Trends in Incidence and Factors Affecting Survival of Patients With Cholangiocarcinoma in the United States

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Abstract

Background: Cholangiocarcinoma (CCA) includes cancers arising from the intrahepatic and extrahepatic bile ducts. The etiology and pathogenesis of CCA remain poorly understood. This is the first study investigating both incidence patterns of CCA from 1973 through 2012 and demographic, clinical, and treatment variables affecting survival of patients with CCA. **Patients and Methods:** Using the SEER database, age-adjusted incidence rates were evaluated from 1973–2012 using SEER*Stat software. A retrospective cohort of 26,994 patients diagnosed with CCA from 1973–2008 was identified for survival analysis. Cox proportional hazards models were used to perform multivariate survival analysis. **Results:** Overall incidence of CCA increased by 65% from 1973–2012. Extrahepatic CCA (ECC) remained more common than intrahepatic CCA (ICC), whereas the incidence rates for ICC increased by 350% compared with a 20% increase seen with ECC. Men belonging to non-African American and non-Caucasian ethnicities had the highest incidence rates of CCA. This trend persisted throughout the study period, although African Americans and Caucasians saw 50% and 59% increases in incidence rates, respectively, compared with a 9% increase among other races. Median overall survival (OS) was 8 months in patients with ECC compared with 4 months in those with ICC. Our survival analysis found Hispanic women to have the best 5-year survival outcome ($P<.0001$). OS diminished with age ($P<.0001$), and ECC had better survival outcomes compared with ICC ($P<.0001$). Patients who were married, were nonsmokers, belonged to a higher income class, and underwent surgery had better survival outcomes compared with others ($P<.0001$). **Conclusions:** This is the most up-to-date study of CCA from the SEER registry that shows temporal patterns of increasing incidence of CCA across different races, sexes, and ethnicities. We identified age, sex, race, marital status, income, smoking status, anatomic location of CCA, tumor grade, tumor stage, radiation, and surgery as independent prognostic factors for OS in patients with CCA.

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Cholangiocarcinomas (CCAs) are rare cancers that arise from the intrahepatic or extrahepatic biliary ductal epithelium, which are classified into intrahepatic or extrahepatic CCAs (ICCs and ECCs, respectively). ECCs are further stratified based on anatomic location into perihilar and distal CCAs. CCA accounts for approximately 10% to 15% of primary hepatic malignancies.¹ In the United States, approximately 5,000 new cases of CCA are diagnosed annually, with relatively equal distribution between ICC and ECC.² Incidence and mor-

talidity of CCA have been reported to be increasing in the United States.³ Although reasons for the increased incidence are unclear, it is thought to be partly from improved diagnostic techniques with higher detection rates and the increased incidence of hepatitis C virus infection.⁴

The etiology and pathogenesis of CCA remain poorly understood. Although most CCAs can arise de novo, risk factors include primary sclerosing cholangitis (PSC), alcohol consumption, liver cirrhosis, and

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chronic viral hepatitis infections.^{2,4-16} The prevalence of CCA increases steadily with age, peaking in the seventh decade.¹⁷ Although prevalence does not vary greatly by race or sex, it has been shown that in the United States, Hispanic men are at the highest risk for CCA¹⁸⁻²⁰ and African American men have the lowest risk, whereas Asians/Pacific Islanders and Caucasians have prevalence rates ranging between these 2 groups.^{20,21} CCA has a high male predominance, except for Hispanic women, who have higher rates of ICC compared with Hispanic men.^{20,22} Cumulative CCA mortality rates have increased by 39% because of increased incidence and mortality rates from ICC, which is reportedly highest in American Indians and Asians.²³

This retrospective study examined the evolving epidemiologic trends in incidence of CCA in the United States, while analyzing the influence of various biographic, demographic, and clinical variables on the survival of patients with CCA.

Patients and Methods

Data Source

CCA-specific data were obtained from the SEER 18 registry, which included cases from 1973 through 2013.²⁴ This registry includes 9.1 million patient records encompassing all cancers, representing approximately 28% of all newly diagnosed cancers in the United States.²⁵ The SEER*Stat statistical software package was used to calculate incidence rates from 1973–2012, which were age-adjusted to the US standard population of 2000. Incidence patterns were further examined by primary site of CCA (ICC or ECC), sex, and ethnicity. Survival analysis was performed using data from the SEER 18 registry database for 1973–2013, by including cases diagnosed from 1973 through 2008. A study endpoint of 2008 was chosen to allow for a minimum of 5 years follow-up, because the last data entry point for this cohort was in December 2013.

Study Population

CCA was defined according to the ICD-O-3 codes of C221 for ICC and C240–249 for ECC. We identified a total of 26,994 patients diagnosed with CCA from 1973–2008 after using age-mandated eligibility criteria of ≥ 18 years. We excluded patients diagnosed with CCA based on clinical judgement alone,

as well as those lacking documentation on ethnicity, survival duration, and smoking status, and those with overlapping lesions of biliary tract. Overlapping lesions were defined as tumors overlapping the boundaries of ≥ 2 categories or subcategories, whose point of origin could not be determined. Gallbladder cancers and combined hepatocellular carcinomas/CCAs were also excluded.

Methods and Variables

The primary endpoint of this study was 5-year overall survival (OS). In patients alive at last follow-up, OS was censored at 60 months. We chose to analyze age as an ordinal variable. Patients were categorized into 4 ethnic groups: Caucasian, African American, Hispanic, and other races, which included American Indian/Alaska Native, Asian, Fiji Islander, Guamanian, Hawaiian, Micronesian, Pacific Islander, Polynesian, and Samoan. Cases were classified into ICC and ECC based on reported primary site. Extrahepatic sites also included ampulla of Vater and biliary tract, not otherwise specified. CCA was divided according to the grade at presentation into well differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III), undifferentiated/anaplastic (grade IV), or unknown. Based on surgery and radiation information in the SEER database, we redefined treatment types into unknown, no treatment, surgery only, radiation only, and surgery and radiation. Patients were divided into quartiles based on “percent of population that ever smoked” reported from their respective counties for 2000 to 2003. The first quartile represents the lowest smoking rate, whereas the fourth quartile represents the highest smoking rate. Similarly, patients were classified into quartiles based on the median family incomes of their respective counties from 2009 to 2013, with the first quartile having the lowest income level and the fourth quartile having the highest.

Statistical Analysis

SEER*Stat version 8.3.2 was used to calculate incidence rates, which were age-adjusted to the US standard population of 2000. Incidence patterns were further stratified according to the primary tumor site, sex, and ethnicity. For survival analysis, patients were stratified by age; sex; ethnicity; primary site, grade, and stage of tumor; surgery; treatment type; current marital status; smoking status; and in-

come level. Descriptive statistics were performed for categorical and ordinal variables using frequencies. Differences among subgroups were evaluated using the chi-square test. The primary outcome was 5-year OS. Cox proportional hazards model was used to perform multivariate analysis and was constructed using age as an ordinal variable. Sex; ethnicity; primary site, grade, and stage of tumor; treatment type; and marital status were treated as categorical variables, whereas smoking status and income level were treated as ordinal variables. Hazard ratios (HRs) and 95% CIs were generated, with an HR <1.0 indicating a survival benefit. All tests of statistical significance were conducted using $P<.05$ as the significance level. Statistical analyses related to survival were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Our selection criteria identified a total of 26,994 patients diagnosed with CCA from 1973–2008 after using age-mandated eligibility criteria of ≥ 18 years and other exclusion criteria as outlined earlier. Within the study cohort, 7,089 had ICC (26.3%) and 19,905 had ECC (73.7%). Median age was 70 years for ICC and 72 years for ECC. Caucasians constituted the predominant racial group in the study cohort. No significant differences were seen in sex or marital status among ICC and ECC subgroups. Patients with ECC received higher rates of surgery with or without radiation compared with those with ICC; 70% of patients with ICC did not receive any kind of radiation or surgical intervention, whereas this number was low at 48% among patients with ECC (Table 1). Unfortunately, staging information was not available in >70% of ECC and ICC cases.

Incidence Patterns

The age-adjusted incidence rates of CCA increased by almost 65% from 1.7 per 100,000 in 1973 through 1975 to 2.8 per 100,000 in 2011 through 2012 (Figure 1). Using data from all available SEER registries for these periods, we noted a continued increase in age-adjusted incidence rates of both ICC and ECC (Figure 2). Age-adjusted incidence rates of ICC increased by 350%: from 0.2 per 100,000 in 1973–1975 to 0.9 per 100,000 in 2011–2012, whereas incidence rates of ECC increased by approximately

Table 1. Demographic, Clinicopathologic, and Treatment Characteristics

Characteristics	ICC (N=7,089; 26.26%)	ECC (N=19,905; 73.74%)	P Value
Median age, y	70	72	–
Race, n (%)			<.0001
Caucasian	4,932 (69.57)	14,271 (71.7)	
African American	494 (6.97)	1,377 (6.92)	
Hispanic	732 (10.33)	2,072 (10.41)	
Other*	931 (13.13)	2,185 (10.98)	
Sex, n (%)			.48
Female	3,432 (48.41)	9,540 (47.93)	
Male	3,657 (51.59)	10,365 (52.07)	
Marital status, n (%)			.87
Married	3,994 (56.34)	11,236 (56.45)	
Not married	3,095 (43.66)	8,669 (43.55)	
Year of diagnosis, n (%)			<.0001
1973–1980	239 (3.37)	1,893 (9.51)	
1981–1990	643 (9.07)	2,741 (13.77)	
1991–2000	2,718 (38.34)	4,915 (24.69)	
2001–2008	3,489 (49.22)	10,356 (52.03)	
Income, quartile, n (%)			<.0001
1st, low	1,556 (21.95)	5,209 (26.17)	
2nd	1,873 (26.42)	5,021 (25.22)	
3rd	1,684 (23.76)	4,997 (25.1)	
4th, high	1,976 (27.87)	4,678 (23.5)	
Smoking, quartile, n (%)			<.0001
1st, low	1,864 (26.29)	4,568 (22.95)	
2nd	1,982 (27.96)	5,393 (27.09)	
3rd	1,612 (22.74)	4,871 (24.47)	
4th, high	1,631 (23.01)	5,073 (25.49)	
Grade, n (%)			<.0001
Well differentiated, I	367 (5.18)	2,120 (10.65)	
Moderately differentiated, II	912 (12.87)	4,762 (23.92)	
Poorly differentiated, III	901 (12.71)	3,392 (17.04)	
Undifferentiated, IV	67 (0.95)	235 (1.18)	
Unknown	4,842 (68.3)	9,396 (47.2)	
Stage, n (%)			<.0001
I	417 (5.88)	1,484 (7.46)	
II	121 (1.71)	1,525 (7.66)	
III	512 (7.22)	782 (3.93)	
IV	714 (10.07)	1,582 (7.95)	
Unknown	5,325 (75.12)	14,532 (73.01)	
Treatment, n (%)			<.0001
Radiation	868 (12.24)	1,588 (7.98)	
Surgery	788 (11.12)	5,924 (29.76)	
Radiation + surgery	247 (3.48)	1,876 (9.42)	
None	4,972 (70.14)	9,641 (48.44)	
Unknown	214 (3.02)	876 (4.4)	

Abbreviations: ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.
*Includes American Indian/Alaska Native, Asian, Fiji Islander, Guamanian, Hawaiian, Micronesian, Pacific Islander, Polynesian, and Samoan.

Trends and Survival in Cholangiocarcinoma

Figure 1. Temporal trends in age-adjusted incidence rates of cholangiocarcinoma from 1973–2012.

20%: from 1.6 per 100,000 in 1973–1975 to 1.9 per 100,000 in 2011–2012. In general, the incidence of ECC was higher than ICC across all time intervals. Sex-based disparities in incidence patterns of CCA were clearly depicted across all time intervals (Figure 3). Age-adjusted incidence rates from 1973–1975 to 2011–2012 increased by 65% in men: from 2 per 100,000 to 3.3 per 100,000, respectively, whereas in women the incidence rates increased by 53%: from 1.5 per 100,000 to 2.3 per 100,000. Among different racial groups, African Americans had the lowest age-adjusted incidence rates followed by Caucasians, who had slightly higher rates, whereas the incidence rate among other races was much higher (Figure 4). All of the groups demonstrated a progressive increase in age-adjusted incidence rates between 1973–1975 and 2011–2012, with Caucasians showing a 59% increase, African

Figure 2. Temporal trends in age-adjusted incidence rates of cholangiocarcinoma by anatomic location. Abbreviations: ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

Figure 3. Temporal trends in age-adjusted incidence rates of cholangiocarcinoma by sex.

Americans a 50% increase, and other races a 9% increase.

Survival Analysis

Median OS in all patients with CCA was 7 months, whereas it was 8 months in ECC and 4 months in ICC. The prognostic significance of several social, clinical, and tumor characteristics is shown in Table 2. In multivariate analysis, age, sex, race, marital status, year of diagnosis, income, smoking, primary tumor site, tumor grade, tumor stage, and treatment type were significantly associated with OS. Women had a significantly lower mortality risk compared with men, and African Americans had the highest mortality risk among the various racial groups studied. Although the 5-year mortality rates were low for the African American population, the adjusted HR indicate that Hispanics had the best survival outcome from CCA.

Figure 4. Temporal trends in age-adjusted incidence rates of cholangiocarcinoma among different ethnic groups.

Table 2. 5-Year Overall Survival Rates

Characteristics	5-Year Mortality Rate, %	Hazard Ratio	95% CI	P Value
Age, y				<.0001
18–34	69.9	Ref=1		
35–49	77.86	1.276	1.075–1.515	
50–64	83.02	1.436	1.216–1.695	
≥65	91.41	1.877	1.592–2.213	
Race				<.0001
Caucasian	89.36	Ref=1		
African American	83.99	1.081	1.027–1.138	
Hispanic	85.46	0.896	0.856–0.938	
Other ^a	89.32	0.903	0.865–0.942	
Sex				<.0001
Female	88.6	Ref=1		
Male	88.08	1.065	1.037–1.094	
Marital status				<.0001
Married	86.64	Ref=1		
Not married	90.5	1.090	1.060–1.120	
Year of diagnosis				
1973–1980	92.17	Ref=1		
1981–1990	89.86	0.888	0.839–0.940	
1991–2000	88.56	0.752	0.713–0.792	
2001–2008	87.23	0.744	0.706–0.784	
Income, quartile				<.0001
1st, low	89.74	Ref=1		
2nd	87.83	0.936	0.899–0.975	
3rd	87.95	0.901	0.868–0.936	
4th, high	87.75	0.856	0.821–0.892	
Smoking, quartile				<.0001
1st, low	86.55	Ref=1		
2nd	89.13	1.070	1.026–1.115	
3rd	87.69	1.030	0.987–1.074	
4th, high	89.77	1.002	0.959–1.047	
Site				<.0001
ICC	94.05	Ref=1		
ECC	86.29	0.856	0.831–0.883	
Grade				<.0001
Well differentiated, I	75.47	Ref=1		
Moderately differentiated, II	79.91	1.287	1.219–1.359	
Poorly differentiated, III	88.26	1.634	1.545–1.728	
Undifferentiated, IV	92.72	1.773	1.563–2.011	
Unknown	93.85	1.358	1.292–1.429	
Stage				<.0001
I	74.17	Ref=1		
II	79.47	1.284	1.190–1.385	
III	87.94	1.365	1.262–1.477	
IV	97.13	1.787	1.670–1.914	
Unknown	89.42	1.4	1.321–1.484	
Treatment				<.0001
None	96.76	Ref=1		
Radiation	96.42	0.693	0.663–0.724	
Surgery	70.28	0.342	0.329–0.355	
Surgery + radiation	75.69	0.360	0.340–0.381	
Unknown	92.75	0.698	0.654–0.745	

Abbreviations: ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

^aIncludes American Indian/Alaska Native, Asian, Fiji Islander, Guamanian, Hawaiian, Micronesian, Pacific Islander, Polynesian, and Samoan.

Marital status also had significant effect on OS, as did income level and smoking status. Improved survival was demonstrated in patients with later years of diagnosis. On multivariate analysis, the HR for mortality of patients diagnosed in 2001–2008 was 0.744 (95% CI, 0.706–0.784) compared with 1973–1980. Tumor character had a significant impact on survival; as expected, patients with poorly differentiated tumors had worse survival than those with moderately or well-differentiated tumors (Table 2). We also found that ECC was associated with a survival benefit compared with ICC (HR, 0.856; 95% CI, 0.831–0.883). Surgery alone (HR, 0.342; 95% CI, 0.329–0.355) or surgery with radiation (HR, 0.360; 95% CI, 0.340–0.381) were associated with significantly better survival outcomes compared with radiation alone (HR, 0.693; 95% CI, 0.663–0.724) or no treatment.

Discussion

This study cohort of patients with CCA from the SEER database demonstrates a persistent increase in the incidence of CCA in the United States from 1973–2012. It confirms the findings reported in earlier studies,^{4,23,26} while expanding the data analyzed to include cases diagnosed up to 2012. Although the highest incidence rates were found in men from non-Caucasian and non-African American ethnic backgrounds, the increase in incidence affected men and women of all racial groups.

The reasons for increased CCA incidence are not clearly delineated. If it is attributed to increasing incidence of PSC,^{13–16} there should have been a shift toward increasing diagnosis of CCA at a younger age and more frequently in women. Our study, similar to a prior study by Shaib et al,⁴ showed that the increasing incidence of CCA was not associated with a shift toward younger age or relatively increased female predisposition. Shaib et al⁴ also examined the increasing incidence of ICC in the United States and suggested a true increase, which could not be completely explained by improved detection alone. Incidence of CCA is known to be exceptionally high in certain parts of the world, including Chile, Bolivia, South Korea, and North Thailand.²⁷ Additionally, other risk factors for CCA, such as parasitic infections (eg, *Clonorchis sinensis*), could have affected the immigrant population from these regions (mostly from Southeast Asia). We were able to confirm

the higher rates of CCA among American Indian/Alaska Natives, Hispanics, and Asians/Pacific Islanders (represented in the ethnic subgroup “others”) compared with African Americans and Caucasians.²⁶

Hepatitis B and C virus infections and liver cirrhosis have all been suggested as potential risk factors for CCA,^{2,4–12} with 3 studies from Asia^{28,29} and Italy⁶ showing these to be associated with increased incidence rates of CCA. However, there have been no studies on CCA and viral infections conducted in the United States, thereby limiting the generalizability of these results to the US population. We could also attribute the increased CCA incidence to ever-improving and more specialized diagnostic modalities developed over the years, but there is a paucity of evidence to support this.

For survival analysis, we used a cohort consisting of 26,994 patients diagnosed with CCA from 1973–2008. As expected, we found tumor characteristics such as primary site, grade, and stage to be associated with survival in CCA. Notably, there was a survival advantage attributable to ECC compared with ICC (HR, 0.856; 95% CI, 0.831–0.883). Survival differences between ICC and ECC may reflect differences in pathogenesis and tumor biology. This is in contrast to the findings of ABC-02 trial, which showed better outcomes for patients with ICC.³⁰ However, SEER represents population cancer registries that consist of unselected patient populations with a great variation in treatments, compared with clinical trials that contain selected populations receiving predefined treatment. Furthermore, ECC is now classified into perihilar and distal ECC, which are managed differently³¹; perihilar and distal ECC were included under a single entity of ECC until the AJCC 7th edition. This study analyzed perihilar and distal ECC as a single entity.

In addition to tumor characteristics, patient features, such as age and sex, also had significant prognostic impact. Ethnicity, which is often described in the literature as having a prominent prognostic role, did have a significant effect on survival. We found Hispanics had a better survival outcome compared with other ethnicities, whereas non-Hispanic blacks had the worst survival outcome. Survival for our youngest age group (18–34 years) was almost 2-fold higher than for the oldest age group (≥ 65 years); this could be representative of higher rates of treatment in younger patients and is unlikely due to any dif-

ferences in tumor biology in the older patients. We could not address the role of systemic chemotherapy on OS in the current study due to lack of information in SEER. Consistent with previous reports, we found women had better survival outcomes than men. However, no definitive molecular pathways have been identified to explain this association.

Other demographic variables, including marital status, income levels, and smoking status, were associated with prognostic implications. Individuals who were married had better survival outcomes than those who were not married (HR, 1.09; 95% CI, 1.060–1.120), and people with higher income levels did better than those with low income (HR, 0.856; 95% CI, 0.821–0.892). These findings are attributable to the availability of good social and economic support. As expected, smoking did worsen the probability of survival.

Multivariate analysis revealed a continued reduction in mortality from 1973–2008, attributable to early diagnosis and improved surgical techniques, along with increased use of chemotherapy and radiation over time. We noted surgery alone or surgery with radiation had the best outcomes in terms of OS. Improvements in the safety of hepatic resection³² and pancreaticoduodenectomy³³ may have resulted in a higher proportion of margin-negative resections, resulting in better oncologic results. Based on our findings, radiation alone did not confer any improvement in OS compared with surgery alone or with radiation, although it showed better results than no treatment. Outcomes for patients undergoing surgery with or without radiation improved over the decades, whereas no improvement was seen with radiation alone (Table 3).

This study has the limitations of being retrospective in nature. The impact of systemic chemotherapy on survival of CCA could not be ascertained in this multivariate analysis due to the lack of chemother-

Table 3. 5-Year Survival Outcomes by Year of Diagnosis and Treatment ($P < .0001$)

Year of Diagnosis	5-Year Mortality Rate, %			
	RT	Surgery	Surgery + RT	No Treatment
1973–1980	95.21	80.47	88.89	97.8
1981–1990	95.37	73.55	85.65	98.49
1991–2000	97.2	70.44	78.98	96.48
2001–2008	96.43	67.19	71.48	96.46

Abbreviation: RT, radiotherapy.

apy-specific information in the SEER database, such as combination regimen, dose, and cycles.

Conclusions

This study identified various biographic, demographic, and clinical variables that have a significant

prognostic influence on OS in patients with CCA. This is the most up-to-date population-based analysis that demonstrates a continued increase in CCA incidence in the United States. The factors causing this increase are not very clear and require large controlled studies to examine the direct role of potential underlying risk factors.

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