Annals of Gastroenterology (2025) **38,** 1-7

Forty-five-year trends in intra- and extrahepatic cholangiocarcinoma: sex- and race-based insights

Rajamanuri Medha[a], Pannala Sai Shanmukha Sreeram[b], Obada, Daaboul[a], Dar Sophia[a], Sundar Rahul[d], Johnson Adejoke[c], Cheema Ayesha[a], Tufail Muhammad Umer[c], Arshad Hafiz Muhammad Sharjeel[a]

Illinois University School of Medicine, Springfield, IL, USA; Staten Island University Hospital, Staten Island, NY, USA; Jacobi Medical Center/North Central Bronx Hospital, NY, USA; Indian Institute of Technology, Madras, India

Abstract

Background A comprehensive review of 45-year trends in intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) in the United States has not been published. Given their rising incidence, our study aimed to analyze trends in incidence and survival, comparing ICC and ECC.

Methods We extracted a 45-year dataset (1975-2020) from the Surveillance, Epidemiology, and End Results database. Age-adjusted incidence rates were calculated using SEERStat®. Annual Percent Change (APC) was estimated via weighted least squares. Relative survival (1- and 5-year) was calculated using the Ederer II method and compared across sexes and races.

Results A significant rise in ICC and ECC incidence was observed in both sexes (APC 3.71 for ICC vs. 6.16 for ECC; P<0.001). In females, ECC incidence increased more than ICC (APC 5.96 vs. 4.09, P<0.05), whereas males showed a fluctuating ECC trend and a steady ICC rise. Survival rates significantly improved across all races and sexes (P<0.05). ICC survival rose from 17.45% to 41.41% (1-year) and 2.83% to 10.99% (5-year), while ECC increased from 30.33% to 41.12% (1-year) and 5.96% to 10.44% (5-year). Among white and other-race females, ECC showed less improvement than ICC. Black individuals lacked statistically significant data.

Conclusions Our study highlights disparities in ICC and ECC incidence, with higher rates in males, but better survival for ECC in males and ICC in females. The underrepresentation of Black individuals warrants further study to explore contributing factors such as risk, access to care, and treatment.

Keywords Cholangiocarcinoma, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, biliary ductal carcinoma, bile duct malignancy

Ann Gastroenterol 2025; 38 (2): 1-7

[a]Southern Illinois University School of Medicine, Springfield, IL, United States (Rajamanuri Medha, Obada, Daboul, Dar Sophia, Cheema Ayesha, Arshad Hafiz Muhammad Sharjeel); [b]Staten Island University Hospital, Staten Island, NY, United States (Pannala Sai Shanmukha Sreeram); [c]Jacobi Medical Center/North Central Bronx Hospital, NY, United States (Johnson Adejoke, Tufail Muhammad Umer); [d]Indian Institute of Technology, Madras, India (Sundar Rahul)

Conflict of Interest: None

Correspondence to: Rajamanuri, Medha, 2305 Boysenberry lane, apt 2, Springfield, IL-62711, USA, e-mail: rajamanurimedha@gmail.com

Received 26 July 2024; accepted 3 February 2025;
published online 28 February 2025

DOI: https://doi.org/10.20524/aog.2025.0951

Introduction

Cholangiocarcinoma (CC) is the second most prevalent primary liver cancer, encompassing a diverse array of malignant tumors arising from the epithelial lining of either the intra- or extrahepatic biliary tract [1]. In Western countries, over half of CC cases originate from the proximal extrahepatic bile ducts, establishing it as the predominant subtype [1]. Regional variations in intrahepatic CC (ICC) incidence are observed, with a higher prevalence in East Asian regions attributed to liver fluke, hepatitis C and hepatitis B [2]. Associated risk factors include hepatolithiasis, biliary cystic disease, alcohol and tobacco use, chemical carcinogens, primary sclerosing cholangitis (PSC) and liver cirrhosis [2-4].

The occurrence of ICC has steadily increased in the United States since 1975. This trend may partly result from improved imaging techniques, including magnetic resonance imaging, computed tomography and cholangioscopy, which have enhanced tumor detection. The sustained rates observed

for patients with early-stage disease, unstaged disease, and tumors smaller than 5 cm confirmed by microscopic evidence strongly suggest a genuine uptick in ICC incidence [5]. In contrast, the age-standardized incidence of extrahepatic CC (ECC) has increased with geographical variation over the past 20 years, particularly notably in countries such as Thailand and Colombia [6]. However, ECC mortality rates have risen more slowly than those for ICC in Western nations [1].

Despite improvements in the 1-year survival rate of CC over time, the 5-year survival rate has shown minimal, if any, significant change, remaining below a 5% increase [7]. Early-stage tumors that are surgically resected are associated with potential cure; however, a substantial number of patients present with advanced disease at diagnosis. The primary contributors to CC mortality include cancer cachexia, liver failure, and recurrent sepsis resulting from biliary obstruction [6].

Racial disparities in cancer survival are evident across various cancer types, including colon, lung, breast, prostate and esophageal cancer [8]. Limited studies assessing racial disparities in ICC consistently show the highest incidence among the Asian group, particularly Asian Pacific Islanders, and a higher incidence among Hispanics compared to non-Hispanic ethnicities [9-12]. Mortality rates are higher among the Hispanic population compared to non-Hispanic populations [10]. However, the underrepresentation of Black populations in Surveillance, Epidemiology, and End Results (SEER) data limits the ability to fully assess racial disparities. Comprehensive studies evaluating racial and sex disparities in CC subtypes are scarce.

Recognizing the need to identify and understand these disparities over time, we conducted a comprehensive study using the SEER program of cancer registries. This study aimed to investigate ICC and ECC incidence over the past 45 years and to provide updated insights into incidental and survival trends across different ethnicities and sexes.

Materials and methods

This observational study utilized data from the SEER program, maintained by the National Cancer Institute, which has collected cancer data since 1975. The SEER database covers approximately 8.3% of the United States population and is well-established for its generalizability. For the incidence analysis, data on ICC and ECC cases diagnosed from 1975-2020 were collected from the incidence-SEER research data, 8 registries, Nov 2022 submission. Demographic characteristics including sex, race and year of diagnosis were of interest. Malignant primary tumors were selected for analysis using specific site and morphology codes for CC.

The transition from ICD-O-2 to ICD-O-3 classification during the study period may have contributed to discrepancies in ICC and ECC case rates. This coding change particularly affected perihilar CCs (pCC), previously classified under ICC and now primarily under ECC. Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.4.2 was used for the data analysis. Age was adjusted to the US 2000 standard population. Rates were initially generated as cases per 100,000 each year, and percent change was calculated using a 1-year interval. Annual percent change (APC) for all years was calculated using the weighted least squares method. The significance level was $P<0.05$ for APC, and confidence intervals were set at 95% for rates and trends.

For survival analysis, data on ICC and ECC cases diagnosed from 1975-2020 were collected from incidence-based mortality-SEER research data, 8 registries, Nov 2022 submission. Relative survival was calculated using the Ederer II method, with 12- and 60-month survival rates analyzed across all sexes, races and years of diagnosis. Data were stratified by sex and race to compare trends. This study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Table 1).

Results

Incidence

The number of cases analyzed for incidence was 7989 for ICC and 3178 for ECC. Overall, in both sexes, the observed increase in age-adjusted annual percent change (APC) was 3.71 for ICC ($P<0.001$) and 6.16 ($P<0.001$) for ECC.

After stratifying for sex in ICC cases, APC was 3.20 ($P<0.05$) for males and 4.09 ($P<0.05$) for females, with males (1.67/100,000 cases in 2020) having a steeper rise in incidence versus a stable rise in females (1.21/100,000 in 2020) (Fig. 1).

For ECC, stratification by sex revealed an APC of 5.96 ($P<0.05$) among females, with an incidence of 0.45/100,000 cases in 2020. Though the incidence among males was 0.66/100,000 cases in 2020, they did not display a statistically significant APC over the last 45 years. Initially, the incidence rates for males and females were gradually rising, but from 2000, males displayed a steeper rise ($P<0.05$) (Fig. 2).

The survival data included 6334 cases for ICC and 2572 for ECC over the past 45 years. Both ICC and ECC demonstrated a significant increase in 12- and 60-month survival rates across all sexes and races from 1975 ($P<0.05$).

For ICC, the survival rate among both sexes has consistently risen. From 1975-2020, the 12-month survival rates rose from 17.45% to 41.41%, while 60-month survival rates rose from 2.83% to 10.99% ($P<0.05$). The difference in 12- and 60-month survival rates for ICC was significantly higher for females than males across all years, with 44.46% and 13.13% for females versus 38.75% and 8.44% for males, respectively, at the end of 2020 (Fig. 3).

For ECC, the 12- and 60-month survival rates among both sexes rose from 30.33% to 41.12% and 5.69% to 10.44%, respectively ($P<0.05$). The difference in 12- and 60-month survival rates for ECC was nearly similar for females and males across all years, with 35.52% and 9.35% for females versus 45.63% and 10.89% for males, respectively, at the end of 2020 (Fig. 4).

From 1975-2020, for both sexes, after stratifying for race, there was a significant improvement in survival among all

Table 1 STROBE checklist for observational studies

Section/Topic	Item No.	Recommendation	Reported on Page (s)
		Title and Abstract	
Title	1a	Indicate the study's design with a commonly used term in the title or the abstract	Yes
Abstract	1b	Provide an informative and balanced summary of what was done and what was found	Yes
		Introduction	
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
		Methods	
Study Design	4	Present key elements of the study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6a	Give the eligibility criteria, and the sources and methods of selection of participants	Yes
	6b	Describe methods of follow-up	Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data Sources/Measurement	8a	For each variable of interest, give sources of data and details of methods of assessment (measurement)	Yes
	8b	Describe comparability of assessment methods if there is more than 1 group	Yes
Bias	9	Describe any efforts to address potential sources of bias	Yes
Study Size	10	Explain how the study size was arrived at	Yes
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes
Statistical Methods	12a	Describe all statistical methods, including those used to control for confounding	Yes
	12b	Describe any methods used to examine subgroups and interactions	Yes
	12c	Explain how missing data were addressed	Not Applicable
	12d	If applicable, describe analytical methods taking account of sampling strategy	Yes
	12e	Describe any sensitivity analyses	Yes
		Results	
Participants	13a	Report numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed)	Yes
	13b	Give reasons for non-participation at each stage	Not Applicable
	13c	Consider use of a flow diagram	Yes
Descriptive Data	14a	Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	Yes
	14b	Indicate the number of participants with missing data for each variable of interest	Yes
	14c	Summarize follow-up time (e.g., average and total amount)	Yes
Outcome Data	15	Report numbers of outcome events or summary measures	Yes
Main Results	16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes
	16b	Report category boundaries when continuous variables were categorized	Yes

(Contd)

Table 1 *(Continued)*

Section/Topic	Item No.	Recommendation	Reported on Page (s)
	16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes
Other Analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Yes
		Discussion	
Key Results	18	Summarize key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalizability	21	Discuss the generalizability (external validity) of the study results	Yes
		Other Information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes

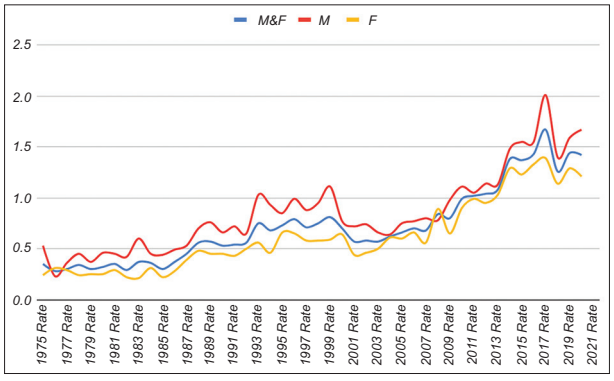

Figure 1 Annual percentage change in intrahepatic cholangiocarcinoma incidence over a 45-year period (1975-2020), showing the trends for both sexes combined, as well as separately for males and females, highlighting disparities and significant differences in the rate of change

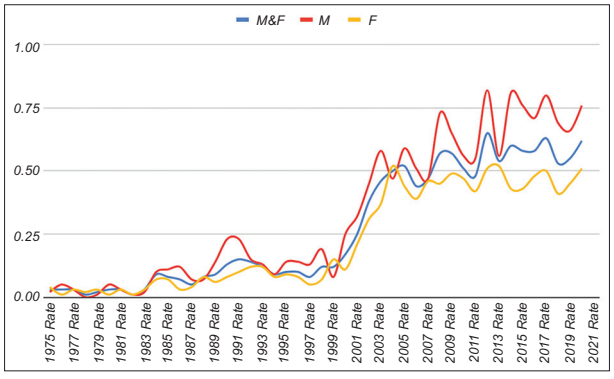

Figure 2 Annual percentage change (APC) in extrahepatic cholangiocarcinoma incidence from 1975-2020, showing the trends for both sexes combined and separately for males and females, indicating significant variations in the APC values across sexes

races for ICC compared to ECC. Among White males, ICC increased from 14.47% to 39.11% and 3.67% to 8.90% for 12- and 60-month survival rates, respectively. Among minority racial groups, the respective rates rose from 16.35% to 37.98% and 0% to 6.87% (P<0.05). White females displayed a 12-month survival rate that increased from 21.80% to 44.67%, and a 60-month survival rate that increased from 2.11% to 11.59%. Among minority-race females, these rates rose from 11.87% to 39.37% and 0% to 13.70% (P<0.05) (Fig.5).

For ECC, among males after stratifying for race, Whites demonstrated an increase in 12-month survival from 33.96% to 46.32% and in 60-month survival from 6.94% to 12.21%. In contrast, the survival rates in minorities were not statistically significant. Females belonging to the White race demonstrated a slight increase and decline in the 12-month survival rate, and a variable 60-month survival rate (P<0.05) (Fig. 6). The data obtained for female minority racial groups were not statistically significant.

It is important to note that our study was unable to extract statistically significant data comparing Blacks with other races among both cohorts.

Discussion

In this section, we aimed to analyze a comprehensive study spanning 45 years on the epidemiology, incidence and survival rates of ICC and ECC in the United States. Our objective is to provide insights into the evolving landscape of these malignancies, particularly focusing on trends in occurrence and survival rates across diverse ethnicities and sexes.

The divergent trends in incidence rates between ICC and ECC can be attributed to factors such as misclassification of CCs, differences in risk factors, early detection and surveillance

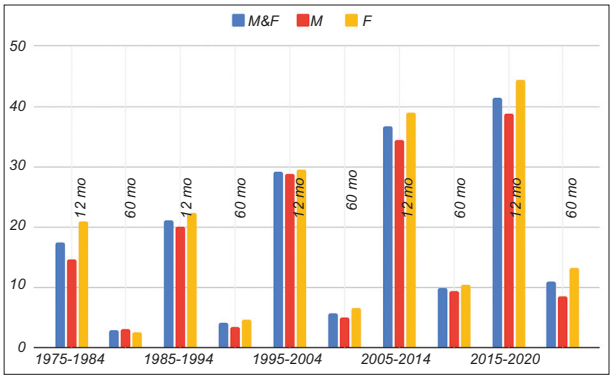

Figure 3 Relative survival rates for intrahepatic cholangiocarcinoma over a 45-year period (1975-2020), categorized by sex. The trends in 1-year and 5-year survival rates for males and females provide insights into sex-based disparities in survival outcomes

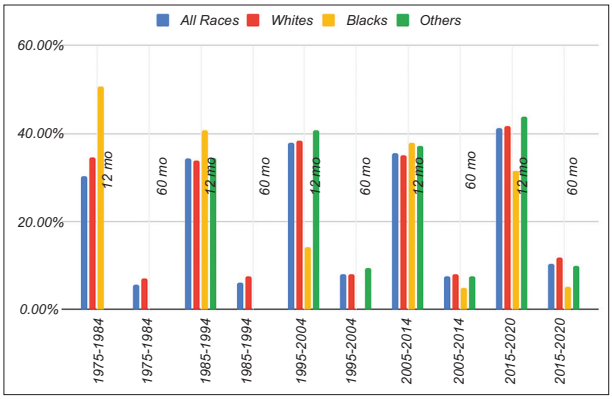

Figure 6 Relative survival rates for extrahepatic cholangiocarcinoma over a 45-year period (1975-2020), categorized by sex and racial categories. The 1-year and 5-year survival trends illustrate the disparities and variations among demographic subgroups

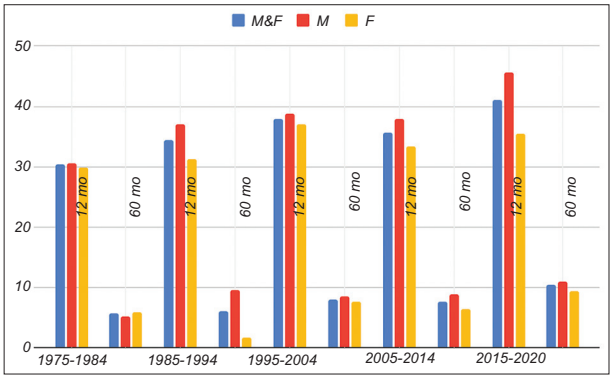

Figure 4 Relative survival rates for extrahepatic cholangiocarcinoma over a 45-year period (1975-2020), categorized by sex. The trends in 1-year and 5-year survival rates for males and females illustrate sex-specific survival differences

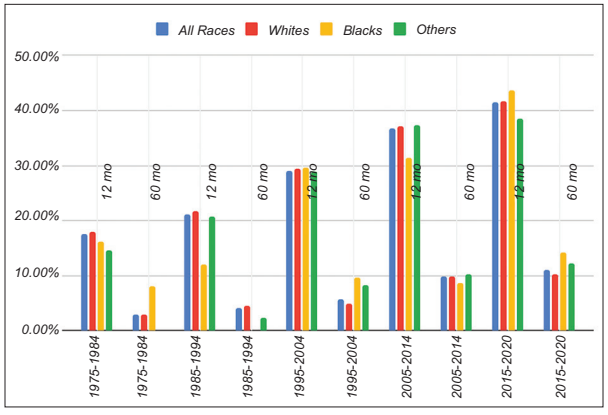

Figure 5 Relative survival rates for intrahepatic cholangiocarcinoma over a 45-year period (1975-2020), categorized by sex and racial groups. The trends in 1-year and 5-year survival rates illustrate the disparities across demographic subgroups

practices, and access to specialized care. For example, transitioning from the ICD-O-2 classification of pCCs to the ICD-O-3 classification led to a decline in ICC incidence and a rise in ECC incidence [13].

Various risk factors, both common and rare, have been associated with CC, often linked to chronic inflammation of the biliary epithelium and bile stasis. Global increases in risk factors such as high alcohol consumption, tobacco smoking, viral infections (hepatitis B and C viruses), obesity, metabolic syndrome and nonalcoholic fatty liver disease have contributed to rising CC rates [14]. PSC is a significant risk factor for both ICC and ECC, while alcohol use and chronic liver diseases such as viral hepatitis and non-alcoholic fatty liver disease are associated with ICC. Conversely, biliary disorders including gallstone disease are more strongly linked to ECC [13,14].

The observed rise in incidence rates for both ICC and ECC in our study aligns with prior studies [12,15-17]. Sex-specific nuances in incidence rates reveal higher rates of ICC in males and stable rates in females, alongside a steeper increase in ECC incidence in males compared to females [6,18]. These disparities underscore the importance of exploring potential etiological factors and implementing targeted preventive strategies, especially considering the higher prevalence of PSC in men [19].

The increasing mortality trend in ICC may be attributed to rising rates of chronic liver diseases such as non-alcoholic fatty liver disease and alcohol-related liver disease, while interventions such as cholecystectomy for gallstone disease may be reducing the risk of ECC [13]. Genetic variations associated with CC contribute to its sporadic nature, with targeted therapies focusing on aberrant expression of proteins such as IDH and FGFR2 in ICC, and mutations like KRAS, TP53 and ELF3 in pCC and distal (dCC) subtypes [20]. These factors underscore the importance of understanding the underlying pathways for guiding the development of targeted therapies to improve patient outcomes [13,20].

Treatment approaches for CCs vary depending on the cancer stage. Curative resection is the preferred option for both ICC and ECC [21]. Neoadjuvant chemotherapy has shown survival benefits for ICC lesions, while pCC and dCC may require extensive hepatopancreatobiliary resection [22,23]. Liver transplantation holds promise for selected patients with localized disease, but the limited organ availability poses challenges [24,25]. Combination systemic chemotherapy, such as cisplatin and gemcitabine, demonstrates efficacy for unresectable disease [26]. Additionally, targeted therapies based on somatic mutations, such as the FDA-approved pemigatinib for unresectable ICC, are emerging [13].

Advancements in aggressive surgical approaches, complete tumor resection and lymph node dissection have led to notable improvements in 1- and 5-year survival rates for both ICC and ECC [27,28]. Emerging chemotherapy regimens have also contributed to progress in non-surgical approaches, albeit not curative [5]. Global trends indicate increasing mortality from ICC, aligned with evolving risk factors and disease classification, whereas mortality from ECC seems to plateau or decrease, possibly because of the increased use of laparoscopic cholecystectomy [29]. However, these highly specialized therapies may not be equally accessible to all, potentially introducing bias in survival outcomes, as noted in our study.

The identified sex disparities in survival rates underscore the need for sex-specific interventions. While ICC mortality rates are higher in males, ECC exhibits comparable survival rates between sexes. Notably, this aligns with observations in Europe, emphasizing the global nature of sex-related survival patterns [29,30]. This issue can be addressed by implementing surveillance, especially in the high-risk population.

A Mayo Clinic study of 830 PSC patients showed that regular imaging surveillance increased overall survival in those diagnosed with CC [31]. Similarly, yearly imaging reduced hepatopancreatobiliary cancers 2-fold in PSC patients with inflammatory bowel disease [32]. Another study across 27 Western centers found scheduled imaging lowered overall mortality risk and improved post-CC diagnosis survival. However, these retrospective studies may be biased. Additionally, serum biomarkers such as carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) can detect CCs, but their effectiveness varies [33]. Clear guidelines are needed for monitoring high-risk patients, especially males with PSC or chronic liver disease. Prospective studies are required to evaluate the clinical and economic effectiveness of surveillance approaches, despite challenges in conducting them due to frequent imaging needs in PSC patients.

The disparities in survival rates among different racial groups warrant attention. While improvements are noted in ICC survival rates among whites, American Indians, Alaskan natives, and Asia/Pacific Islanders, there are limited data on the Black population. These findings highlight potential disparities in access to healthcare, diagnostic delays, or underrepresentation in minority groups [34]. Efforts to address healthcare access and mitigate these disparities are imperative. A study by Munir *et al*, assessing disparities between Black and White patients utilizing the index of dissimilarity, emphasizes the multifaceted nature of sociodemographic influences on mortality rates [35]. Addressing these disparities requires a comprehensive approach involving healthcare policies, awareness programs and improved specialized healthcare access for minority populations.

While this study provides valuable insights, it is not without limitations. The underrepresentation of Black individuals in the dataset underscores the need for more inclusive research practices. Future research should delve into the molecular underpinnings of these CCs, explore the impact of evolving risk factors, and investigate disparities in healthcare access to guide targeted interventions.

In conclusion, our study not only adds to the growing body of evidence on the epidemiology of ICC and ECC, but also emphasizes the importance of considering sex and race-specific nuances in the context of evolving diagnostic and therapeutic landscapes. The observed improvements in survival rates underscore the potential impact of aggressive surgical approaches and emerging chemotherapy regimens, at the same time revealing a potential need for surveillance in the high-risk groups. Addressing disparities in access to healthcare and understanding the sociodemographic influences on outcomes are crucial steps toward improving overall prognosis and reducing the burden of these CCs.

Summary Box

What is already known:

- Intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) are rare but highly lethal malignancies of the bile ducts
- The incidence of ICC has been rising globally, while ECC incidence trends vary by region and demographic factors
- Disparities in survival and incidence rates are influenced by factors such as sex, race, and access to healthcare

What the new findings are:

- A comprehensive analysis of 45-year trends in ICC and ECC using Surveillance, Epidemiology, and End Results (SEER) data highlighted significant sex- and race-based disparities in incidence and survival rates
- ICC incidence rates exhibited a consistent rise among males and females, whereas ECC trends are more variable across sexes
- Survival rates for both ICC and ECC have improved over time, with notable differences observed between demographic groups
- Underrepresentation of Black populations in SEER data underscores the need for more inclusive studies to better understand healthcare disparities

References

1. Pavicevic S, Reichelt S, Uluk D, et al. Prognostic and predictive molecular markers in cholangiocarcinoma. *Cancers (Basel)* 2022;**14**:1026.
2. Yang Y, Zhang X. An overview of extrahepatic cholangiocarcinoma: from here to where? *Front Oncol* 2023;**13**:1171098.
3. Mosconi S, Beretta GD, Labianca R, Zampino MG, Gatta G, Heinemann V. Cholangiocarcinoma. *Crit Rev Oncol Hematol* 2009;**69**:259-270.
4. American Cancer Society. Cancer facts & figures for African Americans 2019-2021. Am Cancer Soc 2019:43. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2019-2021.pdf [Accessed 18 February 2025].
5. Blechacz B. Cholangiocarcinoma: current knowledge and new developments. *Gut Liver* 2017;**11**:13-26.
6. 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.
7. Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol* 2004;**40**:472-477.
8. Tanaka M, Tanaka H, Tsukuma H, Ioka A, Oshima A, Nakahara T. Risk factors for intrahepatic cholangiocarcinoma: a possible role of hepatitis B virus. *J Viral Hepat* 2010;**17**:742-748.
9. Gupta A, Dixon E. Epidemiology and risk factors: intrahepatic cholangiocarcinoma. *Hepatobiliary Surg Nutr* 2017;**6**:101-104.
10. Antwi SO, Mousa OY, Patel T. Racial, ethnic, and age disparities in incidence and survival of intrahepatic cholangiocarcinoma in the United States; 1995-2014. *Ann Hepatol* 2018;**17**:604-614.
11. McLean L, Patel T. Racial and ethnic variations in the epidemiology of intrahepatic cholangiocarcinoma in the United States. *Liver Int* 2006;**26**:1047-1053.
12. Mosadeghi S, Liu B, Bhuket T, Wong RJ. Sex-specific and race/ethnicity-specific disparities in cholangiocarcinoma incidence and prevalence in the USA: an updated analysis of the 2000-2011 Surveillance, Epidemiology and End Results registry. *Hepatol Res* 2016;**46**:669-677.
13. Vithayathil M, Khan SA. Current epidemiology of cholangiocarcinoma in Western countries. *J Hepatol* 2022;**77**:1690-1698.
14. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020;**17**:557-588.
15. Florio AA, Ferlay J, Znaor A, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. *Cancer* 2020;**126**:2666-2678.
16. Javle M, Lee S, Azad NS, et al. Temporal changes in cholangiocarcinoma incidence and mortality in the United States from 2001 to 2017. *Oncologist* 2022;**27**:874-883.
17. Antwi SO, Mousa OY, Patel T. Racial, ethnic, and age disparities in incidence and survival of intrahepatic cholangiocarcinoma in the United States; 1995-2014. *Ann Hepatol* 2018;**17**:604-614.
18. Bergquist A, von Seth E. Epidemiology of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* 2015;**29**:221-232.
19. Garikipati SC, Roy P. (2023, February 6). Biliary tract cholangiocarcinoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
20. Vithayathil M, Bridegwater J, Khan SA. Medical therapies for intrahepatic cholangiocarcinoma. *J Hepatol* 2021;**75**:981-983.
21. Primrose JN, Fox RP, Palmer DH, et al; BILCAP study group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 2019;**20**:663-673.
22. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D; ESMO Guidelines Committee. Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;**27**:v28-v37.
23. de Jong MC, Marques H, Clary BM, et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. *Cancer* 2012;**118**:4737-4747.
24. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012;**143**:88-98.
25. Darwish Murad S, Kim WR, Therneau T, et al. Predictors of pretransplant dropout and posttransplant recurrence in patients with perihilar cholangiocarcinoma. *Hepatology* 2012;**56**:972-981.
26. Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;**362**:1273-1281.
27. Nagino M, Ebata T, Yokoyama Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. *Ann Surg* 2013;**258**:129-140.
28. Choi SB, Kim KS, Choi JY, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. *Ann Surg Oncol* 2009;**16**:3048-3056.
29. Bertuccio P, Malvezzi M, Carioli G, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol* 2019;**71**:104-114.
30. Bertuccio P, Bosetti C, Levi F, Decarli A, Negri E, La Vecchia C. A comparison of trends in mortality from primary liver cancer and intrahepatic cholangiocarcinoma in Europe. *Ann Oncol* 2013;**24**:1667-1674.
31. Ali AH, Tabibian JH, Nasser-Ghodsi N, et al. Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. *Hepatology* 2018;**67**:2338-2351.
32. Trivedi PJ, Crothers H, Mytton J, et al. Effects of primary sclerosing cholangitis on risks of cancer and death in people with inflammatory bowel disease, based on sex, race, and age. *Gastroenterology* 2020;**159**:915-928.
33. Bergquist A, Weismüller TJ, Levy C, et al; International PSC Study Group. Impact on follow-up strategies in patients with primary sclerosing cholangitis. *Liver Int* 2023;**43**:127-138.
34. Ransome E, Tong L, Espinosa J, Chou J, Somnay V, Munene G. Trends in surgery and disparities in receipt of surgery for intrahepatic cholangiocarcinoma in the US: 2005-2014. *J Gastrointest Oncol* 2019;**10**:339-347.
35. Munir MM, Woldesenbet S, Endo Y, et al. Racial segregation among patients with cholangiocarcinoma-impact on diagnosis, treatment, and outcomes. *Ann Surg Oncol* 2023;**30**:4238-4246.