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 (36.0.7)
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.

**** Indicates statistically significant differences of covariate frequency between all subgroups listed ($p < 0{\cdot}05$).

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			
	UC	***CD***	***IC***	***No-IBD***	***UC***	***CD***	***IC***	***No-IBD***
Classical PSC								
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%
sdPSC								
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%
PSC/AIH-overlap								
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			
	UC	*CD*	*IC*	*No-IBD*	*UC*	*CD*	*IC*	*No-IBD*
Classical PSC								
IR; 1st 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%
sdPSC								
IR; 1st 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%
PSC/AIH-overlap								
IR; 1st 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 (0·0.68 – 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
Multi-national			
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
Belgium			
Leuven	Observational	1975 – 2012 [13,14]	240
Canada			
Toronto, ON	Observational	2009 [15]	168
France			
Paris	Observational	2008 [16]	150
Germany			
Heidelberg	Observational / investigative biomarker	2012 [17–21]	281 ***
Hannover	Observational	2006[10]	273
Hamburg and Hannover	Observational	2013[9]	509
Italy			
Multi-regional	Observational	1994 [22]	117
The Netherlands			
Multi-regional	Observational	2008 [23–27]	590 ***
Sweden			
Multi-regional	Observational	1992 [28]	305
Stockholm	Observational	1970 – 2004 [29–31]	604
USA			
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
UK			
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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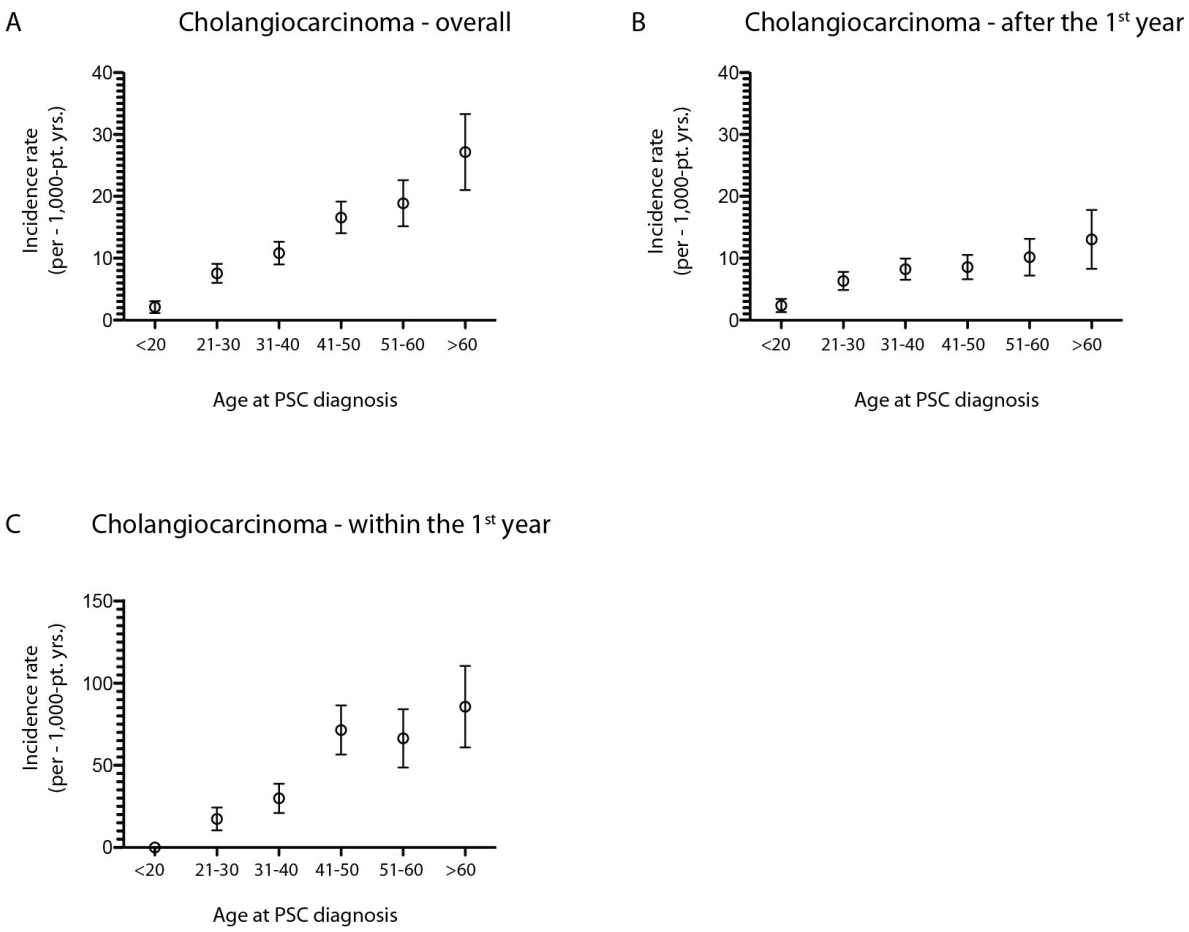
Supplementary Figure 1: Incidence of Cholangiocarcinoma by Age at PSC diagnosis



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].