Cirrhosis and age are key determinants of HCC risk in individuals with primary sclerosing cholangitis: A multi-center longitudinal cohort study

VISUAL ABSTRACT

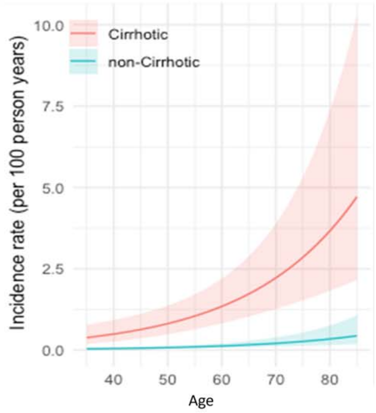
Cirrhosis and age are key determinants of HCC risk in individuals with primary sclerosing cholangitis: A multicenter longitudinal cohort study

Study Population

- 12 European University Centers within the IPSCR-collaboration
- 3,071 PSC patients
- 38,000 patient years of follow-up

	♂ Cirrhosis +		♀ Cirrhosis +	
Age	IR	95%CI	IR	95%CI
45	0.63	0.36-1.12	0.37	0.17-0.79
50	0.81	0.48-1.37	0.47	0.23-0.97
55	1.05	0.64-1.71	0.61	0.31-1.21
60	1.34	0.82-2.20	0.78	0.40-1.54

Result and conclusion



Main findings

- 39 cases of HCC
- 1 per 1,000 patient year
- Most important risk factors are:

Cirrhosis and Age

Co-variate	IRR	95% CI	p-value
Cirrhosis	10.8	5.66. 20.5	0.007
Age	1.05	1.03. 1.08	0.036

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ORIGINAL ARTICLE

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Cirrhosis and age are key determinants of HCC risk in individuals with primary sclerosing cholangitis: A multicenter longitudinal cohort study

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Abbreviations: AIH, autoimmune hepatitis; CCA, cholangiocellular carcinoma; EASL, European Association for the study of the Liver; GBC, gallbladder carcinoma; GEE, generalized estimation equations; IBD, inflammatory bowel disease; IPSCR, the International PSC Registry; IR, incidence rate; IRR, incidence rate ratio; MASLD, metabolic dysfunction–associated steatotic liver disease; PSC, primary sclerosing cholangitis; QIC, Quasi-likelihood Information Criteria; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor.

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Abstract

Background and Aims: The risk of HCC in primary sclerosing cholangitis (PSC) is unclear. Studies indicate a low risk for HCC, questioning the rationale for current HCC surveillance guidelines. This study explores the risk of HCC in a longitudinal multicenter cohort with over 3000 PSC subjects.

Approach and Results: Subjects with well-characterized PSC (n = 3071) were followed at 12 university hospitals within the International PSC Registry (IPSCR) collaboration for a total of 38,387 person-years. Incident HCC was registered. Subjects were followed from PSC diagnosis until death, liver transplantation, diagnosis of hepatobiliary malignancy, or February 2024. *Poisson* regression was used to calculate incidence rate ratios for HCC for the total population and for subgroups of different ages and cirrhosis status. Thirty-nine subjects developed HCC after a mean time of 16.4 years (SD ± 10.7) from PSC diagnosis. In 26 (66.7%) of HCC cases, cirrhosis was diagnosed before HCC. The mean age at HCC diagnosis was 55.6 years (± SD13.1 years), and 28 (71.8%) were male. HCC was associated with cirrhosis (IRR: 10.8, 95% CI: 5.7–20.5) and age (IRR 1.05, 95% CI: 1.03–1.08). At the age of 50, the incidence rate was 0.81 and 0.47 for cirrhotic men and women, respectively. For non-cirrhotic subjects, the risk was low for both men and women and all age groups.

Conclusion: HCC is relatively rare in patients with primary sclerosing cholangitis who do not have cirrhosis, especially in those under the age of 50. Our findings indicate that HCC monitoring for patients with PSC can be tailored based on their age and cirrhosis status.

Keywords: autoimmune liver disease, liver cirrhosis, hepatobiliary cancer, the International PSC Registry, the SweHep collaboration

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic liver disease that increases the risk of hepatobiliary malignancies, particularly cholangiocarcinoma (CCA).[1,2] The natural course of PSC is characterized by progressive inflammation of the bile ducts, leading to stenosis and obstruction of bile flow. Acute symptoms include recurrent pain, pruritus, and cholangitis, while liver cirrhosis is a common end-stage of the disease.[3] Within 15 years of the time of diagnosis, 41% of patients with PSC develop cirrhosis.[4] Despite ongoing research, the underlying pathophysiology of PSC is not fully understood. Currently, no pharmacological treatment is available to cure or halt disease progression or prevent cancer development, and the median transplant-free survival for patients with PSC is estimated to be 13.1–21.3 years.[2,5,6]

The most common malignancies in PSC are CCA and gallbladder cancer (GBC), which can occur without underlying cirrhosis. This contrasts with chronic liver disease in general, for which the most common malignancy is HCC, predominantly occurring in cirrhotic livers.[7] HCC is the fifth most common form of cancer and the third leading cause of cancer-related deaths worldwide.[8] Cancer is the most common cause of death in PSC, and CCA is the most frequent type. Many studies have shown 200–600-fold increased risks of hepatobiliary cancer in comparison to the general population.[1,9] Most of these studies report the overall hepatobiliary cancer risk, including both CCA, GBC, and HCC. CCA is by far the most common,[5] while the risk of HCC in patients with PSC remains unclear. Population-based studies have been of too limited size to specifically assess HCC risk in PSC and to compare that to other etiologies of chronic liver diseases.[10] Studies of small, selected cohorts of patients with PSC have shown varying incidence rates of HCC, ranging from 2.6 to 24 cases per 1000 patient years[11,12] to very low with 1 or 0 cases during follow-up.[2,13] Even among patients with PSC who have developed cirrhosis, the risk of HCC appears to be lower than that in patients with cirrhosis caused by other chronic liver diseases.[14]

Surveillance for hepatobiliary cancer in PSC is a controversial topic. Recently, studies have shown a very low efficacy of annual MRI to detect early stages of CCA and GBC with no impact on cancer-related mortality for patients with PSC.[4,12,15–17] For HCC, the evidence for regular surveillance is even more scarce. Despite this, current guidelines recommend bi-annual ultrasounds for early HCC detection for all patients with cirrhosis and PSC.[18,19] As HCC is a rare complication even within high-risk populations with chronic liver disease, large studies with extensive follow-up are needed to thoroughly address this topic and to better understand the need for HCC surveillance in PSC.

Here we present the results of an international cohort study with 3071 clinically well-characterized patients with PSC and an extensive length of follow-up. The aim of this study is to bring new evidence that describes the risk of HCC development for patients with PSC to better decide when patients with PSC, with or without cirrhosis, benefit from regular HCC surveillance.

METHODS

Study population and collection of data

Clinical data on all patients with new onset of PSC at 12 university hospitals in Finland, Germany, Italy, the Netherlands, Norway, and Sweden were registered within the International PSC Registry (IPSCR) collaboration and the *SweHep* research network.[20] For the present study, data on patients diagnosed with PSC between January 1st, 2000, and February 29th, 2024 was collected from the IPSCG-registry and from local PSC-registries and structured in a common master database at Karolinska University Hospital, Stockholm, Sweden, according to a preset list of variables, including date of birth, sex, PSC phenotype, concurrent inflammatory bowel disease, history of liver transplantation, body mass index, presence of type 2 diabetes, hepatitis B (HBV) and C (HCV) status, cirrhosis diagnosis, and diagnosis of hepatobiliary cancer development. Some data were missing in the prospectively gathered registers and was retrospectively collected for the purpose of the study, including liver elastography and FIB-4. Time of follow-up was defined as time from the first date of PSC diagnosis until the last known clinical contact or until death, date of liver transplantation, or diagnosis of any hepatobiliary malignancy (CCA, GBC, HCC, or pancreatic cancer). Local ethical approval was obtained by all participating sites. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Inclusion and exclusion criteria

Only patients with a well-documented and confirmed diagnosis of large-duct or small-duct PSC and PSC/AIH overlap based on diagnostic cholangiography, histology, or cholestatic biochemical findings were included. Patients with the onset of PSC diagnosis before age 16 years were excluded. Those with concurrent alcohol-associated, metabolic dysfunction–associated steatotic liver disease (MASLD), chronic hepatitis B or C were not excluded for the purpose of this study. Patients with an unknown date of PSC diagnosis or date of last follow-up were considered lost to follow-up and excluded. Subjects with insufficient data to establish age, sex, or tumor type were also excluded. Figure 1 shows an overview of patient inclusion and exclusion, including the number of subjects from each contributing center.

Definitions

HCC in patients with cirrhosis was diagnosed using radiological criteria.[21] HCC in patients without cirrhosis required histologic confirmation.[7] The diagnosis of HCC was made based on each center's established clinical standards in line with guidelines for diagnosing HCC at the time.[22] In cases where the diagnosis date of HCC was noted up to 90 days after liver transplantation, we assumed that the tumor was found in the explanted liver, and the date of HCC diagnosis was then considered to be the date of liver transplantation. Data

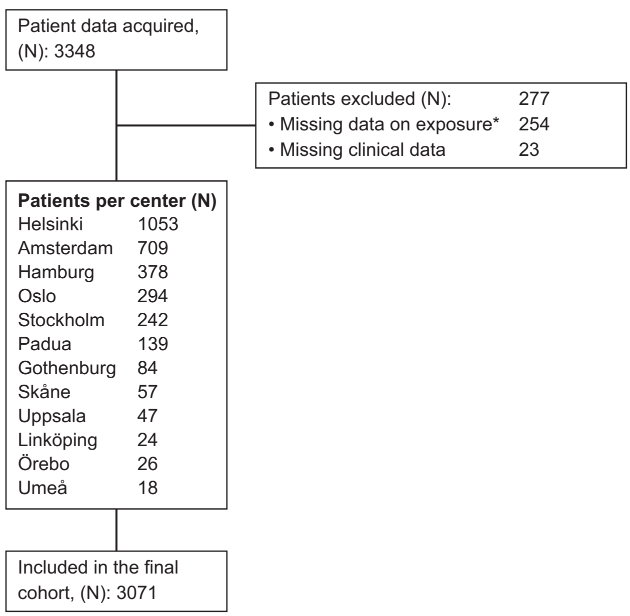

FIGURE 1 Flowchart describing the inclusion of subjects in the final study cohort and the number of subjects from each contributing center in alphabetical order. *Date of PSC diagnosis missing. Abbreviation: PSC, primary sclerosing cholangitis.

on a number of lesions, maximum tumor diameter, and first line of treatment were collected.

Cirrhosis was registered as present at the first known date when any of the following criteria were met: (1) radiologic findings of cirrhosis (eg, irregular liver margins, splenomegaly, variceal splanchnic veins, ascites); (2) clinical signs of cirrhosis and/or portal hypertension (ascites, esophageal varices, hepatic encephalopathy); (3) liver histology (= fibrosis stage F4); or (4) liver stiffness $\geq$15 kPa.[23] Additionally, to identify patients with cirrhosis whose radiological features of cirrhosis had been missed or not reported, we used FIB-4 $>$3.3[24] combined with imaging to retrospectively increase the sensitivity for detecting cirrhosis. With the available data, we were able to calculate FIB-4 scores. For patients with FIB-4 $>$3.3 who were not already registered as having cirrhosis, we conducted a retrospective review of their clinical records. If radiological findings were consistent with cirrhosis, these patients were classified as cirrhotic.

If the cirrhosis diagnosis was recorded within 6 months after liver transplantation or HCC diagnosis, we assumed that cirrhosis was already present at the time of transplantation, HCC diagnosis, or both. We attributed the delayed cirrhosis diagnosis to late registration rather than a new onset of the condition. Data on the presence of portal hypertension or the date of events of decompensated liver function were not available. The presence of HCC surveillance in patients with cirrhosis was defined from a dichotomous variable recorded in the IPSCR and local registries, indicating whether surveillance was adequately performed. Each center registered this variable according to adherence to established clinical procedures. In the registries, surveillance was defined as "included in any kind of surveillance," which included both annual CCA surveillance with MRI and bi-annual imaging for both CCA and HCC surveillance in patients with cirrhosis. Most centers used annual MRI for PSC surveillance, alternated with annual ultrasound, ensuring imaging was performed every 6 months.

Statistical analysis

Summary statistics were used to calculate baseline characteristics, which are reported as either mean with SD, or number with percentage. The dataset was split into multiple observations for each subject, covering all time periods between all events that occur in the data using the *survSplit* function in the package survival[25] for R 4.3.2 (R Core Team, 2023). Data was then submitted to the *geeglm* function in the package *geepack*,[26,27] to estimate generalized estimation equations (GEE), clustered on subjects with robust standard errors, applying a log link and *Poisson* error distribution, with log exposure time as an offset and HCC status as the dependent variable. The estimated coefficients were exponentiated to describe incidence rate ratios (IRR).

The statistical model was developed in 3 stages. First, HCC status was predicted from sex together with linear or 2–4 degrees of freedom natural spline functions of time-varying age, with and without an interaction. For each model, an exchangeable correlation structure was applied, and the Quasi-likelihood Information Criteria (QIC) was calculated. Second, the model with the lowest QIC was selected as a base model, and the time-varying status of cirrhosis was added as a predictor to the model. Finally, the model with exchangeable correlation structure was compared to models with an autoregressive and independent correlation structure, picking the one with the lowest QIC.

As a sensitivity analysis, we used a second model to examine the interaction between age and cirrhosis on HCC risk to assess whether the impact of age on HCC risk varies with the presence of cirrhosis. As a second sensitivity analysis, we excluded all patients who were diagnosed with PSC before age 18 years.

RESULTS

Baseline characteristics

The final cohort consisted of 3071 subjects from 12 centers (Figure 1). Sixty-three percent were male, and the mean age was 36.2 years (SD $\pm$14.5) at the time of PSC diagnosis and 48.7 (SD $\pm$14.7) at the end of the follow-up. The mean length of follow-up was 12.5 years, and the total time of observation was 38,264 person-years. Fifty-eight percent (n = 1791) had ulcerative colitis, and 14% (n = 429) had the Crohn disease diagnosed before or at any time during follow-up. Six hundred and eight subjects (19.8%) were diagnosed with cirrhosis, and 497 (16.2%) underwent a liver transplantation. In 70 subjects, none of whom had HCC, the date of cirrhosis diagnosis was registered on the same day as a censoring event. Diabetes type 2 was present in 5.5% of subjects. Positive serology for HCV or HBV was rare (0.3% and 0.1%, respectively). Table 1 shows a complete report of baseline characteristics.

Characteristics of HCC

In total, 39 subjects (1.3%) developed HCC during follow-up. Seventy-two percent were male and the mean age at HCC diagnosis was 59.5 years (SD $\pm$13.5). Twenty-six (66.7%) had developed cirrhosis at the time of HCC diagnosis. The mean time from diagnosis of PSC to HCC was 16.4 years ($\pm$10.7)

TABLE 1 Description of baseline characteristics of the total study cohort

Total study population	n	3071
PSC	n (%)	2733 (90.0)
Small-duct PSC	n (%)	90 (3.0)
PSC with AIH overlap	n (%)	215 (7.0)
Age at PSC diagnosis, y	Mean (±SD)	36.2 (14.5)
Age at end of follow-up, y	Mean (±SD)	48.7 (14.7)
Sex, male	n (%)	1935 (63.0)
Length of follow-up, y	Mean (±SD)	12.5 (8.3)
Inflammatory bowel disease		
No IBD	n (%)	722 (23.7)
Ulcerative colitis	n (%)	1791 (58.3)
Crohn disease	n (%)	429 (14.0)
Indeterminate colitis	n (%)	111 (3.6)
Cirrhosis diagnosis, ever	n (%)	608 (19.8)
Liver transplantation, ever	n (%)	497 (16.2)
Diabetes type 2, ever	n (%)	114 (5.5)
Body mass index, kg/m^2	Mean (±SD)	24.9 (4.3)
Obesity	n (%)	255 (11.4)
HCV positive	n (%)	6 (0.3)
HBV positive	n (%)	3 (0.1)

Abbreviations: AIH, autoimmune hepatitis; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

and 3.7 years (±4.5) from diagnosis of cirrhosis to HCC. Seven HCC cases had a date of cirrhosis registered within 6 months after the date of HCC. Most HCC cases (88.2%) were included in regular surveillance with imaging, and 21 HCC cases (65.6%) were first detected through surveillance. In total, 24 patients (61.5%) received a potentially curable treatment: 15 (38.5%) liver transplantation, 3 (7.7%) resection, and 6 (15.4%) ablation. Of these, 6 patients died during follow-up, with a mean survival of 47.3 months (±38.1) after HCC diagnosis. Eight patients received palliative treatment or best supportive care, and their mean survival was 11.4 months (SD ±11.0) after HCC diagnosis. Table 2 and Supplemental Table S1, http://links.lww.com/HEP/J782, report characteristics of the HCC cases.

The risk of HCC

The overall long-term risk for HCC in this cohort was 1.01 HCC cases per 1000 person-years. The HCC risk was strongly associated with cirrhosis and age. For patients with cirrhosis, the risk of HCC increased 10-fold (IRR: 10.8, 95% CI: 5.66–20.5, $p=0.007$) and for each life-year the risk increased 5% (IRR: 1.05, 95% CI: 1.03–1.08, $p=0.036$). Although not significant, we also observed a negative correlation between female gender and HCC risk (Table 3).

For patients without cirrhosis, at the age of 50, 60, and 70 years, the annual incidence rate of HCC was 0.08 (95% CI: 0.12–0.05), 0.12 (95% CI: 0.2–0.07), and 0.21 (95% CI: 0.39–0.11) for men, and 0.04 (95% CI: 0.09–0.02), 0.07 (95% CI: 0.14–0.04) and 0.12 (95% CI: 0.25–0.06) for women. For men who had developed cirrhosis, the incidence rate was 0.81 (95% CI: 1.37–0.48) at age 50, 1.34 (95% CI: 2.20–0.82) at age 60, and 2.22 (95% CI: 3.90–1.27) at age 70. For men with cirrhosis, the upper limit of the 95% CI for annual risk of HCC surpassed 1.5% at age 53 (IRR: 0.95, 95% CI: 1.56–0.57). For women with cirrhosis, the incidence rates were 0.47 (95% CI: 0.97–0.23), 0.78 (95% CI: 1.54–0.40), and 1.29 (95% CI: 2.63–0.64), at age 50, 60, and 70, respectively (Figure 2). The IR for all age groups divided by cirrhosis status and sex is shown in Supplemental Table S2, http://links.lww.com/HEP/J782.

Sensitivity analyses

The second model, where we tested for an interaction between age and cirrhosis, did not reveal any significant interaction effect between age and cirrhosis on the risk of HCC ($p=0.12$). Additionally, this model did not show a significant association between cirrhosis and HCC risk ($p=0.07$). Also, we found no association between the risk of HCC and DM2 or between HCC and HBV/HCV status in our cohort when these were added to the multivariate analysis (data not shown).

Three patients who were diagnosed with PSC before age 18 developed HCC 4.3, 13.7, and 29.0 years after PSC diagnosis, respectively. After excluding all patients diagnosed with PSC before age 18 years from the main model, 2775 patients remained, of whom 36 developed HCC. The risk of HCC development was still associated with cirrhosis (IRR: 9.69, 95% CI 4.96–18.9, $p=0.01$) and age (IRR: 1.06, 95% CI: 1.03–1.08, $p=0.035$).

DISCUSSION

In this study, we focused on establishing robust evidence on the long-term risk of HCC in patients with PSC and evaluating the rationale for HCC-specific surveillance in this group of patients. We present the HCC incidence rates from a longitudinal multicenter cohort study with over 3000 subjects with PSC, highlighting that liver cirrhosis and age are the most important risk factors for HCC in PSC.

While the risk of CCA is well established, the true incidence of HCC in PSC is unknown. Current guidelines for HCC surveillance in patients with PSC are primarily based on what is known about the risk in other chronic liver diseases. Our longitudinal multicenter cohort study, including more than 38,000 patient-years of follow-up, confirms that HCC is a rare complication of

TABLE 2 Demographics of HCC cases and tumor characteristics

			Complete data (%)
Total number of HCC cases	n	39	—
Age, y	Mean (±SD)	55.6 (13.1)	39 (100)
Sex, male	n (%)	28 (71.8)	39 (100)
Cirrhosis at time of HCC diagnosis[a]	n (%)	26 (66.7)	39 (100)
Time from diagnosis of PSC to HCC, y	Mean (±SD)	16.4 (10.7)	39 (100)
Time from diagnosis of cirrhosis to HCC, y	Mean (±SD)	5.2 (4.5)	39 (100)
Included in surveillance	n (%)	30 (88.2)	34 (87.2)
HCC diagnosed through surveillance	n (%)	21 (65.6)	32 (82.1)
HCC in explanted liver	n (%)	5 (12.8)	32 (82.1)
Incidental or symptomatic HCC[b]	n (%)	6 (23.1)	32 (82.1)
Number of lesions			33 (84.6)
1	n (%)	25 (64.1)	—
2	n (%)	4 (10.2)	—
≥3	n (%)	4 (10.2)	—
Diameter of largest lesion, mm	Mean (±SD)	32.4 (34.7)	33 (84.6)

[a]In 7 of the 26 HCC cases, the date of cirrhosis was registered after but within 6 months of the HCC date.
[b]Diagnosed by incidence at surveillance (=incidental) or by an imaging prompted by new onset of symptoms (=symptomatic).
Abbreviation: PSC, primary sclerosing cholangitis.

PSC, with an overall incidence of 1.01 per 1000 person-years. Although the HCC risk is higher for patients with PSC compared to that of the general population,[28] it is much lower than the risk of CCA or decompensated cirrhosis in PSC.[2,4] In addition, the risk for HCC in those with cirrhosis was lower in our study compared to that previously reported for cirrhosis in general and in cirrhosis caused by autoimmune disease specifically.[29]

In PSC with cirrhosis, HCC is uncommon before the age of 50. Based on the 95% CI, the annual risk remains below 1.5% for men before age 53 and for women before age 60. We suggest an age cut-off of 50 years for HCC surveillance in PSC to avoid underestimating the risk and to have a clinically practical threshold, consistent with other surveillance guidelines.[30,31]

The non-significant trend toward a lower risk of HCC in women is noteworthy and in line with other chronic liver diseases. However, due to the lack of statistical significance, our data do not support recommending a higher starting age for HCC surveillance in women. Further research on larger cohorts is necessary before gender-specific age limits can be determined. Until then, we propose using the same age threshold of 50 years for both men and women with PSC.

TABLE 3 Longitudinal risk estimates for HCC development with multivariate *Poisson* regression

Covariate	IRR	95% CI	*p*
Cirrhosis	10.8	5.66. 20.5	**0.007**
Age	1.05	1.03. 1.08	**0.036**
Female	0.58	0.29. 1.17	>0.9

Abbreviation: IRR, incidence rate ratio.

Previous data on the incidence of HCC in patients with PSC vary and are limited. In a study by Zenouzi et al[32] no patient developed HCC, which further supported a low risk. However, the size of this study was limited, including only 509 PSC subjects, of which 119 had cirrhosis, and the time of follow-up was <300 person-years. In a prospective study by Villard et al,[13] only one of 512 subjects developed HCC during a mean follow-up of 7 years. In this cohort, only 12% of the PSC patients had cirrhosis. A study of 134 patients with advanced PSC undergoing liver transplantation demonstrated that HCC was present in 3 (2%), all of whom had confirmed cirrhosis prior to HCC diagnosis.[33] Other studies have reported incidence rates of HCC that ranged between 1 and 2.5 cases per 1000 person-year[5,12] up to risks as high as 0.18%–1% annually.[4,11] However, these studies were biased by the high selection of patients with advanced disease who were followed at a tertiary referral center. In addition, all patients with HCC had cirrhosis at the time of cancer diagnosis.

The cost-effectiveness of bi-annual HCC surveillance is a matter of debate. Previous studies in patients with cirrhosis in general have estimated surveillance with ultrasound to be cost-effective when the yearly tumor incidence exceeds 1.5%.[22,34,35] The European Association for the Study of the Liver (EASL) suggests that surveillance is cost-effective at an annual incidence that exceeds 1.5%–3%.[7] In the lack of evidence for PSC specifically, the general guidelines for HCC surveillance are in practice for

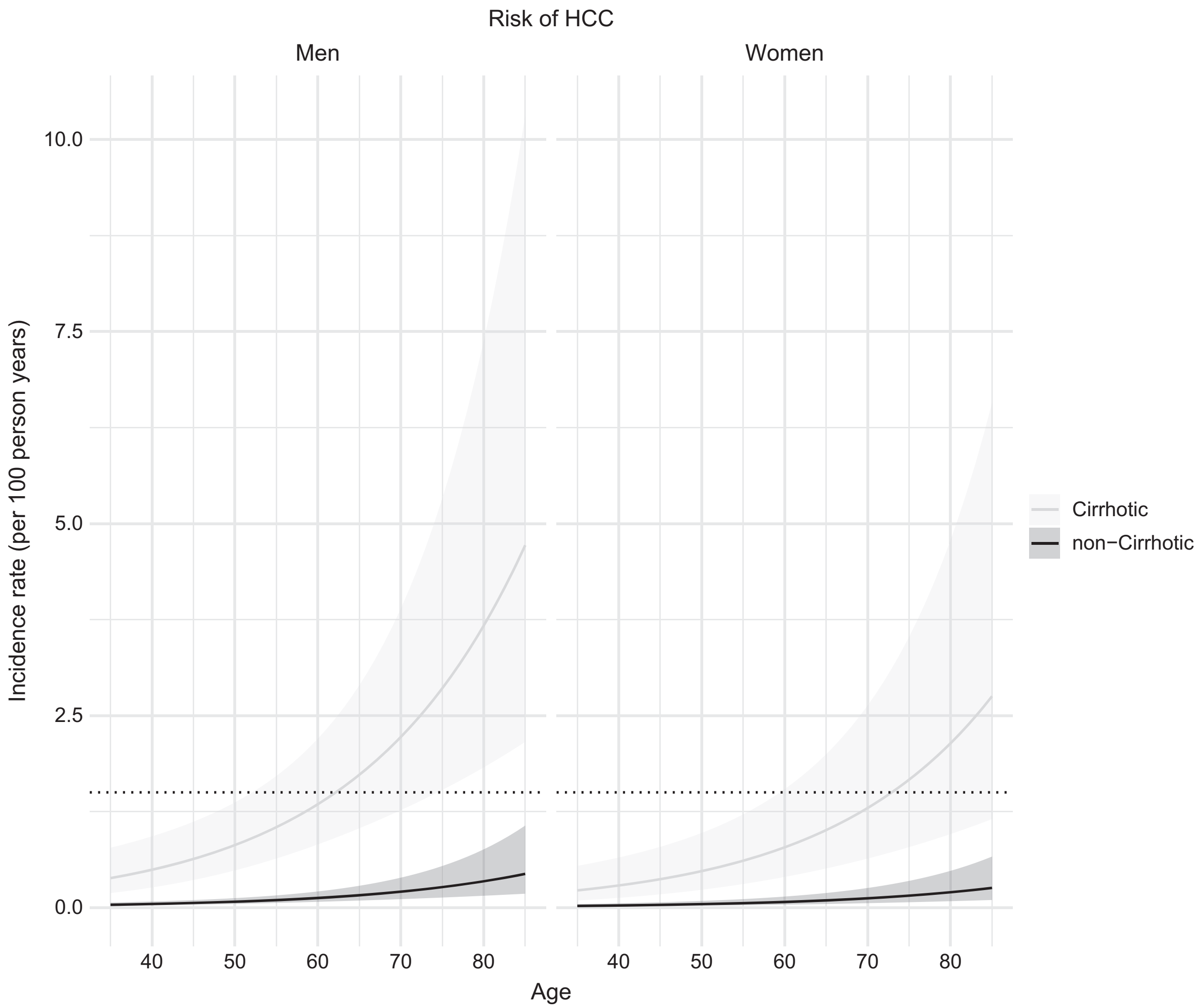

FIGURE 2 Line graph showing incidence rate for HCC (per 100 person-years). Shaded areas show 95% CI. The dotted line denotes a 1.5% annual risk (incidence rate of 1.5 per 100 person years).

patients with PSC as well.[18] However, to date, there is no data to support the cost-effectiveness of this routine. Consequently, when comparing our results to established cost-benefit models, we conclude that bi-annual HCC surveillance is not cost-efficient for patients with PSC below the age of 50, regardless of their cirrhosis status.

This study has several strengths. First, this is one of the largest studies of its kind in PSC, with an extensive follow-up time, which enables a high detection rate of a rare outcome such as HCC. Second, to our knowledge, it is the first study that has statistically established age limits that can be used to determine when to initiate HCC-specific surveillance in PSC. Third, prospective collection of data into a standardized and common database from each center ensures that the material is of high quality and reliable regarding important clinical events and patient characteristics. Also, the diagnosis of PSC and of HCC was based on robust clinical evaluations, which ensures a high internal validity of the study. Fourth, the study's international multicenter design compensates for any regional differences in how PSC-care is organized and ensures a high external validity.

Also, some liabilities need to be addressed. Seven subjects had cirrhosis registered at the same time or after the HCC diagnosis was registered. These cases were included in the longitudinal analysis but did not contribute to a time of exposure since the duration of cirrhosis was unknown. This implies a risk for lead time bias. If so, this would lead to an overestimation of the HCC risk for cirrhotic subjects, but it does not change the interpretation of our main findings. Also, HCC cases without cirrhosis were not manually reviewed to confirm their non-cirrhotic status. As a result, we cannot rule out classification bias, which may lead to an overestimation of HCC risk among non-cirrhotic patients with PSC. We used age at PSC diagnosis <16 as exclusion criteria. Given the chronic natural progression of PSC, a patient diagnosed with PSC at age 16 is likely to have reached adulthood by the time the disease advances to stages involving cirrhosis and when the risk of cancer is higher. The 3 HCC cases in this study, who had their PSC diagnosis established before the age of 18, developed HCC after an average of 15.7 years. Therefore, we argue that using age 16 as the cut-off for PSC diagnosis ensures that we include patients who contribute relevant exposure data. Furthermore, our sensitivity analysis shows that using age 18 as the inclusion cut-off did not change the main findings of this study. We did not exclude subjects with concurrent alcohol use or a concomitant diagnosis of MASLD, which is known to increase the risk of HCC. It can be argued that this would lead to an overestimation of the HCC incidence related to PSC. Our standpoint is that this rather increases the external validity of our results since the patients included are more representative of a real-life clinical setting where patients might have coexisting risk factors for progressive liver disease. The prevalence of type 2 diabetes and obesity was low in our cohort. While we acknowledge that MASLD is highly prevalent in the general population, it was likely lower in this cohort, although we lack accurate data on the presence of hepatic steatosis to confirm this. We believe that concomitant MASLD did not influence our results, and neither MASLD nor diabetes type 2 or obesity were included in the final multivariate regression model. HCV or HBV positivity was low. None of the HCC cases in this study had HBV or HCV infection. Consequently, including these covariates in the multivariate analysis did not impact our primary results, due to the lack of power to detect any such weak associations. Robust data on AIH/PSC overlap, portal hypertension, and events of decompensation were unfortunately lacking and could not be included in the model. However, in a clinical context, if someone with PSC has a concurrent diagnosis known to cause a higher risk for HCC, the specific surveillance guideline for that disease should be applied. In this study, we defined a diagnosis of CCA as a censoring event in the analysis of HCC risk. We decided not to report the CCA-specific incidence since neither the risk for CCA nor the surveillance strategies for CCA in PSC were within the scope of this study. The high incidence of CCA in PSC is well established from the results of multiple previous studies performed in similar patient cohorts and settings as the present one.[36]

CONCLUSIONS

We conclude that the risk of HCC development is low in non-cirrhotic patients with PSC and in cirrhotic patients with PSC under the age of 50 years, with an incidence rate of 0.81 per year. Our findings indicate that HCC surveillance may be less cost-effective in young patients with PSC and cirrhosis compared to those aged 50 years or older. Further research is needed to determine appropriate age thresholds for initiating HCC-specific surveillance in patients with PSC.

AUTHOR CONTRIBUTIONS

Study conception and design: Annika Bergquist, Magnus Holmer, and Michael Ingre. Acquisition of data: All authors. Statistical analysis: Magnus Holmer and Michael Ingre. Analysis and interpretation of data: Annika Bergquist, Magnus Holmer, and Michael Ingre. Drafting of manuscript: Magnus Holmer. Critical revision: All authors. Guarantor of the article: Magnus Holmer. All authors approved the final version of the article, including the authorship list.

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CONFLICTS OF INTEREST

Magnus Holmer advises AstraZeneca. Cyriel Ponsioen consults for Chemomab. He received grants from Perspectum and NGM. Christoph Schramm consults for Agomab, Chemomab, and Pliant. He received grants from the Falk Foundation. Trine Folseraas is on the speakers' bureau for AstraZeneca. Nora Cazzagon consults for, advises, and received grants from Ipsen. She consults for Gilead, Albireo, and Advanz. She consults for and received grants from Orphalan. She consults for GSK. Johan Vessby advises NovoNordisk. Annika Bergquist consults for Ipsen and Onu. The remaining authors have no conflicts to report.

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