


## ORIGINAL ARTICLE

# Risk factors, epidemiology and prognosis of cholangiocarcinoma in Finland

Nina Barner-Rasmussen<sup>1</sup>  | Eero Pukkala<sup>2,3</sup> | Kishor Hadkhale<sup>3</sup> | Martti Färkkilä<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

<sup>2</sup>Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

<sup>3</sup>Faculty of Social Sciences, Tampere University, Tampere, Finland

## Correspondence

Nina Barner-Rasmussen, Department of Gastroenterology, Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, PO box 340, 00280 Helsinki, Finland.  
Email: [nina.barner-rasmussen@hus.fi](mailto:nina.barner-rasmussen@hus.fi)

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## Abstract

**Background:** Cholangiocarcinoma (CCA) is a cancer arising from the intra- and extrahepatic bile ducts. The early stages are often asymptomatic, CCA is frequently diagnosed in an advanced stage and the prognosis of CCA is often dismal.

**Objective:** Our objective was to estimate the incidence of CCA in Finland and to identify risk factors for CCA, with a special interest in primary sclerosing cholangitis (PSC).

**Methods:** We identified all CCA cases during 1974–2018 from the Finnish Cancer Registry and calculated age-standardised incidence rates. Five controls for each case were extracted from the Population Registry, matched by age, gender and municipality of residence at the time of diagnosis. Odds ratios (ORs) for risk factors were estimated with conditional logistic regression and survival estimates with the Kaplan–Meier method.

**Results:** Incidence of CCA remained stable in both genders; the age-standardised rate (World Standard) in 2013–2017 in males and females was 1.7 per 100,000 person years and 1.3 per 100,000 person years, respectively. Primary sclerosing cholangitis carried a 30-fold risk of intrahepatic cholangiocarcinoma (iCCA) and 25-fold risk of extrahepatic cholangiocarcinoma (eCCA). Diabetes, inflammatory bowel disease and liver cirrhosis were associated with iCCA, whereas cholelithiasis and viral hepatitis C were associated with eCCA. The cumulative 5-year survival was 4.6%.

**Conclusions:** The incidence of CCA has been stable. Known risk factors for CCA were confirmed, with PSC having the highest OR. Survival remains poor.

## KEYWORDS

cholangiocarcinoma, epidemiology, liver, primary sclerosing cholangitis, risk factors

## INTRODUCTION

Cholangiocarcinoma (CCA) is a malignant tumour that originates from the epithelial cells of the bile ducts. It is the second most common hepatobiliary malignancy after hepatocellular carcinoma.<sup>1</sup>

CCA is classified into intrahepatic CCA (iCCA), perihilar CCA (pCCA), also known as Klatskin tumours and distal CCA (dCCA). Perihilar CCA and dCCA were previously grouped together as extrahepatic CCA (eCCA).<sup>2</sup> CCA is an aggressive tumour, and the 5-year survival is under 10%; iCCA has a more dismal prognosis than dCCA.<sup>3–5</sup> The

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diagnosis is often made in an advanced state, and only one-third of the patients have a possibility for curative treatment.<sup>6</sup>

There is considerable geographical variation in the age-adjusted incidence of CCA, with the highest incidence in Asia, which has an incidence for iCCA of up to 2.8 per 100,000 person years compared to Western countries of less than 1.2 per 100,000 person years, and for eCCA 2.2 versus 0.8 per 100 000 person years, respectively.<sup>7,8</sup> The incidence of especially iCCA has been shown to increase in many previous studies, even though the results are not consistent.<sup>7,9-12</sup>

When studying the long-term changes in the incidence of CCA, it is important to understand the possibility of its misclassification. It has been reported in many papers that part of the increase in incidence for iCCA could be explained by the World Health Organisation's International Classification of Disease for Oncology (ICD-O) coding. The ICD-O-2 classified pCCA as iCCA instead of eCCA, so it is important to interpret the long-term trends in both iCCA and eCCA with caution.<sup>12-14</sup>

Only a small percentage of CCA cases are associated with known risk factors, while most of the cases are sporadic.<sup>15</sup> Risk factors for CCA include parasitic infections (*Clonorchis sinensis*, *Opisthorchis viverrini*),<sup>16</sup> primary sclerosing cholangitis (PSC), biliary duct cysts, hepatolithiasis, hepatitis B or C and toxins. Probable risk factors are cirrhosis, inflammatory bowel disease (IBD), obesity, diabetes, cholelithiasis, alcohol consumption and smoking. Some of the risk factors are associated with intrahepatic and others with eCCA.<sup>8,9,15,17</sup> In line with IBD, the crude incidence of PSC has also increased in most countries, including Finland.<sup>18,19</sup>

We aimed to determine the incidence of CCA over time and the survival of CCA patients in Finland. We also assessed possible underlying risk determinants for iCCA and eCCA with a special interest in PSC.

## MATERIALS AND METHODS

For case-control analyses on aetiology of CCA, the data on CCA cases diagnosed from 1 January 1971 to 31 December 2014 were retrieved from the population-based countrywide Finnish Cancer Registry. ICD-10 codes C22.1, C24.0, C24.8 and C24.9 were used to identify CCA patients. Information on cancer topography, morphology, staging, treatment and municipality was obtained.

For each CCA case, five controls were extracted from the Population Registry of the Digital and Population Data Services Agency, matched by age, gender and municipality at the time of diagnosis. The controls had to be living in Finland on the date of diagnosis of the CCA case ('index date'). To assess the risk determinants, we linked both the cases and controls to the nationwide patient registry (HILMO) that contains comprehensive healthcare records on inpatients provided by municipal healthcare centres, private healthcare centres and all hospitals. The reports to HILMO include the patient's personal identity code (PIC), admission and discharge dates and discharge diagnoses. The PIC has been given to all residents of Finland since 1967, and it is used as the key in linkages between all main registers in Finland.

### Key summary

#### Established knowledge of this subject

- The incidence of cholangiocarcinoma (CCA) has a high geographical variation
- Several risk factors have been established in previous studies including choledochal cysts and viral hepatitis
- The prognosis is poor with a 5-year survival of around 9%

#### Significant or new findings of this study

- The incidence of CCA in Finland has not increased over time
- Risk factors in Finland were in line with risk factors seen in other studies
- The odds ratio for primary sclerosing cholangitis was 30 for intrahepatic CCA and 25 for extrahepatic CCA

As PSC does not have a disease unique ICD-10 code, PSC diagnoses could not be extracted from HILMO, but we had access to hospital records of all PSC patients in the Helsinki University Hospital (HUS) area from 1990 to 2015.<sup>18</sup> For the current study, we linked those PSC diagnoses done before the index date to all CCA patients and their controls who lived in the HUS area at diagnosis 1990–2014. This region and time-limited case-control subset is used in models for assessing the role of PSC as a risk determinant of CCA.

For survival calculations, we used the same cohort of CCA patients from 1971 to 2014 that served as cases in the case-control study and the HUS subset of the cases. The date of CCA diagnosis was used as the starting point for the survival calculations. The date of death was the outcome event, and the date of emigration or the end of study, 31 December 2014, was used as censoring events. The dates of emigration and death were derived from the Population Registry of the Digital and Population Data Services Agency.

Calculation of the incidences rates of CCA was performed at the end of the study process, when it was possible to use Cancer Registry data until 31 December 2018. Population counts for the incidence calculation were retrieved from Statistics Finland.

Data for the CCA diagnostic code C22.1, C24.0 and C24.9 and morphology codes 8000, 8010, 8020-8021, 8050, 8070, 8140, 8148, 8160-8162, 8180, 8260, 8440, 8460 and 8560, were retrieved. The incidence rates were stratified to (1) histologically confirmed CCA, (2) adenocarcinoma and Klatskin (8140 and 8162) and (3) other morphology codes.

### Statistical methods

The incidence rates were calculated by sex, year, 5-year calendar period, 5-year age group and tumour location. The rates were age standardised to the World Standard Population.

Odds ratios (ORs) and 95% confidence intervals (CIs) for the study variables were estimated with multivariate conditional logistic regression separately for the whole Finland and HUS area. The following variables were available for the whole of Finland: cholelithiasis, diabetes, IBD, liver cirrhosis, viral hepatitis B (HBV) and viral hepatitis C (HCV). Due to high collinearity, IBD and liver cirrhosis were estimated in separate models. Model F1 included cholelithiasis, diabetes, IBD, HBV and HCV. Model F2 included cholelithiasis, diabetes, liver cirrhosis, HBV and HCV.

For the HUS area we also had information on PSC. Due to high collinearity, ORs for IBD, liver cirrhosis and PSC were estimated in separate models. Model H1 included cholelithiasis, diabetes, IBD, HBV and HCV. Model H2 included cholelithiasis, diabetes, liver cirrhosis, HBV and HCV. Model H3 included cholelithiasis, diabetes, PSC, HBV and HCV. Because nobody in the control group had PSC or HBV, unconditional logistic regression was used to estimate ORs for these variables. Cumulative survival was described with Kaplan-Meier estimates. Statistical analyses were made with SPSS 24 and STATA 16 (StataCorp LP).

## RESULTS

### Patient characteristics and survival

We identified 6949 CCA cases from 1971 to 2014. The median age at the time of diagnosis was 73 years (range: 24–103 years) for both sexes combined, 70 years (range: 24–96 years) in male ( $N = 3033$ ) and 76 years (range: 25–103 years) in female ( $N = 3916$ ). The diagnosis was more common in females (56%).

Data on the treatment of CCA patients were missing in 31% of the patients. The stage of CCA was unknown in 2092 (29%), and the disease was known to be localised in only 1039 (15%) and spread in 3835 (55%) of the cases (Table 1). Of the 6949 CCA patients diagnosed during 1971–2014, 6680 (96%) died before the end of 2014. The median time from diagnosis to death was 2.3 months (Figure 1). Cumulative 5-year survival was 5.1% for male and 4.3% for female CCA patients.

In the HUS area, we identified 1246 CCA cases diagnosed in the years 1990–2014. The median age at the time of diagnosis was 71 years (range: 29–100 years) for both sexes combined, 72 years (24–96 years) in male ( $N = 581$ ) and 74 years (25–103 years) in fe-

**TABLE 1** Site, stage at diagnosis and treatment of cholangiocarcinoma in Finland (all regions) 1971–2014, and in HUS area 1990–2014

	All regions 1971–2014		HUS area 1990–2014	
	N	Percentage	N	Percentage
<b>Site</b>				
All	6949	100	1246	100
Intrahepatic	2572	37	621	50
Extrahepatic	3555	51	456	37
Unknown origin	822	12	165	13
<b>Stage</b>				
Localised carcinoma	1039	15	162	13
Only regional lymph node metastases	262	4	47	4
Spread disease	3573	51	619	50
Unknown	2075	30	418	34
<b>Treatment</b>				
Surgery, radical or palliative	1898	27	269	22
Radical surgery	562	8	84	8
Chemotherapy	822	12	215	17
Radiation therapy	341	5	69	6
Combination of different treatments	483	7	333	27
No treatment	2527	36	365	29
No data on treatment	1333	19	327	27

Abbreviation: HUS, Helsinki University Hospital.

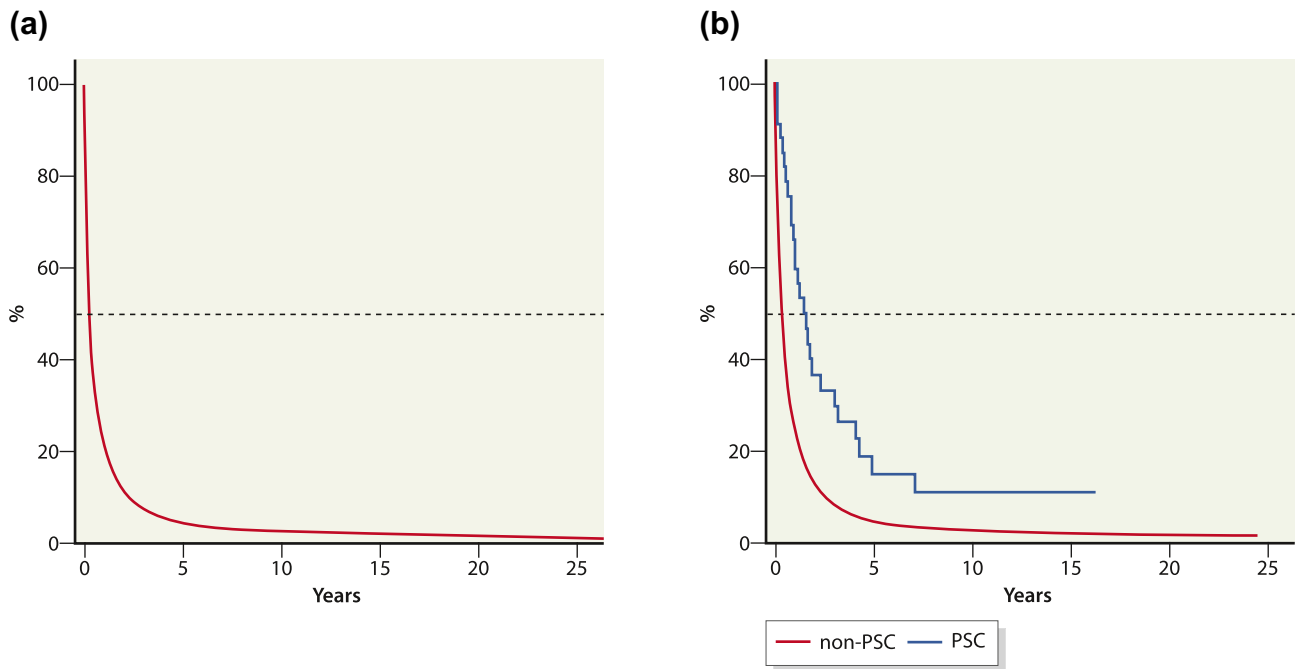
male ( $N = 665$ ). Of the 1246 patients, 1193 (96%) died during the study period. The median time from diagnosis to death was 3.2 months. Cumulative 5-year survival was 5.6% (Figure 1). The study periods for the whole of Finland and the HUS area are different, and therefore, this study does not allow a direct comparison of the results between these two areas.

## Incidence

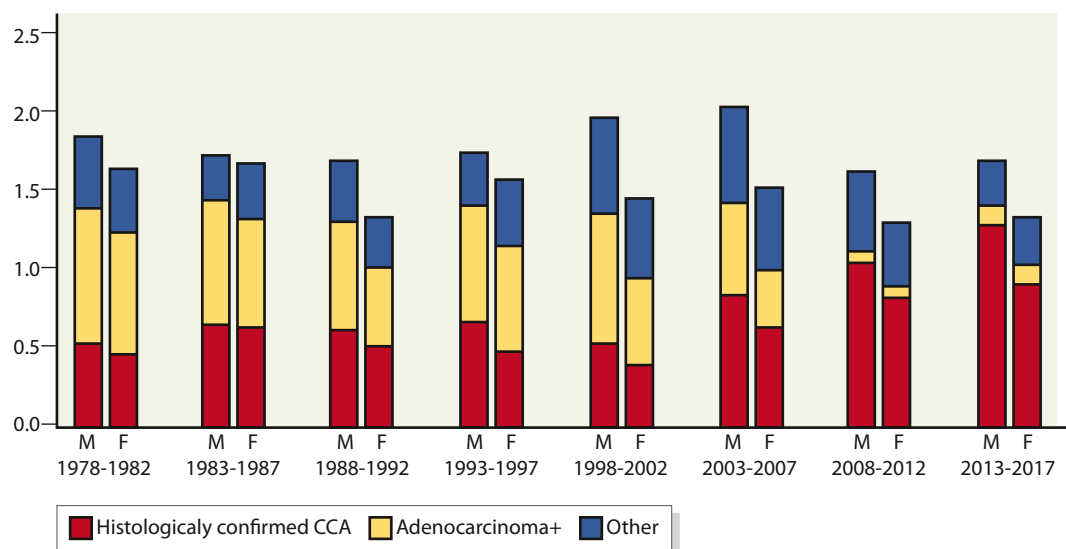
The age-standardised incidence for CCA, histologically confirmed and unconfirmed, among Finnish males in 1978–2017, 1978–1982 and

2013–2017 was 1.8 per 100,000 person years (95% CI: 1.5–2.1), 1.9 per 100,000 (95% CI: 1.3–2.4) person years and 1.7 per 100,000 (95% CI: 1.4–2.0) person years, respectively (Figure 2). The respective rates in females were 1.5 (95% CI: 1.3–1.7), 1.6 (95% CI: 1.4–1.8) and 1.3 (95% CI: 1.1–1.5). The proportion of histologically confirmed CCA increased over time (Figure 3).

The incidence of both iCCA and eCCA in 2013–2017 was higher in males than in females (Figure 3). In males, the incidence of iCCA and eCCA was 1.3 (95% CI: 1.1–1.5) per 100,000 person years and 0.4 (95% CI: 0.3–0.5) per 100,000 person years, respectively. The respective rates for females were 1.0 (95% CI: 0.8–1.2) and 0.3 (95%



**FIGURE 1** Cumulative survival (%) for all cholangiocarcinoma patients in Finland 1978–2014 (a) and for cholangiocarcinoma patients with and without primary sclerosing cholangitis (PSC) in Helsinki University Hospital area 1990–2014 (b)



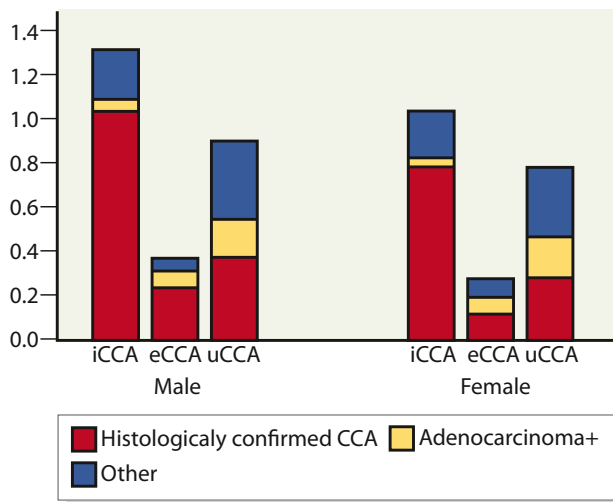
**FIGURE 2** Age-standardised incidence (World Standard) of cholangiocarcinoma (CCA) per 100,000 person years in Finland, by period and gender

CI: 0.2–0.4). During this period, 35% of CCA cases in male and 36% in females were classified as of unknown origin.

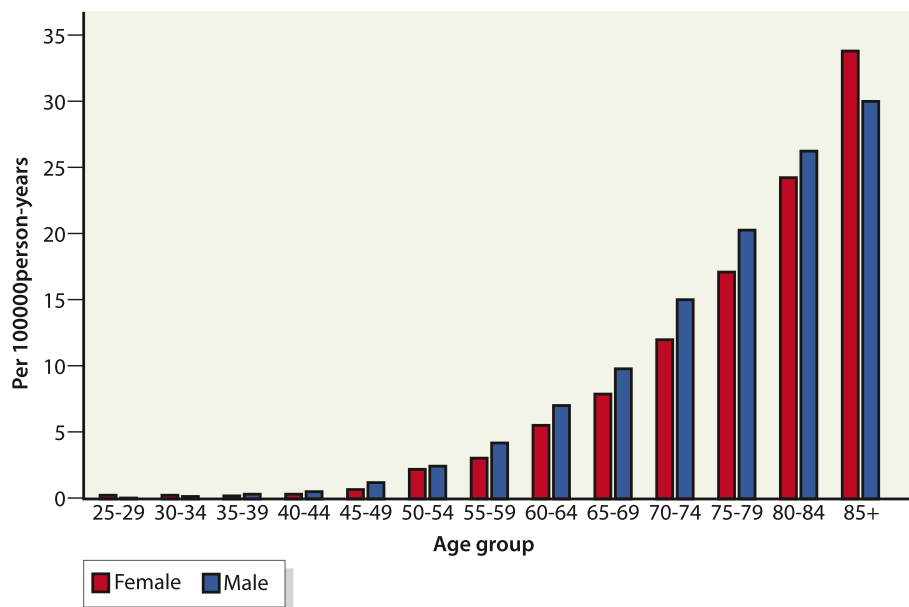
Cholangiocarcinoma is very rarely diagnosed in children or young adults (Figure 4). The incidence rises with age and is highest in the 85+ years category. Males have a higher incidence than females in all age groups except in group 85 years or older.

## Risk factors

The ORs for the concomitant medical conditions are listed in Table 2 for the whole of Finland and Table 3 for the HUS area. The OR for



**FIGURE 3** Age-standardised incidence (World Standard) of cholangiocarcinoma (CCA) 2013–2017 per 100,000 person years, by gender and subclass; intrahepatic CCA (iCCA), extrahepatic CCA (eCCA) and CCA of unknown origin



**FIGURE 4** Incidence of cholangiocarcinoma per 100,000 person years in Finland 1971–2018, by sex and age

IBD in males and in females was 2.7 (95% CI: 2.1–3.5) and 1.3 (95% CI: 0.9–1.7), respectively, in the whole of Finland. In the HUS area, the OR for IBD in males and in females was 7.8 (95% CI: 4.3–14.3) and 2.1 (95% CI: 1.0–4.4), respectively. Primary sclerosing cholangitis is a strong risk factor in both females (OR 36.1, 95% CI: 18.5–70.4) and males (OR: 24.7, 95% CI: 16.3–37.4). For results from the multivariate analysis by sex, see Table S1.

Of the CCA patients in the HUS area, PSC was identified in 33 (2.6%). The median age at the time of diagnosis of CCA was 51 years (range: 29–79 years). Median survival from the diagnosis of CCA to death was 12.4 months, and the cumulative 5-year survival was 3.6% (Figure 4). The median time from PSC diagnosis to CCA was 1.6 years (range: 0–18 years). Of the 33 patients with both PSC and CCA, 23 (70%) had concomitant IBD. In all CCA patients in the HUS area, IBD was diagnosed in 83 CCA patients (6.6%).

## DISCUSSION

In this population-based study, the age-adjusted incidence of CCA did not rise during the study period 1978–2017. The incidence of CCA in the United States rose by 65% from 1973 to 2012,<sup>20</sup> and a much shorter study period in France (2000–2012), the incidence again did not increase.<sup>21</sup>

It was not possible to reliably describe long-term trends in incidence of iCCA and eCCA because of changes in coding over time. Our results for age-standardised iCCA and eCCA incidence rates in 2013–2017 are comparable with the incidence rates for iCCA and eCCA in other Northern European countries.<sup>7</sup>

Risk factors for CCA have not previously been evaluated in Finland. Our ORs for cholelithiasis (2.3) and HCV (1.6) were similar to prior results in other studies.<sup>15</sup> As reported in previous studies, HCV was associated with iCCA. For HBV, the risk increase in our study

**TABLE 2** OR and 95% CI for preceding comorbidity associated with the risk of CCA and CCA subtypes in Finland (all regions) 1971–2014, derived from multivariate analyses

Risk determinant	Subtype of CCA											
	Any CCA (N = 6949)			Intrahepatic (N = 2572)			Extrahepatic (N = 3555)			Unknown (N = 822)		
	Cases (%)	OR	95% CI	Cases (%)	OR	95% CI	Cases (%)	OR	95% CI	Cases (%)	OR	95% CI
Cholelithiasis	1222 (18)	2.3	2.1–2.5	348 (14)	1.8	1.5–2.0	659 (19)	2.6	2.4–2.9	215 (26)	2.6	2.1–3.1
Diabetes	889 (13)	1.0	0.9–1.1	313 (12)	1.1	1.0–1.2	404 (11)	0.8	0.7–0.9	172 (21)	1.7	1.4–2.1
Inflammatory bowel disease	336 (5)	2.0	1.6–2.4	69 (3)	2.6	1.9–3.4	44 (1)	1.4	1.0–2.0	18 (2)	2.0	1.2–3.6
Liver cirrhosis	154 (2)	2.7	2.3–3.1	145 (6)	3.8	3.0–4.7	78 (2)	1.6	1.2–2.1	39 (5)	3.5	2.3–5.3
Hepatitis C	6 (0.1)	1.6	0.6–4.2	4 (0.1)	2.8	0.8–9.5	1 (0.03)	0.7	0.1–5.5	1 (0.1)	1.3	0.1–20.6
Hepatitis B	8 (0.1)	7.0	2.2–21.7	4 (0.1)	5.7	1.3–25.9	3 (0.1)	16.8	1.6–173	1 (0.1)	5.4	0.2–119

Note: The OR for liver cirrhosis is from model F2 including variables cholelithiasis, diabetes, liver cirrhosis, HBV and HCV. All other ORs are from model F1 (cholelithiasis, diabetes, inflammatory bowel disease, HBV and HCV).

Abbreviations: CCA, cholangiocarcinoma; CI, confidence interval; OR, odds ratio.

**TABLE 3** OR and 95% CI associated with the risk of cholangiocarcinoma and CCA subtypes in HUS area, derived from multivariate analyses

Risk determinant	Subtype of cholangiocarcinoma											
	Any (N = 1246)			Intrahepatic (N = 621)			Extrahepatic (N = 456)			Unknown (N = 165)		
	Cases (%)	OR	95% CI	Cases (%)	OR	95% CI	Cases (%)	OR	95% CI	Cases (%)	OR	95% CI
Cholelithiasis	261 (21)	2.5	2.1–2.9	108 (17)	2.0	1.6–2.5	113 (25)	3.0	2.3–3.8	37 (22)	2.7	1.8–4.3
Diabetes	159 (13)	1.4	1.2–1.7	83 (13)	1.6	1.2–2.1	51 (11)	1.1	0.8–1.5	25 (15)	1.7	1.0–2.8
Inflammatory bowel disease	38 (3)	4.5	2.9–7.0	9 (1)	5.7	3.6–9.9	2 (0.4)	3.1	1.3–7.2	4 (2)	2.5	0.5–13.7
Liver cirrhosis	37 (3)	4.3	2.8–6.7	21 (4)	6.0	3.2–11.5	10 (2)	2.2	1.0–4.7	6 (4)	10.0	2.5–40.0
Hepatitis C	3 (0.2)	1.2	0.2–5.7	2 (0.3)	3.1	0.5–18.9	0 (0)	<sup>a</sup>	-	1 (0.6)	3.2	0.3–35.2
Hepatitis B	5 (0.4)	13.8	5.7–33.4	3 (0.4)	10.4	3.3–32.6	1 (0.2)	35.1	4.9–252	1 (0.6)	16.9	2.3–122
Primary sclerosing cholangitis	33 (3)	29.9	21.0–42.4	22 (4)	28.2	18.3–43.4	9 (2)	24.2	12.4–47.2	2 (1)	18.2	4.5–74.0

Note: OR for liver cirrhosis from model H2 (cholelithiasis, diabetes, liver cirrhosis, HBV and HCV). OR for primary sclerosing cholangitis from model H3 (cholelithiasis, diabetes, primary sclerosing cholangitis, HBV and HCV). All other ORs are from model H1, including cholelithiasis, diabetes, inflammatory bowel disease, HBV and HCV.

Abbreviations: CCA, cholangiocarcinoma; CI, confidence interval; HUS, Helsinki University Hospital; OR, odds ratio.

<sup>a</sup>There were no cases of hepatitis C in the extrahepatic CCA group.

was present for both iCCA and eCCA, with a higher OR for eCCA, while in previous studies the OR for iCCA has been higher. The prevalence of HBV in Finland is very low, and the absolute number of HBV patients in our study was accordingly very low.<sup>22</sup>

Finland has the highest incidence of type 1 diabetes in the world, in children under 14 around 60 per 100,000 person years.<sup>23</sup> About 15% of the prevalent diabetes cases in Finland are of type 1.<sup>24</sup> As our study is based on ICD codes, some type 1 diabetics were wrongly diagnosed as type 2, and vice versa, and many patients had ICD codes for both types. Therefore, we pooled diabetes types 1 and 2 together. In previous studies, type 2 diabetes as well as obesity and metabolic syndrome, all of which can lead to non-alcoholic fatty liver disease,<sup>25</sup> have been shown to increase the risk for CCA.<sup>26</sup> Non-alcoholic fatty liver disease can cause steatohepatitis, which may lead to liver cirrhosis and further to an increased risk for CCA.<sup>25</sup>

Primary sclerosing cholangitis is associated with many gastrointestinal malignancies, of which the most dreaded is CCA.<sup>27–29</sup> In previous studies, the risk for CCA has been up to 235- to 400-fold.<sup>18,19</sup> Because PSC does not have a unique ICD code, it is very challenging to reliably identify PSC patients from ICD-code-based registers. In Finland, we have an active search strategy for PSC, and in our previous study, we identified all PSC patients in the HUS area during 1990–2014.<sup>18</sup> This gave us a unique opportunity to study PSC as a risk determinant for CCA in the HUS area, which has not been possible in previous studies.

The median age at the time of diagnosis of CCA in PSC patients was clearly lower than in other CCA patients: 51 versus 73 years. The lifetime risk for CCA in PSC patient is as high as 7%–14%.<sup>13,18</sup> The prognosis of CCA in PSC patients was very poor, and the median time from diagnosis to death was only 1.6 years. There are

several recommendations for surveillance of CCA in PSC patients,<sup>13,30–32</sup> but at present, there is no common consensus for surveillance strategy. It would be of paramount importance to have a working strategy for identifying CCA in PSC at a premalignant stage. Accordingly, it is important to be able to identify the patients at high risk for CCA to better target the biliary dysplasia surveillance. In previous studies, up to half of CCAs are detected already at the time of PSC diagnosis or within 1 year after diagnosing PSC.<sup>33,34</sup> In our study, the proportion of CCA cases with PSC was low, most likely due to the fact that if the first presenting diagnosis is CCA, no further evaluation of the underlying predisposing factor is done. Therefore, PSC might be underdiagnosed as a risk factor for CCA.

Survival in all CCA patients after diagnosis is also poor. The survival estimates for the HUS area are higher than in the whole of Finland, but these two are not comparable, as the HUS area only covers the period 1990–2014 and the data for the whole of Finland also include CCA patients diagnosed from 1971 to 1989.

Inflammatory bowel disease also increases the risk of CCA. In earlier studies, 20%–76% of PSC patients had concomitant IBD.<sup>35,36</sup> In the current data, 69% of the CCA patients with PSC had concomitant IBD, which is in accordance with the rate of IBD in all PSC patients in the area.<sup>18</sup>

## Strengths and limitations of the study

The registries in Finland are of high quality and gave us a comprehensive look at malignancy information, risk determinants and vital status at a nationwide level.<sup>37</sup> A limitation is that the discharge register is for hospitals and not for primary care, and some asymptomatic or mild pre-existing diseases might therefore not be in the register. Another limitation is that the registers do not include information on weight, smoking or alcohol consumption, which are known risk factors for CCA.<sup>38</sup>

## CONCLUSION

The incidence of CCA in Finland has not increased during the study period. The incidence rates of iCCA and eCCA are comparable to the incidence rates in other Northern European countries. Previously known risk factors were identified in this nationwide analysis, with PSC having the strongest association. The prognosis of CCA is poor.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## ETHICS APPROVAL

The local ethics committee of Helsinki University Hospital for Internal Medicine has approved the study protocol, number 278/13/03/01/2009.

## AUTHOR CONTRIBUTIONS

Nina Barner-Rasmussen, Martti Färkkilä and Eero Pukkala: study design and drafting of the manuscript; Nina Barner-Rasmussen, Martti Färkkilä, Eero Pukkala and Kishor Hadkhale: data analysis. All authors: critical revision of the manuscript and interpretation of the data. All authors have approved the final draft submitted. Guarantor of the article: Martti Färkkilä, [martti.farkkila@hus.fi](mailto:martti.farkkila@hus.fi).

## INFORMED CONSENT

No informed consent was required in accordance with Finnish regulations for register-based studies without contact with the study subjects.

## DATA AVAILABILITY STATEMENT

Data subject to third party restrictions.

## ORCID

Nina Barner-Rasmussen  <https://orcid.org/0000-0003-3116-561X>

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Additional supporting information may be found in the online version of the article at the publisher's website.

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