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Risks of colorectal cancer and biliary cancer according to accompanied primary sclerosing cholangitis in Korean patients with ulcerative colitis: a nationwide population-based study

Eun Hye Oh[1], Ye-Jee Kim[2], Minju Kim[2], Seung Ha Park[3], Tae Oh Kim[3], Sang Hyoung Park[4]

[1]Department of Gastroenterology, Hanyang University Guri Hospital, Guri; [2]Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Seoul; [3]Department of Gastroenterology, Haeundae Paik Hospital, Inje University College of Medicine, Busan; [4]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background/Aims: We conducted a nationwide population-based study to investigate incidence rates of colorectal and biliary cancers according to accompanying primary sclerosing cholangitis in Korean ulcerative colitis patients. **Methods:** We used the Health Insurance Review and Assessment claim database from January 2007 to April 2020. Standardized incidence ratios of colorectal and biliary cancers in ulcerative colitis patients were calculated. **Results:** Among 35,189 newly diagnosed ulcerative colitis patients, 1,224 patients were diagnosed with primary sclerosing cholangitis. During the study period, 122 and 52 patients were diagnosed with colorectal and biliary cancers, respectively. Incidences of colorectal cancer were not higher in ulcerative colitis patients than those in the general population (standardized incidence ratios, 0.83; 95% confidence interval, 0.69–0.99), regardless of accompanied primary sclerosing cholangitis (standardized incidence ratio, 0.73; 95% confidence interval, 0.24–1.71). While incidences of biliary cancer were not higher in ulcerative colitis patients than those in the general population (standardized incidence ratio, 1.14; 95% confidence interval, 0.80–1.58), these were much higher with accompanied primary sclerosing cholangitis (standardized incidence ratio, 10.07; 95% confidence interval, 5.75–16.36). Cumulative incidences of colorectal and biliary cancers increased in patients who were diagnosed with ulcerative colitis at an older age. **Conclusions:** In Korean ulcerative colitis patients, colorectal cancer incidences were not higher than those in the general population regardless of accompanied primary sclerosing cholangitis. However, biliary cancer incidences were much higher in ulcerative colitis patients with primary sclerosing cholangitis than in those without, or in the general population. **(Intest Res 2023;21:252-265)**

Key Words: Colitis, ulcerative; Colorectal neoplasms; Biliary tract neoplasms; Cholangitis, sclerosing

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease mainly affecting the colon, which sometimes accompanies primary sclerosing cholangitis (PSC).[1] PSC is a chronic cholestatic liver disease, characterized by progressive destruction of bile ducts by repeated inflammation and fibrosis, leading to cirrhosis.[2] In patients with UC, PSC is usually suspected by elevated serum markers for cholestasis and diagnosed by typical "string-of-pearls" features of the bile duct on cholangiography.[3] Rectal sparing, right-sided colon dominance, pancolitis and backwash ileitis are more common with the accompaniment of PSC in patients with UC.[4,5]

Previous studies have reported that patients with UC have an increased risk of colorectal cancer (CRC), and the risk is re-

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Correspondence to Sang Hyoung Park, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea. Tel: +82-2-3010-5768, Fax: +82-2-476-0824, E-mail: umdalpin@hanmail.net

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ported to increase further in patients with UC and PSC.[6-8] Therefore, it is recommended that patients with UC accompanied by PSC begin surveillance for CRC immediately after the diagnosis of UC, while 8 to 10 years after diagnosis of UC in those without PSC.[9]

With a lifetime prevalence of 5% to 10%, the risk of biliary cancer is reported 1,560-fold higher in PSC patients than that in the general population.[10,11] With a very dismal prognosis of biliary cancer, annual imaging surveillance and serum carbohydrate antigen 19-9 determination is recommended.[9] However, because of the limited number of PSC and biliary cancer cases in patients with UC, reports on the risk of biliary cancer and surveillance recommendation are limited.

Therefore, we conducted a nationwide population-based long-term study to investigate the prevalence of PSC in Korean patients with UC. Moreover, incidences of CRC and biliary cancer according to accompanied PSC were evaluated.

METHODS

1. Ethical Considerations

We conducted this study in compliance with the principles of the Declaration of Helsinki. The study's protocol was reviewed and approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. GURI 2022-09-005). The informed consent was waived.

2. Data Sources

This study used the Korean National Health Insurance (NHI) and Health Insurance Review and Assessment Service (HIRA) claims databases. While the NHI system functions as a single health insurer for all Koreans, the data is collected in the process of reimbursing healthcare institutions and information on all healthcare utilization is stored in a comprehensive database operated by the HIRA. Information on demographic characteristics, principal diagnosis and comorbidity (using 10th International Classification of Disease codes), history of hospitalization and ambulatory care, prescriptions and medical procedures are also included. The data can be considered representative of the medical characteristics of Koreans as the NHI system covers almost 98% of the total population of South Korea.[12]

The NHI operates a patient registration system to relieve the financial burden of medical expenses for patients with severe diseases. Several categories of diseases, including rare intractable diseases (RIDs) and malignancies are included in the system. Diagnosis of the RIDs, including UC and PSC, and malignancies is based on the uniform diagnostic criteria announced by the NHI and is carefully reviewed by the healthcare institution and the NHI before registration. Once registered, the patients can benefit from paying only 5% to 10% of their medical expenses as the rest is reimbursed by the NHI.[13]

Since 1980, nationwide hospital-based cancer incidence data is collected by the Korea Central Cancer Registry established by the Ministry of Health and Welfare. By integrating these data with data from regional cancer registries, the Korea Central Cancer Registry provides annual statistics on cancer incidence and survival via the Korean Statistical Information Service (KOSIS).[14]

3. Identification of Patients with UC and Extraction of Co-variables

We identified patients with UC using the HIRA claims database between January 2007 to April 2020 and a washout period of 1 year (2007) was set to exclude prevalent cases. Only patients who were followed for at least 1 year were included. For more accurate identification of the patients with UC, prescription records of UC medication were used in combination with diagnostic codes.[15,16] Patients who met all of the following criteria were identified as patients with UC: (1) diagnostic codes for UC (K51.0–51.9) in the principal or subsidiary diagnostic field; (2) RID registration code for UC (V131); and (3) prescription of suppository or per oral 5-aminosalicylate >2 times and ≥30 days.

Data on baseline demographic characteristics (age, sex, and year at diagnosis), comorbidities and prescription of UC medications were extracted from the HIRA claims database. The investigated comorbidities and diagnostic codes were as follows: PSC (K83, K87, and V262), hypertension (I10–13, I15), diabetes mellitus (E10–14), coronary vascular disease (I20–25), cerebrovascular disease (I60–69), dyslipidemia (E78) and chronic kidney disease (N18 and dialysis code O701–709).[17]

4. Investigation of Cancer Incidence in the General Population and in Patients with UC

In general population, cancer incidences were investigated as presented on the KOSIS: colon and rectum (C18–20), liver (C22), extrahepatic bile duct and gall bladder (C23–24) (Supplementary Table 1). In the UC cohort defined by the HIRA claims database, incidences of malignancies after diagnosis of UC were investigated using C codes and V193, V194, and V027 codes. Patients with any C code and V193, V194, V027 codes

during the washout period were considered prevalent malignancy cases and excluded from analyses. When calculating standardized incidence ratios (SIRs), the values of 2019 and 2020 were substituted with the value of 2018 because only incidences from 2008 to 2018 were available on the KOSIS at the time of study. When evaluating an incidence of CRC in the UC cohort, patients were censored at the time of colectomy because of reasons other than CRC, such as toxic megacolon.[18]

To find an incidence of biliary cancer including intra- and extrahepatic bile duct cancer and gallbladder cancer in the UC cohort, incident cases were searched using C23–24 codes for extrahepatic bile duct cancer and gall bladder cancer and C22.1 code for intrahepatic bile duct cancer. Meanwhile, the KOSIS only provided the incidence data of C codes with an integer number, and an incidence of C22.1 code was not provided. As C22 code includes other kinds of intrahepatic malignancies, an incidence of intrahepatic biliary cancer (C22.1) was evaluated only in the UC cohort. Therefore, SIR of intra- and extrahepatic biliary cancers (C22.1, 23–24) was not assessable, while that of extrahepatic bile duct cancer and gallbladder cancer (C23–24) was assessable.

5. Statistical Analysis

Categorical variables were expressed as numbers with percentages, and continuous variables were expressed as medians (interquartile ranges) or means ± standard deviations. Kaplan-Meier analysis and log-rank test were performed to compare cumulative incidences among groups. All statistical analyses were performed using SAS Enterprise Guide software Version 7.1 (SAS Institute Inc., Cary, NC, USA) and SPSS version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline Characteristics and Prevalence of PSC in Patients with UC

In this nationwide population-based long-term study, 36,289 patients were defined as patients who were newly diagnosed with UC and followed for more than 1 year. After excluding 1,100 patients as prevalent malignancy cases, the remaining 35,189 patients were finally included in the analyses. Among the study patients, 60.72% (21,368/35,189) were male. The study patients were of a median age of 41 years (interquartile range, 29–54 years) at diagnosis of UC. The most common comorbidity at diagnosis of UC was dyslipidemia (8,024/35,189, 22.80%), and hypertension (5,327/35,189, 15.14%). Altogether, 232 patients (0.66%) had PSC at diagnosis of UC, and the cumulative proportion of comorbid PSC increased to 3.47% (1,226/35,189) during the study period (Table 1).

During the study period, most of the patients used 5-aminosalicylate suppository (27,602/35,189, 78.44%) and per oral formula (30,915/35,189, 87.85%). Less than a quarter (8,456/35,189, 24.03%) used immunomodulators. Proportion of patients with UC who used any kind of biologics was 11.27% (3,963/35,189) and 1,086 patients (3.09%) used more than two kinds of biologics. The most commonly used biologics were infliximab (2,724/35,189, 7.74%) and adalimumab (1,491/35,189, 4.24%) (Table 1).

2. CRC in Patients with UC with or without PSC

Among the study patients, 122 (0.35%) were newly diagnosed with CRC during the study period. The prevalence of CRC was 0.38% (81/21,368) and 0.30% (41/13,821) in male and female patients, respectively. The SIR of CRC in the UC cohort was 0.83 (incidence rate [IR], 55.08/100,000; 95% confidence interval [CI], 0.69–0.99). In terms of sex, the SIRs were 0.77 (IR, 61.21/100,000; 95% CI, 0.61–0.95) and 0.99 (IR, 45.98/100,000; 95% CI, 0.71–1.35) in male and female patients, respectively (Table 2).

In patients with UC without PSC, the prevalence was 0.34% (117/33,968). According to sex, the prevalence was 0.38% (79/20,625) and 0.28% (38/13,343) in the male and female patients, respectively. The SIR in patients with UC without PSC was 0.84 (IR, 54.91/100,000; 95% CI, 0.69–1.00). In terms of sex, the SIRs were 0.79 (IR, 62.04/100,000; 95% CI, 0.62–0.98) and 0.97 (IR, 44.31/100,000; 95% CI, 0.68–1.33) in male and female patients, respectively (Table 2).

In patients with UC accompanied by PSC, the prevalence was 0.41% (5/1,221). According to sex, the prevalence was 0.27% (2/743) and 0.63% (3/478) in male and female patients, respectively. The SIR in patients with UC accompanied by PSC was 0.73 (IR, 59.57/100,000; 95% CI, 0.24–1.71). According to sex, the SIRs were 0.40 (IR, 40.06/100,000; 95% CI, 0.05–1.45) and 1.62 (IR, 88.21/100,000; 95% CI, 0.33–4.75) in male and female patients, respectively (Table 2).

Cumulative incidences of CRC showed significant differences among groups by age at diagnosis of UC ($P<0.001$). The results were similar in male ($P=0.007$) and female ($P<0.001$) patients (Fig. 1). The cumulative incidences had no difference according to accompanied PSC in patients with UC ($P=0.878$). The results were similar in male ($P=0.536$) and female ($P=0.246$) patients (Fig. 2).

https://doi.org/10.5217/ir.2022.00092 • Intest Res 2023;21(2):252-265

Table 1. Baseline Characteristics of Patients Diagnosed with Ulcerative Colitis between January 2008 and April 2020

Characteristics	Total (n = 35,189)	Male (n = 21,368)	Female (n = 13,821)
At diagnosis of ulcerative colitis			
Age at diagnosis of ulcerative colitis (yr)			
Mean ± standard deviation	41.65 ± 16.09	41.58 ± 15.99	41.78 ± 16.24
Median (interquartile range)	41 (29–54)	41 (28–54)	41 (29–53)
Age group			
< 30	9,422 (26.78)	5,794 (27.12)	3,628 (26.25)
30 to < 40	7,160 (20.35)	4,203 (19.67)	2,957 (21.39)
40 to < 50	7,047 (20.03)	4,281 (20.03)	2,766 (20.01)
50 to < 60	6,268 (17.81)	3,898 (18.24)	2,370 (17.15)
≥ 60	5,292 (15.04)	3,192 (14.94)	2,100 (15.19)
Year at diagnosis of ulcerative colitis			
2008.1–2011.12	11,176 (31.76)	6,544 (30.63)	4,632 (33.51)
2012.1–2015.12	12,029 (34.18)	7,323 (34.27)	4,706 (34.05)
2016.1–2019.4	11,984 (34.06)	7,501 (35.10)	4,483 (32.44)
Comorbid disease (at diagnosis of ulcerative colitis)			
Primary sclerosing cholangitis	232 (0.66)	149 (0.70)	83 (0.60)
Hypertension	5,327 (15.14)	3,553 (16.63)	1,774 (12.84)
Diabetes mellitus	3,196 (9.08)	2,158 (10.10)	1,038 (7.51)
Coronary vascular disease	1,361 (3.87)	939 (4.39)	422 (3.05)
Cerebrovascular disease	974 (2.77)	630 (2.95)	344 (2.49)
Dyslipidemia	8,024 (22.80)	5,095 (23.84)	2,929 (21.19)
Chronic kidney disease	163 (0.46)	119 (0.56)	44 (0.32)
Cumulative data during the study period			
Comorbid disease			
Primary sclerosing cholangitis	1,226 (3.47)	746 (3.48)	480 (3.46)
Hypertension	8,940 (25.41)	5,901 (27.62)	3,039 (21.99)
Diabetes mellitus	8,798 (25.00)	5,540 (25.93)	3,258 (23.57)
Coronary vascular disease	3,747 (10.65)	2,434 (11.39)	1,313 (9.50)
Cerebrovascular disease	3,065 (8.71)	1,837 (8.60)	1,228 (8.89)
Dyslipidemia	20,644 (58.67)	12,558 (58.77)	8,086 (58.51)
Chronic kidney disease	571 (1.62)	395 (1.85)	176 (1.27)
Other malignancies	1,276 (3.63)	800 (3.74)	476 (3.44)
Ulcerative colitis treatment			
Conventional therapeutics			
5-Aminosalicylate, suppository	27,602 (78.44)	16,550 (77.45)	11,052 (79.97)
5-Aminosalicylate, per oral	30,915 (87.85)	18,789 (87.93)	12,126 (87.74)
Immunomodulator (thiopurines, methotrexate)	8,456 (24.03)	5,502 (25.75)	2,954 (21.37)
Biologics (any)	3,963 (11.27)	2,531 (11.84)	1,432 (10.36)
Infliximab	2,724 (7.74)	1,724 (8.07)	1,000 (7.24)
Adalimumab	1,491 (4.24)	964 (4.51)	527 (3.81)
Golimumab	468 (1.33)	304 (1.42)	164 (1.19)
Vedolizumab	441 (1.25)	273 (1.28)	168 (1.22)
Ustekinumab	31 (0.09)	20 (0.09)	11 (0.08)
Tofacitinib	272 (0.77)	186 (0.87)	86 (0.62)

Values are presented as number (%) unless indicated otherwise.

Table 2. Risk of Colorectal Cancer in Patients Diagnosed with Ulcerative Colitis with or without PSC[a]

Variable	All	Without PSC	With PSC
Total			
No. of patients	35,189	33,968	1,221
No. of incident cases	122	117	5
Sum of PY	221,484	213,091	8,393
IR (/100,000)	55.08	54.91	59.57
No. of expected cases	146.73	139.91	6.82
SIR	0.83	0.84	0.73
95% CI	0.69–0.99	0.69–1.00	0.24–1.71
Male			
No. of patients	21,368	20,625	743
No. of incident cases	81	79	2
Sum of PY	132,324	127,331	4,992
IR (/100,000)	61.21	62.04	40.06
No. of expected cases	105.53	100.55	4.97
SIR	0.77	0.79	0.40
95% CI	0.61–0.95	0.62–0.98	0.05–1.45
Female			
No. of patients	13,821	13,343	478
No. of incident cases	41	38	3
Sum of PY	89,160	85,759	3,400
IR (/100,000)	45.98	44.31	88.21
No. of expected cases	41.21	39.36	1.85
SIR	0.99	0.97	1.62
95% CI	0.71–1.35	0.68–1.33	0.33–4.75

[a]Censored at the time of colectomy for reasons other than colorectal cancer. PSC, primary sclerosing cholangitis; PY, person-years; IR, incidence rate; SIR, standardized incidence ratio; CI, confidence interval.

3. Intra- and Extrahepatic Bile Duct Cancer and Gallbladder Cancer in Patients with UC with or without PSC

Among the study patients, 52 (0.15%) were newly diagnosed with intra- and extrahepatic bile duct cancer and gallbladder cancer during the study period. The prevalences of intra- and extrahepatic bile duct cancer and gallbladder cancer were 0.14% (29/21,368) and 0.17% (23/13,821) in the male and female patients, respectively. In patients with UC without PSC, the prevalence was 0.08% (26/33,963), 0.07% (14/20,622), and 0.09% (12/13,341) in both sexes, male patients, and female patients, respectively. In patients with UC accompanied by PSC, the prevalence was 1.96% (24/1,226), 2.01% (15/746), and 1.88% (9/480) in both sexes, male patients, and female patients, respectively (Table 3).

Incidence of intra- and extrahepatic bile duct cancer and gallbladder cancer was much higher in patients with UC accompanied by PSC (285.03/100,000) than that in those with UC without PSC (12.12/100,000) and all UC patients (23.32/100,000). Results were similar when analyzing according to sex. In male patients, the incidences were 21.75/100,000, 10.91/100,000, and 299.70/100,000 in all male patients, male patients without PSC, and male patients without PSC, respectively. In female patients, the incidences were 25.65/100,000, 13.91/100,000, 263.52/100,000, respectively (Table 3).

Cumulative incidences of intra- and extrahepatic bile duct cancer and gallbladder cancer showed significant difference among groups by age at diagnosis of UC ($P<0.001$). The results were similar in male ($P<0.001$) and female ($P=0.002$) patients (Fig. 3). Moreover, the cumulative incidences showed significant difference according to accompanied PSC in patients with UC ($P<0.001$). The results were similar in male ($P<0.001$) and female ($P<0.001$) patients (Fig. 4).

4. Extrahepatic Bile Duct Cancer and Gallbladder in Patients with UC with or without PSC

To assess SIR for biliary cancer, we evaluated incidences for extrahepatic bile duct cancer and gallbladder cancer in the UC cohort. In patients with UC, prevalence of extrahepatic bile duct cancer and gallbladder cancer was 0.10% (36/35,189). In terms of sex, the prevalence was 0.18% (23/21,368) and 0.09% (13/13,821) in male and female patients. The SIR in the UC cohort was 1.14 (IR, 16.14/100,000; 95% CI, 0.80–1.58). In terms of sex, the SIR was 1.09 (95% CI, 0.69–1.63; IR, 17.25/100,000) and 1.24 (95% CI, 0.66–2.12; IR, 14.49/100,000) in the male and female patients, respectively (Table 3).

In patients with UC without PSC, the prevalence was 0.06% (20/33,963). According to sex, the prevalence was 0.06% (12/20,622) in male patients, and 0.06% (8/13,341) in female patients. The SIR in patients with UC without PSC was 0.67 (IR, 9.32/100,000; 95% CI, 0.41–1.03). According to sex, the SIR was 0.60 (95% CI, 0.31–1.05; IR, 9.35/100,000) and 0.80 (95% CI, 0.34–1.58; IR, 9.27/100,000) in the male and female patients, respectively (Table 3).

In patients with UC accompanied by PSC, the prevalence was 1.31% (16/1,226). According to sex, the prevalence was 1.47% (11/746) and 1.04% (5/480) in male and female patients, respectively. The SIR in patients with UC with PSC was 10.07 (IR, 189.24/100,000; SIR, 10.07; 95% CI, 5.75–16.36). In terms of sex, SIR was similar in male (IR, 218.82/100,000; SIR, 10.11;

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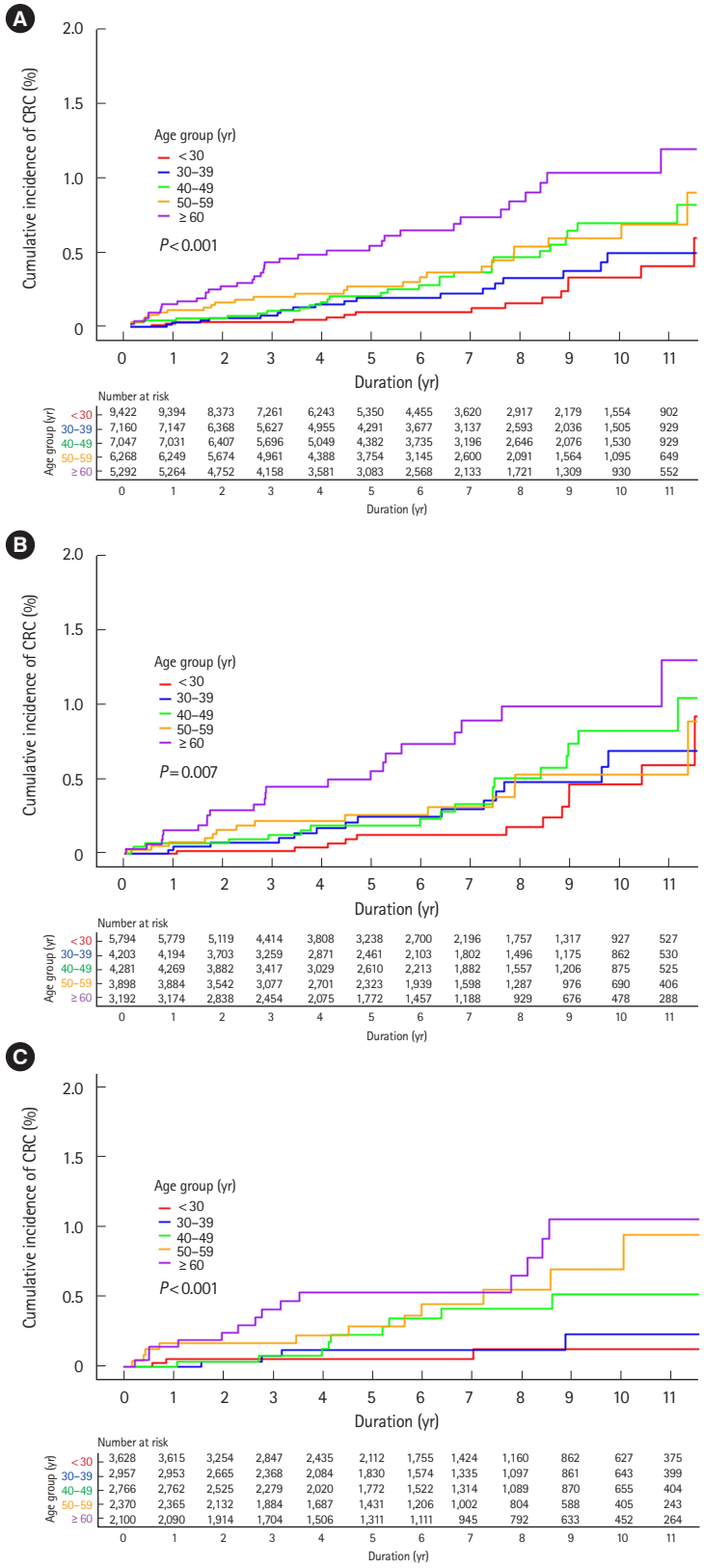

Fig. 1. Cumulative incidence of colorectal cancer (CRC) by age groups. Kaplan-Meier curve for CRC by age group (A) in total (n = 35,189), (B) in male (n = 21,368) and (C) in female (n = 13,821).

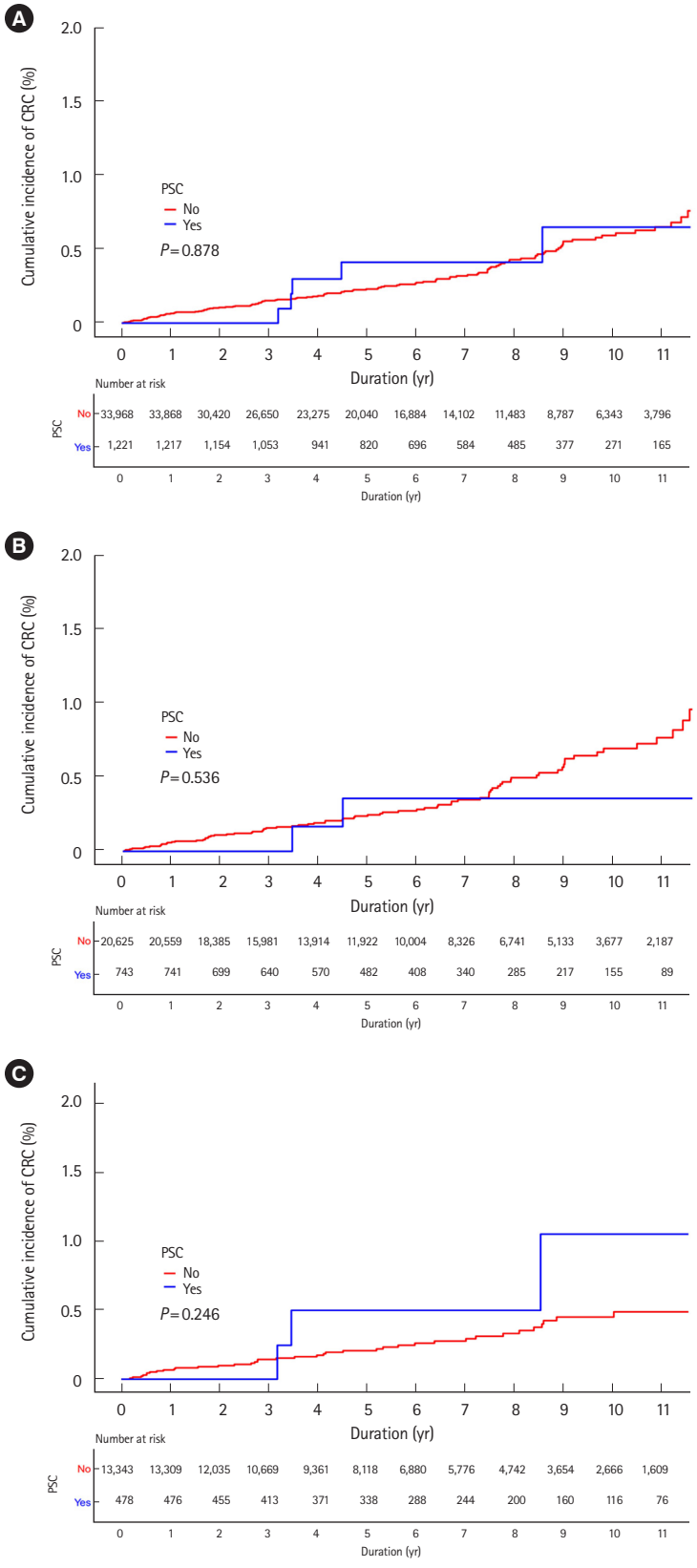

Fig. 2. Cumulative incidence of colorectal cancer (CRC) by primary sclerosing cholangitis (PSC) in patients with ulcerative colitis. Kaplan-Meier curve for CRC by PSC (A) in total (n = 35,189), (B) in male (n = 21,368) and (C) in female (n = 13,821).

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Table 3. Risk of Biliary Cancer in Patients Diagnosed with Ulcerative Colitis with or without PSC

Variable	Intra/extrahepatic bile duct and gall bladder			Extrahepatic bile duct and gall bladder		
	All	Without PSC	With PSC	All	Without PSC	With PSC
Total						
No. of patients	35,189	33,963	1,226	35,189	33,963	1,226
No. of incident cases	52	26	24	36	20	16
Sum of PY	223,013	214,593	8,420	223,079	214,624	8,454
IR (/100,000)	23.32	12.12	285.03	16.14	9.32	189.24
No. of expected cases	NA	NA	NA	31.61	30.03	1.59
SIR	NA	NA	NA	1.14	0.67	10.07
95% CI	NA	NA	NA	0.80–1.58	0.41–1.03	5.75–16.36
Male						
No. of patients	21,368	20,622	746	21,368	20,622	746
No. of incident cases	29	14	15	23	12	11
Sum of PY	133,328	128,323	5,005	133,365	128,338	5,026
IR (/100,000)	21.75	10.91	299.7	17.25	9.35	218.82
No. of expected cases	NA	NA	NA	21.11	20.03	1.09
SIR	NA	NA	NA	1.09	0.60	10.11
95% CI	NA	NA	NA	0.69–1.63	0.31–1.05	5.04–18.09
Female						
No. of patients	13,821	13,341	480	13,821	13,341	480
No. of incident cases	23	12	9	13	8	5
Sum of PY	89,685	86,270	3,415	89,714	86,286	3,427
IR (/100,000)	25.65	13.91	263.52	14.49	9.27	145.86
No. of expected cases	NA	NA	NA	10.50	10.00	0.50
SIR	NA	NA	NA	1.24	0.80	10.00
95% CI	NA	NA	NA	0.66–2.12	0.34–1.58	3.22–23.35

PSC, primary sclerosing cholangitis; PY, person-years; IR, incidence rate; SIR, standardized incidence ratio; CI, confidence interval; NA, not available.

95% CI, 5.04–18.09) and female (IR, 145.86/100,000; SIR, 10.00; 95% CI, 3.22–23.35) patients (Table 3).

DISCUSSION

This nationwide population-based long-term study aimed to investigate the prevalence of PSC and incidences of CRC and biliary cancer according to accompanying PSC in Korean patients with UC. During the 14-year study period, 1,224 patients (3.47%) were diagnosed with PSC among the 35,189 patients with UC. During the study period, 122 patients (0.35%) were newly diagnosed with CRC with SIR of 0.83 (95% CI, 0.69–0.99). Prevalence and cumulative incidence of CRC in patients with UC with accompanied PSC were not higher than those in patients with UC without PSC. During the study period, 52 patients (0.15%) were newly diagnosed with intra- and extrahepatic bile duct cancer and gallbladder cancer. Prevalence and cumulative incidence of intra- and extrahepatic bile duct cancer and gallbladder cancer in patients with UC with accompanied PSC were much higher than those in patients with UC without PSC. During the study period, 36 patients (0.10%) were newly diagnosed with extrahepatic bile duct cancer and gallbladder cancer. Prevalence and cumulative incidence of extrahepatic bile duct cancer and gallbladder cancer in patients with UC with accompanied PSC were much higher than those in UC patients without PSC with SIR of 10.07 (95% CI, 5.75–16.36). Cumulative incidences of CRC and biliary cancer increased in patients who were diagnosed with UC at an older age.

Because some clinical manifestations of UC in patients with

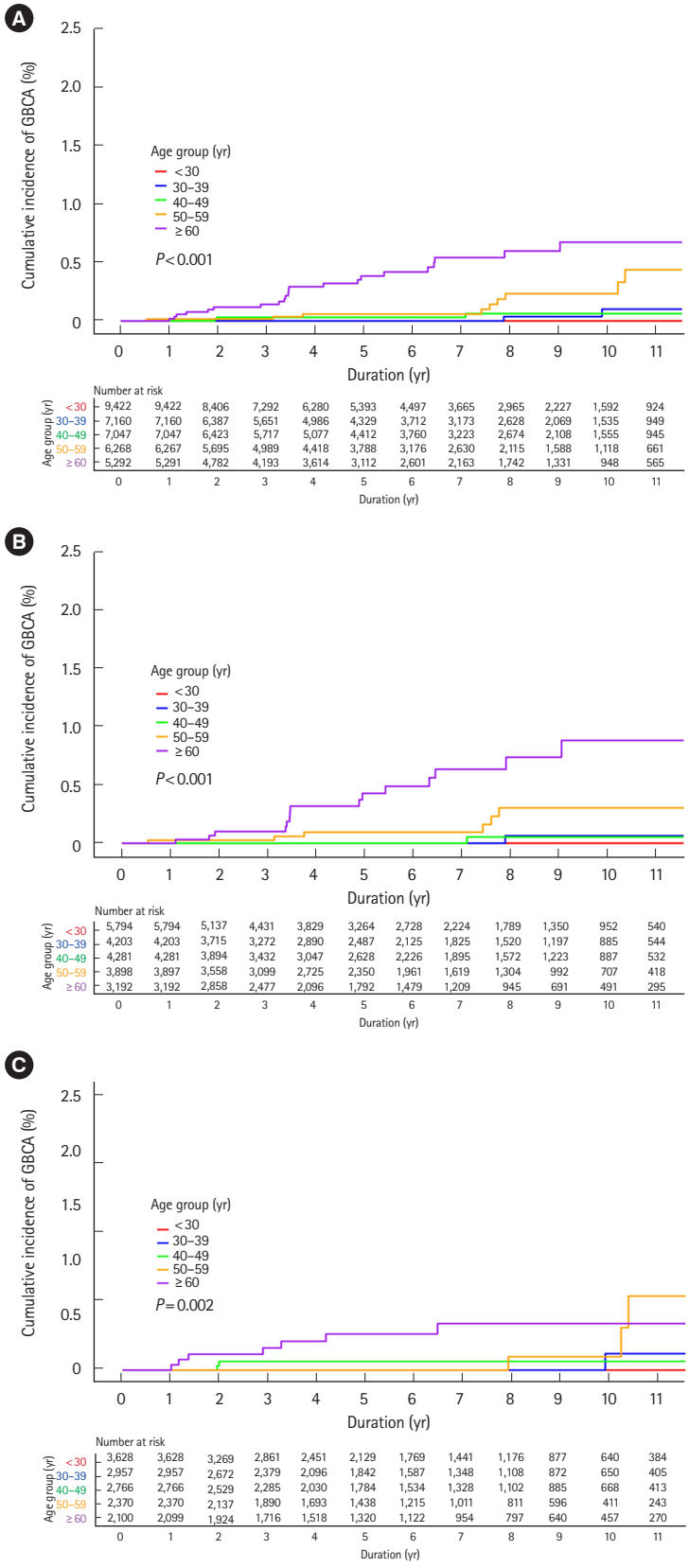

Fig. 3. Cumulative incidence of intra- and extrahepatic bile duct cancer and gallbladder cancer (GBCA) by age groups. Kaplan-Meier curve for biliary cancer by age group (A) in total (n = 35,189), (B) in male (n = 21,368) and (C) in female (n = 13,821).

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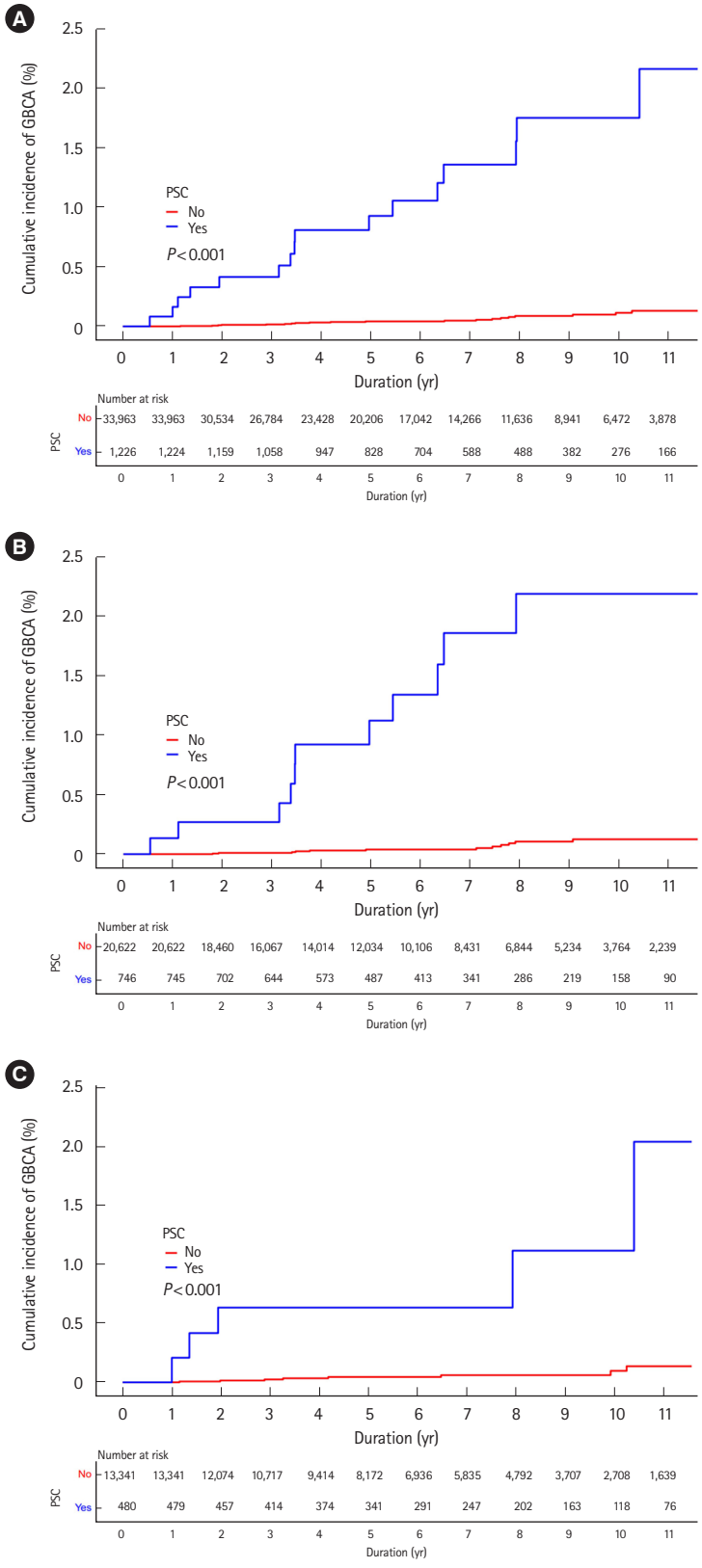

Fig. 4. Cumulative incidence of intra- and extrahepatic bile duct cancer and gallbladder cancer (GBCA) by primary sclerosing cholangitis (PSC) in patients with ulcerative colitis. Kaplan-Meier curve for biliary cancer by PSC (A) in total (n = 35,189), (B) in male (n = 21,368) and (C) in female (n = 13,821).

accompanied PSC are different from those without PSC,[4] and UC and PSC frequently accompany each other,[19] many studies suggested that there could be common factors in the pathogenesis of UC and PSC.[3,20] While the prevalence of PSC in patients with UC is reported to be 3%–8% in Western countries,[3] there are limited studies reporting its prevalence in Asian countries. Retrospective single-center studies from South Korea and Iran reported the prevalence as 1.1%, and 4.3%, respectively, while they included only 21 and 19 patients with UC and PSC, respectively.[4,21] A nationwide study from Japan included 197 PSC patients and reported proportion of comorbid inflammatory bowel disease (IBD) as 34%. However, the study was not able to suggest the prevalence of PSC in patients with UC, and limited because it was conducted based on a questionnaire supplied to patients in only a part of hospitals in Japan.[19] As the prevalence data are lacking in Asian countries, these results might be valuable.

Previous studies have reported an increased risk of CRC in patients with UC. A meta-analysis by Eaden et al.[22] reported that the 4 to 10 times increased incidence of CRC in patients with UC than that of sporadic CRC. However, more recently published papers have reported a declining incidence of CRC in patients with UC.[23,24] In our study, the cumulative incidence of CRC in patients with UC during 14 years of the study period did not increase. Considering studies reporting that the incidence of CRC begins to increase 8 to 10 years after the diagnosis of UC,[25] observation period in our study might not be adequately long to reflect the risk of CRC. However, considering that the incidence of sporadic CRC in Korea and many countries has gradually increased recently,[26,27] which is shown in our data (Supplementary Table 1), the excess risk of CRC in UC might not be significant any longer. Moreover, with the proven role of screening colonoscopy for reducing incidence and mortality of sporadic CRC in the general population,[28-30] regular and frequent surveillance colonoscopy in patients with UC might affect the trend in the incidence of CRC.[23,31,32] The chemopreventive effect of 5-aminosalicylate and advancements in treatment strategies might also have contributed to the decrease of CRC in patients with UC.[6,33,34]

The risk of CRC has been reported to increase further with PSC in patients with UC.[35,36] Previous studies have suggested that the increase might be attributed to the delayed diagnosis of UC because of the subclinical course of UC despite pancolitis in patients with PSC.[7] Several studies also have reported the deleterious effects of bile acid leading to carcinogenesis by inducing DNA damage in exposed cells, including colon cells.[8] Therefore, the European guidelines suggest annual surveillance colonoscopy for patients with PSC from the beginning of PSC diagnosis.[37] However, there are a limited number of studies reporting PSC in patients with UC, and even more a limited number of studies have reported CRC in patients with UC and PSC. Therefore, previous studies might have been limited to identifying whether the risk of CRC increases with accompanying PSC. In this nationwide population-based long-term study, prevalence and cumulative incidence of CRC in patients with UC with accompanied PSC were not higher than those in patients with UC without PSC.

Incidences of PSC are reported to be lower in Asia and Southern Europe, compared to those in the USA and Northern Europe. While the only therapeutics currently available with proven efficacy is ursodeoxycholic acid,[2] the risk of biliary cancer markedly increases in PSC patients,[10,11] and the cancer carries a very dismal prognosis with a 3-year survival rate of <20%.[38] Therefore, annual surveillance with magnetic resonance imaging/cholangiopancreatography or ultrasound and serum carbohydrate antigen 19-9 determination is recommended in PSC patients from the beginning of PSC diagnosis to improve incidence and prognosis of biliary cancer.[9] Even though PSC is an important extra-intestinal manifestation of UC, there are limited reports on the risk of biliary cancer and surveillance recommendations in patients with UC and PSC.[37] A Swiss cohort study reported an increased risk of biliary cancer in IBD patients compared to that in the general population (SIR, 6.3; 95% CI, 1.27–18.41). even though it is uncertain whether PSC was associated with biliary cancer in the study.[39] Another case-controlled single-center study from Sweden reported increased risk of cholangiocarcinoma in patients with UC with PSC, compared to the risk in patients with UC without PSC. The study included only 120 patients with UC (40 with PSC, 80 without PSC) and the mean observation time was 9 years (range, 1–25 years). Ten patients developed cholangiocarcinoma and all cases were included in the UC-PSC group. Although the study can suggest the increased risk of cholangiocarcinoma in the accompaniment of PSC in patients with UC, relative risk could not be assessed.[35] In our study, incidences of biliary cancer were not higher in patients with UC than those in the general population. However, the incidences were >10-fold higher with accompanied PSC in patients with UC.

This study is mainly limited as results of laboratory tests, colonoscopy, or computed tomography were not available from the HIRA claims database. Therefore, variables, such as the extent of UC, stage of CRC, and whether the CRC was spo-

radic or colitis-associated, were not evaluable. Moreover, incidences of non-malignant colorectal tumors and multiplicity of colorectal tumors were not evaluable. Despite the limitation, the dataset has the strength and importance in containing all the information on the use of all forms of medical services in the Korean population. Thereby, the database is frequently used in political decision-making, and academic research in medicine, including that of IBD.[15,40] In addition, the prevalence of comorbidities, such as dyslipidemia and hypertension, might be overestimated because the diseases have no RID codes and medication prescription records were not used in combination when defining the diseases. Another limitation is the impossibility of suggesting the interval of surveillance for CRC and biliary cancer in patients with UC with or without PSC. However, guidelines and recommendations should be established based on the results of rigorous studies with reliable data. Although we were not able to make a clear suggestion for surveillance intervals, we believe that the results of this study might contribute to the production of revised surveillance guidelines that reflect recent trends in UC.

In this nationwide population-based long-term study, incidences of CRC were not higher in patients with UC regardless of accompanied PSC when compared to those in the general population. However, the incidence of biliary cancer increased >10-fold with accompanying PSC in patients with UC compared to that in patients with UC without accompanied PSC or in the general population.

ADDITIONAL INFORMATION

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

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Not applicable.

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ORCID
Oh EH https://orcid.org/0000-0003-4845-9809
Kim YJ https://orcid.org/0000-0002-3307-2970
Kim M https://orcid.org/0000-0003-4600-5352
Park Seung Ha https://orcid.org/0000-0002-5950-2713
Kim TO https://orcid.org/0000-0002-7359-1599
Park Sang Hyoung https://orcid.org/0000-0002-5366-5749

Supplementary Material
Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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