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The Association of Ursodeoxycholic Acid Use With Colorectal Cancer Risk

A Nationwide Cohort Study

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Abstract: Data from preclinical studies suggest that ursodeoxycholic acid (UDCA) has a chemopreventive effect on colorectal cancer (CRC) development, but no large observational study has examined this possibility.

The aim of this study was to investigate the association of UDCA use with CRC risk in a nationwide population-based cohort.

This nationwide population-based cohort study used data from the Taiwan National Health Insurance Research Database for the period from 2000 through 2010. This study included data from 7119 Taiwanese adults who received ≥28 cumulative defined daily doses (cDDDs) of UDCA and 14,238 patients who did not receive UDCA (<28 cDDDs). UDCA nonusers were matched 1:2 for age, sex, enrollment date, and presence of chronic liver disease, viral hepatitis, cholelithiasis, and alcoholic liver disease. The 2 cohorts were followed until December 31, 2010 or occurrence of CRC. Cox proportional hazards regression with robust Sandwich variance estimator, which can cooperate with matching design, was used to examine the association between UDCA use and CRC risk.

During 109,312 person-years of follow-up (median, 5 years), 121 patients had newly diagnosed CRC: 28 UDCA users (76.7 per 100,000 person-years) and 93 nonusers (127.7 per 100,000 person-years) (log-rank test, $P = 0.0169$). After multivariate adjustment for age, UDCA use was associated with a reduced risk of CRC (hazard ratio, 0.60; 95% confidence interval [CI], 0.39–0.92). The adjusted hazard ratios were 0.55 (95% CI, 0.35–0.89), 0.89 (95% CI, 0.36–2.20), and 0.63 (95% CI, 0.16–2.53) for patients with 28 to 180, 181 to 365, and >365 cDDDs, respectively, relative to nonusers.

UDCA use was associated with reduced risk of CRC in a cohort mainly comprising patients with chronic liver diseases. However, further studies are needed to determine the optimal dosage of UDCA.

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Abbreviations: cDDD = cumulative defined daily doses, CRC = colorectal cancer, HCC/ICC = hepatocellular carcinoma and intrahepatic cholangiocarcinoma, HR = hazard ratio, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, LGI = lower gastrointestinal endoscopy, NHIRD = National Health Insurance Research Databases, NSAID = non-aspirin nonsteroidal anti-inflammatory drugs, UDCA = ursodeoxycholic acid.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and fourth leading cause of cancer-related death globally.[1] Although recent advances in screening and treatment have improved CRC survival, the increasing incidence rate of CRC in Asian countries is a major challenge.[2] In Taiwan, CRC is the most common cancer and the third leading cause of cancer-related death. In 2012, there were an estimated 14,965 new CRC cases and 5131 deaths owing to CRC.[3]

CRC development is a multistep process that can take several decades; thus, chemoprevention is a promising strategy for reducing CRC incidence.[4] Epidemiologic studies and clinical trials have shown that aspirin decreases CRC incidence.[5,6] Other agents, including non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), folic acid, calcium, vitamin D, and antioxidants, have been studied, but their effect on CRC incidence has not been determined because of heterogeneity in the populations studied and insufficient duration of follow-up.[7]

Ursodeoxycholic acid (UDCA) is a synthetic bile acid extensively used in the treatment of primary sclerosing cholangitis, primary biliary cirrhosis, and other chronic cholestatic

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liver diseases. UDCA had a chemopreventive effect on colon cancer development in preclinical studies.[8–11] On the basis of those experimental observations, the use of UDCA as a chemoprevention agent has been investigated in diverse populations at risk of CRC, including patients with a history of adenoma removal,[12–14] familial adenomatous polyp,[15] and inflammatory bowel disease.[16–21] The conflicting results of those studies were attributed to differences in UDCA dosing, the small numbers of patients analyzed, methodologic differences between prospective and retrospective studies, and the high proportions of patients excluded from analysis.[22,23] No large-scale epidemiologic studies have investigated this issue.

In Taiwan, which has a population of 23 million, chronic liver disease is a major health problem. The carrier rate of HBsAg in general population has been reported as high as 10% to 15% in 1990s.[24–26] The prevalence rate of hepatitis C in general population was 4.5% in a community-based screening program during 1996 to 2005.[26] One study using back-projection approach estimated that the prevalence rate of hepatitis C in 2012 was 2.8%.[27] To delay development of sequelae such as cirrhosis and hepatocellular carcinoma, several hepatoprotectants, including silymarin and UDCA, are commonly prescribed for patients with chronic liver disease.[28] The high incidence of CRC and common use of UDCA in Taiwan provide a unique opportunity to investigate the association between UDCA use and CRC development. We conducted a nationwide population-based cohort study to compare the risk of CRC development in UDCA users and nonusers.

METHODS

Data Sources

Taiwan began providing compulsory universal health insurance through a national health insurance (NHI) program in 1995. About 22.6 million of Taiwan's 22.96 million people (98% of the total population) were enrolled for some form of health care coverage. The National Health Insurance Administration (NHIA) cooperates with the National Health Research Institute (NHRI) in storing and managing all insurance claims data in the National Health Insurance Research Databases (NHIRDs). The databases comprise of comprehensive information, including birth date, sex, diagnostic codes, surgery or procedures received, medications prescribed, admission date, hospitalizations, discharge date, medical institution codes, and expenditure amounts. In the years 2000 and 2005, the NHRI randomly sampled 1,000,000 patients registered in the NHI, to create the Longitudinal Health Insurance Database (LHID) 2000 and 2005, respectively. There were no statistically significant differences in age, sex, or health care costs between the LHID and the 22.6 million enrolled beneficiaries (http://nhird.nhri.org.tw/date_cohort.htm#1 for LHID 2005, http://nhird.nhri.org.tw/date_cohort.htm#2 for LHID 2000).

This study was approved by the institutional review board of Chang Gung Memorial Hospital (103–6867B). The identification number of each patient had been previously encrypted for protection of privacy; therefore, informed consent was not needed and was waived.

Study Population

Using data extracted from the LHID 2000 and 2005, we conducted a population-based cohort study of patients (age $\geq$20 years) who had received a prescription for UDCA during the period from January 1, 2000 to December 31, 2010. Date of enrollment was defined as the date on which UDCA was initially prescribed. We excluded patients with a CRC diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [*ICD-9-CM*] codes 153, 154) before enrollment (n = 262). For each UDCA user, we randomly selected 2 UDCA nonusers as control patients from the same database. Nonusers were matched for age, sex, enrollment date, and comorbidities related to chronic liver diseases (*ICD-9-CM* codes 571.4, 571.8–571.9), viral hepatitis A (*ICD-9* codes 70.0–70.1), viral hepatitis B (*ICD-9* codes 70.2–70.3), viral hepatitis C (*ICD-9* codes 70.4–70.5, 70.7), cholelithiasis (*ICD-9* code 574), and alcoholic liver disease (*ICD-9* codes 571.0–571.3). All UDCA users and nonusers were observed until a diagnosis of CRC, death, or December 31, 2010, whichever occurred first (Figure 1).

Ascertainment of UDCA Use

Information on all UDCA prescriptions was extracted from the NHRI prescription database. The date of prescription, daily dose, and number of days supplied were collected. Defined daily doses (DDDs) were used in the analysis, as recommended by the World Health Organization.[29] According to the Anatomical Therapeutic Chemical Classification system (ATC)/DDD Index, the DDD of UDCA is 750 mg/day.[30] To indicate duration of UDCA use, cumulative DDD (cDDD) was computed as the sum of dispensed DDD. Patients were categorized into 4 groups by number of cDDDs <28, 28–180, 181–365, >365 to examine the dose–response relationship, and patients who received UDCA for >28 cDDDs were defined as UDCA users.

Ascertainment of CRC

CRC events were identified using codes 153 and 154 of the *ICD-9-CM*. CRC diagnoses were verified by using records in the registry of catastrophic illnesses. In Taiwan, registration of CRC as a catastrophic illness is approved after evaluating pathologic and/or cytologic evidence, and a comprehensive review is conducted to determine eligibility for exemption from all copayments.

Potential Confounders

Comorbidities associated with CRC development included hypertension (*ICD-9* codes 401–404), hyperlipidemia (*ICD-9* code 272), diabetes mellitus (DM) (*ICD-9* code 250), cardiovascular disease (*ICD-9* codes 410–414), and heart failure (*ICD-9* code 428) (32–34). We also assessed prescriptions >28 days for aspirin, NSAIDS (diclofenac, sulindac, indomethacin, acemetacin, aceclofenac, meloxicam, ibuprofen, naproxen, ketoprofen, and mefenamic acid), and statins (atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin, and fluvastatin), which could potentially confound the association between UDCA and CRC risk.[31–36] Given lower gastrointestinal endoscopy (LGI) procedure could be a major confounding variable to detect CRC, patients who underwent LGI with or without biopsy and/or polypectomy were analyzed.

Statistical Analysis

The χ^2 test or unpaired *t* test was used to compare data between the 2 study groups in univariate analysis. The Kaplan–Meier method was used to estimate the time-to-event curve. Survival analysis (log-rank test in univariate analysis and a time-dependent Cox proportional hazards model in multivariate

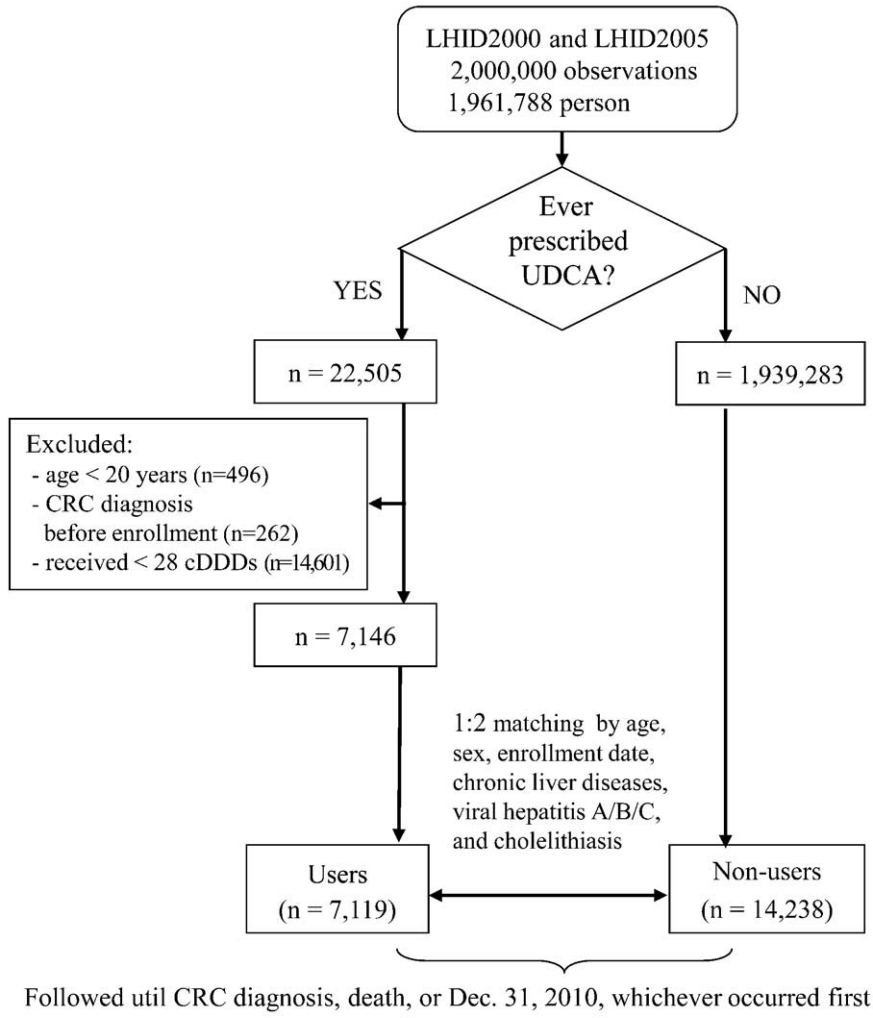

FIGURE 1. Study flowchart. cDDDs = cumulative defined daily doses, CRC = colorectal cancer, LHID = longitudinal health insurance database, UDCA = ursodeoxycholic acid.

analysis with robust Sandwich variance estimator, which can deal with matching data)[37] was used to examine the effect of UDCA on CRC prevention. Forward selection from variables significant in univariate analysis was used to determine the final Cox model. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated afterward. A 2-sided P value of <0.05 was considered to indicate statistical significance. All analyses were performed using SAS statistical software (version 9.3; SAS Institute, Cary, NC).

RESULTS

We identified 7119 UDCA users ($\geq$28 cDDDs) and 14,238 nonusers (Figure 1). The demographic characteristics, comorbidities, and medication use of the patients are presented in Table 1. Overall, mean age was 54 years and 60% of patients were men. Chronic liver diseases were common (78%), followed by cholelithiasis (24%), hepatitis B or C (20%), and alcoholic liver disease (10%). The median follow-up time was 5 years. Because of the matched design, age, sex, the prevalence of the above liver disorders, and follow-up time were comparable between the 2 study groups. Hypertension, hyperlipidemia, DM, and cardiovascular disease were also common in the 2 study groups (prevalence, 10%–50%). The prevalence of hypertension, DM, cardiovascular diseases, and heart failure significantly differed between the 2 groups. NSAIDs had been prescribed for about half of the patients, aspirin for 20%, and statins for 13% to 16% of the patients. There was no significant difference in the rates of NSAID and aspirin prescriptions between the 2 groups. UDCA users had undergone more LGI examinations (3.06% vs 2.13%, $P < 0.001$), whereas no significant difference in terms of biopsy and polypectomy (0.94% vs 0.74%, $P < 0.1307$) was seen.

During 109,312 person-years of follow-up, 121 patients developed CRC (110.7 per 100,000 person-years): 28 UDCA users and 93 nonusers (CRC incidence rate per 100,000 person-years, 76.7 and 127.7, respectively; Table 1). UDCA users had a significantly higher CRC-free rate than did nonusers (log-rank test, $P = 0.0169$; Figure 2).

The unadjusted HR for development of CRC was 0.60 (95% CI, 0.39–0.92) among UDCA users as compared with nonusers. Age, hypertension, DM, and cardiovascular disease were also significantly associated with CRC incidence. The Cox

TABLE 1. Demographics, Comorbidities, and Medication Use Among UDCA Users and Matched Nonusers

	UDCA Users (n = 7119)		Matched Nonusers (n = 14238)		
	n	%	n	%	*P*
Age, y					
20–49	2651	37.24	5307	37.27	0.9969*
50–64	2557	35.92	5116	35.93	
65+	1911	26.84	3815	26.79	
Mean ± sd	54.80 ± 14.80		54.79 ± 14.79		0.9667†
Sex					
Female	2800	39.33	5600	39.33	1.0000*
Male	4319	60.67	8638	60.67	
Comorbidity					
Chronic liver disease	5538	77.79	11076	77.79	1.0000*
Hepatitis A	5	0.07	10	0.07	1.0000*
Hepatitis B	1480	20.79	2960	20.79	1.0000*
Hepatitis C	1469	20.63	2938	20.63	1.0000*
Cholelithiasis	1716	24.10	3432	24.10	1.0000*
Alcoholic liver disease	716	10.06	1432	10.06	1.0000*
Hypertension	3537	49.68	6650	46.71	<0.0001*
Diabetes mellitus	2501	35.13	4140	29.08	<0.0001*
Hyperlipidemia	3004	42.20	5876	41.27	0.1950*
Cardiovascular disease	1901	26.70	4170	29.29	<0.0001*
Heart failure	450	6.32	791	5.56	0.0242*
Medication use					
Aspirin	1392	19.55	2810	19.74	0.7517*
NSAIDs	4031	56.62	8042	56.48	0.8452*
Statin	1153	16.20	1876	13.18	<0.0001*
LGIE					
Colonoscopy, sigmoidoscopy, and rectoscopy examinations	218	3.06	303	2.13	<0.0001*
Biopsy and polypectomy	67	0.94	106	0.74	0.1307*
Follow-up years (median)	5.013		5.005		
Number of CRC	28		93		
Sum of person-years	36488.0		72823.9		
Incidence of CRC‡	76.7		127.7		
95% CI	48.3–105.2		101.8–153.7		

CI = confidence interval, LGIE = lower gastrointestinal examinations, NSAID = nonsteroidal anti-inflammatory drugs, UDCA = ursodeoxycholic acid.

* Chi-squared test.

† Independent *t* test.

‡ incidence per 100,000 person-years.

proportional hazards model showed that age and UDCA use were associated with CRC incidence. The HR among UDCA users was 0.60 (95% CI, 0.39–0.92; Table 2).

We then explored the dose–response relationship among UDCA users. As compared with nonusers, UDCA users with a cDDD between 28 and 180 had the lowest age-adjusted HR (0.55; 95% CI, 0.35–0.89), followed by UDCA users with a cDDD of >365 (age-adjusted HR, 0.63; 95% CI, 0.16–2.53), and UDCA users with a cDDD between 181 and 365 (age-adjusted HR, 0.89; 95% CI, 0.36–2.20) (Table 3).

Because the subjects were predominantly patients with chronic hepatitis—among whom the risk of developing hepatocellular carcinoma and intrahepatic cholangiocarcinoma (HCC/ICC) is higher than in the general population[38–40]—competing risks might be a concern. To examine this possibility, we excluded UDCA users (n = 660) and their matched nonusers (n = 1320) who had received a diagnosis of primary liver cancer (*ICD-9* codes 155.0 and 155.1) before or after the enrollment dates. The remaining numbers of UDCA users and nonusers were 6459 and 12,918, respectively. The CRC incidence rates of these 2 groups were similar to those in the main analysis, and UDCA use remained significant in multivariate analysis (adjusted HR, 0.58; 95% CI, 0.37–0.91; Table 3).

DISCUSSION

To our knowledge, this is the first population-based study of the association of UDCA use with the risk of CRC development. We found that, after age adjustment, CRC risk was 41% lower for UDCA users than for nonusers. We did not observe a dose–response relationship in CRC risk reduction with increasing cumulative UDCA dose.

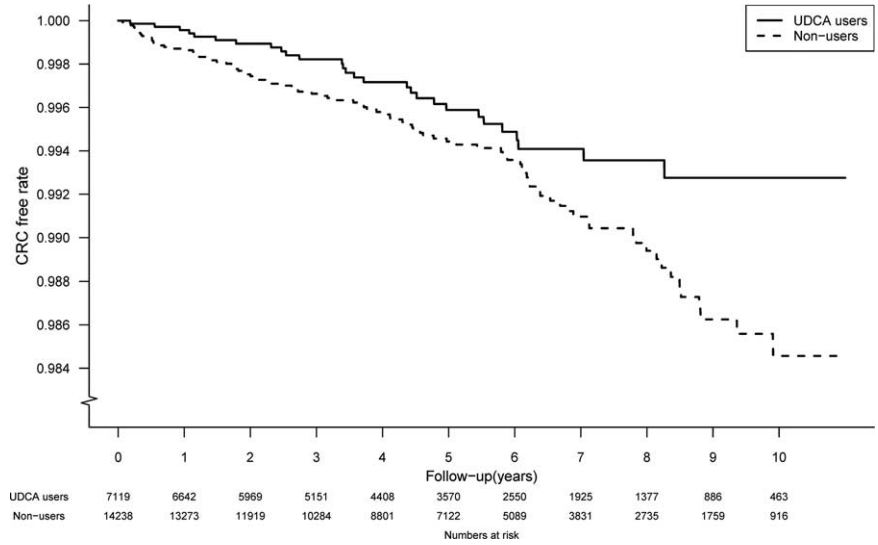

FIGURE 2. Kaplan–Meier curves of event-free probability for colorectal cancer (CRC) among UDCA users and nonusers (n = 21,357) ($P = 0.0169$ by log-rank test).

TABLE 2. Univariate and Multivariate Cox Proportional Hazard Analyses (With Sandwich Variance Estimator) for Developing Colorectal Cancer

	Univariate		Multivariate*	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age, y†				
20–49	1.00 (Reference)		1.00 (Reference)	
50–64	12.66 (3.93–40.71)	<0.0001	12.66 (3.94–40.74)	<0.0001
≥65	25.12 (7.94–79.55)	<0.0001	25.14 (7.94–79.59)	<0.0001
Sex				
Female	1.00 (Reference)			
Male	1.23 (0.85–1.79)	0.2734		
Comorbidity†				
Chronic liver disease	0.66 (0.43–1.02)	0.0584		
Hepatitis A	—	—		
Hepatitis B	0.55 (0.26–1.18)	0.1224		
Hepatitis C	0.68 (0.33–1.39)	0.2911		
Cholelithiasis	0.98 (0.55–1.74)	0.9402		
Alcoholic liver disease	0.82 (0.34–2.02)	0.6697		
Hypertension	2.76 (1.84–4.15)	<0.0001		
Diabetes mellitus	1.72 (1.21–2.46)	0.0026		
Hyperlipidemia	1.25 (0.88–1.78)	0.2152		
Cardiovascular disease	1.70 (1.18–2.44)	0.0042		
Heart failure	1.29 (0.69–2.40)	0.4277		
Medication use				
UDCA	0.60 (0.39–0.92)	0.0185	0.60 (0.39–0.92)	0.0183
Aspirin	1.39 (0.93–2.08)	0.1089		
NSAIDs	0.99 (0.69–1.41)	0.9412		
Statin	1.10 (0.72–1.68)	0.6715		
LGIE				
Colonoscopy, sigmoidoscopy, and rectoscopy examinations	0.76 (0.19–3.09)	0.7057		
Biopsy and polypectomy	1.25 (0.18–9.00)	0.8222		

CI = confidence interval, HR = hazard ratio, LGID = lower gastrointestinal examinations, NSAID = nonsteroidal anti-inflammatory drugs, UDCA = ursodeoxycholic acid.

* Final model was determined using forward selection.

† Time-dependent.

TABLE 3. Dose–response Relationship of Ursodeoxycholic Acid on Colorectal Cancer Risk, and Subgroup Analysis Excluding Patients With Primary Liver Cancer

		CRC		CRC Incidence*		Cox's Model†	
cDDD	Total	n	%	Pyr	Incidence	HR (95% CI)	*P*
Dose–Response Relationship							
<28	14,238	93	0.65%	72823.9	127.71	1.00 (Reference)	
28–180	6045	21	0.35%	30093.1	69.78	0.55 (0.35–0.89)	0.0146
181–365	734	5	0.68%	4127.9	121.12	0.89 (0.36–2.20)	0.8055
>365	340	2	0.59%	2267.1	88.22	0.63 (0.16–2.53)	0.5121
Exclude patients with primary liver cancers from 1996 to 2010							
Nonusers	12,918	86	0.67%	65702.1	130.9	1.00 (Reference)	
UDCA users	6459	25	0.39%	32922.7	75.9	0.58 (0.37–0.91)	0.0168

cDDD = cumulative defined daily doses, CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, pyr = person-years, UDCA = ursodeoxycholic acid.

* Incidence per 100,000 person-years.

† Adjusted for age.

The dose and duration of UDCA use required for chemoprevention has not been carefully studied. In a randomized controlled study, UDCA use (8–10 mg/kg/day) for 3 years did not decrease the overall rate of adenoma recurrence among 1285 patients who had undergone adenoma removal.[13] Another prospective study of UDCA 750 mg/day in 20 patients with colorectal adenoma found no difference in the rate of colorectal mucosal proliferation, as compared with placebo, during a relatively short follow-up period of 6 months.[14] In a retrospective analysis of 59 patients with ulcerative colitis and primary sclerosing cholangitis, UDCA 9 to 10 mg/kg/day for a mean duration of 3.5 years significantly decreased the risk of colonic dysplasia.[18] Two retrospective studies investigated standard UDCA dosages (13–15 mg/kg/day)—one in 116 patients with primary biliary cirrhosis who had undergone adenoma removal, the other in 52 patients with ulcerative colitis and primary sclerosing cholangitis.[12,17] The first study found that standard UDCA dosages (mean duration of administration, 45 months) had beneficial effects on colorectal dysplasia. The second study reported a similar beneficial effect on colorectal dysplasia with a mean follow-up of 42 months. Higher UDCA dosages (28–30 mg/kg/day) were associated with increased risk of colorectal neoplasia in a retrospective analysis of 56 patients with ulcerative colitis and primary sclerosing cholangitis.[16] However, the increase in risk was not significant when patients with possible adenoma-like lesions were excluded from the analysis. Another study showed that high UDCA doses (17–23 mg/kg/day) had no significant effect on CRC or dysplasia in patients with ulcerative colitis and primary sclerosing cholangitis.[21]

The above-mentioned studies were conducted in high-risk populations, such as patients with a history of adenoma removal and ulcerative colitis. The results of these studies thus cannot be generalized to general populations. In the present study, we investigated the chemopreventive effect of UDCA in a cohort mainly with chronic liver diseases and no excess risk of CRC, and DDD was used to estimate UDCA use. The DDD of UDCA is 750 mg; therefore, the estimated daily dose is about 10 to 15 mg/kg. We found that a cDDD between 28 and 180 (the cDDD for most of the patients receiving UDCA) was inversely associated with CRC incidence. Although there was a trend toward risk reduction among patients with >180 cDDDs, the decrease was not significant, probably because of the small number of users at these dose levels.

Most of the present patients had chronic liver disease, which is associated with a high risk of HCC/ICC. Survival is commonly short among patients with HCC/ICC, and thus they may not have time to develop CRC. Such competing risks could affect the results. We attempted to address this competing risk bias by conducting analysis that excluded UDCA users and nonusers with primary liver cancer before or after the enrollment dates. The risk of developing CRC remained lower in users than in nonusers, which indicates that primary liver cancer did not influence the association between UDCA use and CRC risk.

Patients with increasing frequency of medical checkup are more likely to take LGI examinations, which might facilitate the detection of CRC. Our findings found UDCA users indeed had more LGI examinations than nonusers while these procedures were not associated with increased risk of CRC.

The mechanisms by which UDCA use may decrease CRC risk are not well understood. UDCA administration significantly reduced the number of tumor-bearing rats and inhibited tumor development in a rodent model of azoxymethane-induced colon cancer.[8,41] Findings from this azoxymethane model suggest several mechanisms for the effect of UDCA, including suppression of cyclooxygenase-2 through both p21K-ras-dependent and -independent pathways,[42] inhibition of epidermal growth factor receptor signaling,[43,44] reduction of toxic secondary bile acid levels, and upregulation of E-cadherin expression.[45,46]

This study has several strengths. First, the study population was selected by using a computerized database and is therefore highly representative. Moreover, selection bias is unlikely. UDCA nonusers were matched for presence of chronic liver disease, viral hepatitis, and cholelithiasis, as these are common reasons for prescribing UDCA. Therefore, heterogeneity between the user and nonuser groups was reduced. Finally, because data on UDCA use were obtained from a historical database that includes all prescription information before the date of CRC diagnosis, the possibility of recall bias can be excluded.

Several limitations of this study should be noted. First, we lacked detailed information on some risk factors such as

inflammatory bowel disease, cigarette smoking, alcohol consumption, physical activity, body mass index, family CRC history. Second, the prescription did not guarantee drug compliance and anonymization of records impede us to contact patients directly. Third, underestimation of cumulative UDCA dose is likely because drug prescription data before 1996 was not available. To minimize the possible bias, we only included patients who were first prescribed UDCA after 2000. That means that the user group had no history of UDCA prescription for 4 years before starting the study. Fourth, relatively small sample size did not allow us to further examine the effect of UDCA on site-specific CRC. Finally, unmeasured factors that differ between the 2 study groups might be existed.

In conclusion, this population-based study indicates that UDCA use was associated with a 41% reduction in CRC risk in a cohort mainly comprising patients with chronic liver diseases. This suggests that UDCA might have a role in CRC chemoprevention. Prospective studies are needed to confirm these results and determine optimal dosing and duration of treatment.

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