SUPPLEMENTARY RESULTS – SENSITIVITY ANALYSIS

Temporal changes in cholangiocarcinoma incidence and mortality in the United States from 2001–2017

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Patient characteristics

The sensitivity analysis including both topography and histology codes (see Methods for details) yielded 25,606 cases of CCA, from which the 25,599 occurring in adults were analyzed (iCCA, n = 17,095 [66.8%]; eCCA n =8498 [33.2%]; iCCA and eCCA, n = 6 [<0.1%]) (Supplementary Fig. S1). The demographics and disease characteristics of patients with CCA derived from the sensitivity analysis are shown in Supplemental Table S1.

Incidences of CCA, iCCA, and eCCA

The overall age-adjusted incidence of CCA from 2001–2017 was 2.32 per 100,000 person-years (iCCA, 1.54; eCCA, 0.78). The incidence of CCA increased by 46.3% from 2.05 in 2001 to 3.00 in 2017 (Fig. S2A). The annual percentage change (APC) in incidence of CCA showed a significant increase from 2001–2017, a non-significant decline in time period 2001-2006, and significant increases during time periods 2007–2012, and 2013–2017 (Table S2). The age-adjusted incidence of iCCA increased 90.7% (1.18 to 2.25) from 2001–2017; within this period, iCCA incidence remained relatively similar from 2001 (1.18) to 2006 (1.20), and then increased thereafter by 73.1% (1.30 to 2.25) from 2007–2017 (Fig. S2A). Similarly, the APC in incidence of iCCA demonstrated a small, nonsignificant increase from 2001–2006 and then significant increases from 2007–2012 and 2013–2017 (Table S2). The age-adjusted incidence of eCCA decreased by 13.8% from 0.87 in 2001 to 0.75 in 2017 (Fig. S2A), and the APC in eCCA incidence showed a significant decrease from 2001–2006, which was followed by a nonsignificant increase between 2007–2012 and a nonsignificant decline in incidence between 2013–2017 (Table S2). The overall age-adjusted incidence of CUP from 2001–2017 was 3.03, declining 54.4% from 4.65 in 2001 to 2.12 in 2017 (Fig. S2B). The incremental difference

between age-adjusted iCCA and CUP incidences increased monotonically from −3.47 in 2001 to 0.13 in 2017 (Fig. S2B).

The overall age-adjusted incidence of CCA from 2001–2017 increased with patient's age (18–44 years, 0.19; 45–64 years, 2.17; 65–84 years, 8.88; ≥85 years, 11.74) (Fig. S2C). For patients 18–44 years of age, CCA incidence increased by 100.0% from 0.13 in 2001 to 0.26 in 2017; for those ≥85 years of age, incidence decreased by 7.0% from 14.54 in 2001 to 13.52 in 2017. The overall age-adjusted incidence of CCA from 2001–2017 was 2.76 in men versus 1.98 in women, reflecting an increase from 2.61 in 2001 to 3.50 in 2017 (34.1% increase) in men, and from 1.65 in 2001 to 2.58 in 2017 (56.4% increase) in women (Fig. S2D). The overall incidence of CCA from 2001–2017 was 2.97 in Asian/Pacific Islander, 2.28 in White, 2.01 in Black, and 1.92 in American Indian/Alaska native cohorts. The incidence of CCA increased from 3.08 in 2001 to 3.21 in 2017 (4.2%) in Asian/Pacific Islander, 1.98 to 3.03 (53.0%) in White, 1.87 to 2.56 (36.9%) in Black, and decreased from 2.95 to 1.39 (52.9%) in American Indian/Alaska native groups (Fig. S2E).

Prevalence of CCA, iCCA, and eCCA

From 2001–2017, the limited-duration prevalence (LDP) of CCA was 3.96% (Table S3) and was higher for iCCA versus eCCA (2.07% *vs* 1.89%). The LDP of iCCA increased from 2001–2006 (0.87%) to 2007-2012 (1.29%) to 2013-2017 (1.62%), whereas the LDP for eCCA remained relatively stable (2001-2006, 1.17%; 2007-2012, 1.23%; 2013-2017, 1.05%). The LDP of CUP for 2001–2017 was less than that for iCCA (1.40% *vs* 2.07%) (Table S3).

Annual percentage change in mortality due to CCA, iCCA, and eCCA

The APC in annual mortality due to CCA and iCCA both showed significant increases, and APC in mortality due to eCCA declined non-significantly from 2001–2017 (Table S4). The APC in mortality increased significantly in each period (2001–2006, 2007–2012, and 2013–2017) for CCA, increased significantly only in 2007–2012 and 2013–2017 for iCCA, and increased non-significantly in 2001–2006 while decreasing non-significantly in 2007-2012, and 2013–2017 for eCCA (Table S4).

SUPPLEMENTARY TABLES – SENSITIVITY ANALYSIS

Table S1. Baseline demographics and characteristics (sensitivity analysis based on topography and histology codes used by Saha et al[a])

	CCA (N=25,599)[b]	**iCCA (N=17,095)**	**eCCA (N=8,498)**
Age at diagnosis, years			
18–44	969 (3.8)	709 (4.1)	260 (3.1)
45–64	8299 (32.4)	5930 (34.7)	2366 (27.8)
65–84	13,543 (52.9)	8817 (51.6)	4724 (55.6)
≥85	2788 (10.9)	1639 (9.6)	1148 (13.5)
Sex			
Male	13,476 (52.6)	8760 (51.2)	4713 (55.5)
Female	12,123 (47.4)	8335 (48.8)	3785 (44.5)
Race			
White	20,269 (79.2)	13,557 (79.3)	6707 (78.9)
Black	2136 (8.3)	1424 (8.3)	712 (8.4)
American Indian/Alaska Native	207 (0.8)	149 (0.9)	58 (0.7)
Asian/Pacific Islander	2925 (11.4)	1930 (11.3)	994 (11.7)
Unknown	62 (0.2)	35 (0.2)	27 (0.3)
Diagnosis year			
2001–2004	4408 (17.2)	2527 (14.8)	1880 (22.1)
2005–2009	6328 (24.7)	3,964 (23.2)	2,362 (27.8)
2010–2013	6471 (25.3)	4362 (25.5)	2107 (24.8)
2014–2017	8392 (32.8)	6242 (36.5)	2149 (25.3)
Grade at presentation			
Well differentiated (grade I)	1382 (5.4)	672 (3.9)	710 (8.4)
Moderately differentiated (grade II)	5971 (23.3)	2999 (17.5)	2970 (35.0)
Poorly differentiated (grade III)	4964 (19.4)	2994 (17.5)	1970 (23.2)

Undifferentiated/anaplastic (grade IV)	158 (0.6)	96 (0.6)	62 (0.7)
Unknown	13,124 (51.3)	10,334 (60.5)	2786 (32.8)
Cancer stage[c]			
I	3655 (14.3)	2099 (12.3)	1554 (18.3)
II	2272 (8.9)	657 (3.8)	1615 (19.0)
III	3532 (13.8)	2378 (13.9)	1153 (13.6)
IV	4731 (18.5)	3951 (23.1)	780 (9.2)
Unknown	3704 (14.5)	2834 (16.6)	869 (10.2)
Not applicable	0	0	0
Missing[d]	7705 (30.1)	5176 (30.3)	2527 (29.7)

[a]Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S: Intrahepatic Disease on the Rise. *Oncologist.* 2016;21:594-599.

[b]Includes 6 patients (0.1%) who were classified as having both iCCA and eCCA.

[c]The 6th edition of American Joint Committee on Cancer was used to stratify the cancer stages.

[d]Cancer stage stratification data were only available for 2004–2015 diagnosis years and were missing for patients diagnosed in 2001–2003, 2016, and 2017.

Abbreviations: CCA=cholangiocarcinoma; eCCA=extrahepatic cholangiocarcinoma; iCCA=intrahepatic cholangiocarcinoma.

Table S2. Annual percentage changes in incidence of CCA, iCCA, and eCCA (sensitivity analysis based on topography and histology codes used by Saha et al[a])

	Annual percentage change (95% CI), per 100,000 p-y		
	CCA (N=25,599)	**iCCA (N=17,095)**	**eCCA (N=8,498)**
2001–2017	2.87 (2.38–3.36)[b]	4.93 (4.31–5.56)[b]	–0.96 (–1.32 to –0.59)[b]
2001–2006	–0.04 (–1.99 to 1.95)	1.06 (–2.34 to 4.58)	–1.56 (–3.03 to –0.07)[b]
2007–2012	3.07 (1.384.78)[b]	4.72 (2.81–6.67)[b]	0.05 (–2.26 to 2.42)
2013–2017	4.37 (2.226.56)[b]	6.37 (2.40–10.49)[b]	–0.90 (–5.87 to 4.34)

[a]Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S: Intrahepatic Disease on the Rise. *Oncologist.* 2016;21:594-599.

[b]Significant annual percentage changes. Changes were deemed significant if the lower and upper 95% CIs were of same sign, otherwise the change was considered not significant.

Abbreviations: CCA=cholangiocarcinoma; CI=confidence interval; eCCA=extrahepatic cholangiocarcinoma; iCCA=intrahepatic cholangiocarcinoma; p-y=person-years.

Table S3. Prevalence of CCA, iCCA, and eCCA (sensitivity analysis based on topography and histology codes used by Saha et al[a])

	LDP rate,[b] per 100,000 p-y		
	CCA (N=25,599)	**iCCA (N=17,095)**	**eCCA (N=8,498)**
2001–2017	3.96	2.07	1.89
2001–2006	2.04	0.87	1.17
2007–2012	2.52	1.29	1.23
2013–2017	2.67	1.62	1.05

[a]Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S: Intrahepatic Disease on the Rise. *Oncologist.* 2016;21:594-599.

[b]LDP is defined as the number of people alive on a certain day who had a diagnosis of the disease within the past 16 years; as of January 1, 2017. LDP rate was calculated as LDP normalized with averaging 2016 and 2017 populations, then age-adjusted to the US standard population of 2000.

Abbreviations: CCA=cholangiocarcinoma; eCCA=extrahepatic cholangiocarcinoma; iCCA=intrahepatic cholangiocarcinoma; LDP=limited-duration prevalence; p-y=person-years.

Table S4. Annual percentage change in incidence-based mortality due to CCA, iCCA, and eCCA from 2001–2017 (sensitivity analysis based on topography and histology codes used by Saha et al[a])

	Annual percentage change (95% CI), per 100,000 p-y		
	CCA (N=25,599)	**iCCA (N=17,095)**	**eCCA (N=8,498)**
2001–2017	3.08 (2.74, 3.42)[b]	4.75 (4.15, 5.35)[b]	–0.41 (–1.24 to 0.43)
2001–2006	2.16 (0.71–3.63)[b]	0.53 (–2.15 to 3.29)	4.75 (–1.22 to 11.08)
2007–2012	2.51 (0.41–4.65)[b]	4.95 (2.70–7.26)[b]	–2.21 (–4.98 to 0.65)
2013–2017	5.26 (3.56–6.67)[b]	7.32 (5.45–9.22)[b]	–0.42 (–3.63 to 2.89)

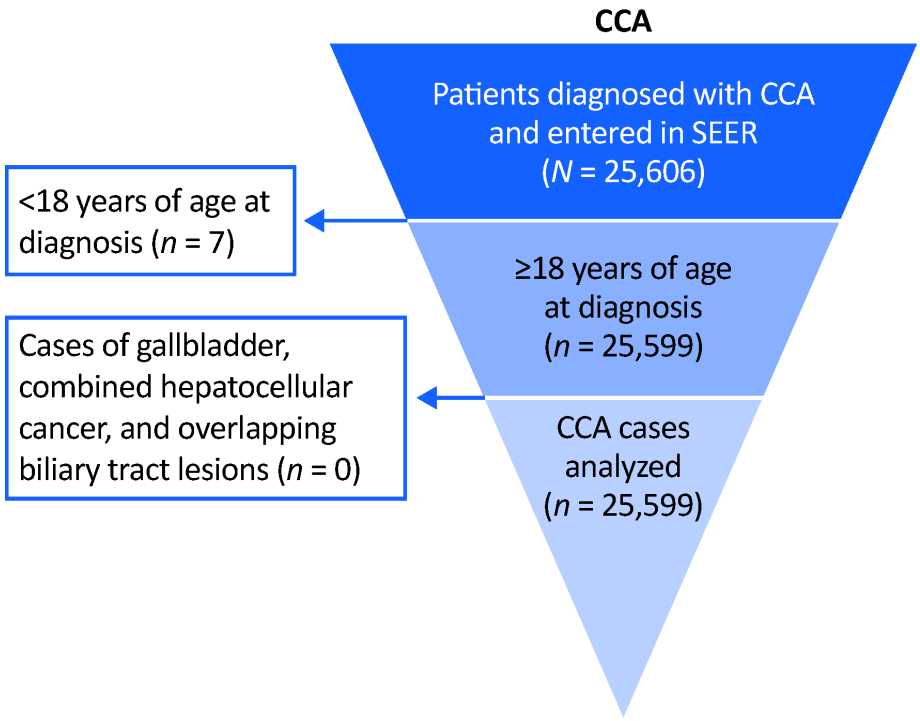
[a]Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S: Intrahepatic Disease on the Rise. *Oncologist.* 2016;21:594-599.

[b]Significant annual percentage changes. Changes were deemed significant if the lower and upper 95% CIs were of same sign, otherwise the change was considered not significant.

Abbreviations: CCA=cholangiocarcinoma; CI=confidence interval; CUP=cancer of unknown primary; eCCA=extrahepatic cholangiocarcinoma; iCCA=intrahepatic cholangiocarcinoma; ND=not determined.

SUPPLEMENTARY FIGURES – SENSITIVITY ANALYSIS

Fig. S1. Patient disposition from a sensitivity analysis conducted based on topography and histology codes used by Saha et al.[a]

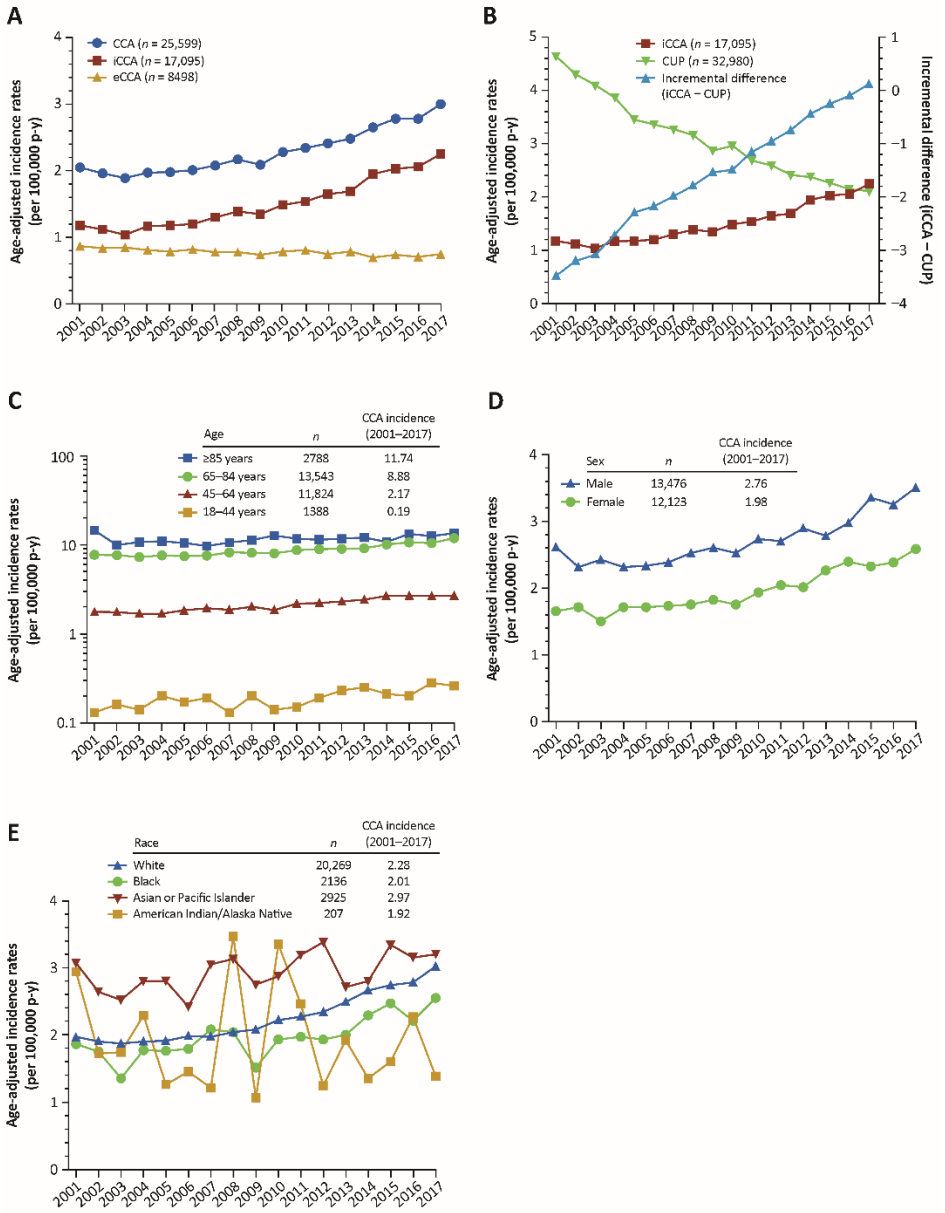


iCCA	17,095	66.8%
eCCA	8498	33.2%
iCCA + eCCA	6	<0.1%

[a]Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S: Intrahepatic Disease on the Rise. *Oncologist.* 2016;21:594-599.

Cases of iCCA were identified using (1) a topography code of C22.0 and histology codes of 8140, 8160, 8161, 8480, 8481, 8500; or (2) a topography code of C22.1 and histology codes of 8000, 8010, 8020, 8140, 8160, 8161, 8260, 8480, 8481, 8490, or 8500. Cases of eCCA were identified using (1) a topography code of C24.1 and histology codes of 8000, 8010, 8020, 8140, 8160, 8161, 8260, 8480, 8481, 8490, 8500; or (2) any diagnoses with topography codes C22.0, C22.1, or C24.0 and a Klatskin tumor histology code of 8162. Abbreviations: CCA=cholangiocarcinoma; CUP=cancer of unknown primary; eCCA=extrahepatic cholangiocarcinoma; iCCA=intrahepatic cholangiocarcinoma; ICD-O-3=International Classification of Diseases for Oncology.

Fig. S2. Age-adjusted incidences of for CCA, iCCA, eCCA (A), CUP (B); incidence of CCA by age (C), sex (D), and race (E) from 2001 to 2017 from a sensitivity analysis conducted based on topography and histology codes used by Saha et al.[a] Also shown in panel B is the incremental difference between age-adjusted iCCA and CUP incidences from 2001 to 2017.



[a]Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S: Intrahepatic Disease on the Rise. *Oncologist.* 2016;21:594-599. Incidence was determined per 100,000 p-y and age-adjusted to the US standard population of 2000. Also shown in panel B is the incremental difference between age-adjusted iCCA and CUP incidences from 2001 to 2017. Note that interpretation of trends in CCA incidence in the American Indian/Alaska Native cohort is limited by the correspondingly small sample size (n=207).

Abbreviations: CCA=cholangiocarcinoma; CUP=cancer of unknown primary; eCCA=extrahepatic cholangiocarcinoma; iCCA=intrahepatic cholangiocarcinoma; p-y=person-year.