

Review

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# Neoplastic risk for liver and colon in primary sclerosing cholangitis

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**How to cite this article:** Lundberg Båve A, Bergquist A. Neoplastic risk for liver and colon in primary sclerosing cholangitis. *Hepatoma Res* 2021;7:58. <https://dx.doi.org/10.20517/2394-5079.2021.27>

**Received:** 1 Mar 2021 **First Decision:** 6 Mar 2021 **Revised:** 18 May 2021 **Accepted:** 2 Jun 2021 **First online:** 9 Jun 2021

**Academic Editors:** Guang-Wen Cao, Annarosa Floreani **Copy Editor:** Yue-Yue Zhang **Production Editor:** Yue-Yue Zhang

## Abstract

Primary sclerosing cholangitis (PSC) is a rare disease that may well be notified as a premalignant condition due to the increased cancer risk. The risk is highest for hepatobiliary cancer and increased by 28-398 times compared to the general population. When comorbidity with inflammatory bowel disease exists, the risk for colorectal cancer is increased 5-12 times and may even be higher after liver transplantation. The cancer risk estimates have decreased with time but vary according to study design. More recent population-based studies have approximated lower cancer risk than previous studies. Higher awareness and earlier detection of PSC together with increased surveillance over time may have influenced risk estimates. Surveillance for PSC patients is recommended for early tumor detection in both the liver and colon to enable curative treatment. The evidence for the efficacy of surveillance for early detection of hepatobiliary cancer is weak and an accepted common strategy worldwide is lacking. The high risk of hepatobiliary cancers has been confirmed repeatedly and future studies in PSC should focus on individualizing follow-up strategies and treatment.

**Keywords:** Epidemiology, inflammatory bowel disease, hepatobiliary cancer, cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma, pancreatic cancer, colorectal cancer

## INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare chronic inflammatory disease of both intra- and extra-hepatic bile ducts. PSC can present at any time in life with a median age of diagnosis in the early 40s. Recent



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population-based studies have estimated incidence and prevalence to 0.5-1.6 and 6-32 per 100,000<sup>[1-3]</sup>. The clinical course of the disease is variable. PSC may be stable and asymptomatic for many years but can progress more rapidly to cirrhosis, liver failure, and development of cancer. Inflammatory bowel disease (IBD) is present in around 70%<sup>[1,4]</sup> and represents a specific phenotype, PSC-IBD<sup>[5-7]</sup>.

PSC can be defined as a premalignant condition<sup>[8,9]</sup>. The high cancer risk in PSC is well established and cancer is the most common cause of death<sup>[1,4,10]</sup>. The risk is highest for bile duct cancer, but increased risks for hepatocellular carcinoma (HCC), pancreatic cancer, and colorectal cancer (CRC) are also reported<sup>[2,11-13]</sup>. Cholangiocarcinoma (CCA) has an aggressive course and poor prognosis with a one-year mortality rate of up to 80%<sup>[14]</sup>. However, in carefully selected patients where liver transplantation following neoadjuvant chemoradiation is performed, a 65% survival after five years is achieved<sup>[15,16]</sup>. Early tumor detection and identification of risk factors for tumor development is of great importance for the individual patient, and the risk of cancer carries a substantial psychological burden in PSC.

In this review, we aim to summarize the current knowledge on the risk of cancer in PSC with a special focus on the liver and gut.

## ASSESSMENT OF CANCER RISK IN PSC

Assessment of cancer risk in PSC is challenging. Factors that contribute to the uncertainty of the actual risk are rarity and heterogeneity of the disease, the variable disease course, diagnostic difficulties to differentiate between benign and malignant biliary strictures, and lack of a specific diagnostic code for PSC.

The majority of studies derive from tertiary centers in western countries where smaller cohorts are retrospectively described. These settings constitute an increased risk for selection and referral bias with a chance of overestimating risks. Population-based studies are warranted for adequate risk estimation. In rare diseases, such as PSC, cases tend to cluster at specialized centers, which influences the detection rate, and true population-based settings are difficult to achieve. Hence, large mixed cohorts may be equally appropriate as a population-based setting.

Registry-based studies of cancer risk in PSC need to be evaluated with special attention. Some studies use the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for PSC diagnosis, entailing risk for misclassification. Confirmation of PSC diagnosis by scrutinization of medical records improves diagnostic precision and study quality. The code for sclerosing cholangitis, K83.0A, in ICD 10 is more specific than in previous ICD versions, but it is still used for secondary causes of sclerosing cholangitis, and its specificity has not been validated in larger cohorts. To increase the specificity when defining PSC, some registry studies combine the diagnoses of cholangitis and IBD or combine ICD code(s) with PSC specific investigations<sup>[11,13]</sup>.

The natural history of PSC has changed over time<sup>[14]</sup>. Increased awareness entails earlier PSC diagnosis, increasing the risk of lead-time bias. Heterogeneity and different phenotypes of the disease also seem to affect cancer risk. Small duct PSC has consistently been reported to be associated with a lower risk of CCA<sup>[16,17]</sup>. A progression of small duct to large duct disease is however seen in about 12% over a mean follow-up time of almost nine years<sup>[17]</sup>. In addition, PSC with features of autoimmune hepatitis (overlap AIH/PSC) have been reported to have a lower cancer risk than large duct PSC<sup>[18,19]</sup>. Consensus regarding the definition of overlap AIH/PSC is lacking and makes the assessment of cancer risk ambiguous. PSC with IBD is associated with higher cancer risk in both liver and colon than PSC alone<sup>[13,19]</sup>. The impact of type of IBD is more uncertain, although PSC-UC is reported with higher CCA risk<sup>[19]</sup>. The influence of sex has also been

discussed, where male sex seems to be associated with a higher risk of CCA<sup>[19]</sup>.

An underestimation of CCA risk may occur due to diagnostic problems in the already fibrotic and strictured biliary tree, especially with decreasing frequency of post-mortem autopsy investigations. Furthermore, liver transplantation for precancerous stages may reduce cancer incidence<sup>[20]</sup>.

## THE RISK OF HEPATOBILIARY CANCER

The risk estimate for hepatobiliary cancers varies remarkably across studies. Risk assessment has been made with comparisons to both general and IBD populations. The highest risk estimates come from early tertiary center studies. A summary of the largest studies evaluating the risk of developing CCA, hepatobiliary cancer, or hepatopancreatobiliary cancer is shown in [Table 1](#).

### Population-based studies

The thus far largest population-based study covering cancer risk in PSC ( $N = 2588$ ) is the national registry study from United Kingdom during 2004-2016 by Trivedi *et al.*<sup>[13]</sup>. PSC patients were identified from an IBD cohort, and the diagnosis of PSC was ascertained by the ICD 10 code for sclerosing cholangitis together with a code of a PSC-related procedure. Overall, 6.5% developed CCA, corresponding to a risk increase of 28 times compared to IBD controls. Cancer incidence increased with age and was highest in individuals older than 60 years. This study is limited by only including PSC patients with IBD.

Two additional large population-based studies have also been published<sup>[1,2]</sup>. First, in the population-based study by Boonstra *et al.*<sup>[1]</sup> from the Netherlands, including 590 PSC patients with a follow-up of more than seven years, 7% developed CCA, of whom 80% died within one year after cancer diagnosis. Older age was a risk factor for CCA, and a 398-fold increased risk compared to the general population was found. Cumulative risk after 10, 20, and 30 years was 6%, 14%, and 20%, respectively. Second, a hospital-based registry study from Finland by Barner-Rasmussen *et al.*<sup>[2]</sup>, comprising nearly one third of the Finnish population, evaluated 580 PSC patients (1990-2015). PSC diagnosis was confirmed by reviewing medical records, and CCA was diagnosed in 4.5%. The risk compared with the general population was sharply increased (SIR = 235, 95%CI: 143-362), and the mean survival after CCA diagnosis was 1.8 years<sup>[2]</sup>.

### Non-population-based studies

The largest non-population-based study was a joint effort within the International PSC Study Group, published by Weismüller *et al.*<sup>[19]</sup> in 2017. More than 7000 PSC patients from mixed populations in western countries were studied. The 10- and 20-year cumulative incidences of hepatopancreatobiliary cancer were 11% and 20%, respectively, which is higher than in the population-based studies. In line with population-based studies, the incidence of cancer increased with age with the highest incidence detected in patients over 60 years. Cancer risks in different PSC phenotypes were compared, and features of autoimmune hepatitis and small duct PSC were associated with a lower risk for hepatobiliary malignancy<sup>[19]</sup>.

In a study from Sweden comprising 604 PSC patients (1970-1998), hepatobiliary malignancies were found in 13%, with a high risk increase compared to the general population (SIR = 161, 95%CI: 120.3-210.1). After excluding the first year of PSC diagnosis, the incidence rate of hepatobiliary cancer was 1.5% per year<sup>[11]</sup>. An extension of this study has recently been performed, but not yet published, with additional PSC-patients ( $N = 1433$ ) and follow-up time (1970-2016). In this updated cohort, compared to matched controls from the general population, the risk of hepatobiliary cancer was also sharply increased (HR = 120.3, 95%CI: 71.6-202.1), with a cumulative incidence at 10, 20, and 30 years after diagnosis of 5%, 13%, and 25%, respectively<sup>[21]</sup>.

**Table 1. Studies assessing the risk for cholangiocarcinoma, hepatobiliary cancer, or hepatopancreatobiliary cancer in patients with primary sclerosing cholangitis**

No. PSC-patients	Setting	Study population	Control group	Study period (Median follow-up time in years)	IBD	Risk estimate (95%CI)	Ref.
7121	Mixed	Multi-national	NA	1980-2010 (7.2)	70%	HR HPBC 15.7 (14.12-17.34)	Weismuller et al. <sup>[19]</sup> 2017
2588	Population	United Kingdom	IBD-patients	2006-2016 (NA)	100%	HR CCA 28.46 HR HCC 21.0 HR PC 5.26	Trivedi et al. <sup>[13]</sup> 2020
1432	Mixed	Sweden	General population	1969-2016 (15.9)	88%	HR HBC 120.9 (72.0-203.1) HR PC 8.0 (3.2-20.2)	Lundberg Båve et al. <sup>[21]</sup> 2021
604	Mixed	Sweden	General population	1970-1998 (5.7)	79%	SIR HBC 161 (120.3-210.1) SIR PC 14.3 (4.7-33.4)	Bergquist et al. <sup>[11]</sup> 2002
590	Population	Netherlands	General population UC-patients (CRC-risk)	2000-2011 (7.7)	68%	SIR CCA 398 (246-608)	Boonstra et al. <sup>[1]</sup> 2013
580	Population	Finland	General population	1990-2015 (NA)	68%	SIR CCA 235 (143-362) SIR HCC 21.6 (4.45-63.1)	Barner-Rasmussen et al. <sup>[2]</sup> 2020
399	Tertiary	United States	NA	2005-2013 (9.4*)	100%	NA	Gulamhusein et al. <sup>[27]</sup> 2016
394	Tertiary	Europe	NA	NA-1998 (4.7)	82%	NA	Boberg et al. <sup>[124]</sup> 2002
370	Tertiary	United Kingdom	NA	1981-2004 (4.9)	85%**	NA	Morris-Stiff et al. <sup>[125]</sup> 2008
305	Mixed	Sweden	NA	NA-1992 (5.3)	81%	NA	Broomé et al. <sup>[28]</sup> 1996
273	Tertiary	Germany	NA	1978-2004 (6.3)	63%	NA	Tischendorf et al. <sup>[10]</sup> 2007
250	Population	United Kingdom	General population	1998-2014 (5.1)	54%	IRR HBC 65.3 (9.5-2810.9)	Liang et al. <sup>[3]</sup> 2017
224	Tertiary	United States	IBD patients	(NA)	100%	OR CCA 55.31 (22.20-137.80) OR PC 11.22 (4.11-30.62)	Ananthakrishnan et al. <sup>[12]</sup> 2014
223	Population	United Kingdom	General population	1987-2002 (NA)	48%	HR HBC 41.52 (11.43-150.80)	Card et al. <sup>[70]</sup> 2008
211	Tertiary	Netherlands	NA	1980-2000 (9 years)	75%	Cum Inc 10 years 9% 20 years 9%	Claessen et al. <sup>[126]</sup> 2009
201	Population	United States	General population	1992-2013 (NA)	NA	OR HBC 1.99 (1.48-2.67)- 7.53 (5.37-10.57)****	McGee et al. <sup>[127]</sup> 2019
195	Population	Denmark	IBD patients	1977-2001 (7.4 years)	100%	HR CCA 190 (54.8-660)	Sørensen et al. <sup>[68]</sup> 2018
194	Population	Sweden	General population	1992-2005	76%	SIR CCA 868 (505-1390) SIR HBC 177 (110-271)	de Valle et al. <sup>[4]</sup> 2012
174	Tertiary	United States	NA	1970-1986 (6 years**)	71%	NA	Wiesner et al. <sup>[128]</sup> 1989

161	Tertiary	United States	General population	1970-1997 (11.5 years)	NA	RR CCA 1560 (780-2 793)	Burak <i>et al.</i> <sup>[34]</sup> 2004
139	Tertiary	United States	NA	1984-1997 (13 years)	61%-80%***	Cum inc 10 years 27%	Ahrendt <i>et al.</i> <sup>[29]</sup> 1999
128	Tertiary	United Kingdom	NA	1984-2011 (9 years)	72%	NA	Chapman <i>et al.</i> <sup>[30]</sup> 2012
126	Tertiary	United Kingdom	NA	1972-1989 (5.8 years)	67%	NA	Farrant <i>et al.</i> <sup>[129]</sup> 1991
125	Population	Sweden	NA	1964-1991 (10 years)	85%	Cum risk 10 years 11.2%	Kornfeld <i>et al.</i> <sup>[31]</sup> 1997

\*Mean; \*\*of patients with CCA; \*\*\*61% in non-CCA and 80% in CCA; \*\*\*\*estimate size depending on intra- or extrahepatic localization. PSC: Primary sclerosing cholangitis; IBD: inflammatory bowel disease; NA: not available; CI: confidence interval; HR: hazard ratio; SIR: standardized incidence ratio; IRR: incidence rate ratio; OR: odds ratio; RR: relative risk; Cum inc: cumulative incidence; Cum risk: cumulative risk; CCA: cholangiocarcinoma; HBC: hepatobiliary cancer; HPBC: hepatopancreatobiliary cancer; PC: pancreatic cancer.

### Risk factors for CCA

Several risk factors for development of CCA have been reported, as presented in [Table 2](#). Older age (> 60 years), male sex, presence of a dominant stricture, and comorbidity with IBD along with raised bilirubin levels are the most consistent risk factors reported<sup>[1,10,11,13,19,22,23]</sup>. The importance of environmental factors for CCA development, such as smoking and alcohol, is less clear and has only been evaluated in a few studies<sup>[24,25]</sup>. Symptoms, hepatomegaly, and raised bilirubin levels should increase the suspicion of an underlying CCA since they are reported to be associated with neoplastic development.

An increased risk for hepatobiliary cancer in patients with colorectal cancer or dysplasia is reported<sup>[1,26,27]</sup>. The association was first described in the early study by Broomé *et al.*<sup>[26]</sup> where 70% of all cases of CCA also developed CRC. In the population-based study by Boonstra *et al.*<sup>[1]</sup>, CRC was a time-dependent risk factor for developing CCA (HR = 4.57, 95%CI: 1.08-19.41); it was significant but with a very wide confidence interval, making generalizability difficult. The increased risk for both cancers in a sub-cohort of individuals raises suspicion of a genetic susceptibility.

Long duration of PSC does not seem to be a risk factor for CCA with up to 66% of CCA or hepatobiliary cancers diagnosed within the first year after PSC diagnosis<sup>[1,2,10,11,13,19,28-32]</sup>. This is likely an effect of length time bias or reverse causation, where the underlying disease shows no evident signs until symptoms of cancer appear. The yearly risk after the first year has been reported to be 0.5%-1.5%<sup>[11,33,34]</sup>. The median time from PSC diagnosis to development of hepatobiliary cancer has been appreciated to be 3-4 years (range: 0.8-21 years)<sup>[33,35]</sup>. This estimation has been made in smaller cohorts with wide distributions of events.

### THE RISK OF GALLBLADDER CANCER

Pathology of the gallbladder is a common finding in patients with PSC, with gallstones, sludge, chronic cholecystitis, and polyps occurring in near half of the patients during the disease course<sup>[36,37]</sup>. Half of all gallbladder mass lesions have been found to be malignant, and the cancer risk increases with polyp size and seems highest in polyps more than 8 mm<sup>[36,38,39]</sup>. The risk for gallbladder cancer (GBC) in PSC has been evaluated in a few studies. In population-based studies, the risk has been reported to be increased 9-fold in PSC-IBD compared to non-PSC-IBD patients in one study<sup>[13]</sup>, and, in another study, it was increased 78 times compared to the general population<sup>[2]</sup>.

### THE RISK OF HEPATOCELLULAR CANCER

Patients with cirrhosis have an increased risk of developing HCC, and risk estimates depend on the underlying liver disease<sup>[40]</sup>. In PSC, the risk for HCC is lower than for CCA. A 20-fold increased risk for

**Table 2. Risk factors for cholangiocarcinoma, hepatobiliary cancer, and hepatopancreatobiliary cancer in patients with primary sclerosing cholangitis**

Risk factor	Increased risk for	Risk estimate (95%CI)	Ref.
Male sex	HPBC	NA, NA, NA	[10,13,19]
IBD	HPBC	NA	[19]
Ulcerative colitis	HPBC	NA	[19]
Symptoms	HBC	NA, NA	[10,28]
Hepatomegaly	HBC	HR = 2.4 (1.6-3.6)	[10]
Persistent elevated bilirubin	HBC	HR = 2.9 (2.9-1.9)	[10]
Elevated bilirubin	HBC	NA, NA	[10,28]
Age at PSC diagnosis	CCA	HR = 1.02 (1.00-1.04), NA, HR [per 10-year increase 1.26 (1.16-1.37)], NA	[1,11,13,27,28]
Duration of IBD	CCA	HR = 1.33 (1.11-1.60), OR = 1.59 (1.12-2.24)	[27,124]
Mayo risk score	CCA	RR = 1.8 (1.0-3.1), NA, NA	[30,33,130]
Variceal bleeding	CCA	RR = 24.2 (3.3-67.1)	[33]
CRC/dysplasia	CCA	HR = 4.57 (1.08-19.41), HR = 1.52 (0.97-2.37), NA	[1,26,27]
Proctocolectomy	CCA	RR = 4.43 (1.29-15.2), HR = 1.53 (1.05-2.22)	[27,33]
Dominant stricture	CCA	HR = 2.3 (1.6-3.3), NA, NA	[10,23,30]
High CA 19-9	CCA	NA, NA, NA	[24,25,30]
Smoking	CCA	NA	[24]
Alcohol	CCA	OR = 2.95 (1.04-8.3)	[25]

CA 19-9: Carbohydrate antigen; CCA: cholangiocarcinoma; CRC: colorectal cancer; HBC: hepatobiliary cancer; HPBC: hepatopancreatobiliary cancer; IBD: inflammatory bowel disease; PSC: primary sclerosing cholangitis.

HCC in comparison to controls is reported from two recent large population-based studies, however information on cirrhosis status was lacking<sup>[2,13]</sup> [Table 1]. In one study of patients undergoing liver transplantation, 2% of the PSC patients were found to have HCC in their explanted liver in comparison to 6% in patients with other benign transplant indications<sup>[41]</sup>. In one study where cirrhosis in PSC was defined mainly by occurrence of esophageal varices, no cases of HCC were found during 292 patient years of follow-up, and a complete analysis of 140 transplants revealed no cases of HCC<sup>[42]</sup>. Longitudinal data from the United States of 830 PSC patients detected 20 (2.4%) patients with HCC during a 9.5-year follow-up, which represented 22% of all hepatobiliary cancers. All HCC cases had late-stage PSC<sup>[43]</sup>. Judging from this evidence, the increased risk for HCC in PSC concerns only those who have developed cirrhosis.

## THE RISK OF PANCREAS CANCER

The first paper describing increased risk for pancreatic cancer in PSC was published in 2002 by Bergquist *et al.*<sup>[11]</sup> and has since been confirmed by others<sup>[12,13,21]</sup> with a risk increase estimated to be 3-14 times higher than in the general population. In IBD cohorts, the risk for pancreatic cancer has been estimated to be 5-8 times higher for IBD-PSC with a decreasing risk with increasing age<sup>[13,44]</sup>. All studies take note of the enlarged risk of misclassifying distal cholangiocarcinoma for pancreatic cancer. Studies on specific risk factors for pancreatic cancer in PSC are lacking.

## SURVEILLANCE FOR EARLY DETECTION OF HEPATOBILIARY CANCER

The high risk and poor prognosis of hepatobiliary malignancies warrants surveillance for early detection. In most centers, image diagnostics of liver and bile ducts, with or without the tumor marker CA 19-9, are performed at least yearly. Ultrasound and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) are the usual imaging methods of choice. MRI/MRCP is superior to ultrasound in evaluating strictures, biliary dilatation, bile duct wall thickening, and infiltrative lesions<sup>[20,45,46]</sup>, as well as for detecting early signs of malignancy<sup>[47]</sup>.

Guidelines support surveillance, albeit evidence for a concrete surveillance strategy is limited and prospective studies of the cost-benefit are needed<sup>[20]</sup>. One large retrospective study from the Mayo Clinic has shown that annual surveillance [imaging with ultrasound, MRI, or computer tomography plus cancer associated antigen (CA) 19-9] was associated with a better survival<sup>[43]</sup>. Patients exposed to surveillance were diagnosed earlier and were available for curative treatment with liver transplantation. Five-year overall survival in this study was 68% in the surveillance and 20% in the non-surveillance group. A lower probability of cancer related adverse events was also found at five-year follow-up<sup>[43]</sup>.

In another large study from the UK<sup>[13]</sup>, a 2-fold reduced risk of cancer related death was associated with annual imaging before cancer diagnosis. The survival benefit after cancer diagnosis disappeared when CCA cases from the first year after PSC diagnosis were excluded. The main benefit from regular surveillance therefore seems to be generated by the early detection of HCC and GBC. Liver transplantation before an overt CCA in non-cirrhotic patients with precancerous stages (high-grade dysplasia) may be beneficial and is recommended in some countries<sup>[48,49]</sup> with posttransplant survival similar to that after liver transplantation due to liver failure<sup>[50]</sup>. In summary, the efficacy of regular surveillance with imaging for early detection of CCA remains to be proven.

The tumor marker CA 19-9 is widely used for surveillance purposes. However, CA 19-9 lacks both sensitivity and specificity, and there is no tumor specific cut-off level<sup>[51-55]</sup>. Longitudinal series with repeated measures of CA 19-9 are contradictory<sup>[52,56]</sup> and increased levels are common in benign disease<sup>[54]</sup>. Normal levels are also frequently seen in patients with CCA. A low intraindividual variability of CA 19-9 over time is reported and the individual levels seem to be affected by genetic differences in the FUT 2/3 genes<sup>[56,57]</sup>. CA 19-9 was evaluated together with imaging in a surveillance program and was found to be a predictor of mortality and CCA-related adverse events, but 70% of the perihilar CCA in this study had low (< 100 U/mL) or normal CA 19-9 levels<sup>[43]</sup>. CA 19-9 is therefore an insufficient marker for regular surveillance for early detection of CCA in PSC<sup>[52,55-58]</sup>.

Due to the high risk of cancer development in gallbladder polyps, current guidelines recommend cholecystectomy in individuals where polyp size is more than 10 mm<sup>[59]</sup>. Cholecystectomy has been suggested to be performed in PSC patients with any polyp size due to the increased malignant potential of smaller lesions<sup>[36,39]</sup>, which is supported by current guidelines<sup>[20,60,61]</sup>. The malignant potential in smaller polyps has recently been questioned in a study of 453 PSC patients where 16% developed smaller gallbladder polyps over 7.7 years and the majority were benign and did not increase in size over time. In most of these patients, a cholecystectomy was not performed, and polyps did not grow significantly over time, suggesting a wait and watch strategy<sup>[37]</sup>. The increased risk for GBC warrants annual screening and cholecystectomy should be performed if polyps are repeatedly found or increasing in size with consideration of surgical risk in more advanced PSC.

## THE RISK OF COLORECTAL CANCER

IBD is present in around 70% of all PSC patients<sup>[1,4]</sup>. The most common subtype is ulcerative colitis (UC), although typical features in PSC patients indicate a unique phenotype<sup>[5,6,7]</sup>. Given the dominant localization of inflammation in the ascending colon, IBD in PSC is often less symptomatic, which is why chronic inflammation may go undetected<sup>[62,63]</sup> and diagnosis be delayed. Frequent surveillance in PSC-IBD may affect risk estimates for CRC since PSC-IBD patients are surveilled to a higher extent than IBD alone<sup>[64]</sup>.

In studies of PSC patients with and without IBD, the risk of CRC has been appreciated to be 5-12 times higher compared to the general population<sup>[1,2,11]</sup>. Estimation of the risk of CRC in PSC-IBD has been done in

two meta-analyses<sup>[65,66]</sup> where the first found a nearly 5-fold increased risk compared to non-PSC IBD (OR = 4.79, 95%CI: 3.58-6.41)<sup>[65]</sup>, whereas the more recent showed a 3-fold increased risk of CRC/dysplasia compared with patients with IBD alone (OR of 3.24, 95%CI: 2.14-4.90)<sup>[66]</sup>. **Table 3** summarizes the most important studies evaluating risk of colorectal cancer in PSC.

Early studies show a high cumulative incidence of CRC in PSC-IBD, up to 40% after 20 years of PSC-IBD disease<sup>[67]</sup>. The CRC incidence rates seem to have decreased over time. Data from more recent studies, such as the population-based study by Boonstra *et al.*<sup>[1]</sup> from 2013, show that 3% of PSC-IBD patients developed CRC at 7-year follow-up and the cumulative risk of high-grade dysplasia or CRC after 10, 20, and 30 years since PSC diagnosis was 3%, 7%, and 13%, respectively. In the study by Sorensen *et al.*<sup>[68]</sup> from 2018, 7% and 9% developed CRC at 10 and 20 years, respectively. Risk estimates often include CRC and both high- and low-grade dysplasia (LGD). This imposes a potential risk of misclassification bias as the assessment of LGD is precarious and embossed by interpersonal interpretation<sup>[69]</sup>.

Despite the well-established increased risk for CRC in PSC-IBD, some studies show conflicting results. Three population-based studies<sup>[3,4,70]</sup> and two tertiary center studies<sup>[6,71]</sup> have not shown increased CRC risk in PSC-IBD.

### **Risk factors for CRC in PSC**

Age is associated with the increased CRC risk in PSC-IBD. In the study by Trivedi *et al.*<sup>[13]</sup>, the CRC risk was 5-fold increased if IBD was diagnosed at an age < 50 and only 2-fold at ages 50-60. CRC also seems to develop at a younger age in PSC-IBD than in non-PSC-IBD. This was illustrated in the study by Boonstra *et al.*<sup>[1]</sup>, where median age at diagnosis of CRC in PSC-IBD was 39 (range: 26-64) compared to 59 (range: 34-73) in IBD controls.

The importance of IBD subtype for the risk of CRC has been discussed in PSC-IBD. Even though it is accepted that IBD in PSC is a phenotype of its own<sup>[6]</sup>, most studies show a higher risk for patients with PSC-UC than with PSC and Crohn's disease. There have been several studies showing diverging results evaluating risk of CRC in PSC patients with Crohn's disease, where some show increased risk<sup>[37,72]</sup> and some do not<sup>[71,73,74]</sup>.

The impact of chronic inflammation on the risk for CRC in PSC is unknown. Increased prevalence of right-sided colon cancers where inflammation generally is dominating in PSC supports that chronic inflammation may be important<sup>[75]</sup>. Previous studies have defined the PSC-IBD phenotype as mild, and early studies show less need of medical treatment<sup>[5,76,77]</sup>. However, a recent study showed similar need for treatment in PSC-IBD and non-PSC-IBD, and active inflammation was shown to be an independent risk factor for CRC in PSC-IBD (HR = 2.39, 95%CI: 1.63-3.49)<sup>[64]</sup>. Other suggested mechanisms than chronic inflammation for malignant development likely involve altered bile composition and colonic microbiome<sup>[78,79]</sup>.

### **Colorectal cancer risk after liver transplantation**

The risk of colonic neoplasia persists and may even escalate after liver transplantation.

A few studies have reported on the high CRC risk in posttransplant PSC-IBD<sup>[80-83]</sup>. The largest study comes from the Nordic countries where colorectal dysplasia or cancer developed in 23% with a median five-year (range: 0-21 years) follow-up after transplantation<sup>[83]</sup>. A meta-analysis from 2013 averaged a 10 times higher risk compared to individuals undergoing liver transplantation for reasons other than PSC<sup>[84]</sup>.



**Table 3. Articles stating risk for colorectal cancer in patients with primary sclerosing cholangitis**

No. PSC-patients	Setting	Study population	Control group	Study period (Median follow-up time in years)	IBD	Risk estimate (95%CI)	Ref.
6268	Population	Denmark	General population/IBD patients	1979-2008 (NA)	100%	RR UC 9.13 (4.52-18.5) CD 2.90 (0.40-20.9)	Jess <i>et al.</i> <sup>[131]</sup> 2012
2588	Population	United Kingdom	IBD patients	2006-2016 (NA)	100%	HR = 2.43 (NA)	Trivedi <i>et al.</i> <sup>[133]</sup> 2020
1432	Mixed	Sweden	General population	1969-2016 (15.9)	88%	HR = 7.5 (5.6-10.0)	Lundberg Båve <i>et al.</i> <sup>[21]</sup> 2021
1022	Meta-analysis	United States Argentina Europe	NA	1992-2015*** (NA)	NA	OR = 3.24 (2.14-4.90)	Zheng <i>et al.</i> <sup>[66]</sup> 2016
604	Mixed	Sweden	General population	1970-1998 (5.7)	79%	SIR = 10.3 (5.3-18.1)	Bergquist <i>et al.</i> <sup>[11]</sup> 2002
590	Population	Netherlands	General population and UC-patients	2000-2011 (7.7)	68%	SIR = 5 (2.02-10.5)	Boonstra <i>et al.</i> <sup>[1]</sup> 2013
580	Population	Finland	General population	1990-2015 (NA)	68%	SIR Colon 5.2 (1.7-12.2) Rectum 5.0 (1.0-14.7)	Barner-Rasmussen <i>et al.</i> <sup>[2]</sup> 2020
564	Meta-analysis	United States Europe	NA	1992-1999*** (NA)	NA	OR = 4.79 (3.58-6.41)	Soetniko <i>et al.</i> <sup>[65]</sup> 2002
293	Mixed	Netherlands United States	IBD patients	2000-2015 (4.1*)	100%	IRR = 2.2 (NA)	Shah <i>et al.</i> <sup>[64]</sup> 2018
277	Mixed	Spain	IBD patients	2006-2018 (13.6)	100%	IR = 3.3/1000 patient years	Guerra <i>et al.</i> <sup>[132]</sup> 2019
250	Population	United Kingdom	General population	1998-2014 (5.1)	54%	IRR = 2.5 (0.8-7.0)	Liang <i>et al.</i> <sup>[3]</sup> 2017
224	Tertiary	United States	IBD patients	(NA)	100%	OR = 5.00 (2.80-8.95)	Ananthakrishnan <i>et al.</i> <sup>[12]</sup> 2014
223	Population	United Kingdom	General population	1987-2002 (NA)	48%	HR** = 2.53 (0.95-6.74)	Card <i>et al.</i> <sup>[70]</sup> 2008
211	Tertiary	Netherlands	NA	1980-2000 (9)	75%	Cum Inc 10 years 9% 20 years 22%	Claessen <i>et al.</i> <sup>[126]</sup> 2009
200	Tertiary	Belgium	NA	NA-2009 (11)	60%	Cum risk 10 years 5.41% 20 years 9.27%	Fevry <i>et al.</i> <sup>[35]</sup> 2012
195	Population	Denmark	IBD patients	1977-2011 (7.4)	100%	HR = 21.4 (9.6-47.6)	Sørensen <i>et al.</i> <sup>[68]</sup> 2018
194	Population	Sweden	General population	1992-2005 (6.5)	76%	HR = 2.87 (0.33-10.4)	De Valle <i>et al.</i> <sup>[4]</sup> 2012

166	Tertiary	United Kingdom	IBD patients	NA	100%	OR UC-PSC 2.7 (0.7-10.1)	Braden <i>et al.</i> <sup>[71]</sup> 2012
132	Tertiary	United States	UC patients	1976-1994 (NA)	100%	RR CRN 3.15 (1.4-7.3)	Shetty <i>et al.</i> <sup>[75]</sup> 1999
125	Population	Sweden	NA	1964-1991 (10)	85%	Cum risk 10 years 16%	Kornfeld <i>et al.</i> <sup>[67]</sup> 1997
75	Tertiary	France	IBD patients	NA-2008 (11.1)	100%	Cum inc 25 years 23.4%	Sokol <i>et al.</i> <sup>[133]</sup> 2008
56	Population	United States	NA	1976-2018 (9.7)	75%	Cum inc 5 years 5.67% 10 years 9.77%	Bakhshi <i>et al.</i> <sup>[32]</sup> 2020
39	Tertiary	Argentina	UC patients	NA (8.5)	100%	Cum Inc 10 years 11% 20 years 18%	Terg <i>et al.</i> <sup>[134]</sup> 2008

\*Mean; \*\*GI cancer; \*\*\*publication year of articles included. PSC: Primary sclerosing cholangitis; IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; GI: gastrointestinal; NA: not available; CI: confidence interval; HR: hazard ratio; SIR: standardized incidence ratio; IR: incidence rate; IRR: incidence rate ratio; OR: odds ratio; RR: relative risk; Cum inc: cumulative incidence; Cum risk: cumulative risk; CRC: colorectal cancer; CRN: colorectal neoplasia.

### Surveillance for CRC

The risk assessment for CRC in IBD is changing and affects follow-up strategies. Duration of IBD has up to recently been the leading measure, and patients with longstanding disease have been included in regular colonoscopy surveillance programs. Recent studies suggest that more attention should be drawn to other risk factors such as presence of a first degree relative with CRC < 50 years of age, active inflammation, strictures, or inflammatory polyps<sup>[74,85-91]</sup>. An index colonoscopy for CRC risk assessment is now recommended in non-PSC-IBD at eight years after IBD diagnosis, and further surveillance is based on the results together with other risk factors<sup>[92]</sup>.

In PSC-IBD, surveillance colonoscopy every or every other year is recommended independent of IBD duration<sup>[93]</sup>. The evidence for the recommendation to start colonoscopy surveillance at onset of PSC diagnosis is scarce<sup>[93-96]</sup>. To what extent heredity, active inflammation, and inflammatory polyps may contribute to CRC risk in PSC-IBD, as well as their potential impact on the surveillance strategy, has not yet been evaluated.

### Chemoprevention

Large studies evaluating chemopreventive treatment for cancer in PSC are lacking.

In a Cochrane report from 2017<sup>[97]</sup>, 22 randomized controlled trials (RCTs) in PSC were evaluated with the primary aim to investigate the effect of different drugs on survival. Cancer was analyzed as a secondary outcome. No evidence of beneficial effect was found for any of the studied drugs (including ursodeoxycholic acid, various immunosuppressants, and antibiotics).

Two well-studied agents sought to be preventive of several cancer forms are aspirin and statins. Reduced risks of CRC and CCA in general have been associated to aspirin exposure<sup>[98-100]</sup>, although studies analyzing dose and time response are still lacking. There is also evidence for aspirin reducing mortality when used as an adjuvant treatment for CRC and CCA<sup>[101,102]</sup>. In PSC, one study has been performed showing borderline significance favoring aspirin as chemoprotective for CCA<sup>[103]</sup>. Statins have not been proven to be risk reducing for CRC in general<sup>[104]</sup>, but evidence is rising for the risk-reducing effect in CCA<sup>[105-107]</sup>, although well-designed RCTs needs to confirm this association before recommendations to a risk population can be made. There is an ongoing randomized controlled trial investigating the efficacy of simvastatin in PSC with the composite endpoint transplantation, CCA, and variceal bleeding (clinicaltrials.gov: NCT04133792).

Chemopreventive treatment in IBD has been evaluated in several studies with somewhat conflicting results. Some studies point towards a protective effect of 5-aminosalicylates in UC patients<sup>[90,108-110]</sup>, whereas one population-based study and two meta-analyses do not<sup>[111-113]</sup>. Considering the elevated risk of CRC in PSC-IBD, the underestimation of inflammatory activity and the beneficial safety profile, 5-ASA is usually recommended in all PSC-IBD patients, despite the lack of robust evidence<sup>[111-113]</sup>. Ursodeoxycholic acid (UDCA) has been evaluated as a potential chemopreventive treatment for CRC in PSC-IBD. Early, small studies indicated a cancer protective effect<sup>[114,115]</sup>, whereas more recent studies have failed to show a beneficiary effect<sup>[73,116,117]</sup>. In a large meta-analysis of eight studies (including three RCTs), no convincing beneficial effect of UDCA for prevention of CRC was found<sup>[118]</sup>. On the contrary, a high dose of UDCA (28-30 mg/kg/day) has been associated with an increased risk of CRC<sup>[119]</sup>. Treatment with UDCA should therefore be governed by the practice for treatment of the liver disease, and UDCA is not recommended as chemoprevention for CRC.

## FUTURE PERSPECTIVES

Albeit convenient for health professionals to use one surveillance template for all patients, the future will likely demand a more individualized strategy. Considering the poor prognosis of advanced CCA and GBC, strategies for chemoprevention, earlier detection, and better treatment are needed. The identification of high-risk patients, who should be identified with new biomarkers/biomarker profiles, is important in future research. The possibility to develop and validate such markers are hampered by few cases, and large collaborative studies are required. There is ongoing research on different markers in serum, among other studies on specific RNA profiles in extracellular vesicles<sup>[120]</sup> and miRNAs<sup>[121]</sup>, as well as proteomics, lipidomics, and metabolomics both in serum and bile<sup>[122]</sup>. Next-generation sequencing on brush samples at ERCP<sup>[123]</sup> may also increase the diagnostic accuracy and be of importance for chemotherapy guidance.

Development and broad implementation of diagnostic means for differentiation between benign and malignant bile duct epithelium with, for example, high-quality MRI, cholangioscopy with targeted biopsies, and genetic markers are additionally important. It should also be pointed out that the lack of treatment to halt the disease progression to cirrhosis is a major future challenge. Identifying drugs delaying the progression of PSC could also potentially reduce the cancer risk in PSC.

The high risk of colorectal cancer in PSC-IBD warrants focus on better understanding of this specific phenotype of IBD and what mechanisms are involved in the malignant process. The impact of long-standing inflammation, inflammatory polyps, and heredity of CRC in PSC-IBD should further be studied and considered in future surveillance strategies for PSC-IBD. The role of the systematic use of chromoendoscopy remains to be established in PSC-IBD as well as different virtual chromoendoscopic techniques such as NBI (narrow band imaging), FICE (Flexible Spectral Imaging Color Enhancement), and i-scans.

## DECLARATIONS

### Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Lundberg Båve A, Bergquist A

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

This work was supported by Swedish Cancer Society, Stockholm County Council, and the Cancer Research Funds of Radiumhemmet.

### Conflicts of interest

Both authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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