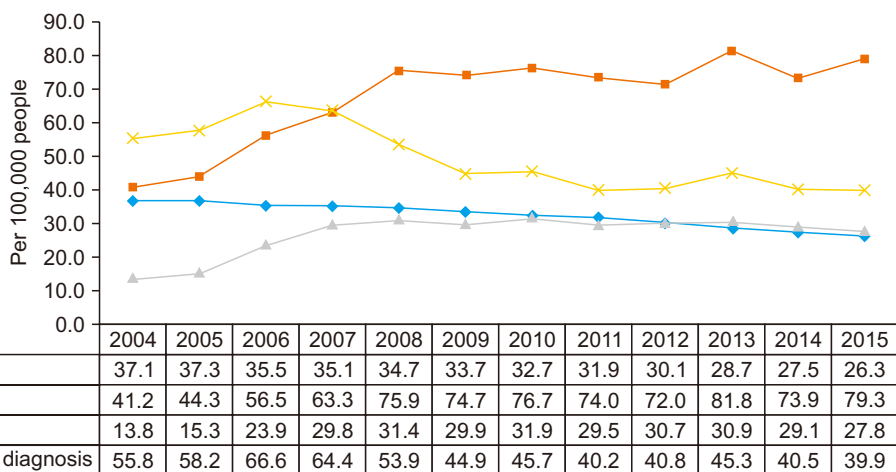
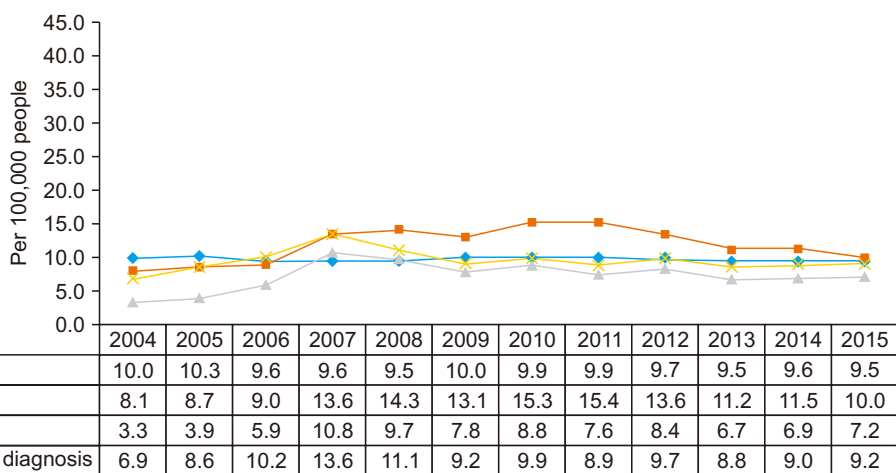


Figure S1. Selection of the study population. NHIS-NSC, National Health Insurance Service-National Sample Cohort. ^aPercentage in cholecystectomy group. ^bPercentage in corresponding.

A



B



C

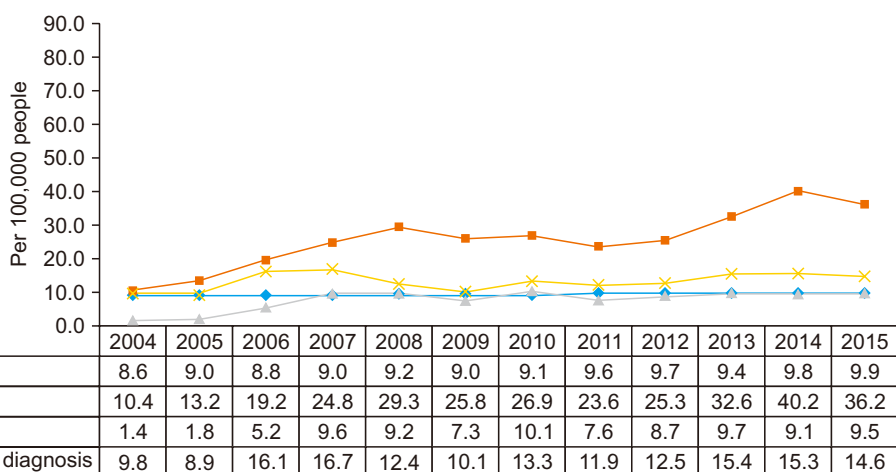


Figure S2. Truncated age-standardized incidence rate of hepatobiliary and pancreatic cancer among adults aged 20 years and older in the national cancer registry and defined in current study. (A) Liver cancer. (B) Biliary tract cancer. (C) Pancreatic cancer. Standard population: middle-year population of 2010.