Received: 8 July 2022 | Revised: 16 September 2022 | Accepted: 21 September 2022

DOI: 10.1002/ijc.34308

CANCER EPIDEMIOLOGY

IJC INTERNATIONAL JOURNAL of CANCER

Personal comorbidities and their subsequent risks for liver, gallbladder and bile duct cancers

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Funding information
European Commission, Grant/Award Number: 856620

Abstract

Many environmental risk factors for hepatobiliary cancers are known but whether they are associated with specific cancer types is unclear. We present here a novel approach of assessing standardized incidence ratios (SIRs) of previously diagnosed comorbidities for hepatocellular carcinoma (HCC), gallbladder cancer (GBC), cholangiocarcinoma (CCA) and ampullary cancer. The 13 comorbidities included alcohol and nonalcohol related liver disease, chronic obstructive pulmonary disease, gallstone disease, viral and other kinds of hepatitis, infection of bile ducts, hepatic and other autoimmune diseases, obesity and diabetes. Patients were identified from the Swedish Inpatient Register from 1987 to 2018, and their cancers were followed from 1997 onwards. SIRs for HCC were 80 to 100 in men and women diagnosed with hepatitis C virus and they were also >10 in patients diagnosed with hepatitis B virus, other kind of hepatitis, hepatic autoimmune disease and nonalcohol related liver disease. Many of these risks, as well as alcohol related liver disease, were either specific to HCC or were shared with intrahepatic CCA. For GBC, CCA and ampullary cancer infection of bile ducts was the main risk factor. Gallstone disease, nonhepatic autoimmune diseases and diabetes were associated with all hepatobiliary cancers.

Abbreviations: CCA, cholangiocarcinoma; CI, confidence interval; GBC, gallbladder cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; NAFLD, nonalcoholic fatty liver disease; O, observed number; PAF, population attributable fraction; SIR, standardized incidence ratio.

The limitations of the study include inability to cover some rare risk factors and limited follow-up time. Many of the considered comorbidities are characterized by chronic inflammation and/or overt immune disturbance in autoimmune diseases. The results suggest that local chronic inflammation and a related immune disturbance is the carcinogenic trigger for all these cancers.

KEYWORDS
alcohol, comorbidity, familial risk, hepatocellular carcinoma, risk factor, smoking

What's new?

Many risk factors have been identified for hepatobiliary cancers, but the role of comorbidities is often neglected. Here, using individual-level, nationwide diagnostic data, the authors found that almost all of 13 major comorbidities were associated with hepatocellular carcinoma and intrahepatic bile duct cancers. Gallstone disease, infection of bile ducts, nonhepatic autoimmune diseases and diabetes were also associated with gallbladder cancer, extrahepatic bile duct cancer and ampullary cancer. The results suggest that local chronic inflammation and related immune disturbance are the carcinogenic trigger for all these cancers. Some associated risks were very high, calling for prevention and intervention measures.

1 | INTRODUCTION

Hepatobiliary cancers include hepatocellular carcinoma (HCC) and biliary tract cancers, including gallbladder cancer (GBC) and cancers of the biliary tract (extrahepatic and intrahepatic bile ducts, also called, CCA) and of the ampulla of Vater (also called ampullary cancer).[1-3] International variation in the incidence of these cancers is largely depending on known risk factors which are to some extent specific for each cancer type.[1,2,4,5] In northern Europe, the incidence in HCC has been relatively low, and in Sweden the incidence in male HCC and female GBC were about were equally common but in recent decades HCC has become more common than GBC.[6]

Globally, chronic infection by hepatitis B (HBV) or C virus (HCV) are the main causes of HCC while in low-risk areas risk factors include alcohol-related liver cirrhosis, obesity, low physical activity, type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), smoking, autoimmune diseases and family history.[1,2,7-11] NAFLD has bidirectional associations with diabetes and obesity related metabolic syndrome, all of which are an increasing global health concern.[12] In spite of the diversity of the risk factors for HCC, most of them share the mechanism of action through chronic inflammation, necroinflammation and the related immune disturbance, estimated to account for 90% of HCC cases.[3,13-15] GBC shares some risk factors with HCC, including obesity and family history, and features important other risk factors, such as gallstone disease, bacterial infections, biliary cysts and other structural abnormalities.[1,16] CCA shares some risk factors with HCC, but associations with alcohol, HBV, and HCV are weaker.[1,5,9,17,18]

Cancer etiology can be interpreted in terms of epidemiologically derived risk factors which may be causal, such as HBV, or may point out to causal pathways, such as gallstones or chronic infections. A more direct way of estimating etiological background is to clinically assign the type of underlying liver disease, which was done in the Swedish national HCC register.[19] It covered years 2009 to 2016 and included 3376 HCC patients, whose etiology was assigned to HCV in 27%, alcohol in 23%, HBV in 5% and diabetes and nonalcohol-induced steatohepatitis both in 4% of cases.[4]

We present here a novel approach using individual-level, nationwide diagnostic data for diseases (comorbidities) that may predispose to hepatobiliary cancer, including infections, alcohol, diabetes, obesity, NAFLD, gallstones and autoimmune diseases. Diagnostic data were collected from the Swedish nationwide hospital discharge register. Patients diagnosed with each comorbidity were followed for subsequent specific hepatobiliary cancer for deriving comorbidity associated relative risks.

2 | MATERIALS AND METHODS

2.1 | Description of comorbidities

Comorbidities were defined as possible risk factors of hepatobiliary cancer as discussed in the Introduction. They were obtained from the Inpatient Register starting in 1987 by which time the register had reached full national coverage.[20] We were not confined to Inpatient Register as Sweden has additionally a national Outpatient Register, operating since 2001, and an almost national-wide Primary Health Care Register in which diagnoses are collected from 21 of 22 regions in Sweden. We found a large number of unrelated patients diagnosed with the current 13 comorbidities from these registers but they had very few subsequent hepatobiliary cancers, probably because the registers were relatively recent. For uniformity and diagnostic accuracy we decided to use patients from the Inpatient Register only.

Comorbidities were identified using codes of the International Classification of Diseases (ICD), between 1987 and 1996 using

ICD-9 and from 1997 onwards ICD-10 (Supplementary Table 1). The selected comorbidities included alcohol related liver disease, chronic obstructive pulmonary disease (COPD), gallstone disease, HBV, HCV, hepatitis of other kind, infection of bile ducts, autoimmune hepatitis, primary biliary cirrhosis, other autoimmune diseases, NAFLD, obesity and diabetes. As national data are not available for smoking and alcohol consumption, chronic obstructive pulmonary disease and alcohol related liver disease were used as proxies. According to a Swedish survey on COPD disease, 89% of men and 64% of women were smokers, with PAFs of 64 and 29%.[21] According to Supplementary Table 1, a total of 3.53 million persons were diagnosed with any of the 13 comorbidities. Persons were assigned to individual comorbidities based on their first diagnosis. The most common comorbidities were other autoimmune diseases (929 000), chronic obstructive pulmonary disease (893 000), diabetes (650 000) and gallstone disease (484 000).

For autoimmune diseases, liver-specific autoimmune hepatitis and primary biliary cirrhosis were analyzed separately and all other 41 types of autoimmune diseases constituted "other autoimmune diseases" as described elsewhere, and listed in Supplementary Table 2 with their ICD codes.[22] None of the autoimmune diseases were significantly associated with a decreased risk of hepatobiliary cancer.

2.2 | Analysis of cancer risks

Cancer data were covered for the years 1997 through 2018 for the whole population of Sweden. Cancers were identified from the Swedish Cancer Registry using ICD-10 codes for primary hepatobiliary cancers but deleting subcodes for cancer in multiple bile ducts and cancer in unspecified bile ducts. The code for HCC was C22.0, for intrahepatic CCA C22.1, for GBC C23.9, for extrahepatic CCA C24.0 (including Klatskin tumors) and for ampulla of Vater C24.1.

The linkages between the different registers were done using the personal identification number, assigned to each resident in Sweden, and replaced by a serial number to preserve people's integrity.

Person-year calculation was started from the first diagnosis of comorbidity from 1997 onwards until a diagnosis of hepatobiliary cancer, death, and emigration or the end of the follow-up in 2018. To test the influence of the follow-up definition for comorbidities (starting in 1987 or 1997) we carried out a sensitivity analysis using both definitions (Supplementary Table 3). The early starting resulted in about 2600 more hepatobiliary cancers and some lower overall standardized incidence ratios (SIRs); a short follow-up is associated with earlier onset disease of higher risk. However, longer follow-up is preferred because of higher case numbers and because of the better chance of coping with the chronic causation of these cancers.

SIRs were calculated as the ratio of observed to the expected number of cases. The expected numbers were calculated from the present dataset for all individuals without the specific comorbidity (ie, most of the Swedish population), and the rates were standardized by 5-year-age, gender, period (5 years group), highest educational level (as a proxy for socioeconomic status) and geographical region.

TABLE 1 Total population and number of case of hepatobiliary cancer in Sweden, 1997 to 2018

	No.	%
Population	13 567 134	100.0
Men	6 821 533	51.3
Women	6 745 601	48.7
All hepatobiliary cancer		
Cases	18 598	
Mean age at diagnosis (±SD)	69.9 ± 12.3	
Incidence rate (per 100 000 person years)[a], 95% CI	4.2, 4.2-4.3	
Men		
Case	10 274	
Mean age at diagnosis (±SD)	68.9 ± 12.3	
Incidence rate (per 100 000 person years)[a], 95% CI	5.0, 4.9-5.1	
Women		
Case	8324	
Mean age at diagnosis (±SD)	71.2 ± 12.2	
Incidence rate (per 100 000 person years)[a], 95% CI	3.5, 3.4-3.6	
Subtypes of hepatobiliary cancer	18 598	100.0
Hepatocellular carcinoma (HCC) (ICD-10 C22.0)	8674	46.6
Intrahepatic bile duce carcinoma (ICD-10 C22.1)	2285	12.3
Gallbladder (ICD-10 C23.9)	4244	22.8
Extrahepatic bile duct (ICD-10 C24.0)	2115	11.4
Ampulla of Vater (ICD-10 C24.1)	1280	6.9
Total numbers of comorbidities preceding diagnosis of hepatobiliary cancer	13 717	100.0
Hepatocellular carcinoma (HCC) (ICD-10 C22.0)	6866	50.1
Intrahepatic bile duce carcinoma (ICD-10 C22.1)	1510	11.0
Gallbladder (ICD-10 C23.9)	2919	21.3
Extrahepatic bile duct (ICD-10 C24.0)	1569	11.4
Ampulla of Vater (ICD-10 C24.1)	853	6.2

[a]Adjusted for World standardized population.

The 95% confidence interval (95% CI) of the SIR was calculated assuming a Poisson distribution. Observed cases (O) indicate the persons for whom the SIR was calculated. SIRs are not comparable with each other because they are calculated using different exposed groups and the numerical ranking should not be taken literally.[23] As each person with a diagnosed comorbidity was entered only once, no double counting was possible. In spite of the limitations with SIR, the measure is commonly used, as it is particularly suitable for small sample sizes, such as many entries here.[24]

When risks were discussed only statistically significant associations (ie, 95%CI did not include 1.00) were referred to.

TABLE 2 Subsequent risk of hepatobiliary cancer (from cancer registry) after comorbidities (from inpatient register) in men, 1997 to 2018

	Hepatocellular carcinoma				Intrahepatic bile duct carcinoma				Gall bladder			Extrahepatic bile duct					Ampulla of Vater			
Diagnosis of comorbidities	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	**O**		**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Alcohol-related liver disease	1080	9.05	8.51	9.60	78	2.33	1.84	2.90	43	1.20	0.87	1.62	37	1.24	0.87	1.71	21	1.28	0.79	1.96
Chronic obstructive pulmonary disease	513	1.65	1.51	1.80	120	1.37	1.14	1.64	185	1.11	0.96	1.29	102	1.21	0.98	1.46	74	1.51	1.19	1.90
Gallstone disease	512	1.46	1.33	1.59	241	2.38	2.09	2.70	1414	9.38	8.89	9.88	329	3.65	3.27	4.07	217	4.13	3.60	4.72
Hepatitis B virus	212	49.07	42.69	56.15	20	15.04	9.17	23.26	3	2.42	0.46	7.16	4	4.04	1.05	10.45	1	1.85	0.00	10.62
Hepatitis C virus	925	84.63	79.26	90.27	29	7.84	5.24	11.27	3	0.83	0.16	2.47	7	2.41	0.95	4.98	4	2.60	0.68	6.72
Hepatitis of other kind	180	35.57	30.57	41.17	18	11.69	6.91	18.51	8	3.07	1.31	6.07	7	5.15	2.04	10.66	4	5.13	1.33	13.26
Infection of bile ducts	130	7.66	6.40	9.10	271	67.08	59.33	75.57	336	35.82	32.09	39.87	520	151.60	138.85	165.22	218	96.04	83.71	109.68
Autoimmune hepatitis	18	30.51	18.04	48.31	1	4.00	0.00	22.93	0				0				0			
Primary biliary cirrhosis	84	42.00	33.50	52.02	4	4.55	1.18	11.75	3	1.52	0.29	4.49	2	2.47	0.23	9.08	1	2.27	0.00	13.03
Other autoimmune diseases	1306	2.41	2.28	2.54	412	2.52	2.28	2.78	476	1.54	1.40	1.68	265	1.68	1.48	1.90	130	1.41	1.18	1.68
Nonalcohol related liver disease	99	24.50	19.92	29.84	9	7.63	3.46	14.54	5	2.78	0.88	6.53	1	0.94	0.00	5.41	2	3.39	0.32	12.47
Obesity	88	1.76	1.41	2.17	31	1.73	1.18	2.46	45	1.91	1.39	2.56	23	1.61	1.02	2.42	5	0.67	0.21	1.58
Diabetes	1719	4.05	3.86	4.25	276	2.45	2.17	2.76	398	1.87	1.69	2.06	272	2.40	2.13	2.71	176	2.61	2.24	3.03
All of above	6866	3.73	3.64	3.82	1510	2.85	2.71	3.00	2919	3.17	3.06	3.29	1569	3.14	2.98	3.29	853	2.93	2.74	3.14

Note: Case number in the total population are from Table 1.
Abbreviations: CI, confidence interval; O, observed; SIR, standardized incidence ratio.

TABLE 3 Subsequent risk of hepatobiliary cancer (from cancer registry) after comorbidities (from inpatient register) in women, 1997 to 2018

	HCC				Intrahepatic bile duce carcinoma				Gall bladder				Extrahepatic bile duct				Ampulla of Vater			
Diagnosis of comorbidities	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Alcohol-related liver disease	137	9.07	7.62	10.73	15	1.46	0.81	2.41	19	1.06	0.64	1.66	7	0.90	0.35	1.85	4	1.02	0.26	2.63
Chronic obstructive pulmonary disease	190	1.94	1.68	2.24	63	1.27	0.97	1.62	128	1.02	0.85	1.21	54	1.19	0.89	1.55	35	1.44	1.00	2.01
Gallstone disease	195	1.47	1.27	1.69	146	2.27	1.92	2.67	1097	9.29	8.75	9.86	193	3.65	3.16	4.21	109	3.79	3.11	4.57
Hepatitis B virus	49	61.25	45.30	81.02	7	13.21	5.24	27.37	2	2.63	0.25	9.68	1	2.86	0.00	16.38	1	5.26	0.00	30.17
Hepatitis C virus	185	101.09	87.05	116.77	10	6.85	3.26	12.64	1	0.45	0.00	2.58	3	2.91	0.55	8.62	0			
Hepatitis of other kind	67	41.61	32.25	52.87	6	6.82	2.45	14.94	4	1.94	0.51	5.02	2	2.67	0.25	9.81	3	7.32	1.38	21.66
Infection of bile ducts	49	8.51	6.29	11.25	104	43.51	35.55	52.74	201	27.88	24.16	32.01	245	129.63	113.91	146.93	97	84.35	68.40	102.92
Autoimmune hepatitis	13	41.94	22.24	71.92	0				0				0				0			
Primary biliary cirrhosis	67	48.55	37.62	61.68	4	5.19	1.35	13.43	3	1.60	0.30	4.75	2	2.90	0.27	10.66	1	2.70	0.00	15.49
Other autoimmune diseases	413	2.28	2.07	2.52	172	1.74	1.49	2.02	310	1.26	1.12	1.41	126	1.41	1.18	1.68	64	1.33	1.02	1.69
Nonalcohol related liver disease	39	36.45	25.91	49.87	5	8.20	2.59	19.28	2	1.49	0.14	5.49	0				1	3.70	0.00	21.23
Obesity	23	1.26	0.80	1.90	17	1.47	0.86	2.37	33	1.71	1.17	2.40	9	1.05	0.48	2.00	3	0.69	0.13	2.04
Diabetes	362	3.62	3.26	4.02	96	1.95	1.58	2.38	276	1.93	1.71	2.17	109	2.32	1.91	2.80	61	2.38	1.82	3.06
All of above	1789	3.21	3.06	3.36	645	2.22	2.05	2.40	2076	3.03	2.90	3.16	751	2.93	2.73	3.15	379	2.74	2.47	3.03

Note: Case number in the total population are from Table 1.

Abbreviations: CI, confidence interval; O, observed; SIR, standardized incidence ratio.

3 | RESULTS

The characteristics of the study population are described in Table 1. The total population was 13.6 million covering years 1997 to 2018 with 18 598 hepatobiliary cancers at a mean diagnostic age of 69.9 years. Incidence rates were 5.0/100000 for men and 3.5/100000 for women. The specific types of cancer were 46.6% HCC, 12.3% intrahepatic CCA, 22.8% GBC, 11.4% extrahepatic CCA and 6.9% ampullary cancer.

Male cancer risks for each of 13 comorbidities are shown in Table 2. The overall SIRs were increased for all cancer types, being highest for HCC (3.73) and lowest for intrahepatic CCA (2.85). Accordingly, 5/13 comorbidities (gallstone disease, hepatitis of other kind, infection of bile ducts, other autoimmune disease and diabetes) conferred a risk at all subsites. For HCC all comorbidities were associated with a significant risk and for intrahepatic CCA all comorbidities but autoimmune hepatitis conferred an increased risk. Many of the SIRs were very high for HCC, including any type of hepatitis (eg, HCV 84.63), alcohol and NAFLD and hepatic autoimmune diseases. Alcohol related liver disease and NAFLD were associated only with the risk of HCC and intrahepatic CCA; these cancers were also increased after primary biliary cirrhosis, but autoimmune hepatitis increased only risk of HCC. Gallstone disease was associated with a high risk of GBC (9.38), infection of bile ducts was associated with a very high risk of extrahepatic CCA (151.60) and ampullary cancer (96.04).

Female risks are shown in Table 3. Case numbers were much lower than for men but, nevertheless, the results between sexes were very uniform and no comorbidity showed a significant sex difference. For women, 4/13 comorbidities (gallstone disease, infection of bile ducts, other autoimmune diseases and diabetes) conferred a risk at all subsites, and infection of bile ducts was associated with high risk at all sites. Obesity was associated only will GBC.

4 | DISCUSSION

The novelty of the present study is that we were able to use a large number medically diagnosed comorbidities to assess cancer risks in all main types of hepatobiliary cancers. Comorbidities were collected from a national Inpatient Register in a country of high quality medical care, accessible to the population at large.[20] This contrasts with the literature focused on one type of cancer and usually a single risk factor. In the published studies on HCC the risks factors or comorbidities have included HVB and HCV, smoking, alcohol, nonalcoholic liver disease, autoimmune disease and physical inactivity.[10,25-30] For GBC, gallstone disease has been the subject of many studies while for CAA risks of smoking, alcohol and some comorbidities have been analyzed.[1,5,9,18]

The coverage of patients diagnosed with severe medical conditions, such as gallstone disease, infection of bile ducts, autoimmune disease and diabetes was probably reasonably high. Nonalcoholic liver disease has been histologically verified in 8892 Swedish patients in years 1966 to 2015 with subsequent 153 HCCs; the present patient number was 5536 with 138 HCCs.[28] Nonalcoholic liver disease may have overlapping patients diagnosed with obesity and diabetes. The estimated number of Swedish patients with chronic HCV infection has been given at 57 040 between years 1990 and 2015, compared with our figure of 25 035 (serological diagnosis for HCV has been possible after 1989). Even though inpatient data may lack half of HCV patients, the diagnosed HCC cases (N = 1110) were not as much lower than the 1758 liver cancers (including unspecified cases not recorded in the Cancer Registry) in the HCV cohort.[31] The prevalence of alcohol related liver disease was 280 000 patients which was 2.1% of the 13.6 million inhabitants included in the study. These patients are most likely at the highest cancer risk among all alcohol consumers (SIR was 9.05 for men and 9.07 for women) but alcohol related cancers were certainly diagnosed in a wider population which were missed. Alcohol related liver disease targeted specifically HCC as only male intrahepatic CCA was additionally modestly increased (SIR 2.35) in this population. We were not able to cover structural anomalies of bile ducts which are known to be associated with a high cancer risk at the affected sites.[18] COPD is not a perfect proxy for smoking, as pointed out in Methods, but nevertheless the present SIRs of COPD for HCC (1.65 for men and 1.95 for women) were close to 1.55 for current smokers from pooled analysis of 81 studies.[25]

The study has several limitations. We were not able to cover all susceptible individuals because they did not received medical treatment (eg, most alcohol consumers and smokers), no codes were available for a comorbidity (eg, primary sclerosing cholangitis) or because follow-up time was limited in these cancers where chronic stimulation and cirrhosis may take decades to transform into cancer; for example in HCV the maximal HCC risk was reached after 40 years of infection.[31] However, even if the follow-up was started in 1987, the Swedish Inpatient Register does not exclude patients diagnosed before 1987. Thus, it is possible that many patients had their first comorbidity diagnosis well before 1987, after which date they were captured by the Inpatient Register. The inclusion of hospitalized patients in the study probably imply that the observed risks at least for alcohol and smoking related cancers were higher compared with average consumers. However, inclusion of hospitalized patients guarantees diagnostic accuracy as many of the comorbidities requires specialist diagnostics. Another important limitation is that the results apply only to the population under study.

Positive bias in the context of medical surveillance is commonplace but it is unlikely to be a serious confounder for the fatal cancers included.[32] The present results allow some important conclusions. First, the spectrum of comorbidities influence the associated cancers; alcohol and nonalcohol liver disease, any type of hepatitis and hepatic autoimmune disease increased vastly HCC, gallstone disease targeted GBC and infection of bile ducts caused cancer in the linings of these ducts. This was altogether a textbook example of local chronic stimulation as a cause of cancer.[3,13-15] Second, chronic obstructive pulmonary disease, a proxy for smoking, obesity and diabetes, nonspecifically associated with a modest or low risk of many cancer types.

Are there means of preventing hepatobiliary cancer other than moderation in alcohol consumption, avoidance of overweight, maintaining physical activity, and stopping smoking? Prevention of viral hepatitis would require avoidance of intravenous drug use with dirty

needles, condom use, and encouragement to infected persons to seek and keep medical contacts.[33] HBV vaccines are effective, and antiviral therapies can be used for infected persons with HBV and HCV. Various screening options have been considered for cirrhotic patients with liver autoimmune diseases.[34] Aspirin use has been reported to reduce the risk of HCC to a relative risk of 0.62, according to a recent meta-analysis.[35] Aspirin, other nonsteroidal anti-inflammatory drugs, and statin may have even stronger effects in reducing the risk of GBC and CCA.[36,37] Considering the very high risk of bile duct infection on CCA, data would be urgently needed to intervene with the harmful sequelae after such infections.

In conclusion, patients diagnosed with the selected 13 comorbidities from the national Inpatient Register had high risks of subsequent specific hepatobiliary cancer. The individual comorbidities were associated with site-specific cancers, alcohol- and nonalcohol related liver disease and any type of hepatitis increased the risk of HCC, gallstone disease affected GBC, and infection of bile ducts increased CCA, suggesting local chronic stimulation as a carcinogenic mechanism not only in HCC but in all hepatobiliary cancers. The contribution of autoimmune diseases in all hepatobiliary cancers underscores the mechanistic role of immune disturbance.[15]

AUTHOR CONTRIBUTIONS

Design: Kari Hemminki, Kristina Sundquist, Jan Sundquist and Xinjun Li. Acquisition of data: Kristina Sundquist and Jan Sundquist. Statistical analysis and interpretation: Xinjun Li and Kari Hemminki. Manuscript writing: Kari Hemminki, Asta Försti, Vaclav Liska and Akseli Hemminki. Approval of the final text: All authors. The work reported in the paper has been performed by the authors unless clearly reported in the text.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

Supported by the European Union's Horizon 2020 Research and Innovation Program, No. 856620, The Swedish Research Council, Jane and Aatos Erkko Foundation, Finnish Cancer Organizations, University of Helsinki, Helsinki University Central Hospital, Novo Nordisk Foundation, Päivikki and Sakari Sohlberg Foundation, Sigrid Juselius Foundation, the Cooperation Program, research area SURG and National Institute for Cancer Research—NICR (Program EXCELES, ID Project No. LX22NPO5102), funded by the European Union—Next Generation EU.

CONFLICT OF INTEREST

Akseli Hemminki is shareholder in Targovax ASA. Akseli Hemminki is employee and shareholder in TILT Biotherapeutics Ltd. The other authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

For cancer data please contact Swedish Board of Health and Welfare. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The study was approved by the Regional Ethical Review Board in Lund, February 6, 2013 (Reference 2012/795 and later amendments). 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.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hemminki K, Sundquist K, Sundquist J, et al. Personal comorbidities and their subsequent risks for liver, gallbladder and bile duct cancers. *Int J Cancer*. 2023;152(6):1107-1114. doi:10.1002/ijc.34308