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ORIGINAL ARTICLE

Autoimmune diseases as comorbidities for liver, gallbladder, and biliary duct cancers in Sweden

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Abstract

Background: Autoimmune diseases are associated with many cancers but there is a lack of population-based studies with different autoimmune diseases that have a long follow-up. This is also true of hepatobiliary cancers, which include hepatocellular cancer (HCC) and rarer entities of gallbladder cancer (GBC), intra- and extrahepatic cholangiocarcinoma (iCCA and eCCA), and ampullary cancer.

Methods: Diagnostic data on 43 autoimmune diseases were collected from the Swedish Inpatient Register from 1987 to 2018, and cancer data were derived from the national cancer registry from 1997 onward. Relative risks were expressed as standardized incidence ratios (SIRs).

Results: In a population of 13.6 million, 1.1 million autoimmune diseases were diagnosed and subsequent hepatobiliary cancer was diagnosed in 3191 patients (17.2% of cancers). SIRs for HCC were 2.73 (men) and 2.86 (women), 3.74/1.96 for iCCA, 2.65/1.37 for GBC, 2.38/1.64 for eCCA, and 1.80/1.85 for ampullary cancer. Significant associations between autoimmune disease and HCC were observed for 13 autoimmune diseases, with the highest risks being for autoimmune hepatitis (48.92/73.53, men/women) and primary biliary cirrhosis (38.03/54.48). GBC was

increased after six autoimmune diseases, with high SIRs for ulcerative colitis (12.22/3.24) and men with Crohn disease (9.16). These autoimmune diseases were also associated with a high risk of iCCA, which had seven other associations, and eCCA, which had five other associations. Ampullary cancer occurrence was increased after four autoimmune diseases.

Conclusion: An autoimmune disease is a common precursor condition for hepatobiliary cancers. This calls for careful control of autoimmune disease symptoms in each patient and encouragement to practice a healthy lifestyle.

KEYWORDS
comorbidity, discharge data, hepatocellular cancer, immune disturbance, risk factor

INTRODUCTION

Hepatobiliary cancers include hepatocellular carcinoma (HCC), biliary tract cholangiocarcinoma (CCA), gallbladder cancer (GBC), and cancer of the ampulla of Vater (ampullary cancer).[1,2] The large international variation in the incidence of these cancers can be explained by the differential distribution of known risk factors, which for HCC include chronic infection by hepatitis B (HBV) or hepatitis C virus (HCV) in developing countries, and alcohol, other lifestyle factors, and family history in developed countries.[1–5] Since 2009, Sweden has had a national HCC register reporting what the causes for HCC were ascribed to: HCV in 30%, alcohol in 25%, and HBV in 6% of the patients.[6] Diabetes and nonalcoholic liver disease have been reported since 2013, and they each accounted for close to 4% of HCC; for a large proportion of patients, no cause could be assigned. In a study from the United States (Florida), HCV was the leading cause of HCC among men and women (50% and 43%, respectively), followed by metabolic and alcohol-related disorders.[7] For CCA and GBC, the risk factors are different, but liver flukes are a prominent risk factor in developing countries.[8] GBC shares some risk factors with HCC, including obesity, and features other risk factors, such as gallstone disease, bacterial infections, and structural abnormalities, including biliary cysts.[1,9] For CCA, associations with alcohol, HBV, and HCV are weaker than for HCC but biliary infections play an important role.[1,8,10–12]

Despite the diverse risk factors, most share the mechanism of chronic inflammation, which is estimated to account for 90% of HCC cases.[3,13] Recent work has revealed similarities between the cellular landscapes of chronic inflammation and tumor microenvironment.[14–18]

Autoimmune diseases are characterized by aberrations in the immune system that lead to the loss of tolerance to self-antigens and to immune attacks on its own normal proteins.[19] There are close to 100 types of autoimmune diseases, some of which are rare but, jointly, their prevalence has been estimated at 3% to 5% of the total population.[19] Cancer risk is increased in many patients with autoimmune diseases because of related disturbances in immune surveillance.[20] This applies also to hepatobiliary cancers, which are increased in many patients with autoimmune diseases and specificity as to the type of autoimmune disease and cancer (e.g., HCC risk is vastly increased in patients with autoimmune hepatitis and primary biliary cirrhosis).[21,22] Another cause of cancer in certain patients with autoimmune diseases is the immunosuppressive medication used to control the underlying disease.[23,24]

We present here an updated nationwide Swedish study on hospitalized patients with autoimmune diseases (total, 929,000) and their subsequent hepatobiliary cancers (total, 18,598). Forty-three different autoimmune diseases were included and with an extended follow-up time of 8 years, the patient numbers were more than two times higher than in our previous study.[21] The current patient numbers are only second to a recent US study on patients diagnosed at more than 66 years of age that had a somewhat different set of autoimmune diseases compared with the present patient group.[22] The advantages of the present study are its nationwide coverage with a long follow-up.

MATERIALS AND METHODS

Information on autoimmune diseases was obtained from the National Inpatient Register, which started in 1987. This included 43 types of autoimmune diseases, as described elsewhere.[25] However, Takayasu disease, thrombotic thrombocytopenia, angiitis hypersensitive, and chorea minor were not associated with any hepatobiliary cancer; therefore, the analysis covered 39 autoimmune diseases. The International Classification of Diseases (ICD) codes used to identify autoimmune diseases are shown in Table S1. The first diagnosed autoimmune disease was considered in the basic analysis. Cancer data were available from the Swedish Cancer Registry for 1997–2018. ICD version 10 codes were used for primary hepatobiliary cancers because it was the first one specifying a code for intrahepatic CCA (iCCA). Other codes were for HCC, GBC, extrahepatic CCA (eCCA), and cancer of the ampulla of Vater (ampullary cancer). To confirm the accuracy of the HCC ICD-10 codes (for the possible inclusion of metastatic cancers or biliary cancers) or for iCCA, we included, in addition to the ICD-10 codes, SNOMED codes 81703 for HCC and 81603 for iCCA. Information from the two registers was linked at the individual level via the national 10-digit civic registration number. In the linked data set, civic registration numbers were replaced with serial numbers to ensure anonymity.

Person-year calculation began from the first diagnosis of autoimmune disease in 1997 until a diagnosis of hepatobiliary cancer,

death, emigration, or end of the follow-up in 2018. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases. The expected numbers were calculated from the present data set for all individuals without a specific autoimmune disease (i.e., most of the Swedish population), and the rates were standardized by every 5-year age, sex, period (5-year calendar period), highest educational level (as a proxy for socioeconomic status), and geographical region. The 95% CI of the SIR was calculated assuming a Poisson distribution. Observed cases (marked as O in the tables) indicate the persons for whom the SIR was calculated. In a sensitivity analysis, additional adjustments were done for patients who had been hospitalized for alcohol-related disease (ICD-10 codes F10, K70), chronic obstructive pulmonary disease (codes J40-J47), and obesity (codes E65-E68). The motivation to perform this analysis was to test whether the associations between autoimmune disease and hepatobiliary cancer could be confounded by the known risk factors of hepatobiliary cancer. Because data were not available for smoking, chronic obstructive pulmonary disease was used as a proxy. Among Swedish patients with chronic obstructive pulmonary disease, 89% of men and 64% of women were smokers, and the population-attributable fractions were 64% and 29%.[26]

A separate analysis was performed of patients diagnosed with two different autoimmune diseases, but that only considered autoimmune diseases that were individually significantly associated with hepatobiliary cancer. However, the case numbers were so few that underreporting of second autoimmune diseases may be likely, and therefore no results were shown. When risks were discussed, only statistically significant associations were referred to (i.e., 95% CI did not include 1.00).

The study was approved by the Regional Ethical Review Board in Lund February 6, 2013 (Reference 2012/795 with subsequent supplementations). Guidelines of the Helsinki Declaration were followed. The study was conducted in accordance with the approved guidelines with an explicit statement that no informed consent was required. The study is a national register-based study on pseudonymous (deidentified) personal data.

RESULTS

The number of patients diagnosed with individual autoimmune diseases (first diagnosis) is shown in Table S1. The total number was 1.096 million, with psoriasis being the most prevalent (181,000), followed by Hashimoto thyroiditis (153,000), type 1 diabetes (144,000), and rheumatoid arthritis (102,000). The characteristics of the study population are described in Table 1. The total population was 13.6 million and covered the period 1997–2018, with 18,598 hepatobiliary cancers at a mean diagnostic age of 69.9 years. A total of 3191 hepatobiliary cancers of a total of 18,598 cancers (17.2%) had a prior diagnosis of an autoimmune disease. Age-standardized incidence rates for hepatobiliary cancers were 5.01/100,000 for men and 3.51/100,000 for women; the incidence of HCC was three times higher in men and GBC was less than half compared with women. The specific types of cancer were 60.4/29.6% (male/female) HCC, 11.0/13.9% iCCA, 11.1/37.3% GBC, 10.6/12.3% eCCA, and 6.9/6.9% ampullary cancer. The mean follow-up time between autoimmune disease and cancer was 8.0 years.

Age-standardized incidence rates for hepatobiliary cancers in the total population, in patients diagnosed with an autoimmune disease and in those not diagnosed with an autoimmune disease are shown in Table 2. The overall incidence difference in hepatobiliary cancer between autoimmune disease patients and patients without an autoimmune disease was 1.64; it was highest for iCCA (2.39) and lowest for GBC (1.25).

Relative risks of subsequent hepatobiliary cancer after the first diagnosed autoimmune disease are shown in Table S2. The combined male and female risks were 2.73 and 1.92, respectively. Both male and female risk were significantly increased after nine individual autoimmune diseases, whereas only male risk increased after three autoimmune diseases compared with one autoimmune disease only with more female risk.

Risks for specific hepatobiliary cancer are shown in Table 3, considering only autoimmune diseases with at least 30 cases or some significant associations. Male and female data are presented on top of each other to ease comparison and to support biological plausibility when data for the sexes agree. The overall SIRs were increased for all cancer types but showed sex differences: SIRs for HCC were 2.73 (men) and 2.86 (women), 3.74/1.96 for iCCA, 2.65/1.37 for GBC, 2.38/1.64 for eCCA, and 1.80/1.85 for ampullary cancer. The differences between sexes were statistically significant (i.e., 95% CIs did not overlap) for sites other than HCC and ampullary cancer. Type 1 diabetes was the most common autoimmune disease for HCC, eCCA, and ampullary cancer, whereas for iCCA and GBC ulcerative colitis was the most common.

In Table 3, type 1 diabetes was associated with all types of hepatobiliary cancers and Hashimoto thyroiditis was associated with all female cancers. For HCC, the highest risks were observed after autoimmune hepatitis (48.92/73.53, men/women) and primary biliary cirrhosis (38.03/54.48). Significant associations between autoimmune disease and HCC were observed for 13 autoimmune diseases, of which all but four were concordant for sexes; Hashimoto thyroiditis and rheumatoid arthritis were significant for women only and localized scleroderma and pernicious anemia were significant for men only. Among concordant associations, high risks were observed for immune thrombocytopenic purpura (10.34/6.72) and type 1 diabetes (5.13/4.92). For iCCA, nine associations were significant; of these, the highest were for autoimmune hepatitis (25.00/9.84), ulcerative colitis (14.33/5.51), and Crohn disease (6.31/4.61). Graves' disease was associated only with men (6.06). GBC was increased after six autoimmune diseases, with high SIRs for ulcerative colitis (12.22/3.24), male Crohn disease (9.16), and male pernicious anemia (6.74). For eCCA, seven associations were significant; of these, the highest were for male autoimmune hepatitis (9.09), ulcerative colitis (7.06/4.44), and Crohn disease (3.97/3.53). The only significant association (8.51) of myasthenia gravis was eCCA. The rare ampullary cancer was increased after four autoimmune diseases, including type 1 diabetes (2.94/3.82), male celiac disease (4.60), female Hashimoto thyroiditis, and female rheumatoid arthritis.

TABLE 1 Total population and number of cases of hepatobiliary cancer in Sweden, 1997–2018

	No.	%	Incidence rate (per 100 000 person-years)[a], 95% CI
Population	13 567 134	100.0	
Men	6 821 533	51.3	
Women	6 745 601	48.7	
Number of patients with hepatobiliary cancer			
Case	18 598		
Mean age at diagnosis (± SD)	69.9 ± 12.3		
Incidence rate (per 100 000 person-years)[a], 95% CI			4.24, 4.18–4.30
Hepatocellular carcinoma (ICD-10 C22.0)	8674	46.6	2.02, 1.98–2.07
Intrahepatic bile duct carcinoma (ICD-10 C22.1)	2285	12.3	0.56, 0.54–0.59
Gallbladder (ICD-10 C23.9)	4244	22.8	0.89, 0.87–0.92
Extrahepatic bile duct (ICD-10 C24.0)	2115	11.4	0.47, 0.45–0.49
Ampulla of Vater (ICD-10 C24.1)	1280	6.9	0.28, 0.27–0.30
Subsequent hepatobiliary cancer in autoimmune patients			
Cases	3191		
Mean follow-up (years ± SD)	8.1 ± 7.2		
<1	513	16.1	
1–4	881	27.6	
5–9	803	25.2	
≥10	994	31.2	
Men			
Case	10 274		
Mean age at diagnosis (±SD)	68.9 ± 12.3		
Incidence rate (per 100 000 person-years)[a], 95% CI			5.01, 4.91–5.11
Hepatocellular carcinoma (ICD-10 C22.0)	6207	60.4	3.04, 2.96–3.12
Intrahepatic bile duct carcinoma (ICD-10 C22.1)	1132	11.0	0.59, 0.56–0.63
Gallbladder (ICD-10 C23.9)	1143	11.1	0.53, 0.49–0.56
Extrahepatic bile duct (ICD-10 C24.0)	1088	10.6	0.52, 0.49–0.55
Ampulla of Vater (ICD-10 C24.1)	704	6.9	0.33, 0.30–0.35
Subsequent hepatobiliary cancer of autoimmune patients			
Cases	1723		
Mean follow-up (years ± SD)	8.2 ± 7.2		
<1	238	13.8	
1–4	484	28.1	
5–9	462	26.8	
≥10	539	31.3	
Women			
Case	8324		
Mean age at diagnosis (±SD)	71.2 ± 12.2		
Incidence rate (per 100 000 person-years)[a], 95% CI			3.51, 3.44–3.59
Hepatocellular carcinoma (ICD-10 C22.0)	2467	29.6	1.07, 1.03–1.11

TABLE 1 (Continued)

	No.	%	Incidence rate (per 100 000 person-years)[a], 95% CI
Intrahepatic bile duct carcinoma (ICD-10 C22.1)	1153	13.9	0.54, 0.51–0.57
Gallbladder (ICD-10 C23.9)	3101	37.3	1.23, 1.19–1.28
Extrahepatic bile duct (ICD-10 C24.0)	1027	12.3	0.43, 0.40–0.45
Ampulla of Vater (ICD-10 C24.1)	576	6.9	0.24, 0.22–0.26
Subsequent hepatobiliary cancer of autoimmune patients			
Cases	1468		
Mean follow-up (years ± SD)	8.0 ± 7.1		
<1	275	18.7	
1–4	397	27.0	
5–9	341	23.2	
≥10	455	31.0	

Abbreviation: ICD, International Classification of Diseases.
[a]Adjusted for world standardized population.

TABLE 2 Incidence rate (per 100 000 person-years) of hepatobiliary cancer in Sweden, 1997–2018

	All			With a history of autoimmune diseases			Without autoimmune diseases		
	Rate[a]	95% CI		Rate[a]	95% CI		Rate[a]	95% CI	
Total case of hepatobiliary cancer	4.24	4.18	4.30	6.67	6.45	6.89	3.93	3.87	3.99
Subtypes of hepatobiliary cancer									
Hepatocellular carcinoma (ICD-10 C22.0)	2.02	1.98	2.07	3.19	3.04	3.34	1.86	1.82	1.90
Intrahepatic bile duce carcinoma (ICD-10 C22.1)	0.56	0.54	0.59	1.26	1.15	1.37	0.49	0.47	0.51
Gallbladder (ICD-10 C23.9)	0.89	0.87	0.92	1.09	1.01	1.18	0.87	0.85	0.90
Extrahepatic bile duct (ICD-10 C24.0)	0.47	0.45	0.49	0.76	0.68	0.83	0.44	0.42	0.46
Ampulla of Vater (ICD-10 C24.1)	0.28	0.27	0.30	0.37	0.32	0.42	0.27	0.25	0.28

Abbreviation: ICD, International Classification of Diseases.
[a]Adjusted for world standardized population.

Association of follow-up time for autoimmune diseases and hepatobiliary cancer risk is presented in Table 4. The overall risk was highest (6.76) at follow-up of less than 5 years, when the least number of cancers was diagnosed. At longer follow-up times, the risk increased, reaching 2.31 at follow-up over 10 years.

For confirmation of the specificity of the ICD-10 codes used by the Swedish Cancer Registry, we analyzed male risks for HCC and iCCA after each autoimmune disease by comparing results when only the ICD-10 code was used with those when the specific SNOMED codes (81703 and 81603, respectively) were also used (Table S3). Applying SNOMED codes slightly reduced the case numbers because of missing SNOMED codes on some patients, but overall the SIRs were in excellent agreement.

As a sensitivity analysis, we additionally adjusted data in Table S2 for inpatient data on chronic obstructive pulmonary disease, alcoholism, and obesity in Table S4. The overall risk for hepatobiliary cancers decreased from 2.29 to 2.27 and, for most associations, the change was only in decimals of SIR. However, the exceptions were autoimmune hepatitis and primary biliary cirrhosis. The risk associated for these autoimmune diseases decreased in patients with alcohol-related comorbidity.

As another control, we repeated the analysis of HCC after removing patients diagnosed with HBV and HCV (Table S5). The results are quite similar to those in Table 2. Overall risks for HCC in Table 2 were 2.73 for men and 2.86 for women. After removal of the patients with viral infections, the risks were 2.64 and 2.83, respectively.

DISCUSSION

The novel findings of the present study included substantially higher overall associations of autoimmune diseases with all hepatobiliary cancers compared with previous studies; large male excess risks in

TABLE 3 Subsequent risk of hepatobiliary cancer after autoimmune disorders, 1997–2018

		Hepatocellular carcinoma				Intrahepatic bile duct carcinoma				Gallbladder				Extrahepatic bile duct				Ampulla of Vater			
Autoimmune disorders	**Sex**	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Ankylosing spondylitis	Men	15	1.27	0.71	2.10	4	1.83	0.48	4.72	2	1.09	0.10	4.02	2	0.90	0.09	3.33	2	1.48	0.14	5.45
Ankylosing spondylitis	Women	5	3.09	0.97	7.26	0				4	1.79	0.46	4.62	1	1.16	0.00	6.67	1	2.22	0.00	12.74
Autoimmune hepatitis	Men	91	**48.92**	**39.39**	**60.09**	8	**25.00**	**10.68**	**49.50**	1	3.45	0.00	19.77	3	**9.09**	**1.71**	**26.91**	0			
Autoimmune hepatitis	Women	75	**73.53**	**57.83**	**92.20**	6	**9.84**	**3.54**	**21.55**	3	2.04	0.38	6.04	0				1	3.45	0.00	19.77
Celiac disease	Men	11	1.49	0.74	2.68	3	2.13	0.40	6.30	0				1	0.71	0.00	4.07	4	**4.60**	**1.20**	**11.89**
Celiac disease	Women	9	**2.23**	**1.01**	**4.26**	5	2.03	0.64	4.78	6	1.11	0.40	2.43	3	1.43	0.27	4.23	0			
Chronic rheumatic heart disease	Men	16	**1.76**	**1.00**	**2.87**	1	0.67	0.00	3.82	0				1	0.60	0.00	3.45	0			
Chronic rheumatic heart disease	Women	5	1.33	0.42	3.12	3	1.88	0.35	5.55	2	0.35	0.03	1.28	2	1.17	0.11	4.30	0			
Crohn disease	Men	34	**2.10**	**1.45**	**2.93**	19	**6.31**	**3.79**	**9.88**	24	**9.16**	**5.86**	**13.65**	12	**3.97**	**2.04**	**6.96**	4	2.13	0.55	5.50
Crohn disease	Women	15	**2.50**	**1.39**	**4.13**	17	**4.61**	**2.68**	**7.39**	13	1.53	0.81	2.62	11	**3.53**	**1.75**	**6.33**	3	1.83	0.34	5.41
Diabetes mellitus type 1	Men	376	**5.13**	**4.62**	**5.67**	56	**4.15**	**3.13**	**5.39**	28	**2.22**	**1.47**	**3.21**	48	**3.42**	**2.52**	**4.53**	26	**2.94**	**1.92**	**4.31**
Diabetes mellitus type 1	Women	89	**4.92**	**3.95**	**6.05**	21	**2.15**	**1.33**	**3.29**	49	**1.85**	**1.37**	**2.45**	24	**2.56**	**1.64**	**3.81**	19	**3.82**	**2.29**	**5.97**
Giant-cell arteritis	Men	9	1.13	0.51	2.16	4	2.70	0.70	6.99	0				4	2.47	0.64	6.38	0			
Giant-cell arteritis	Women	8	1.34	0.57	2.65	4	1.28	0.33	3.30	13	1.48	0.79	2.54	1	0.31	0.00	1.78	2	1.14	0.11	4.18
Grave	Men	9	1.01	0.46	1.92	10	**6.06**	**2.89**	**11.19**	5	**3.36**	**1.06**	**7.89**	2	1.18	0.11	4.33	2	1.89	0.18	6.94
Graves' disease	Women	14	1.07	0.58	1.80	7	0.87	0.35	1.81	21	1.14	0.71	1.75	13	**1.88**	**1.00**	**3.23**	8	2.17	0.93	4.30
Hashimoto thyroiditis	Men	28	1.47	0.98	2.13	10	**2.80**	**1.33**	**5.17**	4	1.14	0.30	2.94	9	**2.33**	**1.05**	**4.43**	4	1.66	0.43	4.29
Hashimoto thyroiditis	Women	84	**2.55**	**2.03**	**3.16**	44	**2.27**	**1.65**	**3.05**	70	**1.51**	**1.18**	**1.91**	30	**1.68**	**1.13**	**2.39**	25	**2.53**	**1.64**	**3.74**
Immune thrombocytopenic purpura	Men	33	**10.34**	**7.12**	**14.54**	1	1.67	0.00	9.55	0				1	1.56	0.00	8.96	2	5.13	0.48	18.86
Immune thrombocytopenic purpura	Women	8	**6.72**	**2.87**	**13.31**	0				2	1.20	0.11	4.43	1	1.69	0.00	9.72	1	3.13	0.00	17.91
Localized scleroderma	Men	4	**5.48**	**1.43**	**14.17**	0				0				0				0			
Localized scleroderma	Women	1	1.08	0.00	6.16	0				3	2.24	0.42	6.63	1	2.13	0.00	12.20	0			
Myasthenia gravis	Men	2	0.81	0.08	2.98	0				0				4	**8.51**	**2.21**	**22.01**	0			
Myasthenia gravis	Women	1	1.23	0.00	7.08	1	2.22	0.00	12.74	1	0.83	0.00	4.78	1	2.44	0.00	13.98	0			
Pernicious anemia	Men	11	**3.16**	**1.57**	**5.68**	0				6	**6.74**	**2.43**	**14.77**	1	1.61	0.00	9.25	0			
Pernicious anemia	Women	4	2.55	0.66	6.59	1	1.75	0.00	10.06	0				1	1.54	0.00	8.82	0			

TABLE 3 (Continued)

		Hepatocellular carcinoma				Intrahepatic bile duct carcinoma				Gallbladder				Extrahepatic bile duct				Ampulla of Vater			
Autoimmune disorders	**Sex**	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Polymyalgia rheumatica	Men	31	1.42	0.96	2.01	5	1.31	0.41	3.08	8	1.66	0.71	3.29	8	1.83	0.78	3.63	7	2.36	0.94	4.90
Polymyalgia rheumatica	Women	14	0.94	0.51	1.58	11	1.66	0.82	2.98	26	1.16	0.76	1.71	3	0.42	0.08	1.24	5	1.23	0.39	2.89
Primary biliary cirrhosis	Men	27	**38.03**	**25.04**	**55.40**	0				1	7.14	0.00	40.94	0				0			
Primary biliary cirrhosis	Women	73	**54.48**	**42.70**	**68.52**	4	**4.94**	**1.28**	**12.77**	3	1.45	0.27	4.29	2	2.74	0.26	10.08	1	2.63	0.00	15.08
Psoriasis	Men	162	**2.30**	**1.96**	**2.69**	29	**2.17**	**1.45**	**3.12**	15	1.41	0.79	2.33	17	1.26	0.73	2.02	11	1.37	0.68	2.46
Psoriasis	Women	51	**2.01**	**1.50**	**2.64**	18	1.08	0.64	1.71	46	1.30	0.95	1.73	17	1.20	0.70	1.92	13	1.76	0.93	3.02
Rheumatoid arthritis	Men	44	1.12	0.81	1.50	11	1.61	0.80	2.89	5	0.67	0.21	1.58	6	0.81	0.29	1.78	8	1.67	0.71	3.30
Rheumatoid arthritis	Women	51	**1.56**	**1.16**	**2.06**	29	**1.67**	**1.12**	**2.40**	53	1.09	0.81	1.42	24	1.47	0.94	2.19	19	**2.20**	**1.32**	**3.44**
Systemic lupus erythematosus	Men	5	**3.50**	**1.10**	**8.22**	0				1	3.70	0.00	21.23	2	7.41	0.70	27.24	0			
Systemic lupus erythematosus	Women	9	**3.91**	**1.77**	**7.46**	4	2.88	0.75	7.44	7	2.06	0.82	4.27	0				0			
Ulcerative colitis	Men	77	**2.35**	**1.86**	**2.94**	86	**14.33**	**11.46**	**17.71**	66	**12.22**	**9.45**	**15.56**	43	**7.06**	**5.11**	**9.52**	6	1.58	0.57	3.46
Ulcerative colitis	Women	23	**2.46**	**1.56**	**3.69**	32	**5.51**	**3.76**	**7.78**	43	**3.24**	**2.34**	**4.36**	22	**4.44**	**2.78**	**6.74**	1	0.38	0.00	2.16
Any autoimmune disorders	Men	1035	**2.73**	**2.57**	**2.91**	259	**3.74**	**3.30**	**4.23**	175	**2.65**	**2.27**	**3.08**	172	**2.38**	**2.04**	**2.76**	82	**1.80**	**1.43**	**2.24**
Any autoimmune disorders	Women	572	**2.86**	**2.63**	**3.11**	225	**1.96**	**1.72**	**2.24**	395	**1.37**	**1.24**	**1.51**	172	**1.64**	**1.41**	**1.91**	104	**1.85**	**1.51**	**2.24**

Note: Bolding indicates that the 95% CI does not include 1.00.

Abbreviations: ICD, International Classification of Diseases; O, observed; SIR, standardized incidence ratio.

TABLE 4 Subsequent risk of hepatobiliary cancer after autoimmune disorders according to the length of follow-up time, 1997–2018

	<1				1-4				5-9				> = 10			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Addison disease	0				2	1.26	0.12	4.63	2	1.52	0.14	5.57	2	0.94	0.09	3.47
Ankylosing spondylitis	6	**6.74**	**2.43**	**14.77**	8	1.26	0.54	2.50	9	1.29	0.59	2.47	13	1.13	0.60	1.94
Autoimmune hepatitis	23	**69.70**	**44.12**	**104.73**	38	**18.72**	**13.24**	**25.71**	38	**23.31**	**16.49**	**32.02**	89	**30.38**	**24.39**	**37.39**
Celiac disease	4	**3.57**	**0.93**	**9.23**	11	1.38	0.69	2.48	15	**1.79**	**1.00**	**2.97**	12	1.20	0.62	2.10
Chronic rheumatic heart disease	2	0.88	0.08	3.25	14	1.19	0.65	1.99	9	1.13	0.51	2.15	5	0.69	0.22	1.63
Crohn disease	13	**7.69**	**4.08**	**13.19**	30	**2.53**	**1.71**	**3.61**	34	**2.76**	**1.91**	**3.86**	75	**3.15**	**2.48**	**3.95**
Dermatitis herpetiformis	1	5.56	0.00	31.85	1	0.78	0.00	4.44	2	1.54	0.15	5.66	5	**3.40**	**1.07**	**8.00**
Diabetes mellitus type 1	161	**14.45**	**12.31**	**16.87**	218	**3.27**	**2.85**	**3.73**	205	**3.47**	**3.01**	**3.98**	152	**2.80**	**2.38**	**3.29**
Discoid lupus erythematosus	0				2	1.12	0.11	4.11	3	1.69	0.32	4.99	2	1.06	0.10	3.89
Giant-cell arteritis	12	**4.62**	**2.37**	**8.09**	18	1.17	0.69	1.85	9	0.77	0.35	1.47	6	0.87	0.31	1.92
Glomerular nephritis chronic	3	3.85	0.73	11.39	7	1.38	0.55	2.87	4	0.79	0.20	2.03	8	1.03	0.44	2.04
Glomerular nephritis acute	2	9.52	0.90	35.02	2	1.48	0.14	5.45	1	0.76	0.00	4.38	5	2.51	0.79	5.91
Grave disease	6	2.10	0.76	4.60	26	1.32	0.86	1.94	27	1.47	0.97	2.14	32	1.34	0.91	1.89
Guillain-Barre syndrome	2	7.41	0.70	27.24	0				1	0.68	0.00	3.87	3	2.04	0.38	6.04
Hashimoto thyroiditis	115	**10.00**	**8.26**	**12.01**	97	**1.46**	**1.18**	**1.78**	53	1.11	0.83	1.45	43	1.31	0.94	1.76
Immune thrombocytopenic purpura	8	**11.59**	**4.95**	**22.96**	20	**5.28**	**3.22**	**8.16**	15	**5.47**	**3.05**	**9.05**	6	2.31	0.83	5.06
Localized scleroderma	1	4.17	0.00	23.88	5	2.91	0.92	6.84	1	0.68	0.00	3.93	2	1.53	0.14	5.61
Multiple sclerosis	2	2.06	0.19	7.58	6	0.81	0.29	1.77	8	0.94	0.40	1.85	13	0.92	0.49	1.58
Myasthenia gravis	2	4.76	0.45	17.51	1	0.38	0.00	2.16	3	1.43	0.27	4.23	4	1.86	0.48	4.81
Pemphigoid	1	0.87	0.00	4.98	4	0.84	0.22	2.16	4	1.84	0.48	4.77	1	1.06	0.00	6.10
Pernicious anemia	5	**5.38**	**1.70**	**12.65**	10	1.97	0.94	3.63	3	1.01	0.19	2.99	6	2.34	0.84	5.14
Polymyalgia rheumatica	23	**3.15**	**1.99**	**4.73**	50	1.19	0.89	1.58	25	0.91	0.59	1.34	20	1.23	0.75	1.90
Polymyositis/dermatomyositis	2	8.33	0.79	30.65	4	3.01	0.78	7.78	2	1.75	0.17	6.45	0			
Primary biliary cirrhosis	21	**58.33**	**36.05**	**89.32**	22	**10.23**	**6.40**	**15.52**	23	**12.30**	**7.79**	**18.48**	45	**20.83**	**15.19**	**27.90**
Psoriasis	27	**2.78**	**1.83**	**4.05**	110	**1.57**	**1.29**	**1.89**	119	**1.70**	**1.41**	**2.03**	123	**1.89**	**1.57**	**2.26**
Rheumatoid arthritis	20	**2.10**	**1.28**	**3.25**	74	1.17	0.92	1.47	70	1.25	0.98	1.58	86	**1.42**	**1.13**	**1.75**
Sarcoidosis	5	**4.50**	**1.42**	**10.60**	8	1.04	0.44	2.05	4	0.51	0.13	1.32	11	1.01	0.50	1.81
Sjögren syndrome	4	3.28	0.85	8.48	7	0.82	0.33	1.71	8	1.02	0.44	2.02	7	0.90	0.36	1.86
Systemic lupus erythematosus	2	4.35	0.41	15.99	9	**2.89**	**1.31**	**5.52**	6	1.99	0.72	4.37	11	**2.33**	**1.16**	**4.18**
Ulcerative colitis	35	**11.08**	**7.71**	**15.42**	71	**3.16**	**2.47**	**3.98**	96	**4.05**	**3.28**	**4.95**	197	**4.84**	**4.19**	**5.56**
Wegener granulomatosis	1	3.03	0.00	17.37	4	2.06	0.54	5.33	0				1	0.58	0.00	3.35
All	513	**6.76**	**6.19**	**7.37**	881	**1.85**	**1.73**	**1.98**	803	**1.95**	**1.82**	**2.09**	994	**2.31**	**2.17**	**2.46**

Note: Bolding indicates that the 95% CI does not include 1.00. Autoimmune diseases with fewer than 6 cases were excluded, but included in total numbers.

Abbreviations: ICD, International Classification of Diseases; O, observed; SIR, standardized incidence ratio.

iCCA, GBC, and eCCA; and several specific associations for individual autoimmune diseases.[21,22] In the largest study published so far, the overall risk of HCC was 1.61 (sexes combined) and for other sites the risks were approximately 1.20 except for ampullary cancer, which was 1.02 (not significant).[22] These can be compared with the present SIRs of 2.73/2.86 HCC (men/women), 3.74/1.96 for iCCA, 2.65/1.37 for GBC, 2.38/1.64 for eCCA, and 1.80/1.85 for ampullary cancer. Sex-specific risks were not considered in the previous studies, and these were substantial for iCCA, GBC, and eCCA in this study. In Table 1, we present the incidence rates for all hepatobiliary cancers, and these show a 3-fold male excess for HCC, a 2-fold female excess for GBC, and a relatively even incidence for the other cancers and

thus apparently not explaining sex differences for associations with autoimmune diseases.

Association between autoimmune disease and liver cancer may arise because immune disturbance and the related chronic inflammation are shared risk factors for both diseases.[17] Autoimmune diseases are chronic conditions, and their treatment may potentially increase cancer risk. The evidence for cancer risk is strong for immunosuppressive agents, such as azathioprine and mycophenolate mofetil, and less so for biologicals, such as anti-tumor necrosis factor therapy; methotrexate is known to cause nonmelanoma skin cancer.[11,12] In the context of chronic medical conditions, surveillance bias is always possible but it is less likely for aggressive cancers, such as hepatobiliary cancers.[27] It has been also suggested that some associations may arise because of "reverse causation" (i.e., preexisting cancer may contribute to autoimmunity).[21] However, the distribution of cases throughout follow-up times did not lend support to this mechanism.

HCC was the main target of autoimmune hepatitis and primary biliary cirrhosis, but autoimmune hepatitis also affected biliary ducts, particularly as iCCA; primary biliary cirrhosis affected iCCA in women. Our adjustment for alcoholism markedly decreased the risks of HCC after autoimmune hepatitis and primary biliary cirrhosis, suggesting that alcohol intake interacts with these autoimmune diseases to increase the risk of HCC, as has been reported in a review.[28] The common mechanism is likely to be that all these factors promote cirrhosis as the pathway to HCC.[28] Immune thrombocytopenic purpura was associated with a high and specific risk of HCC, which has been observed in previous studies.[13,14] The mechanism is not known, but platelet destruction takes place in the spleen and liver, which may lead to congestion and chronic inflammation.[29] Type 1 diabetes was the only autoimmune disease that increased the risk of all hepatobiliary cancers in men and women; Hashimoto thyroiditis did that in women only. Crohn disease and ulcerative colitis increased the risk of all but ampullary cancers. These common high-risk cancers were the main contributors to the male excess risk in iCCA, GBC, and eCCA. The rare ampullary cancer showed site-specific associations related to its location in the duodenal wall in the mouth of the biliary and pancreatic duct: it was associated with type 1 diabetes and celiac disease, the latter of which has small intestinal manifestations.[30]

Limitations of the study include sample size for rare autoimmune diseases and cancers and follow-up time to allow for chronic immunostimulation for cancer initiation. Table 4 showed that the risks started to increase after the peak in year 1 after autoimmune disease diagnosis, suggesting that the high risks of cancer in year 1 were due to concomitant diagnosis of the two diseases and the slow increase in cancer until more than 10 years was the time for chronic immunostimulation. Even if the risks were highest in the first year of diagnosis, these hepatobiliary cases included only 16% of all associated cases. Left-truncation of data is a likely contributor to the high risks in the first year of follow-up. For example, diagnostics of HCV has been possible only since 1989 in Sweden, and many autoimmune diseases had diagnostic codes first in ICD-10.[31] Thus, longer follow-up times would be needed for a proper analysis of time trends between autoimmune disease and hepatobiliary cancer risk.

In conclusion, autoimmune diseases preceded diagnosis of hepatobiliary cancer in 17.2% of patients with this cancer, and the overall risk was 2.29. Although the risks of hepatic autoimmune diseases for HCC and iCCA are well known, the high risks posed by autoimmune diseases such as type 1 diabetes, Crohn disease, and ulcerative colitis to most types of hepatobiliary cancers are less well known. Survival in hepatobiliary cancers is poor and there are two principal ways to try and prevent these cancers in patients with autoimmune diseases.[32] One is to tackle autoimmune disease by prevention and treatment that suppress autoimmune manifestations and inflammation.[33] The second option is to tackle risk factors of hepatobiliary cancer with the assumption that risk factors add up, as has been suggested for hepatic autoimmune diseases, alcohol consumption, and smoking.[28,34]

AUTHOR CONTRIBUTIONS

Kari Hemminki: Design, statistical analysis and interpretation, and manuscript writing. **Kristina Sundquist:** Design and data acquisition. **Jan Sundquist:** Design and data acquisition. **Asta Försti:** Statistical analysis and interpretation. **Akseli Hemminki:** Manuscript writing. **Xinjun Li:** Design and statistical analysis and interpretation. Approval of the final text: All authors.

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CONFLICT OF INTEREST STATEMENT

A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics, Ltd. The other authors declare no conflicts of interest.

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