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Original Article

Increased Risk of Cancer after Cholecystectomy: A Nationwide Cohort Study in Korea including 123,295 Patients

Yoon Jin Choi[1], Eun Hyo Jin[2], Joo Hyun Lim[2], Cheol Min Shin[3], Nayoung Kim[3,4], Kyungdo Han[5], and Dong Ho Lee[3,4]

[1]Department of Internal Medicine, Yonsei University College of Medicine, [2]Department of Internal Medicine, Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, [4]Department of Internal Medicine, Liver Research Institute, Seoul National University College of Medicine, and [5]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea

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Corresponding Author

Dong Ho Lee
ORCID https://orcid.org/0000-0002-6376-410X
E-mail dhljohn@yahoo.co.kr

Kyungdo Han
ORCID https://orcid.org/0000-0002-9622-0643
E-mail hkd917@naver.com

Background/Aims: Contradictory findings on the association between cholecystectomy and cancer have been reported. We aimed to investigate the risk of all types of cancers or site-specific cancers in patients who underwent cholecystectomy using a nationwide dataset.

Methods: Subjects who underwent cholecystectomy from January 1, 2007, to December 31, 2014, who were older than 20 years and who underwent an initial baseline health check-up within 2 years were enrolled. Those who were diagnosed with any type of cancer before the enrollment or within 1 year after enrollment were excluded. Ultimately, patients (n=123,295) who underwent cholecystectomy and age/sex matched population (n=123,295) were identified from the database of the Korean National Health Insurance Service. The hazard ratio (HR) and 95% confidence interval (CI) for cancer were estimated, and Cox regression analysis was performed.

Results: The incidence of cancer in the cholecystectomy group was 9.56 per 1,000 person-years and that in the control group was 7.95 per 1,000 person-years. Patients who underwent cholecystectomy showed an increased risk of total cancer (adjusted HR, 1.19; 95% CI, 1.15 to 1.24; p<0.001), particularly leukemia and malignancies of the colon, liver, pancreas, biliary tract, thyroid, pharynx, and oral cavity. In the subgroup analysis according to sex, the risk of developing cancers in the pancreas, biliary tract, thyroid, lungs and stomach was higher in men than in women.

Conclusions: Physicians should pay more attention to the possibility of the occurrence of secondary cancers among patients who undergo cholecystectomy. **(Gut Liver 2022;16:465-473)**

Key Words: Neoplasms; Cholecystectomy; Gallbladder; Incidence

INTRODUCTION

Cholecystectomy is the standard surgical procedure for gallstone removal from symptomatic patients.[1] The recent adoption of the laparoscopic approach for cholecystectomy has made cholecystectomy one of the most commonly performed operations worldwide. A total of 750,000 cholecystectomies are performed annually in the United States.[2] Western lifestyles and diets can contribute to the increase in the prevalence of gallstones.[3]

Gallbladder removal can lead to a more continuous flow of bile juice to the small bowel or colon. Cholecystectomy promotes the negative feedback of bile acid production from the liver.[4] The long-term medical consequences of cholecystectomy are not completely elucidated. An increasing body of literature has proposed that cholecystectomy may increase the risk of developing cancers, particularly neoplasm of the colon[5] and pancreas.[6] However, studies about the association between cholecystectomy and colon cancers have shown inconsistent findings. The reasons for such conflicting findings are the relatively small number of participants and short follow-up periods. In this study, we aimed to determine whether cholecystectomy is related to an increased risk of cancers of any site. We used a nation-

wide population-based registry dataset from the Korean National Health Insurance Service (NHIS), which enabled us to gain sufficient statistical power.

MATERIALS AND METHODS

1. Database

This retrospective cohort study relied on data from the Korean NHIS database. Approximately 97% of the Korean population is registered with the Korean NHIS, which is a single public health insurance program managed by the Korean government. The NHIS database contains beneficiary information, the eligibility database (age, sex, socioeconomic variables, type of eligibility, and income level), medical treatment database (based on the medical bills that were claimed by medical service providers for their medical expenses), and health examination database (blood pressure, height, weight, waist circumference, and values of serum fasting glucose and total cholesterol [mg/dL] and questionnaires on lifestyle and behavior).

Moreover, Korean researchers can use the NHIS database after approval by the official review committee. The present study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (IRB number: X-2003/601-904). Informed consent was waived because the study was based on routinely collected medical claims data.

2. Study population

The subjects who had undergone cholecystectomy from January 1, 2007 to December 31, 2014, who were older than 20 years and who had undergone an initial baseline health check-up within 2 years were enrolled in the study. The study population was followed until December 31, 2017 (end of the follow-up period) or censored at any cancer. Cholecystectomy operations were identified using corresponding insurance claims codes (Q7380). A total of 123,295 control subjects were 1:1 matched for age and sex with the 123,925 subjects who underwent cholecystectomy. The matched control participants were evaluated at the same time as each cholecystectomy group participant (index date). In both groups, patients with a diagnosis code for cancer before the index date were omitted to exclude subjects with a history of any cancer. Subjects who were diagnosed with cancers within 1 year after enrollment were excluded (1-year lag period).

Patients with cancer were diagnosed by medical doctors using specific international classification of disease (ICD)-10 codes and intractable and rare diseases (IRDs) codes: oral cavity (ICD-10 C00-C14), larynx (C32), esophagus (C15), stomach (C16), colon (C18), rectum (C19-20), liver (C22), biliary tract (C24), pancreas (C25), lung (C33-34), skin (C43), breast (C50), cervix uteri (C53), corpus uteri (C54), ovary (C56), prostate (C61), testis (C62), kidney (C64), bladder (C67), central nervous system (C70-72), thyroid (C73), non-Hodgkin lymphoma (C82-86), multiple myeloma (C90), and leukemia (C91-95).

3. Covariates

Age groups were classified using 10-year intervals, with a total of seven designated age groups. Lifestyle factors, such as smoking status or body mass index, were obtained from medical check-up data. These factors were identified based on the data available in the first 2-year data before surgery. Diabetes mellitus was defined based on claim for diabetes (E11-E14 and anti-diabetes medication) or fasting plasma glucose level ≥126 mg/dL. Hypertension was defined as claim for hypertension (I10-I15 and antihypertensive medication) or systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg. Dyslipidemia was defined based on at least one claim per year for E78 or lipid-lowering medication. We also analyzed the characteristics of the subjects undergoing cholecystectomy stratified according to sex.

4. Statistical analyses

We presented the basic characteristics of the study population using descriptive statistics. The chi-square test or Fisher exact test was used to compare age and comorbidities between the cholecystectomy and control groups as categorical variables. The incidence of cancer between the two groups was calculated per 1,000 person-years. We analyzed the hazard ratio (HR) and 95% confidence interval (CI) of cancer after cholecystectomy, and the Cox regression analysis was subsequently performed. The HR was adjusted for age, sex, smoking status, body mass index, hypertension, diabetes mellitus, and dyslipidemia. We also analyzed the characteristics of the subjects undergoing cholecystectomy stratified according to age group and sex. All statistical analyses were performed using the SAS version 9.4 software package (SAS Institute, Cary, NC, USA), and results with two-sided p-values of <0.05 were considered significant.

RESULTS

1. Characteristics of the study population

From the 471,602 cases undergoing cholecystectomy during 2007 to 2014, those who have not underwent the

baseline health check-up within 2 years before the surgery (n=323,214), those who were <20 years old (n=28) and those who were diagnosed with any type of cancer during the preceding years (n=21,999) were excluded. To clarify the temporal relationship, 3,066 patients who were diagnosed with cancers within 1 year after cholecystectomy were excluded. Finally, a total of 123,295 patients who underwent cholecystectomy and 123,295 matched comparison subjects were included in the analysis (Fig. 1). Their mean age was 52.79±13.21 years, and 54.02% of the study population was male. The cholecystectomy group had a lower proportion of current smokers and higher body mass index than the control group. The cholecystectomy group included a higher proportion of individuals with hypertension, diabetes mellitus or dyslipidemia than the control group (Table 1).

2. Cancer risk in patients who underwent cholecystectomy relative to the matched control group

In the total study population, the mean follow-up period after a 1-year lag of cholecystectomy was 4.59±2.44 years (4.58±2.44 years for the cholecystectomy group and 4.61±2.44 years for the control group). The maximum follow-up interval after cholecystectomy was 7 years.

The incidence of total combined cancers in the cholecystectomy group was 9.56 per 1,000 person-years and that in the control group was 7.95 per 1,000 person-years. The adjusted HR (aHR) for total combined cancers in the cholecystectomy group versus the control group was 1.19 (95% CI, 1.15 to 1.24; p<0.001) (Table 2, Fig. 2).

When we evaluated the risk for intestinal cancers according to the removal of the gallbladder or not, people

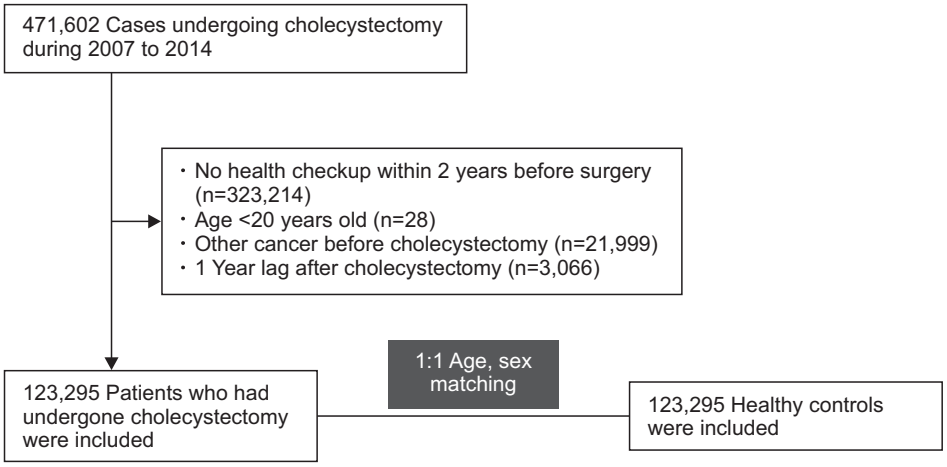

Fig. 1. Flowchart of the study population.

Table 1. Baseline Characteristics of the Study Participants from the Korean National Health Insurance Service

Variable	Healthy control (n=123,295)	Cholecystectomized patients (n=123,295)	p-value
Age, mean±SD, yr	52.79±13.21	52.79±13.21	NS
Age group, No. (%), yr			NS
20–29	3,874 (3.14)	3,874 (3.14)	
30–39	16,208 (13.15)	16,208 (13.15)	
40–49	30,478 (24.72)	30,478 (24.72)	
50–59	33,482 (27.16)	33,482 (27.16)	
60–69	23,481 (19.04)	23,481(19.04)	
70–79	13,509 (10.96)	13,509 (10.96)	
≥80	2,263 (1.84)	2,263 (1.84)	
Male sex, No. (%)	66,600 (54.02)	66,600 (54.02)	NS
BMI, mean±SD, kg/m^2	23.91±3.17	24.56±3.34	<0.001
Glucose, mean±SD, mg/dL	99.62±24.02	100.87±24.98	<0.001
Diabetes, No (%)	14,331 (11.62)	18,888 (15.32)	<0.001
Smoking status, No. (%)			<0.001
Non	75,968 (61.61)	75,309 (61.08)	
Ex-smoker	20,065 (16.27)	22,081 (17.91)	
Current	27,262 (22.11)	25,905 (21.01)	

BMI, body mass index; NS, not significant.

Table 2. Incidences and Adjusted Hazard Ratios of All 23 Cancers and Site-Specific Cancers

Cancer type	Cholecystectomy	No.	Event	Duration*	IR†	HR (95% CI)‡
All-site cancer	No	123,295	4,512	567,857	7.95	1 (reference)
	Yes	123,295	5,397	564,814	9.56	1.19 (1.15–1.24)
Oral cavity	No	123,295	58	578,377	0.10	1 (reference)
	Yes	123,295	99	577,830	0.17	1.76 (1.27–2.43)
Larynx	No	123,295	28	578,459	0.05	1 (reference)
	Yes	123,295	41	577,937	0.07	1.50 (0.92–2.43)
Esophagus	No	123,295	71	578,411	0.12	1 (reference)
	Yes	123,295	61	577,928	0.11	0.93 (0.66–1.31)
Stomach	No	123,295	724	576,758	1.26	1 (reference)
	Yes	123,295	800	575,910	1.39	1.10 (0.99–1.22)
Colon	No	123,295	690	576,914	1.20	1 (reference)
	Yes	123,295	777	576,026	1.35	1.11 (1.00–1.23)
Rectum	No	123,295	313	577,697	0.54	1 (reference)
	Yes	123,295	301	577,251	0.52	0.94 (0.81–1.11)
Liver	No	123,295	456	577,835	0.79	1 (reference)
	Yes	123,295	747	576,759	1.30	1.60 (1.42–1.80)
Biliary tracks	No	123,295	180	578,304	0.31	1 (reference)
	Yes	123,295	273	577,601	0.47	1.50 (1.24–1.82)
Pancreas	No	123,295	376	577,945	0.65	1 (reference)
	Yes	123,295	469	577,234	0.81	1.22 (1.07–1.40)
Lung	No	123,295	658	577,578	1.14	1 (reference)
	Yes	123,295	707	576,993	1.23	1.13 (1.02–1.26)
Skin	No	123,295	13	578,502	0.02	1 (reference)
	Yes	123,295	24	578,003	0.04	1.77 (0.90–3.48)
Breast	No	56,695	362	264,731	1.37	1 (reference)
	Yes	56,695	422	264,569	1.60	1.14 (0.99–1.31)
Cervix uteri	No	56,695	79	265,535	0.30	1 (reference)
	Yes	56,695	67	265,542	0.25	0.84 (0.60–1.16)
Corpus uteri	No	56,695	57	265,564	0.21	1 (reference)
	Yes	56,695	62	265,541	0.23	1.00 (0.69–1.44)
Ovary	No	56,695	100	265,528	0.38	1 (reference)
	Yes	56,695	87	265,542	0.33	0.85 (0.63–1.13)
Prostate	No	66,600	444	311,753	1.42	1 (reference)
	Yes	66,600	477	311,236	1.53	1.05 (0.92–1.20)
Testes	No	66,600	17	312,767	0.05	1 (reference)
	Yes	66,600	8	312,336	0.03	0.44 (0.19–1.03)
Kidney	No	123,295	122	578,252	0.21	1 (reference)
	Yes	123,295	103	577,814	0.18	0.80 (0.62–1.04)
Bladder	No	123,295	158	578,136	0.27	1 (reference)
	Yes	123,295	178	577,670	0.31	1.13 (0.91–1.40)
CNS	No	123,295	80	578,440	0.14	1 (reference)
	Yes	123,295	75	577,940	0.13	0.95 (0.69–1.30)
Thyroid	No	123,295	537	576,641	0.93	1 (reference)
	Yes	123,295	813	575,237	1.41	1.47 (1.31–1.64)
NHL	No	123,295	106	578,293	0.18	1 (reference)
	Yes	123,295	110	577,821	0.19	1.02 (0.78–1.33)
MM	No	123,295	48	578,448	0.08	1 (reference)
	Yes	123,295	59	577,968	0.10	1.21 (0.82–1.77)
Leukemia	No	123,295	64	578,430	0.11	1 (reference)
	Yes	123,295	96	577,914	0.17	1.46 (1.06–2.01)

IR, incidence rate; HR, hazard ratio; CI, confidence interval; CNS, central nervous system; NHL, non-Hodgkin lymphoma; MM, multiple myeloma.
*Person-years; †Per 1,000 person-years; ‡Adjusted for age, sex, diabetes, body mass index, and current smoking.

who underwent cholecystectomy had an increased HR for developing malignancy in the colon, liver, pancreas and biliary tracks (colon cancer aHR, 1.11; 95% CI, 1.00 to 1.23; liver cancer aHR, 1.60; 95% CI, 1.42 to 1.80; pancreatic cancer aHR, 1.22; 95% CI, 1.07 to 1.40; and biliary tract cancer aHR, 1.50; 95% CI, 1.24 to 1.82). No significant associations were found between cholecystectomy and esophageal, gastric or rectal cancer (esophageal cancer aHR, 0.93; 95% CI, 0.66 to 1.31; gastric cancer aHR, 1.10; 95% CI, 0.99 to 1.22; and rectal cancer aHR, 0.94; 95% CI, 0.81 to 1.11).

With regard to non-gastrointestinal cancers, the risks for lung cancer, thyroid cancer, oral cancer and leukemia were increased among those who underwent cholecys-

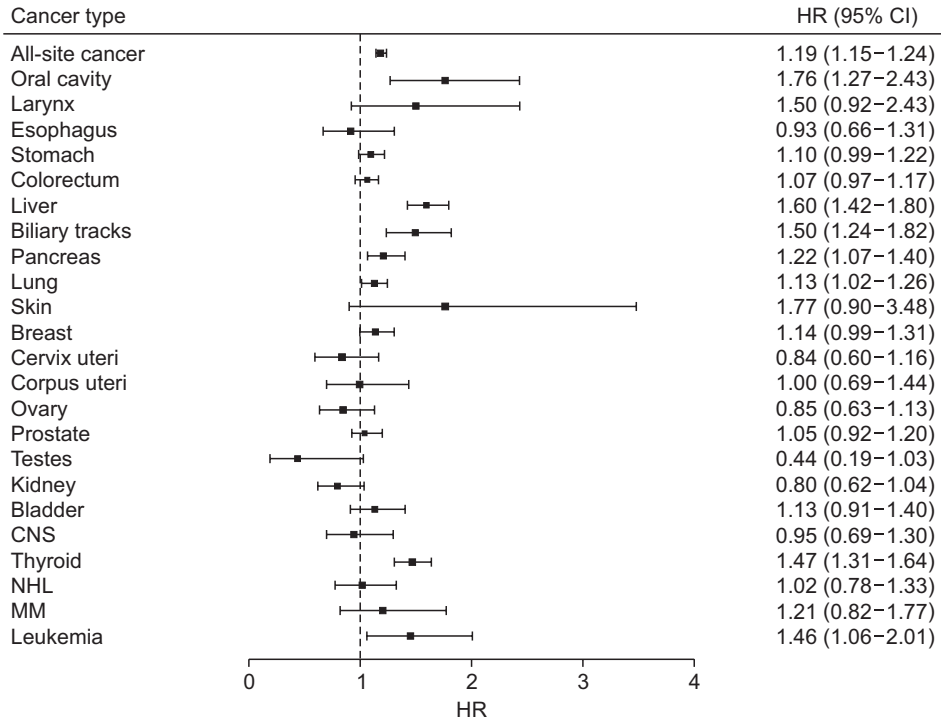

Fig. 2. Hazard ratios for the associations of cholecystectomy with all sites of cancers and site-specific cancers. HR, hazard ratio; CI, confidence interval; CNS, central nervous system; NHL, non-Hodgkin lymphoma; MM, multiple myeloma.

tectomy compared with non-cholecystectomized patients (lung cancer aHR, 1.13; 95% CI, 1.02 to 1.26; thyroid cancer aHR, 1.47; 95% CI, 1.31 to 1.64; oral cancer aHR, 1.76; 95% CI, 1.27 to 2.43; and leukemia aHR, 1.46; 95% CI, 1.06 to 2.01). Cancers in the breast, uterine cervix and corpus, prostate, larynx, testes, kidney, bladder, nerves and skin, lymphoma and multiple myeloma did not show significant associations with cholecystectomy (Fig. 2).

In order to secure a longer follow-up period, only those who underwent cholecystectomy between 2007 and 2009 were analyzed again. The mean follow-up period after a 1-year lag of cholecystectomy was 7.86±1.69 years. Despite the subgroup analysis, a history of cholecystectomy was associated with a similar trend in the risk of cancers (Supplementary Table 1).

3. Subgroup analysis by sex

According to sex, we calculated the aHR for cancers after cholecystectomy compared with the matched non-cholecystectomy group (Table 3). The male and female patients who underwent cholecystectomy showed aHR values of total combined cancers of 1.20 (95% CI, 1.14 to 1.26) and 1.18 (95% CI, 1.11 to 1.26), respectively, compared with each control group.

When the risk was evaluated according to specific sites, cancers in the liver, oral cavity and thyroid remained positively associated with cholecystectomy. However, the excessive risks for the development of cancers in the pancreas, biliary tract and lung among cholecystectomized persons were observed only in men, not in women (Table 3).

When the study populations were divided according to sex, no association was found between cholecystectomy and increased risk for leukemia, colon or rectal cancer regardless of sex. However, men showed an excessive risk for stomach cancer after cholecystectomy compared with men who did not undergo cholecystectomy (aHR, 1.17; 95% CI, 1.04 to 1.32).

DISCUSSION

This is one of the largest population-based cohort studies to examine the association between cholecystectomy and 24 types of cancers. The study results indicated that the incidence of cancer was higher in subjects who underwent cholecystectomy than those in the aged- and sex-matched control group (aHR, 1.19). Those who underwent cholecystectomy were likely to develop cancers in the colon, liver, pancreas, biliary tracts, oral cavity, thyroid and lung. Moreover, the excessive risk for these cancers was observed mostly in men than in women.

The following is the basis for research on the change in the risk of gastrointestinal cancer after cholecystectomy. Cholecystectomy changes bile flow[7] and increases bile salt exposure[8] to intestine. After cholecystectomy, 100% of the hepatic bile enters the duodenum.[9] During the enterohepatic circulation, anaerobic bacteria promote 7α-dehydroxylation of hydrophilic primary bile acids

Table 3. Incidences and Adjusted Hazard Ratios According to Sex

Cancer type	Cholecystectomy	Male (n=66,600)				Female (n=56,695)			
		Event	Duration*	IR†	HR (95% CI)‡	Event	Duration*	IR†	HR (95% CI)‡
All-site cancer	No	2,691	306,919	8.77	1 (reference)	1,821	260,938	6.98	1 (reference)
	Yes	3,209	304,915	10.52	1.20 (1.14–1.26)	2,188	259,899	8.42	1.18 (1.11–1.26)
Oral cavity	No	42	312,687	0.13	1 (reference)	16	265,691	0.06	1 (reference)
	Yes	67	312,207	0.21	1.69 (1.14–2.49)	32	265,623	0.12	1.94 (1.06–3.55)
Larynx	No	26	312,725	0.08	1 (reference)	2	265,734	0.01	1 (reference)
	Yes	41	312,238	0.13	1.61 (0.98–2.65)	0	265,699	0.00	0 (0.00–0.00)
Esophagus	No	68	312,679	0.22	1 (reference)	3	265,732	0.01	1 (reference)
	Yes	53	312,244	0.17	0.84 (0.59–1.21)	8	265,684	0.03	2.85 (0.75–10.79)
Stomach	No	524	311,495	1.68	1 (reference)	200	265,264	0.75	1 (reference)
	Yes	615	310,686	1.98	1.17 (1.04–1.32)	185	265,225	0.70	0.92 (0.75–1.13)
Colon	No	414	311,841	1.33	1 (reference)	276	265,072	1.04	1 (reference)
	Yes	476	311,050	1.53	1.13 (0.99–1.29)	301	264,976	1.14	1.07 (0.91–1.26)
Rectum	No	222	312,195	0.71	1 (reference)	91	265,501	0.34	1 (reference)
	Yes	213	311,781	0.68	0.93 (0.77–1.13)	88	265,470	0.33	0.96 (0.72–1.30)
Liver	No	333	312,297	1.07	1 (reference)	123	265,538	0.46	1 (reference)
	Yes	542	311,390	1.74	1.59 (1.39–1.83)	205	265,369	0.77	1.63 (1.30–2.04)
Biliary track	No	106	312,662	0.34	1 (reference)	74	265,643	0.28	1 (reference)
	Yes	175	312,056	0.56	1.65 (1.30–2.11)	98	265,545	0.37	1.30 (0.96–1.75)
Pancreas	No	238	312,415	0.76	1 (reference)	138	265,530	0.52	1 (reference)
	Yes	315	311,806	1.01	1.31 (1.10–1.55)	154	265,428	0.58	1.09 (0.86–1.37)
Lung	No	490	312,132	1.57	1 (reference)	168	265,447	0.63	1 (reference)
	Yes	540	311,582	1.73	1.19 (1.05–1.34)	167	265,412	0.63	0.98 (0.79–1.22)
Skin	No	8	312,784	0.03	1 (reference)	5	265,718	0.02	1 (reference)
	Yes	13	312,323	0.04	1.61 (0.66–3.90)	11	265,680	0.04	2.05 (0.71–5.94)
Kidney	No	92	312,596	0.29	1 (reference)	30	265,657	0.11	1 (reference)
	Yes	71	312,205	0.23	0.73 (0.54–1.00)	32	265,609	0.12	1.01 (0.61–1.67)
Bladder	No	125	312,458	0.40	1 (reference)	33	265,677	0.12	1 (reference)
	Yes	145	312,035	0.46	1.17 (0.92–1.49)	33	265,635	0.12	0.98 (0.61–1.60)
CNS	No	50	312,742	0.16	1 (reference)	30	265,698	0.11	1 (reference)
	Yes	39	312,305	0.12	0.83 (0.54–1.26)	36	265,634	0.14	1.14 (0.70–1.86)
Thyroid	No	141	312,364	0.45	1 (reference)	396	264,276	1.50	1 (reference)
	Yes	238	311,589	0.76	1.63 (1.33–2.02)	575	263,648	2.18	1.41 (1.24–1.61)
NHL	No	62	312,647	0.20	1 (reference)	44	265,645	0.17	1 (reference)
	Yes	68	312,209	0.22	1.09 (0.77–1.54)	42	265,612	0.16	0.94 (0.61–1.44)
MM	No	30	312,747	0.10	1 (reference)	18	265,702	0.07	1 (reference)
	Yes	44	312,296	0.14	1.43 (0.89–2.28)	15	265,672	0.06	0.82 (0.41–1.64)
Leukemia	No	36	312,736	0.12	1 (reference)	28	265,694	0.11	1 (reference)
	Yes	56	312,265	0.18	1.51 (0.99–2.30)	40	265,649	0.15	1.41 (0.87–2.30)

IR, incidence rate; HR, hazard ratio; CI, confidence interval; CNS, central nervous system; NHL, non-Hodgkin lymphoma; MM, multiple myeloma.
*Person-years; †Per 1,000 person-years; ‡Adjusted for age, sex, diabetes, body mass index, and current smoking.

converting them into hydrophobic secondary bile acids, deoxycholic acid and lithocholic acid. Depending on the concentration, hydrophobic secondary bile acids can cause cholestasis or encourage apoptosis and DNA damage.[10] Moreover, deoxycholic acid has carcinogenic and mutagenic properties.[11,12]

First, studies on the relationship between cholecystectomy and cancer risk have been conducted most frequently in colorectal cancer. Except for some studies,[13,14] most researches have reported the consistent findings that cholecystectomy increases the risk of colon cancer, but is not related to the risk of rectal cancer. A meta-analysis of 10 cohort studies has recently reported an increased risk for colon cancer up to 30% compared with the non-cholecystectomized group.[5] Studies that were previously had published as having no association between cholecystectomy and colorectal cancer also showed similar trends, when colon was divided into colon and rectum.[15-17]

The reason for this discrepancy in the effect of cholecystectomy even on one organ has been often explained by the reduced amount of bile flow according to increasing distance from the common bile duct. For instance, A Swedish nationwide cohort study showed that the risk remains for adenocarcinoma and carcinoids of the small bowel, and

right-sided colon cancer, but not distal bowel cancer.[18] This difference might be the expression of molecular and biological differences between colon and rectal cancer.[19]

According to the bile exposure-theory, the increased bile flow into the duodenum can flow backward to the stomach and esophagus. One large U.S. case-control study including 1 million cancer cases reported that gallstones and cholecystectomy are associated with increased risk for noncardiac gastric cancer but not for esophageal squamous-cell carcinoma, esophageal adenocarcinoma or gastric cardia adenocarcinoma,[15] which are consistent with the results of the present study.

Meanwhile, although the hepatobiliary tract, as well as gastrointestinal systems is part of the digestive system, it is difficult to explain with the increasing bile exposure-hypothesis. The findings of the relationship between cholecystectomy and cancers in the hepatobiliary system are also contradictory.[20] Moreover, aside from pancreatic cancers, other cancers have not been investigated thoroughly. A previous U.S. study reported that cholecystectomy is associated with increased risks for pancreatic cancer, hepatocellular carcinoma and cholangiocarcinoma.[15] Some animal studies have reported that secondary bile acids or metabolites may have a carcinogenic effect in the liver,[21] and pancreas.[22] On the other hand, gallstones are strongly associated with an increased development of extrahepatic cancers.[23,24] Given that calculus cholecystitis is the leading cause of cholecystectomy,[25] similar epidemiologic features shared by cholelithiasis and neoplasm of biliary tract or liver cancers. Several papers have reported that cholelithiasis itself, not cholecystectomy, increases the risk of cancer,[26,27] others showed gallstone was no association with cancer of the cecum or ascending colon.[18] Due to the inaccuracy of the operational definition of cholelithiasis using the claimed data, the present study did not analyze the relationship between carrying gallstone and cancer, but (female) sex, old age, and obesity, which are known risk factors for gallstone, were included as covariates.

Besides neoplasms of digestive tract, the present study showed those who underwent cholecystectomy were more likely to develop cancers in the thyroid, lung, oral cavity and pharynx or leukemia in the present study. To our knowledge, no studies have evaluated the association between cholecystectomy and these cancers.

As other mechanisms of increasing cancer incidence after cholecystectomy, other than direct exposure to bile, is altered metabolic or endocrine pathways. As described previously, bile acids are synthesized from cholesterol in the liver and further metabolized by the gut microbiota into secondary bile acids. Bile acid synthesis is under negative feedback control through activation of the nuclear receptor farnesoid X receptor in the ileum and liver.[28] Bile acids act important signaling molecules in the host. These signaling functions influence lipid and cholesterol metabolism, energy metabolism, immune homeostasis, and intestinal electrolyte balance. Bile acids can also modulate gut microbial composition.[29] In a recent study comparing the intestinal microbiota of the three groups of gallstone carriers, cholecystectomy-patients and normal subjects, cholecystectomy but not gallstone carrier status is associated with decreased beta-diversity along with a decrease in beneficial microorganisms and an increase in harmful microorganisms.[30]

This study has several limitations. Despite additional subgroup analysis, the relatively short follow-up period is a disadvantage. We could not rule out the possibility that the individuals who received cholecystectomy were more eager to undergo health screening than the matched control, leading to more diagnoses of cancers. Although this study used age- and sex-matched control group, confounding factors, such as infection, diet pattern or alcohol consumption, were not included for the control. Similar epidemiologic features shared by cholelithiasis, such as physical inactivity or over-nutrition, may contribute to the positive association between cholecystectomy and an increased development of the certain subtype of cancers. Although several studies have published results showing significant associations even when these variables are corrected,[31,32] ultimately, research is needed to find the mechanism.

The strengths of our study include the use of a large data set, which provided us good statistical power to investigate less common cancer sites. Our study also had high data quality because cancer diagnosis was double checked using IRDs codes. The diagnosis must be based on the IRD-defined diagnostic criteria provided by the national health insurance system and reviewed by the corresponding healthcare institution. The present research represents one of the few nationwide studies evaluating the risk for 24 different types of cancers after cholecystectomy with controlling for known common cancer risk factors.

The current study demonstrates an association between cholecystectomy and the subsequent risk of cancers in the colon, liver, pancreas, biliary tracts, thyroid, lung, pharynx and oral cavity and leukemia. The risk of developing cancers in the pancreas, biliary tracts, thyroid, lung and stomach is higher in men than in women. This study may recommend careful observation of other cancers that may develop following cholecystectomy. However, the results of this study require careful interpretation because the follow-up period is short and correction for all possible compounding factors is impossible. Further studies for true mechanism are warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study design: Y.J.C., D.H.L. Data handling and statistical analysis: K.H. Drafting the manuscript: Y.J.C. Revising a manuscript: E.H.J., J.H.L., C.M.S., N.K. Editing a manuscript: D.H.L. All authors approved the final version of the manuscript before submission.

ORCID

Yoon Jin Choi https://orcid.org/0000-0002-1922-9388
Eun Hyo Jin https://orcid.org/0000-0002-2126-3315
Joo Hyun Lim https://orcid.org/0000-0002-8437-096X
Cheol Min Shin https://orcid.org/0000-0003-2265-9845
Nayoung Kim https://orcid.org/0000-0002-9397-0406
Kyungdo Han https://orcid.org/0000-0002-9622-0643
Dong Ho Lee https://orcid.org/0000-0002-6376-410X

SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl210009.

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