

Supplementary Table 1: Patient Characteristics by Gender *

A) Demographics and phenotype **		
	Men (n = 4661)	Women (n = 2454) ***
Age at diagnosis: ****		
- Mean	37 yrs. (SD: 15)	40 yrs. (SD: 16)
- <= 20 yrs.	660 (14.2%)	278 (11.4%)
- 21 – 30 yrs.	1065 (22.8%)	442 (18.0%)
- 31 – 40 yrs.	1084 (23.3%)	532 (21.7%)
- 41 – 50 yrs.	904 (19.4%)	531 (21.7%)
- 51 – 60 yrs.	550 (11.8%)	403 (16.4%)
- > 60 yrs.	397 (8.5%)	266 (10.8%)
PSC sub-phenotype: ****		
- classical PSC	4231 (90.8%)	2160 (88.0%)
- small duct PSC	158 (3.4%)	96 (3.9%)
- PSC / AIH variant	271 (5.8%)	198 (8.1%)
Diagnosis year:		
- 1980 – 1984	144 (3.1%)	73 (3.0%)
- 1985 – 1989	304 (6.5%)	120 (4.9%)
- 1990 – 1994	524 (11.2%)	248 (10.1%)
- 1995 – 1999	937 (20.1%)	477 (19.4%)
- 2000 – 2004	1176 (25.2%)	623 (25.4%)
- 2005 – 2010	1576 (33.8%)	913 (37.2%)
IBD phenotype at baseline: ****		
- ulcerative colitis	1935 (45.4%)	823 (36.0)
- Crohn’s disease	362 (8.5%)	233 (9.5)
- indeterminate colitis	76 (1.8%)	37 (1.6)
- no IBD	1890 (44.3%)	1190 (52.1)
IBD phenotype at end of follow-up: ****		
- ulcerative colitis	2818 (61.0)	1168 (48.1)
- Crohn’s disease	466 (10.1)	318 (13.1)
- indeterminate colitis	143 (3.1)	67 (2.8)
- no IBD	1193 (25.5)	874 (36.0)
B) Clinical events ****	Incidence rate per-100-pt. yrs. (95%. C.I.)	
Liver transplantation or death	5.58 (5.34-5.82)	5.16 (4.83-5.48)
Hepatopancreatobiliary malignancy		
- overall	1.55 (1.41-1.68)	1.10 (0.94-1.25)
- cholangiocarcinoma	1.28 (0.86-1.71)	0.90 (0.43-1.37)

* Data presented as absolute number (%) unless otherwise indicated.

** Data presented only for patients in whom complete respective data are available.

*** Six patients did not have gender data documented

**** Indicates statistically significant differences of covariate frequency between all subgroups listed ($p < 0.05$).

Supplementary Table 2: Patient Characteristics by PSC Sub-phenotype *

A) Demographics and phenotype **			
	Classical PSC (n= 6397)	Small-duct PSC (n = 254)	PSC / AIH variant (n = 470)
No. of men	4232 (66.2%)	158 (62.2%)	271 (57.8%)
Age at diagnosis:			
- Mean	39 yrs. (SD: 15.4)	37yrs. (SD: 14.8)	32 yrs. (SD: 15)
- < 20 yrs.	779 (12.2%)	35 (13.8%)	126 (26.8%)
- 21 – 30 yrs.	1323 (20.7%)	59 (23.2%)	126 (26.8%)
- 31 – 40 yrs.	1456 (22.8%)	68 (26.8%)	93 (19.8%)
- 41 – 50 yrs.	1327 (20.8%)	43 (16.9%)	65 (13.8%)
- 51 – 60 yrs.	884 (13.8%)	32 (12.6%)	37 (7.9%)
> 60 yrs.	625 (9.8%)	17 (6.7%)	23 (4.9%)
Diagnosis year:			
- 1980 – 1984	213 (3.3%)	2 (0.8%)	2 (0.4%)
- 1985 – 1989	404 (6.3%)	9 (3.5%)	11 (2.3%)
- 1990 – 1994	723 (11.3%)	18 (7.1%)	32 (6.8%)
- 1995 – 1999	1287 (20.1%)	47 (18.5%)	80 (17.0%)
- 2000 – 2004	1603 (25.1%)	79 (31.1%)	120 (25.5%)
- 2005 – 2010	2167 (33.9%)	99 (39.0%)	225 (47.9%)
IBD phenotype at baseline:			
- ulcerative colitis	2535 (43.2%)	67 (27.9%)	159 (36.2%)
- Crohn’s disease	545 (9.3%)	24 (10.0%)	26 (5.9%)
- indeterminate colitis	98 (1.7%)	6 (2.5%)	9 (2.1%)
- no IBD	2694 (45.9%)	143 (59.6%)	245 (55.8%)
IBD phenotype at end of study:			
- ulcerative colitis	3682 (58.1%)	85 (33.5%)	222 (47.7%)
- Crohn’s disease	718 (11.3%)	30 (11.8%)	38 (8.2%)
- indeterminate colitis	185 (2.9%)	7 (2.8%)	18 (3.9%)
- no IBD	1750 (27.6%)	132 (52.0%)	187 (40.2%)
B) Clinical events **			
Incidence rate per-100-pt. yrs. (95%. C.I.)			
Liver transplantation or death	5.62 (5.42 -5.83)	2.32 (1.67 – 3.00)	4.70 (3.97 – 5.43)
Hepatopancreatobiliary malignancy			
-overall	1.52 (1.41 –1.63)	0.20 (0.00 –0.39)	0.43 (0.20 – 0.65)
- cholangiocarcinoma	1.25 (0.90–1.60)	No cases	0.37 (0.16 – 0.58)

* Data presented as absolute number (%) unless otherwise indicated.

** Data presented only for patients in whom complete respective data are available.

Supplementary Table 3: Patient Characteristics by IBD phenotype (at baseline) *

A) Demographics and phenotype **				
	Ulcerative colitis (n = 2761)	Crohn's Disease (n= 595)	Indeterminate (n = 113)	No IBD (n = 3082)
No. of men	1935 (70.2)	362 (60.8)	76 (67.3)	1890 (61.4)
Age at diagnosis:				
- Mean	37 yrs. (SD: 15)	38 yrs. (SD: 16)	35 yrs. (SD: 14)	40 yrs. (SD: 16)
- <= 20 yrs.	410 (14.8%)	91 (15.3%)	17 (15.0%)	350 (11.4%)
- 21 – 30 yrs.	646 (23.4%)	125 (21.0%)	36 (31.9%)	585 (19.0%)
- 31 – 40 yrs.	671 (24.3%)	136 (22.9%)	24 (21.2%)	660 (21.4%)
- 41 – 50 yrs.	510 (18.5%)	116 (19.5%)	17 (15.0%)	664 (21.6%)
- 51 – 60 yrs.	336 (12.2%)	74 (12.4%)	13 (11.5%)	452 (14.7%)
- > 60 yrs.	188 (6.8%)	53 (8.9%)	6 (5.3%)	368 (12.0%)
PSC sub-phenotype:				
- classical PSC	2535 (91.8%)	545 (91.6%)	98 (86.7%)	2694 (87.4%)
- small duct PSC	67 (2.4%)	24 (4.0%)	6 (5.3%)	143 (4.6%)
- PSC / AIH variant	159 (5.8%)	26 (4.4%)	9 (8.0%)	245 (7.9%)
Diagnosis year:				
- 1980 – 1984	75 (2.7%)	9 (1.5%)	4 (3.5%)	91 (3.0%)
- 1985 – 1989	166 (6.0%)	23 (3.9%)	6 (5.3%)	167 (5.4%)
- 1990 – 1994	327 (11.8%)	41 (6.9%)	16 (14.2%)	299 (9.7%)
- 1995 – 1999	561 (20.3%)	104 (17.5%)	15 (13.3%)	620 (20.1%)
- 2000 – 2004	705 (25.5%)	165 (27.7%)	27 (23.9%)	783 (25.4%)
- 2005 – 2010	927 (33.6%)	253 (42.5%)	45 (39.8%)	1122 (36.4%)
B) Clinical events **	Incidence rate per-100-pt. yrs. (95% C.I.)			
Liver transplantation or death	5.36 (5.06-5.67)	3.89 (3.30-4.47)	4.47 (3.07-5.88)	5.82 (5.51-6.13)
Hepatopancreatobiliary malignancy				
-overall	1.48 (1.31-1.64)	1.21 (0.88-1.55)	1.43 (0.62-2.24)	1.34 (1.19-1.50)
- cholangiocarcinoma	1.22 (0.72-1.72)	1.02 (0.03-2.02)	1.19 (0.00-3.07)	1.11 (0.60-1.62)

* Data presented as absolute number (%) unless otherwise indicated.

** Data presented only for patients in whom complete respective data are available.

Supplementary Table 4: Incidence Rates (IR) per-100-pt. yrs. of Liver transplantation / Death According to Phenotype

Event: liver transplantation / death								
	Male				Female			
	<i>UC</i>	<i>CD</i>	<i>IC</i>	<i>No-IBD</i>	<i>UC</i>	<i>CD</i>	<i>IC</i>	<i>No-IBD</i>
<i>Classical PSC</i>								
IR:	5.5	4.3	4.6	6.3	5.3	3.4	5.5	5.7
1y survival:	94%	96%	97%	92%	95%	96%	100%	94%
5y survival:	77%	80%	82%	71%	79%	85%	73%	77%
10y survival:	59%	67%	73%	55%	61%	72%	62%	60%
20y survival:	30%	52%	37%	31%	23%	67%	40%	35%
<i>sdPSC</i>								
IR:	2.5	0.0	0.0	2.2	2.7	4.0	0.0	2.5
1y survival:	96%	100%	100%	99%	100%	100%	100%	95%
5y survival:	96%	100%	100%	89%	100%	88%	100%	86%
10y survival:	96%	100%	100%	89%	75%	88%	-	80%
20y survival:	84%	-	-	82%	56%	-	-	67%
<i>PSC/AIH-overlap</i>								
IR:	4.1	4.8	2.1	3.9	5.2	6.6	0.0	5.5
1y survival:	96%	100%	100%	96%	97%	92%	100%	96%
5y survival:	86%	92%	83%	78%	79%	61%	-	81%
10y survival:	73%	69%	83%	68%	69%	41%	-	56%
20y survival:	45%	69%	-	55%	30%	41%	-	29%

**Supplementary Table 5: Incidence Rates (IR) per-100-pt. yrs. of HPB malignancy
According to Phenotype**

Event: hepatopancreatobiliary (HPB) malignancy *								
	Male				Female			
	<i>UC</i>	<i>CD</i>	<i>IC</i>	<i>No-IBD</i>	<i>UC</i>	<i>CD</i>	<i>IC</i>	<i>No-IBD</i>
<i>Classical PSC</i>								
IR; 1 st yr. only:	3.1	2.2	3.5	3.8	2.2	2.1	1.9	2.6
IR; overall:	1.6	1.6	1.4	1.7	1.5	0.6	1.5	1.1
1y survival:	96%	97%	95%	94%	97%	97%	97%	96%
5y survival:	92%	92%	93%	90%	92%	96%	91%	92%
10y survival:	86%	87%	93%	86%	86%	95%	78%	90%
20y survival:	70%	73%	82%	75%	68%	95%	78%	83%
<i>sdPSC</i>								
IR; 1 st yr. only:	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IR; overall:	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.5
1y survival:	100%	100%	100%	100%	100%	100%	100%	100%
5y survival:	100%	100%	100%	100%	100%	100%	100%	98%
10y survival:	100%	100%	100%	100%	89%	100%	-	92%
20y survival:	100%	-	-	100%	89%	-	-	92%
<i>PSC/AIH-overlap</i>								
IR; 1 st yr. only:	1.5	6.5	0.0	0.7	0.0	0.0	0.0	0.8
IR; overall:	0.7	2.0	0.0	0.2	0.2	1.2	0.0	0.1
1y survival:	96%	92%	100%	99%	100%	100%	100%	99%
5y survival:	94%	81%	100%	98%	98%	89%	-	99%
10y survival:	94%	81%	100%	98%	98%	89%	-	99%
20y survival:	94%	81%	-	98%	98%	-	-	99%

* For HPB malignancy, IR are provided for events in the 1st year only as well as overall

Supplementary Table 6: Univariate Risk Factors for Disease Progression *

Risk factor	Crude Hazard Ratio (95% C.I.)	p value
A) Liver transplantation / death		
Age at diagnosis **	1.022 (1.019 – 1.025)	< 0.0001
Gender		
Male	1 (reference)	
Female	0.88 (0.81– 0.96)	0.002
PSC sub-phenotype		
- classical PSC	1 (reference)	
- small duct PSC	0.30 (0.21 – 0.42)	< 0.001
- PSC / AIH variant	0.81 (0.68 – 0.96)	0.015
IBD phenotype (baseline)		
- ulcerative colitis	1 (reference)	
- Crohn's disease	0.64 (0.53 – 0.76)	<0.0001
- indeterminate	0.86 (0.61 – 1.22)	0.40
- no IBD	1.01 (0.93 – 1.10)	0.89
IBD phenotype (prior-to-endpoint) ***		
- ulcerative colitis	1 (reference)	
- Crohn's disease	0.62 (0.52 – 0.72)	< 0.001
- indeterminate	0.91 (0.68 – 1.21)	0.52
- no IBD	0.90 (0.83 – 0.99)	0.03
B) Hepatopancreatobiliary malignancy		
Age at diagnosis **	1.03 (1.03 – 1.04)	< 0.001
Gender		
Male	1 (reference)	
Female	0.68 (0.57 – 0.80)	< 0.001
PSC biliary phenotype		
- classical PSC	1 (reference)	
- small duct PSC	0.15 (0.06 – 0.40)	< 0.001
- PSC / AIH variant	0.26 (0.15 – 0.44)	< 0.001
IBD phenotype (baseline)		
- ulcerative colitis	1 (reference)	
- Crohn's disease	0.73 (0.54 – 0.96)	0.04
- indeterminate	1.09 (0.61 – 1.94)	0.77
- no IBD	0.88 (0.75 – 1.04)	0.14
IBD phenotype (prior-to-endpoint) ***		
ulcerative colitis	1 (reference)	
- Crohn's disease	0.68 (0.51 – 0.91)	0.008
- indeterminate	0.94 (0.55 – 1.61)	0.82
- no IBD	0.77 (0.65 – 0.92)	0.004

*All analysis stratified by geographical region of participating centre and adjusted by patient year of diagnosis.

** Per 1-yr. increase in age.

*** Assessed as a time-dependent covariate

Supplementary Table 7: Previously published clinical outcome studies in PSC *

Geographical location	Study type	Study period or last reported follow-up date – previously reported	Maximum No. pts. – previously reported
<i>Multi-national</i>			
Italy, Norway, Spain, Sweden, UK	Observational	1998 ^{1,2}	394
Scandinavia	Clinical trial	2009 ^{3–5}	219 **
Finland, the Netherlands, Norway, UK	Investigative biomarker	2012 ⁶	305
Germany and Sweden	Observational	1989 – 2008 (Germany) ^{7,8} 1992 – 2005 (Sweden)	345
Germany and Norway	Observational	2014 ¹¹	638
Germany and Norway	Investigative biomarker	2006 – 2015 (Germany) ¹² 2008 – 2012 (Norway)	318
<i>Belgium</i>			
Leuven	Observational	1975 – 2012 ^{13,14}	240
<i>Canada</i>			
Toronto, ON	Observational	2009 ¹⁵	168
<i>France</i>			
Paris	Observational	2008 ¹⁶	150
<i>Germany</i>			
Heidelberg	Observational / investigative biomarker	2012 ^{17–21}	281 ***
Hannover	Observational	2006 ¹⁰	273
Hamburg and Hannover	Observational	2013 ⁹	509
<i>Italy</i>			
Multi-regional	Observational	1994 ²²	117
<i>The Netherlands</i>			
Multi-regional	Observational	2008 ^{23–27}	590 ***
<i>Sweden</i>			
Multi-regional	Observational	1992 ²⁸	305
Stockholm	Observational	1970 – 2004 ^{29–31}	604
<i>USA</i>			
Multi-regional	Clinical trial	2009 ^{32–34}	150
Multi-regional	Observational	1995 – 2005 ³³	784
Minnesota	Observational	1970 – 1997 ^{36,37}	174
California	Observational	2000 – 2006 ³⁸	169
<i>UK</i>			
London	Observational	2011 ³⁹	128
London	Observational	1990 – 2009 ⁴⁰	96
London	Observational	1972 – 1989 ⁴¹	169

* Comprises PSC cohorts ~ / ≥100 patients, which have contributed data to the international PSC Study Group (IPSCSG). Presented reports are likely to include those wherein more than one publication stems from a given cohort.

** Includes post-hoc outcome analysis of patients included in prior clinical trials.

*** Includes a subset of patients subject to an open-label study of endoscopic biliary intervention.

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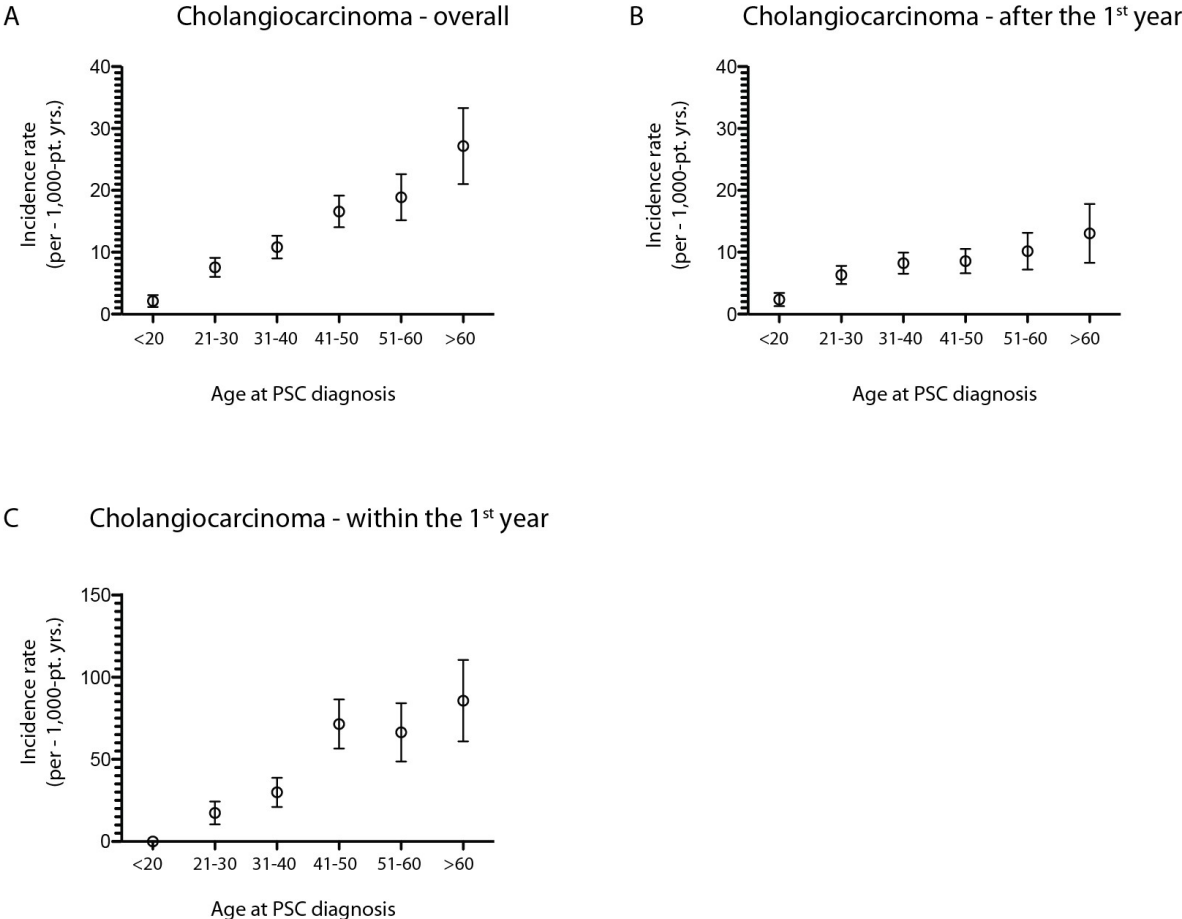
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Supplementary Figure 1: Incidence of Cholangiocarcinoma by Age at PSC diagnosis

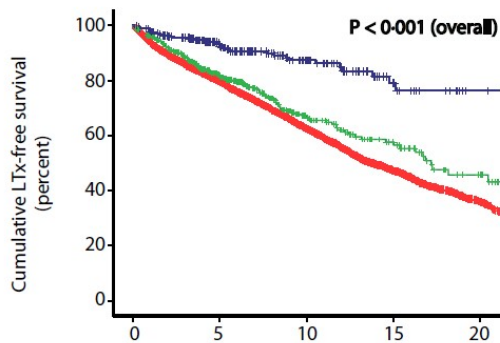


Incidence rates of cholangiocarcinoma (CCA) according to the age at PSC diagnosis are presented for all cases in [A], excluding CCA cases diagnosed in the first year of PSC diagnosis [B] and restricted analysis to events within the first year of PSC diagnosis [C].

Supplementary Figure 2: Incidence of Clinical Events According to PSC Phenotype

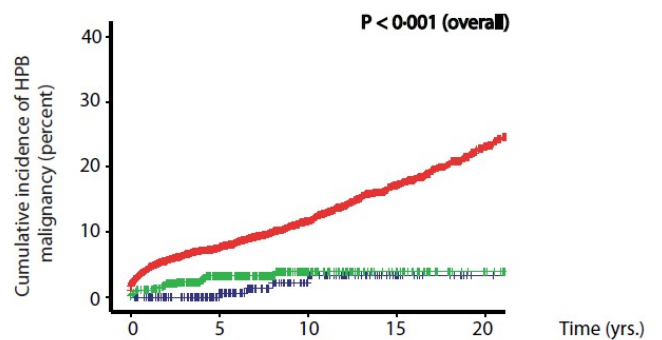
Kaplan-Meier estimates illustrating [A] transplant-free survival and [B] incidence rate of hepatopancreatobiliary malignancy, stratified according to PSC phenotype at diagnosis (unadjusted) Patients with unknown malignancy status at time of study completion were excluded from analysis in [B].

A



— Small duct PSC	254	165	84	30	10
— PSC / AIH overlap	470	261	116	51	21
— Classical PSC	6397	3756	1930	861	342

B



	247	161	81	29	9	Pts. at risk
	460	254	111	46	17	Pts. at risk
	6122	3542	1802	789	308	Pts. at risk