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Risk of gastrointestinal cancers in patients with primary Sjögren's syndrome in Korea: a nationwide retrospective cohort study

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Abstract

Background The risk of non-Hodgkin's lymphoma in patients with primary Sjögren's syndrome (pSS) is well established. However, the association between pSS and the risk of gastrointestinal cancers remains underexplored. This study aims to assess the risk of gastrointestinal cancers in pSS patients in Korea compared with the general population.

Methods We included 320,082 participants from National Health Insurance Service-National Sample Cohort (NHIS-NSC) database. Of these, there were 850 patients with pSS and 319,232 in the non-pSS group. All participants were followed-up until 2019 or the development of gastrointestinal cancers, whichever occurred first. Hazard ratio (HR) and 95% confidence intervals (95% CI) for gastrointestinal cancers were calculated by multivariable Cox proportional hazards models.

Results Compared with the non-pSS group, patients with pSS had a higher risk of developing all gastrointestinal cancers, but the association did not reach statistical significance (adjusted HR: 1.240, 95% CI: 0.990–1.543). Site-specific analyses showed that pSS patients had a higher risk of colorectal cancer (adjusted HR: 1.597, 95% CI: 1.122–2.273) and pancreatic cancer (adjusted HR: 2.294, 95% CI: 1.267–4.151). The association was found to be more prominent in females and elderly (aged ≥ 60) individuals according to subgroup analyses.

Conclusions pSS was associated with increased risks of colorectal and pancreatic cancers, particularly among females and older adults. Further research should explore the underlying mechanisms and the impact of pSS duration and severity on cancer risk.

Keywords Cohort studies, Sjögren's syndrome, Gastrointestinal neoplasms, Neoplasms, Proportional hazards models

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Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized primarily by dry eyes (xerophthalmia) and dry mouth (xerostomia) [1]. Due to the systemic inflammation caused by pSS, patients suffer from various symptoms including dysphagia, arthralgia, and myalgia [1], which lower their quality of life and impose a financial burden [2]. One of the key life-threatening complications is non-Hodgkin lymphoma, caused by the persistent activation of autoimmune B cells [3]. According to a recent pooled analysis of 15 cohort studies, the standardized incidence ratio (SIR) of non-Hodgkin lymphoma in pSS patients was 8.78 [95% confidence interval (CI): 5.51–13.99] times higher compared with the general population [4].

Gastrointestinal manifestations such as dysphagia, dyspepsia, atrophic gastritis, pancreatitis, and autoimmune hepatitis are prevalent among pSS patients [5]. These complications arise because pSS involves the exocrine glands in the gastrointestinal tract and leads to increased inflammation in the intestines [5, 6]. These facts have led researchers to examine the association between pSS and gastrointestinal cancer, but the link is still ambiguous. Zhong et al. identified only five studies investigating the link between pSS and all gastrointestinal cancers [7–11], and the combined results showed null association [12]. A major limitation of all five studies was the lack of adjustment for lifestyle behaviors like smoking and alcohol consumption. Lifestyle behaviors are highly important risk factors for gastrointestinal cancers, constituting 35.2–59.8% of the population attributable fraction [13]. Another limitation is the limited number of studies addressing site-specific cancer risks in pSS patients. To our knowledge, few studies estimated SIRs for colon [7, 8, 10, 14], liver [7, 9, 15], gallbladder [7, 8], and pancreatic [7, 9, 10] cancers, respectively. Moreover, despite the known differences in pSS across sex and age, there is little published data containing stratified analyses.

Thus, the primary aim of this study is to evaluate the risk of all gastrointestinal cancers, as well as site-specific gastrointestinal cancers, in patients with pSS, while adjusting for lifestyle behaviors. Moreover, we conducted subgroup analyses to investigate how sex and age altered the risk of gastrointestinal cancer in patients with pSS.

Methods

Database

The study was based on a database from the National Health Insurance Service–National Sample Cohort (NHIS-NSC). The NHIS-NSC is a cohort database that contains health information on 2.2% of eligible Korean citizens from 2002 to 2019 [16]. The database includes basic demographic information, all healthcare utilization, including hospitalizations and outpatient visits, diagnoses, prescriptions, and biennial health examination results [16]. Any researcher can conduct population studies using this vastly informative database after obtaining permission from the National Health Insurance Sharing Service to use NHIS-NSC.

The Institutional Review Board (IRB) of Kyung Hee University Hospital deliberated and approved this study (IRB No. KHUH 2023-04-023). The IRB waived informed consent because this study used registry-based database.

Definition of patients with pSS and study population

Supplementary Fig. 1 shows the steps for selecting study participants. At first, 351,252 individuals who underwent a health examination between January 1, 2005 and December 31, 2006 were selected for study. Subsequently, 26,361 individuals who had previously been diagnosed with gastrointestinal cancers (International Classifications of Diseases, 10th revision [ICD-10] code C15–C26) were excluded [17]. To exclude patients with secondary Sjögren's syndrome, 4779 patients who diagnosed with Sjögren's syndrome as a secondary diagnosis during the entire observation period were excluded. The NHIS-NSC included both primary and secondary diagnoses for each hospital visits. For example, systemic lupus erythematosus may recorded as a primary diagnosis, with Sjögren's syndrome listed only as a secondary diagnosis. Finally, 320,082 people were included in the study, of which 850 were patients with pSS. Patients with pSS were identified using the ICD-10 code 'M35.0' for Sjögren's syndrome [17], diagnosed prior to the period of index date.

Outcome

In this study, the primary endpoint was the incidence of new gastrointestinal cancer cases, defined by corresponding ICD-10 diagnosis codes; gastric (C16), colorectal (C18–C20), liver (C22), gallbladder (C23–C24), and pancreatic (C25) cancers [17]. Follow-up started from the baseline date and ended at the earliest of either the diagnosis of gastrointestinal cancers, death, or December 31, 2019.

Covariates

The NHIS-NSC included basic demographic information, such as age and sex. Anthropometric examinations, health behavior information, and blood test results were obtained from participants' national health examinations in 2005–2006. Body mass index (BMI) was calculated by dividing weight by the square of participant height (kg/m^2). A trained healthcare worker measured systolic and diastolic blood pressure (BP) twice and used the lower number. Fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), and total cholesterol were measured from blood tests taken after an 8-hour fast.

Smoking status, alcohol consumption, and physical activity were defined based on self-reported questionnaire surveys during the health examination. The smoking status was categorized into three groups: never smoker, former moker, and current smoker. Alcohol consumption was categorized into the two groups: <2 days per week, ≥2 days per week. Physical activity was categorized into the three groups: none, 1–4 days per week, and ≥5 days per week.

Statistical analysis

Baseline characteristics of the participants in the study are shown using mean ± (standard deviation) and median (interquartile range) for continuous variables, and count (percentage) for categorical variables. Baseline characteristics between participants non-pSS and those with pSS were compared using the Student's t-tests and the chi-square tests. Kaplan-Meier plots were employed to illustrate the cumulative incidence of gastrointestinal cancers in patients with pSS in comparison to those without pSS. The difference in gastrointestinal cancer incidence between the two groups was assessed utilizing the log-rank test.

Multivariable Cox proportional-hazard models were used to assess the association between pSS and gastrointestinal cancers. Adjusted hazard ratios (aHRs) and 95 CIs for gastrointestinal cancers were calculated using multivariable models adjusting for age, sex, BMI, fasting blood glucose, systolic BP, total cholesterol, GGT, smoking status, alcohol consumption, and physical activity. Subgroup analyses based on age (<60, ≥60) and sex were performed using the identical Cox model. To determine how the impact of pSS on gastrointestinal cancers varies by age and sex, moderation analyses employed a Cox proportional hazards model, integrating interaction terms (pSS status × age × sex). Statistical significance was set at a two-sided *P* value below 0.05. All statistical analyses were carried out employing SAS software (version 9.4, SAS Institute, Cary, NC, USA).

Results

In a total of 320,082 participants, there were 850 (0.27%) patients with pSS (Table 1). Compared with the non-pSS population, patients with pSS were more likely to be female (64.47%), older (57.37 ± 9.38), never smokers (82.14%), and drink alcohol < 2 days per week (93.29%).

In Supplementary Fig. 2, a notably higher cumulative incidence of all gastrointestinal cancers was observed in the pSS group (*P* for log rank test < 0.001). Table 2 presented the associations between pSS and gastrointestinal cancer risk. Within the non-pSS group, there were 24,855 incident cases of gastrointestinal cancer over 4,118,769.45 person-years, whereas the pSS group recorded 79 incident cases over 10,806.41 person-years. The incidence rates per 10,000 person-years were 60.35 for the non-pSS group and 73.10 for those with pSS. Compared with the non-pSS group, the pSS group showed an increased risk of all gastrointestinal cancer, though this was not statistically significant (aHR: 1.240, 95% CI: 0.990–1.553). Upon examining site-specific gastrointestinal cancers, pSS group statistically significant increased risks of colorectal cancer (aHR: 1.597, 95% CI: 1.122–2.273) and pancreatic cancer (aHR: 2.294, 95% CI: 1.267–4.151).

Subgroup analyses by age and sex were performed. In subgroup analyses by sex, the increased risk of all gastrointestinal cancers (aHR: 1.562, 95% CI: 1.189–2.051), colorectal cancer (aHR: 1.913, 95% CI: 1.246–2.939), and pancreatic cancer (aHR: 3.302, 95% CI: 1.710–6.375) within the pSS group was notably significant exclusively among females (Table 3). In subgroup analyses by age (Table 4), the significant increased risk of all gastrointestinal cancer (aHR: 1.429, 95% CI: 1.242–1.644) in the pSS group was observed among individuals aged 60 years or older. Additionally, compared with non-pSS group, an increased risk of gastric cancer (aHR: 1.500, 95% CI: 1.175–1.914), colorectal cancer (aHR: 1.343, 95% CI: 1.043–1.730), and pancreatic cancer (aHR: 1.764, 95% CI: 1.134–2.744) in the pSS group (Table 4). The risk of gastrointestinal cancers was evaluated across eight groups, stratified by pSS status, age, and sex (Supplementary Fig. 3). When comparing males without pSS under the age of 60, there appeared to be a tendency towards a decreased risk of gastrointestinal cancers in females. However, these trends shifted to null associations in females with pSS, except for the risk of gastric cancer.

Discussion

In our study, we observed that pSS was associated with increased risks of colorectal cancer and panceratic cancer. Subgroup analyses by sex indicated that these associations were more prominent among females. Among individuals aged ≥60, there was a significant increase in the risk of all gastrointestinal cancers, gastric cancer, colorectal cancer, and pancreatic cancer in the pSS group compared with the non-pSS group. These findings underscore the importance of monitoring gastrointestinal cancer risk in patients with pSS, particularly among older adults and females.

Several studies explored the association between pSS and gastrointestinal cancer. A meta analysis that combined data of five studies reported no significant association between pSS and all gastrointestinal cancers (pooled SIR: 1.10, 95% CI: 0.86–1.41) [12]. While earlier studies were limited by relatively short follow-up [7, 9], our study with a longer follow-up duration (mean 12.90 ± 3.01 years) and adjustment for multiple covariates similarly found no statistically significant association. Unlike previous studies, we conducted subgroup

Table 1 Baseline characteristics of study participants

Characteristic	Total *n* = 320,082	Non-pSS *n* = 319,232	pSS *n* = 850	*P* value
Follow-up year	12.90 ± 3.01	12.90 ± 3.01	12.71 ± 3.28	
Person -year	4,129,575.86	4,118,769.45	10,806.41	
Age (years)	55.31 ± 9.20	55.31 ± 9.20	57.37 ± 9.38	< 0.001
Sex				< 0.001
Male (%)	182,920 (57.15)	182,618 (57.21)	302 (35.53)	
Female (%)	137,162 (42.85)	136,614 (42.79)	548 (64.47)	
BMI (kg/m^2)	23.96 ± 2.89	23.96 ± 2.89	23.92 ± 2.82	0.640
Fasting blood glucose (mg/dL)	98.08 ± 26.91	98.08 ± 26.92	98.03 ± 22.35	0.951
Systolic BP (mmHg)	126.18 ± 16.77	126.18 ± 16.77	126.10 ± 17.49	0.889
Diastolic BP (mmHg)	78.68 ± 10.78	78.69 ± 10.78	77.81 ± 10.71	0.018
Total cholesterol (mg/dL)	198.54 ± 36.67	198.54 ± 36.67	197.80 ± 37.61	0.560
AST (U/L)	24.00 (20.00–29.00)	24.00 (20.00–29.00)	24.00 (20.00–28.60)	0.388
ALT (U/L)	21.00 (16.00–29.00)	21.00 (16.00–29.00)	21.00 (15.00–28.00)	0.101
GGT (U/L)	24.00 (16.00–40.00)	24.00 (16.00–40.00)	21.00 (15.00–33.00)	< 0.001
Smoking status				< 0.001
Never (%)	214,642 (71.09)	213,989 (69.63)	653 (82.14)	
Former smoker (%)	28,110 (9.31)	28,052 (9.32)	58 (7.30)	
Current smoker (%)	59,184 (19.60)	59,100 (19.63)	84 (10.57)	
Alcohol consumption				0.001
< 2 days per week (%)	280,977 (89.59)	280,212 (89.58)	765 (93.29)	
≥ 2 days per week (%)	32,649 (10.41)	32,594 (10.42)	55 (6.71)	
Physical activity				< 0.001
None (%)	154,883 (48.39)	154,453 (48.38)	430 (50.59)	
1–4 days per week (%)	131,875 (41.20)	131,553 (41.21)	322 (37.88)	
≥ 5 days per week (%)	33,324 (10.41)	33,226 (10.41)	98 (11.53)	

Data are presented as means (standard deviation), medians (interquartile range), or numbers (percentages)

Abbreviations: *pSS* primary Sjögren's Syndrome, *BMI* body mass index, *BP* blood pressure, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* γ-glutamyltransferase

P-values are determined using Student's t-test for continuous variables and χ^2 test for categorical variables

Table 2 Hazard ratios and 95% confidence intervals for the incidence of gastrointestinal cancers according to pSS status

Type of cancer	Group	Person-year	Cases	Incidence rate/10,000 person-year	Hazard ratios (95% confidence interval)	
					Unadjusted model	Adjusted model
All gastrointestinal cancer	Non-pSS (*n* = 319,232)	4,118,769.45	24,855	60.35	1.000 (Reference)	1.000 (Reference)
	pSS (*n* = 850)	10,806.41	79	73.10	1.211 (0.971–1.510)	1.240 (0.990–1.553)
Gastric cancer	Non-pSS	4,224,441.35	8139	19.27	1.000 (Reference)	1.000 (Reference)
	pSS	11,288.66	13	11.52	0.602 (0.350–1.035)	0.689 (0.400–1.188)
Colorectal cancer	Non-pSS	4,220,849.31	7748	18.36	1.000 (Reference)	1.000 (Reference)
	pSS	11,128.28	32	28.76	1.565 (1.106–2.215)	1.597 (1.122–2.273)
Liver cancer	Non-pSS	4,225,720.60	6817	16.13	1.000 (Reference)	1.000 (Reference)
	pSS	11,161.48	22	19.71	1.219 (0.802–1.853)	1.165 (0.759–1.789)
Gallbladder cancer	Non-pSS	4,260,181.24	2354	5.53	1.000 (Reference)	1.000 (Reference)
	pSS	11,314.91	6	5.30	0.961 (0.431–2.140)	0.948 (0.426–2.113)
Pancreatic cancer	Non-pSS	4,266,872.83	1845	4.32	1.000 (Reference)	1.000 (Reference)
	pSS	11,349.59	12	10.57	2.447 (1.387–4.316)	2.294 (1.267–4.151)

Multivariable adjusted model was adjusted for age, sex, BMI, systolic BP, fasting blood glucose, total cholesterol, GGT, smoking status, alcohol consumption, and physical activity

Abbreviations: *pSS* primary Sjögren's Syndrome, *BMI* body mass index, *BP* blood pressure, *GGT* γ-glutamyltransferase

Table 3 Hazard ratios and 95% confidence intervals for the incidence of gastrointestinal cancers according to pSS status after stratifying by sex

Type of cancer	Group	Male (*n* = 182,920)		Female (*n* = 137,162)	
		Unadjusted model	Adjusted model	Unadjusted model	Adjusted model
All gastrointestinal cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	0.912 (0.612–1.360)	0.845 (0.566–1.260)	1.607 (1.233–2.095)	1.562 (1.189–2.051)
Gastric cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	0.704 (0.336–1.476)	0.664 (0.317–1.394)	0.713 (0.320–1.588)	0.717 (0.322–1.599)
Colorectal cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	1.252 (0.673–2.327)	1.168 (0.628–2.173)	1.954 (1.285–2.972)	1.913 (1.246–2.939)
Liver cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	0.910 (0.409–2.022)	0.816 (0.366–1.819)	1.443 (0.883–2.357)	1.392 (0.838–2.312)
Gallbladder cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	-	-	1.604 (0.719–3.580)	1.652 (0.740–3.687)
Pancreatic cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	1.060 (0.265–4.237)	0.955 (0.239–3.826)	3.607 (1.932–6.734)	3.302 (1.710–6.375)

Multivariable adjusted model was adjusted for age, sex, BMI, systolic BP, fasting blood glucose, total cholesterol, GGT, smoking status, alcohol consumption, and physical activity

Abbreviations: *pSS* primary Sjögren's Syndrome, *BMI* body mass index, *BP* blood pressure, *GGT* γ-glutamyltransferase

Table 4 Hazard ratios and 95% confidence intervals for the incidence of gastrointestinal cancers according to pSS status after stratifying by age

Type of cancer	Group	Age < 60 (*n* = 219,760)		Age ≥ 60 (*n* = 100,322)	
		Unadjusted model	Adjusted model	Unadjusted model	Adjusted model
All gastrointestinal cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	0.965 (0.671–1.389)	1.070 (0.738–1.550)	1.239 (0.939–1.636)	1.429 (1.242–1.644)
Gastric cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	0.624 (0.281–1.387)	0.824 (0.370–1.835)	0.500 (0.238–1.049)	1.500 (1.175–1.914)
Colorectal cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	1.114 (0.600–2.068)	1.277 (0.686–2.376)	1.666 (1.096–2.533)	1.343 (1.043–1.730)
Liver cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	1.220 (0.675–2.204)	1.141 (0.613–2.123)	1.101 (0.610–1.987)	1.286 (0.916–1.719)
Gallbladder cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	0.802 (0.200–3.210)	0.865 (0.216–3.463)	0.903 (0.339–2.403)	0.928 (0.560–1.539)
Pancreatic cancer	Non-pSS	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
	pSS	1.551 (0.501–4.804)	1.733 (0.557–5.390)	2.551 (1.323–4.916)	1.764 (1.134–2.744)

Multivariable adjusted model was adjusted for age, sex, BMI, systolic BP, fasting blood glucose, total cholesterol, GGT, smoking status, alcohol consumption, and physical activity

Abbreviations: *pSS* primary Sjögren's Syndrome, *BMI* body mass index, *BP* blood pressure, *GGT* γ- glutamyltransferase

analyses by age and sex, and found significant associations in females and the elderly. This could be attributed to the greater severity of pSS in females. Several studies have reported that extraglandular manifestations are more commonly observed in female pSS patients than in male pSS patients [18]. Extraglandular manifestations refer to systemic symptoms that occur outside of the primary exocrine glands, including synovitis, myositis, and cutaneous vasculitis [19]. These symptoms indicate higher severity of pSS and are major components of the EULAR Sjögren's syndrome disease activity index (ESSDAI), a severity assessment tool for pSS [20]. The precise biological mechanisms remain unclear, but it is known that lower estrogen levels after menopause contribute to these sex differences [18]. Reduced estrogen post-menopause can promote B cell proliferation and autoantibody production, while decreasing the protective and anti-inflammatory effects previously provided by premenopausal estrogen [18].

The prominent association between pSS and all gastrointestinal cancers in participants aged ≥ 60 may be explained by the longer duration of pSS. pSS is a gradually progressing disease. Lee and colleagues proposed a working model of pSS through the following stages: pre-disease (Stage 0), the appearance of glandular symptoms (Stage 1), the onset of extraglandular manifestations (Stage 2), a nd the development of lymphoma (Stage 3) [21]. This indicates that pSS severity may worsen with time, possibly increasing cancer risk. A single-center retrospective cohort study from Turkey revealed that pSS patients diagnosed with cancer had a mean duration of 9.30 ± 5.2 years, which was longer compared with 7.25 ±

4.6 years in those without cancer [22]. However, no studies have yet evaluated cancer risk based on the duration of pSS. Future research should address this knowledge gap.

When examining site-specific cancers, we found an increased risk of colorectal cancer in pSS patients. This result contrasts with findings from previous studies. Most studies observed a null association between pSS and the incidence of colorectal cancer [8, 10, 14]. A study in Taiwanese population including 15,636 pSS patients reported a significant lower risk (SIR: 0.6, 95% CI: 0.5–0.8) of colorectal cancer in pSS patients than in the general population [7]. This difference could be due to our adjustment for BMI, smoking, alcohol consumption and physical activity in the multivariable Cox-proportional hazard model, which previous studies did not consider [7]. pSS may contribute to increased intestinal inflammation and intestinal permeability [23]. Additionally, microbiota dysbiosis is commonly observed in pSS patients [24]. The disturbance of the intestinal epithelial barrier and microbiome imbalance can contribute to the development of colorectal cancer [25].

We observed a significant association with an increased risk of pancreatic cancer in pSS patients. This observation also contradicts earlier cohort studies that reported an null association between pSS and the risk of pancreatic cancer [7, 9, 10]. However, a retrospective cohort study has demonstrated an elevated risk of acute pancreatitis in pSS patients [26]. Recent epidemiologic evidence suggests that acute pancreatitis increases the risk of pancreatic cancer [27, 28]. Therefore, pSS may increase the risk of pancreatic cancer by mediating acute pancreatitis. Further research is warranted.

This study has multiple strengths and clinical implications. To the best of our knowledge, this is the first study to estimate the risk of gastrointestinal cancers in pSS patients after adjusting for BMI, smoking, alcohol consumption, and exercise. This study has another strength of longer observation period, with an average follow-up of more than 12 years. As a result, we were able to observe the development of gastroinctestinal cancers among 850 pSS patients. Furthermore, we identified that pSS patients who aged ≥ 60 and females are at a higher risk of developing gastrointestinal cancers.

In the Republic of Korea, the National Cancer Screening Program (NCSP) provides annual colorectal cancer screening for adults aged ≥ 50 years using fecal immunochemical testing followed by colonoscopy for positive cases, and biennial gastric cancer screening for adults aged ≥ 40 years with either upper gastrointestinal endoscopy or an upper gastrointestinal series [29]. Because our study was based on the NHIS-NSC claims database, gastrointestinal cancers identified in both the pSS and non-pSS groups likely include cases detected through the NCSP as well as those diagnosed symptomatically or incidentally. Patients with pSS have regular rheumatology visits and more frequent healthcare utilization, which may indicate greater health awareness and higher participation rates in the NCSP. This could introduce detection bias, which is likely to be more pronounced for gastric and colorectal cancers targeted by the NCSP.

However, this study also has several limitations. Firstly, we were unable to account for dietary factors, which is another significant covariate affecting gastrointestinal cancers. The NHIS-NSC database we used did not include information on individual dietary habits. Future research should incorporate dietary factors to provide a more comprehensive analysis. Secondly, due to the lack of clinical information, we could not consider the clinical characteristics and immunologic markers of pSS patients. In patients with pSS, high ESSDAI scores and cryobulinemia are directly linked to mortality and prognosis [30]. In addition, because the NHIS-NSC provides data starting from 2002, we were unable to determine the duration of pSS. Thirdly, as the study was limited to Korean population, the findings cannot be extrapolated to other populations. The incidence of pSS in Korea is reported to be 2.34 per 100,000 population annually, which is lower than the incidence in the United States (5.8 per 100,000 population) and Taiwan (6.0 per 100,000 population) [31–33]. The incidence of gastrointestinal cancers in Koreans also differs from Western populations. Koreans have higher age-standardized rates for cancers of the stomach, and liver but lower rates for cancers of the colon, rectum, and pancreas [34].

Conclusion

In conclusion, we found that pSS was associated with increased risks of colorectal cancer and pancreatic cancer in Korean population. These associations were prominent among females and individuals aged ≥ 60 years. Further studies in other populations are needed to verify these findings.

Abbreviations

pSS	primary Sjögren's syndrome
SIR	Standardized incidence ratio
CI	Confidence interval
NHIS-NSC	National Health Insurance Service–National Sample Cohort
IRB	Institutional Review Board
ICD-10	International Classifications of Diseases, 10th revision
BMI	Body mass index
BP	Blood pressure
AST	Aspartate aminotransferase, ALT: alanine aminotransferase
GGT	γ-glutamyltransferase
aHRs	Adjusted hazard ratios
ESSDAI	EULAR Sjögren's syndrome disease activity index

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Soonsu Shin wrote the first and final draft of this manuscript. Soonsu Shin, Min-Ho Kim, Chang-Mo Oh, Dosang Cho, and Jae-Hong Ryoo contributed to the interpretation of data and results. Min-Ho Kim and Jae-Hong Ryoo contributed to the statistical analysis. Jae-Hong Ryoo contributed to the acquisition of funding. Chang-Mo Oh, and Jae-Hong Ryoo contributed to the supervision and management of research. All authors critically reviewed the manuscript.

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Data availability
The authors do not have permission to distribute the data. Data from the Korean National Health Insurance Service (NHIS) can be accessed through the Health Insurance Data Service website (http://nhiss.nhis.or.kr). Researchers need to submit a study proposal for institutional review board approval, which will be assessed by the NHIS review committee.

Declarations

Ethics approval and consent to participate
The Institutional Review Board (IRB) of Kyung Hee University Hospital deliberated and approved this study (IRB No. KHUH 2023-04-023). The IRB waived informed consent because this study used registry-based database.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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