의학석사 학위논문

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A population-based cohort study

담낭절제술 및 충수돌기절제술 후 대장암 발생위험 - 인구기반 코호트 연구

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이 논문을 의학석사 학위논문으로 제출함

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Abstract

The risk of colorectal cancer incidence after cholecystectomy or appendectomy: A population-based cohort study

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Introduction: Cholecystectomy and appendectomy are the most commonly performed general surgery techniques that are thought to be associated with colorectal cancer, but such associations have been controversial because of protopathic bias. In this study, we investigated the association between cholecystectomy or appendectomy and the

subsequent risk of colorectal cancer in the Korean population focusing on protopathic bias.

Methods: A retrospective cohort study was conducted using the National Health Insurance Service–National Sample Cohort (NHIS-NSC) of Korea; this cohort was followed up from January 1, 2002, until the date of colorectal cancer incidence, loss to follow up or until December 31, 2015. The exposure status of cholecystectomy and appendectomy was treated as a time-varying covariate. Cox proportional hazard regression models stratified by the follow-up time and applying different lag periods (0 to 5 years) after surgery were performed to investigate the association between cholecystectomy or appendectomy and the colorectal cancer incidence after adjusting for age, sex, and comorbidities such as diabetes mellitus and inflammatory bowel disease.

Results: In total, 707,663 individuals were included for analysis. The study population was followed up for an average of 13.66 years, and 4,324 incidental colorectal cancer cases were identified. The risk of colorectal cancer was increased in the first year of cholecystectomy (HR: 1.71; 95% CI: 1.01-2.89), but no association was shown thereafter. By considering the latency period after cholecystectomy, the hazard ratios of

colorectal cancer were 0.94 (95% CI: 0.70-1.24) without a lag period and 0.88 (95% CI: 0.54-1.44) with 5 years of lag. The risk of colorectal cancer was increased in the first three years after appendectomy. Within one year of appendectomy, the hazard ratio of colorectal cancer was 4.22 (95% CI: 2.87-6.20). When applying the latency period after appendectomy, the risk of colorectal cancer was elevated in a model without a lag period (HR: 1.44; 95% CI: 1.14-1.83) and was not associated in a model with a lag period (HR with one year of lag: 1.02; 95% CI: 0.76-1.38). The elevated risk of cancer within three years of appendectomy was more prominent in patients with colon cancer than in those with rectal cancer.

Conclusion: The risk of colorectal cancer was increased only in the first year of cholecystectomy, likely due to the protopathic bias that an early sign of colorectal cancer mimics a sign of gallbladder disease. After appendectomy, the risk of colorectal cancer was not associated after three years but was increased in the first three years and was prominent in colon cancer, implying that appendicitis as an early sign of colorectal cancer and appendectomy as a cause of colorectal cancer was less likely. The risk of colorectal cancer was not associated with cholecystectomy or appendectomy after

considering protopathic bias.

Keywords: Cholecystectomy; Appendectomy; Colorectal cancer; Causality; Cohort study

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Contents

List of Tables

List of Figures

Introduction

Epidemiology of colorectal cancer

Colorectal cancer is the third leading cancer worldwide, and its incidence and mortality vary with ethnicity as well as with geographic region (1-5). According to GLOBOCAN 2012 (2, 3), the age-standardized incidence rate of colorectal cancer was 20.6 per 100,000 in men and 14.3 per 100,000 in women, accounting for the third and second highest incidence rates, respectively, in 2012.

In Korea, colorectal cancer was the third most prevalent cancer with the third highest incidence rate in 2015 (6). The age-standardized incidence rate was 30.4 per 100,000 following thyroid and stomach cancer, and it rose by 6.0% annually from 1999 to 2010 and has been decreasing by 4.9% annually from 2010 (6). Stratified by sex, the age-standardized incidence rates were 40.2 per 100,000 and 22.2 per 100,000 in men and women, respectively (6).

Risk factors of colorectal cancer

There are well-established risk factors related to colorectal cancer (1). Age and sex are closely associated with the risk of colorectal cancer. The risk of colorectal cancer is increased by aging, and both the incidence and mortality are higher in men than in women.

Family history is a known risk factor of colorectal cancer. Individuals with a first-degree relative with colorectal cancer have a 1.72-fold elevated risk of colorectal cancer. If there were more family members that had first-degree relatives with colorectal cancer, the risk would be higher (7).

Inherited factors play a role in colorectal cancer progression (1). Individuals who have conditions of familiar adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) were reported to have an increased risk of colorectal cancer. Both FAP and HNPCC are caused by gene defects involving tumor progression.

Some medical conditions are known to be associated with colorectal cancer development. Diabetes mellitus is thought to increase colorectal cancer risk by high levels of insulin. Type 2 diabetes mellitus is due to insulin resistance, resulting in a high

level of insulin in the bloodstream. Insulin plays a role as a growth factor for colonic mucosa, so a high level of insulin can accelerate the growth of tumor cells in the colon (8).

Inflammation and colorectal cancer are well known for being closely related (9, 10). Particularly, the association between inflammatory bowel disease covering ulcerative colitis and Crohn's disease and colorectal cancer is well established (1, 11, 12). Furthermore, it is well known that the administration of anti-inflammatory drugs has a protective effect on colorectal cancer development (13).

Environmental factors known to increase the risk of colorectal cancer include smoking, heavy alcohol drinking, processed meat intake, low physical activity and obesity (1, 14).

Association between cholecystectomy/appendectomy and colorectal cancer

Cholecystectomy and appendectomy are two of the most commonly performed surgeries in Korea (15); these are performed under general anesthesia and involve the removal of an inflamed organ within the digestive tract. The association between these

surgeries and colorectal cancer has been of interest because of the possible mechanism.

Bile acid, which is synthesized in the liver and stored in the gall bladder, has been known to be carcinogenic for colorectal cancer (16-18). Following a cholecystectomy, bile acid could flow into the intestine continuously because of the lack of a bile reservoir. This could increase the exposure time between the intestinal mucosa and bile acid (19), leading an altered risk of colorectal cancer development.

The appendix is thought to have an immune function in the bowel (20). Because inflammation is considered a mechanism in the development of colorectal cancer (10, 21, 22), the risk of colorectal cancer can be changed after appendectomy.

In addition, surgery itself can depress the immune function in the colon, leading to increased susceptibility to colorectal cancer development (23).

Previous studies on the association between cholecystectomy/ appendectomy and colorectal cancer

Studies investigating the association between cholecystectomy and the risk of colorectal cancer have been reported continuously (Table 1) (24-34). Some of these studies have indicated a modest increased risk of colorectal cancer after cholecystectomy (27-29, 31, 34), but others have reported no association (25, 26, 30, 32, 33), and only one study reported a decreased risk (24).

The association between appendectomy and the risk of colorectal cancer has been studied, and an increased incidence of colorectal cancer after appendectomy was found (Table 2) (35-38). Only one study reported no association between appendectomy and colorectal cancer, but the risk increased with a shorter follow-up time (39).

Table 1. Previous studies investigating the association between cholecystectomy and the risk of colorectal cancer

Author (Year)	Study design	Number in the study population	Exposure	Outcome (Cancer subsite)	Results
Nogueira L (2014) (24)	Case-control	Case: 150,054 Control: 100,000	Cholecystectomy	Colorectal cancer	OR: 0.97 (0.92-1.02)
				Proximal colon cancer	OR: 1.06 (0.99-1.12)
				Distal colon cancer	OR: 0.93 (0.86-1.00)
				Rectal cancer	OR: 0.85 (0.78-0.92)
Shang J (2016) (25)	Case-control	Case: 5,847 Control: 4,970	Cholecystectomy	Colorectal cancer	OR: 0.88 (0.73-1.08)
Jørgensen T (1992) (26)	Cohort	5,347	Cholecystectomy	Colorectal cancer	OR: 0.87 (0.53-1.43)
			Gallstone	Colorectal cancer	OR: 1.59 (1.04-2.45)

Table 1. Continued

Author (Year)	Study design	Number in the study population	Exposure	Outcome (Cancer subsite)	Results
Schernhammer, E. S (2003) (27)	Cohort	85,184	Cholecystectomy	Colorectal cancer	RR: 1.19 (0.98-1.44)
				Colon cancer	RR: 1.17 (0.91-1.51)
				Rectal cancer	RR: 1.58 (1.05-2.36)
Shao T (2005) (28)	Cohort	Exposed: 55,960	Cholecystectomy	Colorectal cancer	HR: 1.32 (1.16-1.48)
		Unexposed: 574,668		Colon cancer	HR: 1.51 (1.30-1.74)
				Rectal cancer	HR: 1.00 (0.85-1.17)
Chen YK (2014) (29)	Cohort	Exposed: 15,545	Cholecystectomy	Colorectal cancer	HR: 1.56 (1.12-2.17)
		Unexposed: 62,180			

Table 1. Continued

Author (Year)	Study design	Number in the study population	Exposure	Outcome (Cancer subsite)	Results
Peng YC (2017) (30)	Cohort	Exposed: 525 Unexposed: 525	Cholecystectomy in IBD patients	Colorectal cancer	HR: 0.76 (0.25-2.32)
Giovannucci E (1993) (31)	Meta-analysis	38 studies	Cholecystectomy	Total	RR: 1.22 (1.08-1.38)
				Cohort	RR: 0.97 (0.82-1.14)
				Case-control	RR: 1.34 (1.14-1.57)
Zhao C (2012) (32)	Meta-analysis	10 studies	Cholecystectomy	Colorectal adenoma	RR: 1.17 (0.92-1.48)

*IBD: Inflammatory bowel disease.

Table 1. Continued

Author (Year)	Study design	Number in the study population	Exposure	Outcome (Cancer subsite)	Results
Chiong C (2012) (33)	Meta-analysis	42 studies	Cholecystectomy	Rectal cancer	OR: 1.14 (0.92-1.41)
			Cholelithiasis	Rectal cancer	OR: 1.33 (1.02-1.73)
Zhang Y (2017) (34)	Meta-analysis	10 studies	Cholecystectomy	Colorectal cancer	RR: 1.22 (1.08-1.38)
				Colon cancer	RR: 1.30 (1.07-1.58)
				Rectal cancer	RR: 1.09 (0.89-1.34)

Table 2. Previous studies investigating the association between appendectomy and the risk of colorectal cancer

Author (Year)	Study design	Number in the study population	Exposure	Outcome (Cancer subsite)	Results
Lai HW (2006) (35)	Case-control	1,873	Appendectomy	Colon cancer	OR: 38.5
Emre Ergul (2009) (36)	Case-control	Case: 455	Appendectomy	Rt. colon cancer	OR: 3.607 (2.056-6.330)
		Control: 166	Appendectomy	Lt. colon cancer	OR: 2.537 (1.544-4.168)
			Appendectomy	Rectal cancer	OR: 3.232 (1.670-6.254)
Wu SC (2015) (37)	Cohort	Exposed: 75,979	Appendectomy	Colorectal cancer	HR: 1.14 (1.02-1.28)
		Unexposed: 303,640			

Table 2. Continued

Author (Year)	Study design	Number in the study population	Exposure	Outcome (Cancer subsite)	Results
Wu SC (2015) (38)	Cohort	Exposed: 130,374	Appendectomy	Colorectal cancer	HR (Male): 16.8 (8.19-34.3)
		Unexposed: 260,746		Colorectal cancer	HR (Female): 12.3 (5.57-27.2)
Huan Song (2016) (39)	Cohort	480,382	Appendectomy	Colon cancer	SIR: 1.03 (0.99-1.07)
			Appendicitis	Colon cancer	SIR: 1.00 (0.95-1.06)

Objective of this study

In observational studies, the results with the presence of bias do not reflect true association (40, 41). Particularly, studies investigating the factors associated with cancer development need a long latency period because cancer requires time from exposure to develop (41-43). Protopathic bias, also called reverse causation, is a bias such that the exposure is a result of the early manifestation of the targeted disease (40). Thus, protopathic bias, which is the possibility that both cholecystectomy and appendectomy resulted from colorectal cancer, should be considered, and the latency period between these surgeries and colorectal cancer was needed in the analyses. However, such consideration was not properly managed, or the management differed from study to study. This bias in previous studies might explain the inconclusive results.

In this study, we investigated the association between cholecystectomy or appendectomy and the risk of subsequent colorectal cancer considering protopathic bias. First, we evaluated bias by considering the time after cholecystectomy and appendectomy. Additionally, we estimated the risk of colorectal cancer after cholecystectomy and appendectomy considering bias by applying the lag period.

Methods

Data source

National Health Insurance Service (NHIS) is a unique medical insurance claim system in Korea covering over 97% of the Korean population. This system provided a sample cohort from the National Health Insurance Service–National Sample Cohort (NHIS-NSC) for research purposes. The cohort comprises approximately one million individuals, accounting for 2% of randomly selected health insurance subscribers and Medicare recipients in Korea. The NHIS-NSC contains all medical resource utilization information such as surgery, drug prescriptions, and disease diagnoses from 2002 to 2015. It also contains demographic factors for each individual that included age, sex, residence, and medical insurance premiums. The NHIS-NSC also contains medical check-up data comprising questionnaires for the participants' medical conditions and laboratory results. The details of the cohort are mentioned elsewhere (44).

Identification of colorectal cancer

We identified colorectal cancer cases using the 10th International Classification of Disease (ICD-10). However, when we compared the age-standardized incidence rate of colorectal cancer defined by only ICD-10 with that of the national cancer registry data, we found an approximately 3-fold higher incidence rate because of false-positive data (Figure 1). Therefore, subjects who simultaneously had a diagnostic code of colorectal cancer [C18-20] and the claim code of its treatment were selected as colorectal cancer cases. Treatments for colorectal cancer include surgery, chemotherapy and radiation therapy and are listed in Table 3. We also compared our definition with that of the national cancer registry data after age standardization. Age standardization was performed using the 2010 mid-year population in Korea. The incidence rate of our definition of colorectal cancer was lower than that of the national cancer registry data, but the trend showed similar results (Figure 2). Colorectal cancer cases were categorized into colon cancer [C18] and rectosigmoid colon cancer [C19-20] based on ICD-10.

Identification of cholecystectomy and appendectomy

Cholecystectomy and appendectomy were identified by the insurance claim code for these surgeries. Cholecystectomy covered cholecystectomy [Q7380] and radical cholecystectomy of gallbladder cancer [Q7410]. Appendectomy covered appendectomy-simple [Q2861], appendectomy-perforated [Q2862], and removal of appendiceal abscesses with periappendiceal abscess drainage [Q2863]. The first date of the claim was defined as the surgery index date in this study.

Table 3. List of colorectal cancer treatments in the National Health Insurance Service

Operation	Claim codes
Rt. or Lt. hemicolectomy	QA671, Q2671
Subtotal colectomy	Q1261, Q1262
Total colectomy	QA672, Q2672
Segmental resection	QA673, Q2673
Colectomy with proximal colostomy and distal stump	QA679, Q2679
Transanal Rectal tumor resection	Q2891
Transsacral or parasacral rectal tumor resection	Q2890
Abdominal approach rectal tumor resection	Q2892
Transanal endoscopic microsurgery of rectal tumor resection	Q2893
Anterior resection	QA921, Q2921
Low anterior resection	Q2927, QA922, Q2922
Abdominoperineal resection	QA921, Q2923
Abdominal pull-through operation	QA924, Q2924
Total coloprotectomy with ileostomy	QA925, Q2925
Total coloprotectomy with ileal pouch-anal anastomosis	QA926, Q2926

Table 3. Continued

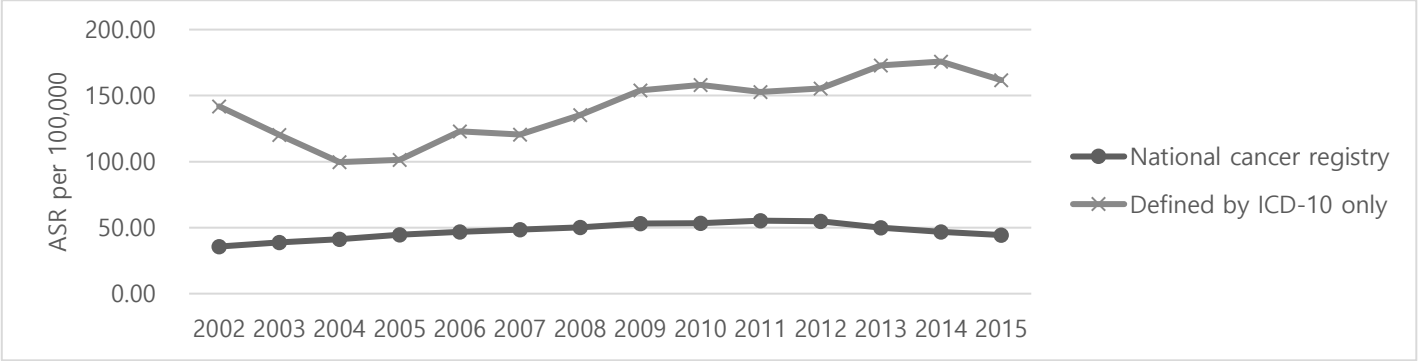
Chemotherapy	Claim codes
Capecitabine	122701ATB, 122702ATB
5-FU	161430BIJ, 161431BIJ, 161432BIJ
Leucovorin	566132BIJ, 566134BIJ, 622630BIJ, 622631BIJ, 622632BIJ, 521001BIJ, 521002BIJ
Irinotecan	177430BIJ, 177431BIJ, 177432BIJ, 177433BIJ, 177434BIJ, 177435BIJ, 177436BIJ, 177437BIJ
Bevacizumab	554330BIJ, 554331BIJ
Cetuximab	556430BIJ
Oxaliplatin	205830BIJ, 205834BIJ,

205803BIJ, 205832BIJ

Table 3. Continued

Radiation therapy (claim codes)
HD051, HD054, HD052, HD055, HD053, HD056, HD057, HD058, HD059, HD061, HD071, HD072, HD073, HD080, HD081, HD081, HD082, HD083, HD084, HD085, HD086, HD087, HD088, HD089, HD111, HD112, HZ271

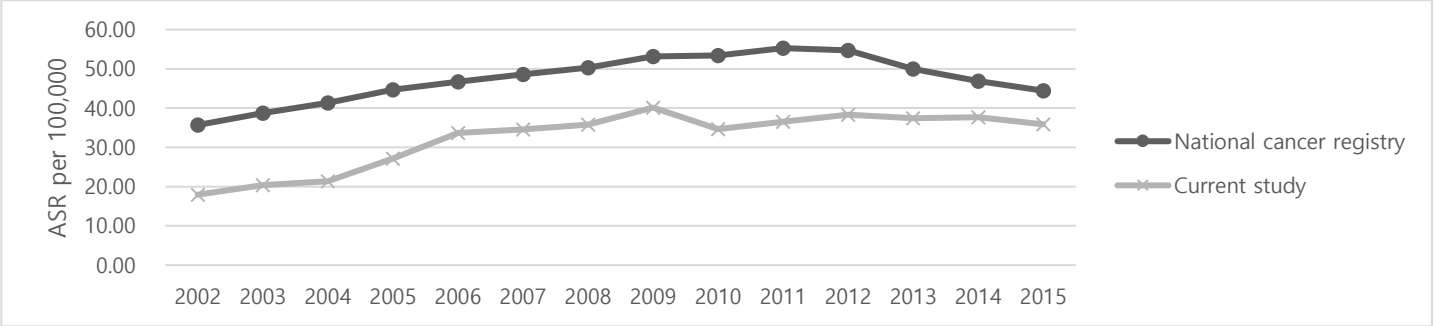
Figure 1. Truncated age-standardized incidence rate (ASR) of colorectal cancer among adults aged 20 years and older in the national cancer registry and defined by only ICD-10



Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
National cancer registry	35.69	38.73	41.34	44.68	46.73	48.63	50.30	53.17	53.43	55.28	54.72	50.00	46.85	44.42
Defined by ICD-10 only	141.96	120.28	99.63	101.45	122.83	120.50	135.31	153.89	158.16	152.83	155.51	172.86	175.78	161.82

*Age standardized using the 2010 mid-year population of Korea.

Figure 2. Truncated age-standardized incidence rate (ASR) of colorectal cancer among adults aged 20 years and older in the national cancer registry and current study



Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
National cancer registry	35.69	38.73	41.34	44.68	46.73	48.63	50.30	53.17	53.43	55.28	54.72	50.00	46.85	44.42
Current study	17.95	20.37	21.38	27.12	33.65	34.61	35.77	40.13	34.65	36.52	38.35	37.44	37.70	35.84

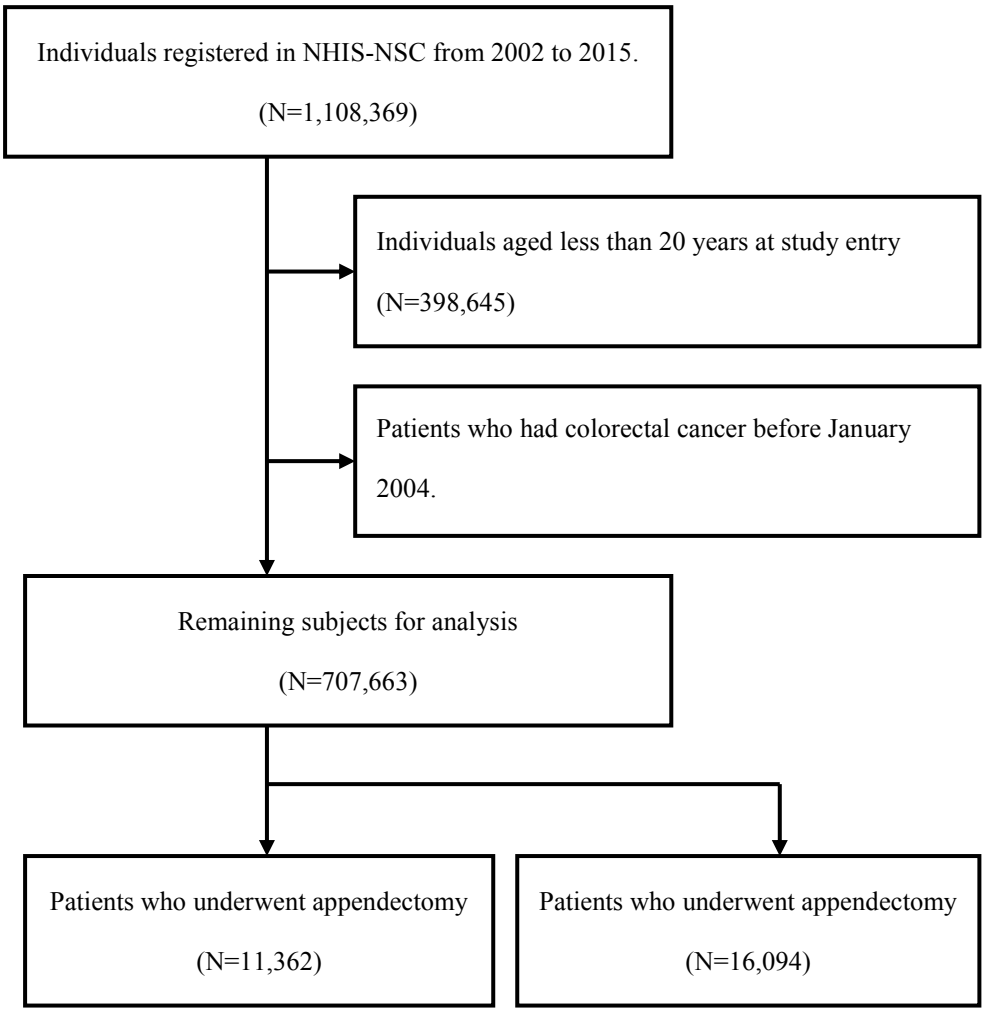
*Age standardized using the 2010 mid-year population of Korea.

Study design and population

We designed a retrospective cohort study using the NHIS-NSC from 2002 and 2015 with subjects aged older than 20 years. To identify only incidental cases of colorectal cancer, we excluded subjects with a diagnostic code of colorectal cancer [C18-C20] before January 2004 because they were thought to have a colorectal cancer priory.

A total of 1,108,369 subjects were included in the original cohort, and 707,663 subjects remained after exclusion of prevalent colorectal cancer cases (N=2,082) and subjects aged less than 20 years at study entry (N=398,624) (Figure 3). A total of 11,362 subjects had cholecystectomy, and 16,094 subjects had appendectomy during the study period. The study population was followed up until the end of the follow up or development of colorectal cancer, whichever occurred first.

Figure 3. Selection of the study population



Covariates

We also extracted the factors known to be associated with colorectal cancer: diabetes mellitus (DM), inflammatory bowel disease (IBD), smoking status, alcohol consumption and body mass index (BMI) (1, 11, 45). Individuals with DM were defined as using ICD-10 (E10-14) and prescription hypoglycemic agents at the same time during the first 2 years of study entry. Individuals who had two claims per year of IBD based on the ICD-10 (K50, K51) in the first 2 years were defined as IBD patients. Information about lifestyle factors such as smoking status, alcohol consumption, and BMI could be obtained from the medical check-up data. These factors were identified based on the data available in the first 2 years of study. BMI was categorized into two groups, less than and more than 25 kg/m^2, based on the WHO classification of overweight. However, over 70% of the medical check-up data were missing; thus, reliable results could not be gained with more than half of the data missing. Therefore, we considered these lifestyle factors not in the main analysis but in the sensitivity analysis, restricting the subjects to those who had available medical check-up data.

Statistical analysis

Chi-square tests and t-tests were used to compare the baseline characteristics between patients who had had cholecystectomy during the study period and those who had not; the same procedures were also completed for appendectomy patients.

We calculated the age-standardized incidence rates of colorectal cancer separately for the total study population, cholecystectomy patients, and appendectomy patients. To consider the latency period, colorectal cancer cases from 0 to 5 years after cholecystectomy or appendectomy were selected to calculate the incidence rates. Age-standardized incidence rates were calculated using the mid-year Korean population in 2010 as the standard population. The standardized incidence ratio was compared with the incidence in the study population, and 95% confidence intervals (CIs) were calculated by Poisson distribution.

In risk estimation, we defined the status of cholecystectomy and appendectomy as time-varying covariates, so that each individual was followed up as a nonexposure of cholecystectomy or appendectomy until the date of surgery. In this manner, we could consider the immortal time bias that could easily occur in the dynamic cohort (46-51).

The risk of colorectal cancer after cholecystectomy or appendectomy was evaluated by a time-dependent Cox proportional hazard regression model adjusted for sex, DM, and IBD. Age was chosen as a time scale in the Cox model because colorectal cancer is an age-related disease (52, 53). Thus, the risk was estimated by comparison between subjects who had the same age. Initially, we evaluated the risk of colorectal cancer stratified by the follow-up time after cholecystectomy or appendectomy to estimate the risk depending on the follow-up time after surgery to determine protopathic bias. In addition, we applied the latency period after cholecystectomy or appendectomy in the Cox model considering protopathic bias and evaluating the risk of colorectal cancer after surgery. We also calculated the risk of colorectal cancer stratified by anatomical site based on the ICD-10: colon cancer (C18) and rectal cancer (C19-20). The proportional hazard assumption was checked by Schoenfeld residual plots. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Sensitivity analysis

Only 181,933 subjects had available medical check-up data in the first 2 years of the

study. We performed sensitivity analysis with these subjects to consider the lifestyle factors. Baseline characteristics were compared in the same way with the main analysis. In this analysis, hazard ratios were computed by a time-dependent Cox proportional hazard regression model adjusted for sex, DM, IBD, smoking status, alcohol consumption, and BMI. The colorectal cancer risk stratified by anatomical site was also computed in this analysis.

Results

Main analysis

In total, 707,633 subjects were included in the final analysis and had an average of 13.66 years of follow-up time, and 4,324 subjects developed colorectal cancer during the study period. The subjects were followed up an average of 5.37 years after cholecystectomy and an average of 6.90 years after appendectomy. Forty-eight cases and sixty-nine cases of colorectal cancer were identified after cholecystectomy and appendectomy, respectively. The baseline characteristics comparing patients with or without cholecystectomy or appendectomy are shown in Table 4. Subjects with cholecystectomy tended to be older and have DM compared with those without. Those with appendectomy tended to be younger than those without and free of DM compared with those without.

The age-standardized incidence rate (ASR) of colorectal cancer in the study population was 44.46 per 100,000 person-years for adults aged 20 years and older (Table 5). The ASRs after cholecystectomy or appendectomy were 52.60 or 66.75 per 100,000 person-years, respectively. The ASRs in cholecystectomy patients were nonsignificantly

lower than those in the total study population, although they were significantly low among cholecystectomy patients with 1 or 2 years of lag. The ASRs in the appendectomy cohort tended to be lower with a longer lag period applied.

Stratified by the follow-up time since cholecystectomy, the risk of colorectal cancer was significantly elevated in first year (HR: 1.71; 95% CI: 1.01-2.89) (Table 6, Figure 4). However, it showed no association after one year of cholecystectomy. The risk levels of colon cancer [C18] and rectal cancer [C19-C20] were also elevated in the first year of cholecystectomy, although they were not statistically significant (Table 7, Table 8, Figure 4). The risk of colorectal cancer after cholecystectomy applying different lag periods showed no association regardless of the lag periods applied (Table 9, Figure 5). The hazard ratios were 0.94 (95% CI: 0.70–1.24) without applying a lag period and 0.88 (95% CI: 0.54-1.44) with applying 5 years of lag. These results were also similar to those stratified by anatomical site of colorectal cancer (Table 10, Table 11, Figure 5).

The risk of colorectal cancer was significantly elevated in the first year (HR: 4.22; 95% CI: 2.87-6.20) and from two to three years (HR: 2.34; 95% CI: 1.36-4.03) after appendectomy (Table 12, Figure 6). The risk of colorectal cancer was increased in the

follow-up period from one to two years, but it was not statistically significant (HR: 1.19; 95% CI: 0.57-2.50). Classified by the anatomical site of colorectal cancer, this risk elevation was also observed in colon cancer (Table 13, Figure 6). The risk of rectal cancer in the first year of appendectomy was increased, but it was not statistically significant (HR: 1.90; 95% CI: 0.79-4.56) (Table 14, Figure 6). Considering this risk elevation period, the risk levels of colorectal cancer after appendectomy applying different lag periods are shown in Table 15. The risk of colorectal cancer was elevated after appendectomy without applying a lag period (HR: 1.44; 95% CI: 1.14-1.83), but it was not statistically significant when applying lag periods (Table 15, Figure 7). The risk of colon cancer was also increased in a model without a lag period (Table 16, Figure 7). However, in the case of rectal cancer, no association was shown whether or not a lag period was (Table 17, Figure 7).

The hazard ratios for each adjusted covariate are shown in Table 18. Women had a lower risk of colorectal cancer than men did, and subjects who had DM or IBD showed an increased risk but not it was not statistically significant. The assumption of the proportional hazard assumption was checked by the Schoenfeld residual plot presented

in Figure 8 and Figure 9. Because there was no pattern with time, we determined that the risk models fit the proportional hazard assumption for both cholecystectomy and appendectomy.

Table 4. Characteristics of the study population, the National Health Insurance Service-National Sample Cohort (NHIS-NSC) 2002-2015

	Total, N (%)	Cholecystectomy, N (%)			Appendectomy, N (%)		
		(-)	(+)	p-value*	(-)	(+)	p-value*
Total N	707,663	696,301 (98.39)	11,362 (1.61)		691,569 (97.73)	16,094 (2.27)	
Age† (mean, SD)	41.70 (14.7)	41.60 (14.7)	47.78 (14.6)	<0.001	41.76 (14.7)	39.09 (14.4)	<0.001
Sex							
Male	347,411 (49.1)	341,792 (49.1)	5,619 (49.5)	0.437	339,458 (49.1)	7,953 (49.4)	0.407
Female	360,252 (50.9)	354,509 (50.9)	5,743 (50.5)		352,111 (50.9)	8,141 (50.6)	
Comorbidities							
Diabetes mellitus	22,944 (3.2)	22,211 (3.2)	733 (6.5)	<0.001	22,653 (3.3)	291 (1.8)	<0.001
Inflammatory bowel disease	361 (0.1)	354 (0.1)	7 (0.1)	0.614	347 (0.1)	14 (0.1)	0.041

*p-value was calculated by chi-square tests for categorical values and t-tests for continuous values; †Age at study entry.

Table 5. Follow-up duration, number of events and age-standardized incidence rate of colorectal cancer

	N	Person-years	N of events	ASR*	SIR	95% CI
Total	707,663	9,668,662	4,324	44.46	1.00	reference
Cholecystectomy (no lag periods)	11,362	61,043	48	52.60	0.79	(0.58-1.04)
Cholecystectomy (1 year of lag)	10,015	50,392	34	37.03	0.65	(0.45-0.91)
Cholecystectomy (2 years of lag)	8,756	41,020	30	42.19	0.68	(0.46-0.97)
Cholecystectomy (3 years of lag)	7,598	32,840	25	30.06	0.69	(0.44-1.01)
Cholecystectomy (4 years of lag)	6,511	25,792	21	32.96	0.71	(0.44-1.09)
Cholecystectomy (5 years of lag)	5,464	19,823	16	38.83	0.68	(0.39-1.11)

Table 5. Continued

	N	Person-years	N of events	ASR*	SIR	95% CI
Appendectomy (no lag periods)	16,094	111,125	69	66.75	1.18	(0.92-1.49)
Appendectomy (1 year of lag)	15,022	95,590	43	47.74	0.82	(0.60-1.11)
Appendectomy (2 years of lag)	13,954	81,116	36	41.98	0.79	(0.55-1.09)
Appendectomy (3 years of lag)	12,702	67,784	23	20.12	0.59	(0.37-0.88)
Appendectomy (4 years of lag)	11,527	55,659	18	19.22	0.55	(0.32-0.86)
Appendectomy (5 years of lag)	10,344	44,722	13	16.48	0.48	(0.25-0.82)

ASR; Age-standardized incidence rate.

*Age-standardized with the mid-year Korean population in 2010.

Table 6. Risk of colorectal cancer after cholecystectomy based on the follow-up time

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Cholecystectomy	Nonexposure	9,600,974	4,276	1.00 (reference)	1.00 (reference)
	0~1 year	10,650	14	1.71 (1.01 - 2.89)	1.71 (1.01 - 2.89)
	1~2 years	9,372	4	0.54 (0.20 - 1.45)	0.54 (0.20 - 1.44)
	2~3 years	8,181	5	0.76 (0.32 - 1.83)	0.76 (0.32 - 1.82)
	3~4 years	7,065	4	0.68 (0.26 - 1.82)	0.68 (0.26 - 1.82)
	4~5 years	5,966	5	0.99 (0.41 - 2.39)	0.99 (0.41 - 2.38)
	5~ years	19,808	16	0.88 (0.54 - 1.44)	0.88 (0.54 - 1.44)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 7. Risk of colon cancer [C18] after cholecystectomy based on the follow-up time

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Cholecystectomy	Nonexposure	9,600,974	2,539	1.00 (reference)	1.00 (reference)
	0~1 year	10,650	8	1.65 (0.82 - 3.30)	1.64 (0.82 - 3.29)
	1~2 years	9,372	3	0.69 (0.22 - 2.13)	0.69 (0.22 - 2.13)
	2~3 years	8,181	4	1.02 (0.38 - 2.72)	1.02 (0.38 - 2.71)
	3~4 years	7,065	1	0.29 (0.04 - 2.04)	0.29 (0.04 - 2.03)
	4~5 years	5,966	3	1.00 (0.32 - 3.09)	0.99 (0.32 - 3.08)
	5~ years	19,808	7	0.64 (0.31 - 1.35)	0.64 (0.31 - 1.35)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 8. Risk of rectal cancer [C19-20] after cholecystectomy based on the follow-up time

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Cholecystectomy	Nonexposure	9,600,974	1,822	1.00 (reference)	1.00 (reference)
	0~1 year	10,650	6	1.72 (0.77 - 3.83)	1.71 (0.77 - 3.82)
	1~2 years	9,372	2	0.64 (0.16 - 2.54)	0.63 (0.16 - 2.53)
	2~3 years	8,181	1	0.36 (0.05 - 2.53)	0.36 (0.05 - 2.52)
	3~4 years	7,065	3	1.21 (0.39 - 3.74)	1.20 (0.39 - 3.73)
	4~5 years	5,966	2	0.94 (0.24 - 3.76)	0.94 (0.23 - 3.74)
	5~ years	19,808	9	1.18 (0.61 - 2.26)	1.17 (0.61 - 2.26)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

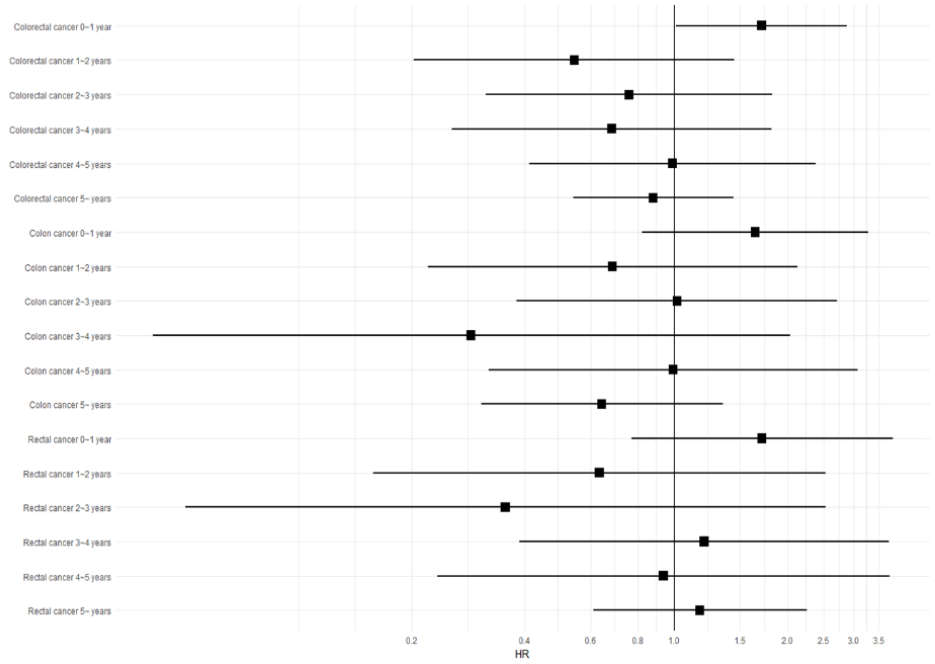


Figure 4. Risk of site-specific colorectal cancer based on the follow-up time

Table 9. Risk of colorectal cancer after cholecystectomy applying different lag periods

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Cholecystectomy (no lag period)	61,043	48	0.94 (0.71-1.25)	0.94 (0.70-1.24)
Cholecystectomy (1 year of lag)	50,385	34	0.79 (0.56-1.11)	0.79 (0.56-1.10)
Cholecystectomy (2 years of lag)	41,008	30	0.84 (0.59-1.21)	0.84 (0.59-1.20)
Cholecystectomy (3 years of lag)	32,824	25	0.86 (0.58-1.28)	0.86 (0.58-1.27)
Cholecystectomy (4 years of lag)	25,774	21	0.91 (0.59-1.40)	0.90 (0.59-1.39)
Cholecystectomy (5 years of lag)	19,805	16	0.88 (0.54-1.44)	0.88 (0.54-1.44)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 10. Risk of colon cancer [C18] after cholecystectomy applying different lag periods

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Cholecystectomy (no lag period)	61,043	26	0.85 (0.58-1.25)	0.85 (0.58-1.25)
Cholecystectomy (1 year of lag)	50,385	18	0.70 (0.44-1.12)	0.70 (0.44-1.11)
Cholecystectomy (2 years of lag)	41,008	15	0.71 (0.42-1.17)	0.70 (0.42-1.17)
Cholecystectomy (3 years of lag)	32,824	11	0.64 (0.35-1.15)	0.63 (0.35-1.14)
Cholecystectomy (4 years of lag)	25,774	10	0.72 (0.39-1.34)	0.72 (0.39-1.34)
Cholecystectomy (5 years of lag)	19,805	7	0.65 (0.31-1.36)	0.64 (0.31-1.35)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 11. Risk of rectal cancer [C19-20] after cholecystectomy applying different lag periods

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Cholecystectomy (no lag period)	61,043	23	1.06 (0.70-1.60)	1.06 (0.70-1.59)
Cholecystectomy (1 year of lag)	50,385	17	0.93 (0.58-1.50)	0.93 (0.58-1.50)
Cholecystectomy (2 years of lag)	41,008	15	0.99 (0.60-1.65)	0.99 (0.60-1.65)
Cholecystectomy (3 years of lag)	32,824	14	1.14 (0.67-1.93)	1.14 (0.67-1.92)
Cholecystectomy (4 years of lag)	25,774	11	1.13 (0.62-2.04)	1.12 (0.62-2.03)
Cholecystectomy (5 years of lag)	19,805	9	1.18 (0.61-2.27)	1.17 (0.61-2.26)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

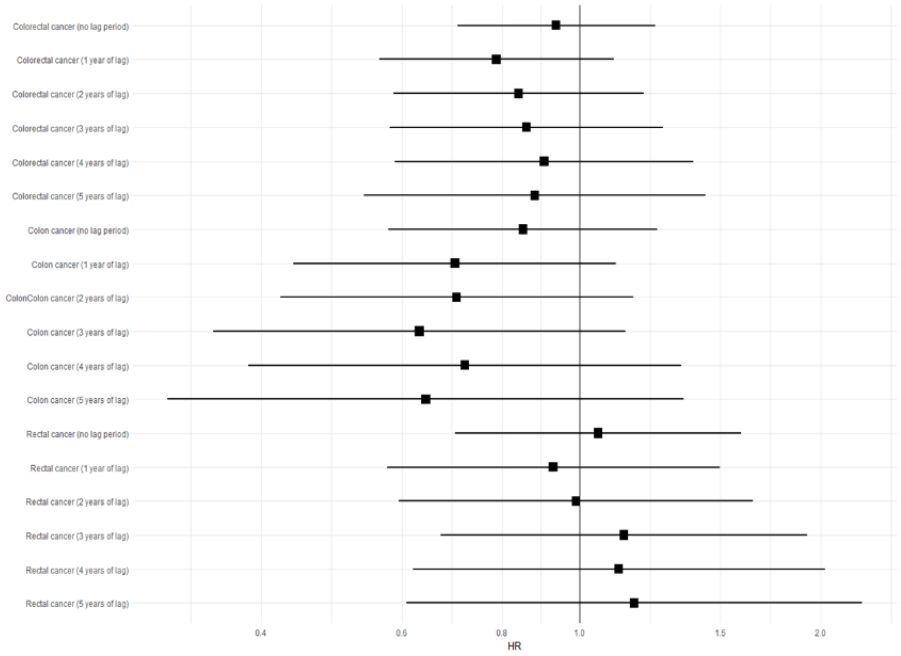


Figure 5. Risk of site-specific colorectal cancer after cholecystectomy applying different lag periods

Table 12. Risk of colorectal cancer after appendectomy based on the follow-up time

	Follow-up time	Person-years	N. of event	Crude HR (95% CI)	Adjusted HR* (95% CI)
Appendectomy	Nonexposure	9,550,906	4,255	1.00 (reference)	1.00 (reference)
	0~1 year	15,534	26	4.21 (2.86-6.18)	4.22 (2.87-6.20)
	1~2 years	14,474	7	1.19 (0.57-2.49)	1.19 (0.57-2.50)
	2~3 years	13,332	13	2.33 (1.35-4.02)	2.34 (1.36-4.03)
	3~4 years	12,157	5	0.97 (0.40-2.33)	0.97 (0.40-2.33)
	4~5 years	10,933	5	1.05 (0.44-2.53)	1.06 (0.44-2.54)
	5~ years	44,694	13	0.63 (0.37-1.09)	0.63 (0.37-1.09)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 13. Risk of colon cancer [C18] after appendectomy based on the follow-up time

	Follow-up time	Person-years	N. of event	Crude HR (95% CI)	Adjusted HR* (95% CI)
Appendectomy	Nonexposure	9,550,906	2,515	1.00 (reference)	1.00 (reference)
	0~1 year	15,534	21	5.74 (3.73-8.81)	5.74 (3.74-8.82)
	1~2 years	14,474	6	1.72 (0.77-3.82)	1.72 (0.77-3.83)
	2~3 years	13,332	8	2.42 (1.21-4.84)	2.42 (1.21-4.85)
	3~4 years	12,157	2	0.65 (0.16-2.61)	0.65 (0.16-2.62)
	4~5 years	10,933	4	1.42 (0.53-3.79)	1.42 (0.53-3.79)
	5~ years	44,694	9	0.74 (0.38-1.42)	0.74 (0.38-1.42)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 14. Risk of rectal cancer [C19-C20] after appendectomy based on the follow-up time

	Follow-up time	Person-years	N. of event	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendectomy	Nonexposure	9,550,906	1,824	1.00 (reference)	1.00 (reference)
	0~1 year	15,534	5	1.89 (0.79-4.54)	1.90 (0.79-4.56)
	1~2 years	14,474	1	0.40 (0.06-2.81)	0.40 (0.06-2.83)
	2~3 years	13,332	6	2.53 (1.14-5.64)	2.54 (1.14-5.67)
	3~4 years	12,157	4	1.81 (0.68-4.83)	1.82 (0.68-4.86)
	4~5 years	10,933	1	0.49 (0.07-3.51)	0.50 (0.07-3.53)
	5~ years	44,694	4	0.45 (0.17-1.21)	0.46 (0.17-1.22)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

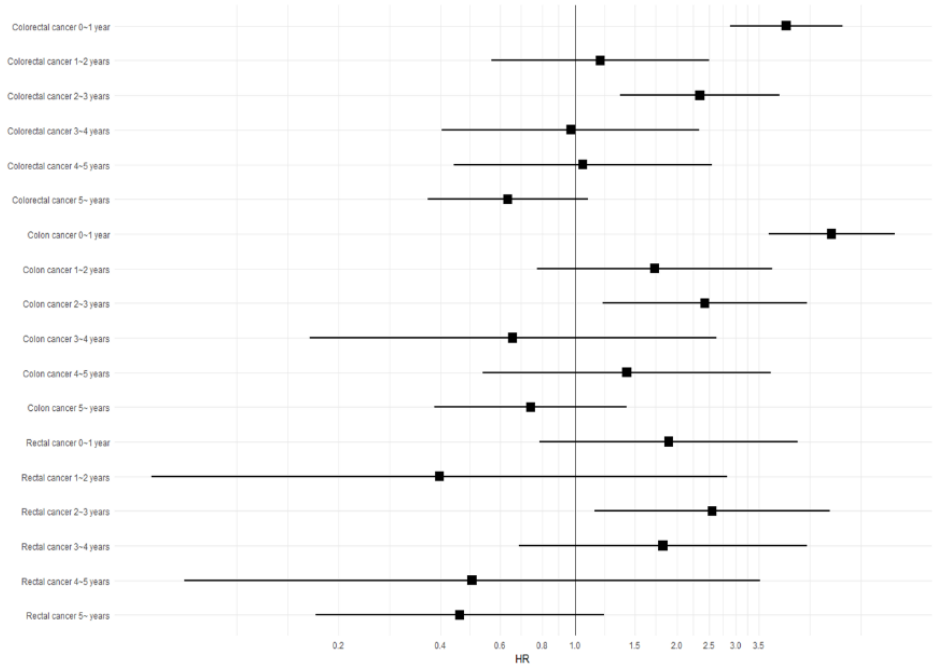


Figure 6. Risk of site-specific colorectal cancer after appendectomy based on the follow-up time

Table 15. Risk of colorectal cancer after appendectomy applying different lag periods

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Appendectomy (no lag period)	111,125	69	1.44 (1.13-1.82)	1.44 (1.14-1.83)
Appendectomy (1 year of lag)	95,580	43	1.02 (0.76-1.38)	1.02 (0.76-1.38)
Appendectomy (2 years of lag)	81,097	36	0.99 (0.72-1.38)	1.00 (0.72-1.38)
Appendectomy (3 years of lag)	67,758	23	0.75 (0.50-1.13)	0.75 (0.50-1.13)
Appendectomy (4 years of lag)	55,627	18	0.71 (0.45-1.12)	0.71 (0.45-1.13)
Appendectomy (5 years of lag)	44,687	13	0.63 (0.37-1.08)	0.63 (0.37-1.09)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 16. Risk of colon cancer [C18] after appendectomy applying different lag periods

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Appendectomy (no lag period)	111,125	50	1.75 (1.32-2.32)	1.76 (1.33-2.32)
Appendectomy (1 year of lag)	95,580	29	1.16 (0.80-1.67)	1.16 (0.80-1.67)
Appendectomy (2 years of lag)	81,097	23	1.07 (0.71-1.61)	1.07 (0.71-1.61)
Appendectomy (3 years of lag)	67,758	15	0.82 (0.50-1.37)	0.82 (0.50-1.37)
Appendectomy (4 years of lag)	55,627	13	0.86 (0.50-1.48)	0.86 (0.50-1.48)
Appendectomy (5 years of lag)	44,687	9	0.73 (0.38-1.41)	0.73 (0.38-1.41)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

Table 17. Risk of rectal cancer [C19-20] after appendectomy applying different lag periods

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Appendectomy (no lag period)	111,125	21	1.02 (0.66-1.57)	1.03 (0.67-1.58)
Appendectomy (1 year of lag)	95,580	16	0.89 (0.54-1.46)	0.90 (0.55-1.46)
Appendectomy (2 years of lag)	81,097	15	0.97 (0.59-1.62)	0.98 (0.59-1.63)
Appendectomy (3 years of lag)	67,758	9	0.69 (0.36-1.33)	0.69 (0.36-1.33)
Appendectomy (4 years of lag)	55,627	5	0.46 (0.19-1.11)	0.46 (0.19-1.11)
Appendectomy (5 years of lag)	44,687	4	0.45 (0.17-1.21)	0.46 (0.17-1.21)

*Adjusted for sex, diabetes mellitus, and inflammatory bowel disease.

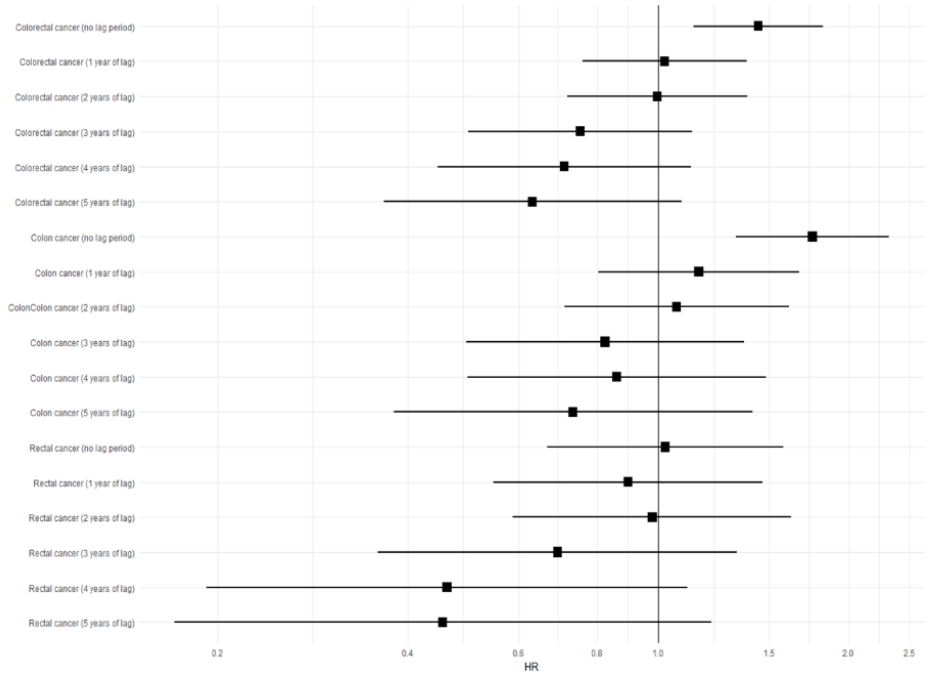


Figure 7. Risk of site-specific colorectal cancer after appendectomy applying different lag periods

Table 18. Hazard ratios of the incidence of colorectal cancer adjusted for sex, diabetes mellitus, and inflammatory bowel disease

Covariates		N	Person-years	N of events	Age- and sex-adjusted HR (95% CI)
Sex	Male	347,411	4,729,917	2,604	1.00 (reference)
	Female	360,252	4,932,128	1,720	0.49 (0.46-0.52)
Diabetes mellitus	(-)	684,719	9,365,067	3,986	1.00 (reference)
	(+)	22,944	296,977	338	1.04 (0.93-1.16)
Inflammatory bowel disease	(-)	707,302	9,657,200	4,320	1.00 (reference)
	(+)	361	4,844	4	1.24 (0.46-3.30)

Figure 8. Schoenfeld residual plot of cholecystectomy to check proportional assumption

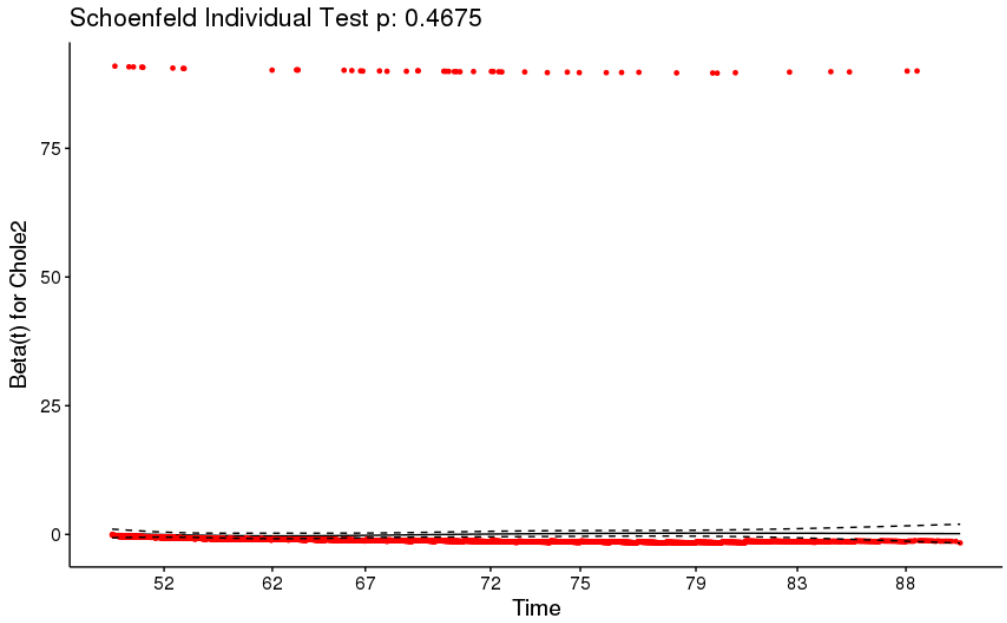
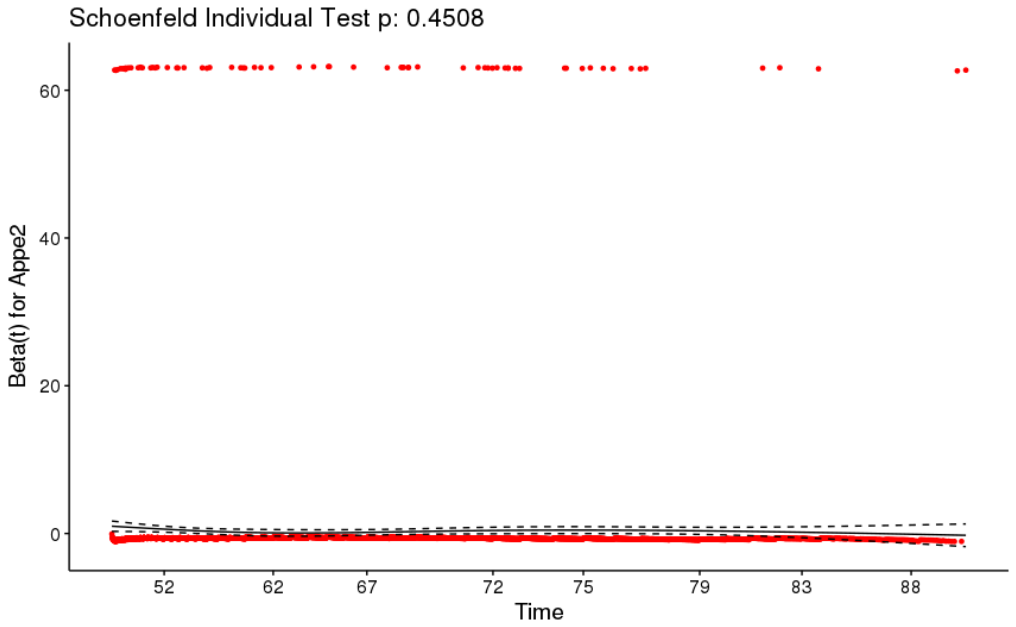


Figure 9. Schoenfeld residual plot of cholecystectomy to check proportional assumption



Sensitivity analysis

The characteristics of subjects with available medical check-up data in the first 2 years and those without are shown in Table 19. Subjects with medical check-up data were older than subjects without and tended to be male. Additionally, they tended to have more DM and IBD than those who did not have medical check-up data. The comparison of the baseline characteristics among subjects with medical check-up data is shown in Table 20. The cholecystectomy patients were younger, and the appendectomy patients were older. Regarding lifestyle factors, the patients who had cholecystectomy tended to be nonsmokers, never drinkers and have higher BMI values, while patients who had appendectomy tended to be nonsmokers and current drinkers. The hazard ratios of the incidence of colorectal cancer for these covariates are shown in Table 21. Subjects who drank alcohol, smoked and were obese showed an elevated risk of colorectal cancer compared with those who did not. Women had a higher risk of colorectal cancer than men did. DM and IBD did not show statistically significant results.

Although the samples were restricted to subjects with available medical check-up data, the results were similar to those of the main analysis. The risk of colorectal cancer was

elevated in the first year of cholecystectomy in sensitivity analysis, and it was elevated in colon cancer but not in rectal cancer (Table 22, Table 23, Table 24). After applying lag periods, the risk of colorectal cancer was not associated with cholecystectomy regardless of the lag periods in both colon and rectal cancer (Table 25, Table 26, Table 27). In the case of appendectomy, the risk of colorectal cancer and colon cancer was elevated in the first year, while that of rectal cancer was not (Table 28, Table 29, Table 30). In the sensitivity analysis, the hazard ratios after applying lag periods did not show statistical significance regardless of the lag period applied and were classified by the anatomical site of the cancer (Table 31, Table 32, Table 33).

Table 19. Characteristics between subjects with medical check-up data and those without

	Medical check-up data (N, %)		
	Absent	Present	p-value*
Total N	525,730 (74.3)	181,933 (25.7)	
Age† (mean, SD)	41.03 (15.1)	43.63 (13.5)	<0.001
Sex			
Male	239,391 (45.5)	108,020 (59.4)	<0.001
Female	286,339 (54.5)	73,913 (40.6)	
Comorbidities			
Diabetes mellitus	16,313 (3.1)	6,631 (3.6)	<0.001
Inflammatory bowel disease	249 (0.0)	112 (0.1)	0.021

*p-value was calculated by chi-square tests for categorical values and t-tests for continuous values; †age at study entry.

Table 20. Characteristics of the subjects restricted to those with available medical check-up data

	Total, N (%)	Cholecystectomy, N (%)			Appendectomy, N (%)		
		(-)	(+)	p-value*	(-)	(+)	p-value*
Total N	181,933	178,695 (98.22)	3,238 (1.78)		177,573 (97.60)	4,360 (2.40)	
Age† (mean, SD)	43.63 (13.5)	43.54 (13.4)	48.92 (13.1)	<0.001	43.68 (13.5)	41.76 (13.6)	<0.001
Sex							
Male	108,020 (59.4)	106,068 (59.4)	1,952 (60.3)	0.287	105,376 (59.3)	2,644 (60.6)	0.084
Female	73,913 (40.6)	72,627 (40.6)	1,286 (39.7)		72,197 (40.7)	1,716 (39.4)	
Comorbidities							
Diabetes mellitus	6,631 (3.6)	6,429 (3.6)	202 (6.2)	<0.001	6,545 (3.7)	86 (2.0)	<0.001
Inflammatory bowel disease	112 (0.1)	108 (0.1)	4 (0.1)	0.151	108 (0.1)	4 (0.1)	0.416

Table 20. Continued

	Total, N (%)	Cholecystectomy, N (%)			Appendectomy, N (%)		
		(-)	(+)	p-value*	(-)	(+)	p-value*
Smoking							
Missing	4,169 (2.3)	4,101 (2.3)	68 (2.1)	0.001	4,050 (2.3)	119 (2.7)	0.040
Never	107,090 (58.9)	105,115 (58.8)	1,975 (61.0)		104,543 (58.9)	2,547 (58.4)	
Past	17,042 (9.4)	16,706 (9.3)	336 (10.4)		16,597 (9.3)	445 (10.2)	
Current	53,632 (29.5)	52,773 (29.5)	859 (26.5)		52,383 (29.5)	1,249 (28.6)	
Alcohol							
Missing	2,885 (1.6)	2,834 (1.6)	51 (1.6)	<0.001	2,805 (1.6)	80 (1.8)	0.001
Never	86,196 (47.4)	84,505 (47.3)	1,691 (52.2)		84,256 (47.4)	1,940 (44.5)	
Current	92,852 (51.0)	91,356 (51.1)	1,496 (46.2)		90,512 (51.0)	2,340 (53.7)	

Table 20. Continued

	Total, N (%)	Cholecystectomy, N (%)			Appendectomy, N (%)		
		(-)	(+)	p-value*	(-)	(+)	p-value*
BMI							
Missing	107 (0.1)	106 (0.1)	1 (0.0)	<0.001	104 (0.1)	3 (0.1)	0.633
Normal (BMI<25)	125,336 (68.9)	123,400 (69.1)	1,936 (59.8)		122,305 (68.9)	3,031 (69.5)	
Obesity (BMI≥25)	56,490 (31.0)	55,189 (30.9)	1,301 (40.2)		55,164 (31.1)	1,326 (30.4)	

*p-value was calculated by chi-square tests for categorical values and t-tests for continuous values; †age at study entry.

Table 21. Hazard ratios of the incidence of colorectal cancer adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking, alcohol consumption and obesity among subjects with medical check-up data

Covariates		N	Person-years	N of events	Age- and sex-adjusted HR (95% CI)
Sex	**Male**	108,020	1,481,532	863	1.00 (reference)
	Female	73,913	1,019,069	393	0.45 (0.40-0.51)
DM	**(-)**	175,302	2,413,300	1,151	1.00 (reference)
	(+)	6,631	87,300	105	1.06 (0.87-1.30)
IBD	**(-)**	181,821	2,499,092	1,255	1.00 (reference)
	(+)	112	1,509	1	0.86 (0.12-6.08)
Alcohol	**Never drinker**	86,196	1,181,172	605	1.00 (reference)
	Current drinker	92,852	1,279,938	630	1.41 (1.25-1.60)
	Missing	2,885	39,491	21	1.01 (0.65-1.56)

Table 21. Continued

Covariates		N	Person-years	N of events	Age- and sex-adjusted HR (95% CI)
Smoking	**Never smoker**	107,090	1,473,155	722	1.00 (reference)
	Past Smoker	17,042	233,840	146	1.12 (0.93-1.36)
	Current Smoker	53,632	736,273	363	1.24 (1.08-1.43)
	Missing	4,169	57,333	25	0.94 (0.63-1.40)
Obesity	**Normal**	125,336	1,721,976	798	1.00 (reference)
	Obesity	56,490	777,163	457	1.14 (1.01-1.28)
	Missing	107	1,462	1	1.12 (0.16-7.99)

Table 22. Risk of colorectal cancer after cholecystectomy based on the follow-up time among subjects with medical check-up data

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR* (95% CI)
Cholecystectomy	Nonexposure	2,483,065	1,241	1.00 (reference)	1.00 (reference)
	0~1 year	3,045	6	2.40 (1.07-5.35)	2.39 (1.07-5.32)
	1~2 years	2,687	1	0.44 (0.06-3.09)	0.43 (0.06-3.08)
	2~3 years	2,361	4	1.96 (0.73-5.22)	1.94 (0.73-5.18)
	3~4 years	2,023	0		
	4~5 years	1,719	0		
	5~ years	5,686	4	0.69 (0.26-1.85)	0.69 (0.26-1.83)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 23. Risk of colon cancer [C18] after cholecystectomy based on the follow-up time among subjects with medical check-up data

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Cholecystectomy	Nonexposure	2,483,065	710	1.00 (reference)	1.00 (reference)
	0~1 year	3,045	4	2.77 (1.04-7.40)	2.73 (1.02-7.29)
	1~2 years	2,687	1	0.76 (0.11-5.37)	0.74 (0.10-5.27)
	2~3 years	2,361	3	2.56 (0.82-7.95)	2.51 (0.81-7.80)
	3~4 years	2,023	0		
	4~5 years	1,719	0		
	5~ years	5,686	2	0.59 (0.15-2.38)	0.58 (0.15-2.32)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 24. Risk of rectal cancer [C19-C20] after cholecystectomy based on the follow-up time among subjects with medical check-up data

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Cholecystectomy	Nonexposure	2,483,065	560	1.00 (reference)	1.00 (reference)
	0~1 year	3,045	2	1.78 (0.44-7.13)	1.80 (0.45-7.21)
	1~2 years	2,687	0		
	2~3 years	2,361	1	1.08 (0.15-7.70)	1.09 (0.15-7.74)
	3~4 years	2,023	0		
	4~5 years	1,719	0		
	5~ years	5,686	2	0.78 (0.19-3.12)	0.79 (0.20-3.15)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 25. Risk of colorectal cancer after cholecystectomy applying different lag periods among subjects with medical check-up data

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Cholecystectomy (no lag period)	17,521	15	0.94 (0.56-1.56)	0.93 (0.56-1.55)
Cholecystectomy (1 year of lag)	14,475	9	0.67 (0.35-1.28)	0.66 (0.34-1.27)
Cholecystectomy (2 years of lag)	11,786	8	0.71 (0.36-1.43)	0.71 (0.35-1.42)
Cholecystectomy (3 years of lag)	9,424	4	0.44 (0.16-1.16)	0.43 (0.16-1.15)
Cholecystectomy (4 years of lag)	7,405	4	0.54 (0.20-1.45)	0.54 (0.20-1.44)
Cholecystectomy (5 years of lag)	5,685	4	0.69 (0.26-1.85)	0.69 (0.26-1.83)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 26. Risk of colon cancer [C18] after cholecystectomy applying different lag periods among subjects with medical check-up data

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Cholecystectomy (no lag period)	17,521	10	1.08 (0.58-2.02)	1.06 (0.57-1.98)
Cholecystectomy (1 year of lag)	14,475	6	0.76 (0.34-1.71)	0.75 (0.34-1.67)
Cholecystectomy (2 years of lag)	11,786	5	0.77 (0.32-1.85)	0.75 (0.31-1.81)
Cholecystectomy (3 years of lag)	9,424	2	0.37 (0.09-1.50)	0.37 (0.09-1.46)
Cholecystectomy (4 years of lag)	7,405	2	0.47 (0.12-1.86)	0.45 (0.11-1.82)
Cholecystectomy (5 years of lag)	5,685	2	0.60 (0.15-2.38)	0.58 (0.14-2.32)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 27. Risk of rectal cancer [C19-C20] after cholecystectomy applying different lag periods among subjects with medical check-up data

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Cholecystectomy (no lag period)	17,521	5	0.70 (0.29-1.68)	0.70 (0.29-1.70)
Cholecystectomy (1 year of lag)	14,475	3	0.50 (0.16-1.54)	0.50 (0.16-1.55)
Cholecystectomy (2 years of lag)	11,786	3	0.60 (0.19-1.86)	0.60 (0.19-1.87)
Cholecystectomy (3 years of lag)	9,424	2	0.49 (0.12-1.96)	0.49 (0.12-1.97)
Cholecystectomy (4 years of lag)	7,405	2	0.61 (0.15-2.45)	0.62 (0.15-2.48)
Cholecystectomy (5 years of lag)	5,685	2	0.78 (0.20-3.13)	0.79 (0.20-3.16)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 28. Risk of colorectal cancer after appendectomy based on the follow-up time among subjects with medical check-up data

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendectomy	Nonexposure	2,470,332	1,243	1.00 (reference)	1.00 (reference)
	0~1 year	4,202	6	3.06 (1.37-6.82)	3.07 (1.38-6.85)
	1~2 years	3,908	1	0.53 (0.08-3.78)	0.53 (0.08-3.79)
	2~3 years	3,605	2	1.11 (0.28-4.45)	1.12 (0.28-4.47)
	3~4 years	3,302	0		
	4~5 years	2,973	1	0.63 (0.09-4.48)	0.63 (0.09-4.49)
	5~ years	12,278	3	0.42 (0.13-1.29)	0.42 (0.13-1.29)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 29. Risk of colon cancer [C18] after appendectomy based on the follow-up time among subjects with medical check-up data

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendectomy	Nonexposure	2,470,332	710	1.00 (reference)	1.00 (reference)
	0~1 year	4,202	5	4.47 (1.85-10.77)	4.50 (1.87-10.84)
	1~2 years	3,908	1	0.93 (0.13-6.58)	0.93 (0.13-6.62)
	2~3 years	3,605	1	0.97 (0.14-6.90)	0.98 (0.14-6.95)
	3~4 years	3,302	0		
	4~5 years	2,973	1	1.10 (0.15-7.79)	1.10 (0.15-7.80)
	5~ years	12,278	2	0.48 (0.12-1.94)	0.48 (0.12-1.92)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 30. Risk of rectal cancer [C19-C20] after appendectomy based on the follow-up time among subjects with medical check-up data

	Follow-up time	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendectomy	Nonexposure	2,470,332	561	1.00 (reference)	1.00 (reference)
	0~1 year	4,202	1	1.13 (0.16-8.01)	1.13 (0.16-8.01)
	1~2 years	3,908	0		
	2~3 years	3,605	2	2.47 (0.62-9.90)	2.47 (0.62-9.91)
	3~4 years	3,302	0		
	4~5 years	2,973	0		
	5~ years	12,278	1	0.31 (0.04-2.20)	0.31 (0.04-2.20)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 31. The risk of colorectal cancer after cholecystectomy applying different lag periods among subjects with medical check-up data

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendectomy (no lag period)	30,269	13	0.81 (0.47-1.39)	0.81 (0.47-1.39)
Appendectomy (1 year of lag)	26,064	7	0.49 (0.23-1.03)	0.49 (0.23-1.03)
Appendectomy (2 years of lag)	22,153	6	0.49 (0.22-1.08)	0.49 (0.22-1.08)
Appendectomy (3 years of lag)	18,547	4	0.38 (0.14-1.01)	0.38 (0.14-1.01)
Appendectomy (4 years of lag)	15,252	4	0.45 (0.17-1.21)	0.45 (0.17-1.21)
Appendectomy (5 years of lag)	12,276	3	0.42 (0.13-1.29)	0.42 (0.13-1.29)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 32. Risk of colon cancer [C18] after cholecystectomy applying different lag periods among subjects with medical check-up data

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendectomy (no lag period)	30,269	10	1.08 (0.58-2.01)	1.08 (0.58-2.01)
Appendectomy (1 year of lag)	26,064	5	0.61 (0.25-1.47)	0.61 (0.25-1.47)
Appendectomy (2 years of lag)	22,153	4	0.56 (0.21-1.50)	0.56 (0.21-1.50)
Appendectomy (3 years of lag)	18,547	3	0.49 (0.16-1.53)	0.49 (0.16-1.53)
Appendectomy (4 years of lag)	15,252	3	0.59 (0.19-1.84)	0.59 (0.19-1.83)
Appendectomy (5 years of lag)	12,276	2	0.48 (0.12-1.93)	0.48 (0.12-1.92)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Table 33. Risk of rectal cancer [C19-C20] after cholecystectomy applying different lag periods among subjects with medical check-up data

	Person-years	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendectomy (no lag period)	30,269	4	0.55 (0.21-1.48)	0.55 (0.21-1.48)
Appendectomy (1 year of lag)	26,064	3	0.47 (0.15-1.47)	0.47 (0.15-1.47)
Appendectomy (2 years of lag)	22,153	3	0.54 (0.18-1.69)	0.55 (0.18-1.70)
Appendectomy (3 years of lag)	18,547	1	0.21 (0.03-1.51)	0.21 (0.03-1.51)
Appendectomy (4 years of lag)	15,252	1	0.25 (0.04-1.80)	0.25 (0.04-1.81)
Appendectomy (5 years of lag)	12,276	1	0.31 (0.04-2.20)	0.31 (0.04-2.21)

* Adjusted for sex, diabetes mellitus, inflammatory bowel disease, smoking status, alcohol consumption, and obesity.

Discussion

In our population-based cohort study, the risk of colorectal cancer was associated with cholecystectomy only in the first year. One year after cholecystectomy, no association was found between cholecystectomy and colorectal cancer. This result suggested the possibility of bias. If there is a true association between cholecystectomy and colorectal cancer, the risk would be elevated constantly after one year. The result of elevated risk in the first year of cholecystectomy can be explained by protopathic bias. Gallbladder disease, the reason for cholecystectomy, and colorectal cancer have similar features. Thus, cautious consideration of colorectal cancer could be performed when the symptoms of gallbladder disease occur, and the misdiagnosis of the early sign of colorectal cancer as gallbladder disease was also reported previously (54-56). The results were interrupted by protopathic bias in the analysis of cholecystectomy and colorectal cancer, and it was shown in the results of models applying different lag periods. We found no association between cholecystectomy and subsequent colorectal cancer regardless of the lag period applied. However, the hazard ratio of the model without applying a lag period was slightly higher than the hazard ratios of the other models, indicating that the involvement of risk elevation in first year after cholecystectomy.

In our study, appendectomy increased the risk of colorectal cancer, especially in the first year, and it was prominent for colon cancer. Although the risk elevation was not statistically significant in the second year of appendectomy, the risk seemed to be increased until three years after appendectomy. The risk of colorectal cancer was not associated with appendectomy after 3 years. In addition, this risk elevation was significant only in colon cancer, not in rectal cancer. In conclusion, the risk of colon cancer was elevated in first 3 years and was not associated with appendectomy in the followed time, implying the possibility of reverse causation. When we applied a lag period after appendectomy, this protopathic bias was shown prominently. The risk of colorectal cancer was increased without applying a lag period, which resulted from the involvement of the elevated risk in the first 3 years. Therefore, the results with less than 3 years of lag period could be biased. Previous studies concerning appendectomy and the risk of colorectal cancer showed an elevated risk regardless of the lag period applied (35-38). However, their risk elevation was more prominent with a shorter lag and toward null with a longer lag in those results. Only one study reported no association between appendectomy and colorectal cancer with one year of lag (39). However, this study also reported an increased risk ratio with a shorter follow-up time, although it was not statistically significant. These results were consistent with those of our study, implying

that appendectomy as a cause of colorectal cancer was less likely. The result that only risk elevation in colon cancer was significant supported this explanation. The mass in the right-sided colon cancer could result in the obstruction of the lumen of the appendix, likely leading to appendiceal inflammation. Therefore, the results that colon cancer risk was elevated in the short term might imply that appendicitis, the reason for appendectomy, could be an early sign of colorectal cancer.

Our study shows several strengths. First, this study used nationally representative data sources, and the sample comprised approximately 700,000 individuals older than 20 years. Second, we controlled possible biases that could arise easily in the longitudinal study statistically (47, 49). We considered delayed entry and various exposure times using time-varying setting (50). In this manner, we could control immortal time bias with the possibility of being interrupted in the previous studies. Additionally, we chose age as the time scale in the analysis. Previous studies did not consider age as the time scale in their analysis, but it could distort the results (53). Third, the analysis focusing on the follow-up period provided evidence that bias was involved in the association. By this evidence, we applied different lag periods from 0 to 5 years after surgery, so that we could consider protopathic bias. Thus, we found that considering a lag period is necessary when investigating the association between cholecystectomy and

appendectomy and colorectal cancer, providing a clue of the underlying mechanism. Finally, the study design of the retrospective cohort study using insurance claim data resulted in no recall bias.

However, our study also had limitations. Because we used claims data, the identification of colorectal cancer might not be precise. However, our comparison of the incidence of colorectal cancer between our definition and that of the national cancer register data showed a similar but underestimated trend. This underestimation could lead to misclassification bias and push the result toward null. Although we analyzed over 700,000 subjects, there was an insufficient number of newly developed colorectal cancer cases among the cholecystectomy or appendectomy patients because colorectal cancer is a rare disease, and there was an insufficient number of surgery cases, which could explain why our results did not show statistical significance. To secure statistical power, 20-fold more subjects are needed (57). Cholecystectomies and appendectomies performed before 2002 could not be identified in this study. Because these surgeries do not need long-term follow up after surgery, it was impossible to obtain patients' histories of these surgeries by claims data. Thus, there might be more surgery cases in the nonsurgery cohort, and this bias might render the results null. Additionally, we could not consider other possible confounding factors. However, the hazard ratios changed little

when we adjusted for DM and IBD, and lifestyle factors in sensitivity analysis. In this manner, we could predict that if other confounding factors were considered, the result may not have changed much. Finally, the follow-up time after cholecystectomy and appendectomy in our study might not be sufficient to develop colorectal cancer that needs at least 5 to 10 years for carcinogenic change (1). If there is a significant association between the surgeries and colorectal cancer, the risk change will be shown with a longer follow-up period.

Conclusion

The risk of colorectal cancer was not associated with cholecystectomy. However, the risk of colorectal cancer was elevated in the first year after cholecystectomy, likely due to gallstone disease. The risk of colorectal cancer after appendectomy was significantly increased when applying no lag period, but it showed no association when applying over 1 year of lag. The cause may be that appendicitis is the reason for appendectomy and could be the early manifestation of colorectal cancer and that appendectomy is a less likely cause of colorectal cancer. To be protected from bias in the analysis focusing on exposure such as surgery and colorectal cancer risk, lag periods after surgery are

necessary.

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요약

담낭절제술과 충수돌기절제술은 대장암 발생 위험과의 상관관계에 대하여 그 가능성에 의해 연구가 많이 되어왔다. 담즙산의 대사산물이 대장암 발생의 발암물질임이 알려짐에 따라 담낭절제술 후 변화하는 담즙산의 대사과정으로 인해 대장암 발생 위험의 변화가 관심이 되어갔고, 위장관의 면역기관으로 알려진 충수와 이를 절제함으로써 생길 것이라 예상되는 위장관내 면역체계변화로 인해 충수돌기절제술과 대장암과의 상관관계에 대한 관심이 증가하였다. 하지만 기존의 연구에서는 일관된 결과를 보여주고 있지 못한데, 이는 연구과정에서 발생할 수 있는 비뚤림으로 인한 것으로 생각된다. 이 연구에서는 국민건강보험공단의 표본코호트 자료를 이용하여 담낭절제술, 충수돌기절제술과 대장암 발생위험과의 상관관계를 규명하였고, 이에 비뚤림의 영향을 고려하였다.

국민건강보험공단의 2002년부터 2015년까지의 보험청구자료 및 건강검진자료를 바탕으로 한국 국민의 2%를 표본추출 한 자료를 이용하여 후향적 코호트를 구축하였다. 20세 이상을 대상으로 대장암의 과거력이 있을 것으로 판단되는 2004년 이전에 대장암으로 청구된 사람들은 제외하여 연구를 진행하였다. 연구대상자는 담낭절제술, 충수돌기절제술을 시행 받기

전까지는 비노출군, 시행 받은 후부터 노출군으로 정의하여 대장암의 발생여부를 추적관찰 하여 인과관계를 확인하였다. 이때 추적관찰시간에 따라 층화하여 시간에 따른 위험도의 변화를 추정하였고, 또한 이 결과를 바탕으로 수술 이후 시간간격을 고려하여 대장암 발생 위험도를 확인하였다. 각 노출상태에 따라 시간종속 콕스회귀분석를 시행하여 위험도와 95% 신뢰구간을 계산하였다.

총 707,663명의 대상자가 연구에 등록되었으며, 평균 13.66년 추적관찰 되었고, 그 중 4,324명이 대장암으로 발생되었다. 대장암 발생의 위험도는 담낭절제를 받은 군은 받지 않은 군에 비하여 1년사이에 발생위험이 유의하게 증가하였으나 (HR: 1.71, 95% CI: 1.01-2.89), 그 이후의 기간에서는 유의성이 관찰되지 않았다. 담낭절제술 이후 시간간격을 두지 않고 분석하였을 때는 그 위험도는 0.94 (0.70-1.24)으로 유의하지 않았고, 이는 시간간격을 두더라도 유의하지 않았다. 충수돌기절제술을 받은 군은 1년이내 대장암의 발생위험이 4.22배 증가하였고, 이는 직장암보다는 우측 대장암에서 더 유의하게 관찰이 되었다. 충수돌기절제술 이후 시간간격을 두지 않은 분석에서는 대장암 발생 위험도가 1.44배 증가하였으나, 시간간격을 두었을 때는 유의하게 증가하지 않았다.

대장암의 발생 위험도는 담낭절제술을 시행한 군에서 1년이내에만 유의하게 증가하였는데, 이는 담낭절제술이 원인이라기보다 담석에 의한 증상과 대장암 증상의 유사성 때문이라고 생각되며, 이 영향을 고려하여 시간간격을 두고 분석하였을 때 유의하지 않음을 볼 때 담낭절제술은 대장암의 발생과 관련이 없을 것으로 생각된다. 또한 충수돌기절제술을 시행한 군은 1년이내 발생률이 유의하게 증가하고, 이후에는 유의하지 않음을 보았을 때 충수돌기절제술이 대장암의 원인이기 보다 충수돌기염이 대장암의 선행사건일 가능성이 높다. 이에 대한 영향을 고려하여 충수돌기술 이후 대장암의 발생위험을 시간간격을 고려하여 분석하였을 때, 통계적으로 유의한 결과가 보이지 않음을 보았을 때 충수돌기술 자체가 대장암의 원인일 가능성을 떨어진다.

주요어 : 대장암, 담낭절제술, 충수돌기절제술, 코호트 연구

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