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ORIGINAL RESEARCH—CLINICAL

Widening Health Disparities: Increasing Cholangiocarcinoma Incidence in an Underserved Population

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BACKGROUND AND AIMS: Cholangiocarcinoma is a relatively rare malignancy with high mortality. In the U.S., incidence rates of cholangiocarcinoma have increased, particularly affecting younger age groups and Hispanic and Asian individuals. We investigated the incidence of cholangiocarcinoma in a largely under-represented, minority population. **METHODS:** We performed a retrospective cohort study from 2005 to 2017 among adults in a county-funded healthcare system in Harris County, Texas. Incidence rate ratios were computed to compare age-standardized rates using U.S. standard population between 2 time periods: 2005–2011 and 2012–2017. **RESULTS:** We identified 139 cholangiocarcinoma cases (64% intrahepatic, 36% extrahepatic). The median age at diagnosis was 57 years; 62% were Hispanic, and 56% were born outside the U.S. The incidence rate increased from 1.2 to 2.4 per 100,000 person-years (rate ratio 2.1 [95% confidence interval {CI}: 1.5, 3.0]). Hispanic individuals and those aged 40–69 years had the highest rate of incidence increase (respectively, rate ratio: 2.5 [95% CI: 1.6, 4.0] and rate ratio: 2.0 [95% CI: 1.2, 3.0]) between time periods. In 2012–2017, the risk of cholangiocarcinoma among patients with diabetes was 1.4 times relative to those without (relative risk: 1.4; 95% CI: 1.1, 1.5) and 1.2 times among those who were overweight/obese relative to those who were not (relative risk: 1.2; 95% CI: 1.1, 1.6). **CONCLUSION:** Incidence of cholangiocarcinoma doubled during the 12-year study period, with Hispanic and middle-aged individuals disproportionately affected. Individuals with diabetes mellitus and those who were overweight or obese had a high risk of being diagnosed with cholangiocarcinoma in the later time period. Further studies should focus on preventing and improving earlier diagnosis of cholangiocarcinoma among Hispanics.

Keywords: Cholangiocarcinoma; Incidence Rates; Hispanic; Health Disparities

Introduction

Cholangiocarcinoma is a relatively rare malignancy of the bile ducts and has high mortality rates.[1] Cholangiocarcinoma is thought to arise after a chronic inflammatory process in the bile ducts and can be anatomically divided into intrahepatic and extrahepatic.[2,3] Before 2000, anatomical classification differed under the use of International Classification of Diseases (ICD) for Oncology, second edition, when perihilar or Klatskin tumors were often classified as intrahepatic and subsequently caused erroneous incidence rates with over-representation of intrahepatic cholangiocarcinoma cases.[2–4]

Risk factors for cholangiocarcinoma include diabetes, obesity, cirrhosis, viral hepatitis, tobacco use, and alcohol consumption.[1] Diabetes and obesity are highly prevalent risk factors that have been shown to increase the risk of cholangiocarcinoma. Studies by Li et al reported that diabetes is associated with a 74% increased risk of cholangiocarcinoma[5] and obesity is associated with a 52% increased risk.[6] Other risk factors, such as primary sclerosing cholangitis, bile duct cysts, and parasitic infections including *Opisthorchis viverrini* or *Clonorchis sinensis*, are less prevalent in the general population but confer especially high risk for cholangiocarcinoma.[1,2,7]

Previous studies have noted increasing incidence of cholangiocarcinoma, particularly among certain subpopulations.[3,8–12] A study using the National Cancer Institute's Surveillance, Epidemiology, and End Results data found that age-adjusted incidence rates for cholangiocarcinoma increased in the U.S. between 1973 and 2012, with intrahepatic cholangiocarcinoma rates increasing from 0.44 to 1.18 per 100,000 and extrahepatic cholangiocarcinoma rates increasing from 0.95 to 1.02 per 100,000.[3] A more recent study reported similar increasing trends for intrahepatic cholangiocarcinoma through 2014.[8] Among race/ethnic groups in the U.S., Asian and Hispanic

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; RR, relative risk.

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individuals have been found to have higher incidence rates of cholangiocarcinoma than non-Hispanic white individuals.[3] While incidence has been noted to rise nationally among these subgroups, we wanted to investigate changing incidence and risk among a predominately ethic minority and underserved population.

We assessed the trend in age-standardized incidence rates of cholangiocarcinoma between 2005 and 2017 in the Houston-based Harris Health System (Harris County, Texas). Houston is the fourth largest city in the United States, and the Harris Health System is one of the largest county-funded healthcare institutions in the country. We undertook this study to provide insight into cholangiocarcinoma incidence that has changed among an ethnically diverse and underserved population. This study aimed to investigate the increasing incidence of cholangiocarcinoma among a high-risk population over a 12-year period.

Methods

Study Cases

We performed a retrospective cohort study among adults aged 18 years and older diagnosed with cholangiocarcinoma from October 2005 to October 2017. The study took place within a large, county-funded healthcare system in Harris County, Texas. This healthcare system cares for patients who are mostly uninsured (54%) and patients who belong to racial minority groups (90%).[13] All cholangiocarcinoma cases were obtained through a prospectively maintained Harris Health System Cancer Registry. Age-specific (the number of cases divided by person-years at risk in specific age category) and age-adjusted incidence rates (sum of expected cases in standard U.S. population across all age categories) per 100,000 were computed.

Cholangiocarcinoma cases were identified using the International Classification of Diseases for Oncology, third edition, histology codes 8160/3.[14] Anatomical location was identified according to ICD-10 topography codes. Intrahepatic cholangiocarcinoma was defined by codes C22.0 (liver) and C22.1 (intrahepatic bile duct). Extrahepatic cholangiocarcinoma was defined by codes C24.0 (extrahepatic bile duct) and C24.9 (biliary tract). Gallbladder carcinoma cases were excluded. Stage of disease was determined after discussion at a multidisciplinary tumor board and classified using the American Joint Committee on Cancer staging system.[15]

Demographic and cholangiocarcinoma-related risk factors were obtained through manual review of the electronic health record. Race/ethnicity was self-reported and classified as non-Hispanic white, non-Hispanic Black, Hispanic/Latino, Asian, Middle Eastern, or unknown. Nativity or place of birth was determined and categorized as born within or outside the U.S. Other study variables were derived from data in electronic medical records and included comorbidities of hepatitis B virus infection, hepatitis C virus infection, cirrhosis, diabetes mellitus, history of tobacco use, history of heavy alcohol use, and body mass index (BMI). Heavy alcohol use was defined as greater than 8 drinks per week according to the National Institute on Alcohol Abuse and Alcoholism definition of moderate to heavy alcohol consumption.[16] Overweight or obesity was defined as BMI of 25 or greater based on height and weight data collected closest to the time of cholangiocarcinoma diagnosis.

The Institutional Review Boards at Baylor College of Medicine and Harris Health System approved this study. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical Analysis

We a priori elected to contrast 2 cohorts each including 6 years of cholangiocarcinoma diagnoses to assess any changes in incidence: the first period from 2005 to 2011 and the second period from 2012 to 2017. To assess associations of categorical variables such as gender, age, race/ethnicity, nativity, stage, and anatomic location with cholangiocarcinoma in the 2 time periods, we performed Pearson's Chi square test of independence (or Fisher exact test in case of assumption violation). In case of significant associations between these variables and the time period, the strength of association was also assessed through Phi and Cramer's V. The risk ratios of cholangiocarcinoma between 2 cumulative incidences in different ethnic groups, whether born in the U.S. or not, and having different comorbid conditions, were assessed for the 2 different time periods (relative risk [RR]). The RR for each race category was relative to all other races. Nativity RR was computed for those born outside the U.S. vs those born in the U.S. as reference category (for each of the 2 time periods). The RR for comorbid conditions were for "Yes" responses, with "No" as reference category.

We used county-level census data[17] to compute age-specific and age-standardized incidence rates for each of the 2 study periods using U.S. standard population. We retrieved person-years at risk based on age groups, race/ethnicity, and gender to compute incidence rates per 100,000. Incidence rate ratios were computed to compare incidence rates between the 2 time periods. The population of Harris County served as denominator. All statistical testing was carried out at the significance level of $P < .05$ through IBM SPSS package (IBM SPSS statistics for windows, 2020, IBM Corp, Armonk, NY).

Results

We identified a total of 139 cases of cholangiocarcinoma diagnosed from 2005 to 2017 (40 patients in 2005–2011 and 99 in 2012–2017). Patient demographic and clinical characteristics are outlined in Table 1. The overall cohort was 50% female, 57% younger than 60 years at diagnosis, 62% Hispanic, and 56% born outside the U.S. The majority of those born outside the U.S. were born in Central America (n = 62, 79%), most commonly Mexico (55%) followed by El Salvador (17%). The median age at diagnosis was 57 years. The distributions of gender, age, and race/ethnicity and anatomic location were not different between the 2 time periods. Conversely, there were significant differences in nativity between the 2 time periods. Significantly more individuals diagnosed with cholangiocarcinoma in 2012–2017 were born outside the U.S. than those diagnosed in 2005–2011 (67% vs 56%; *P*-value .014). One patient had primary sclerosing cholangitis. The majority of patients were diagnosed at stage 4 (60% in 2005–2011 and 61% in

Table 1. Demographic and Clinical Characteristics of Cholangiocarcinoma Cohort[a]

	Overall		2005–2011		2012–2017		
	N = 139		N = 40		N = 99		
Characteristic	n	%	n	%	n	%	*P*-value
Sex							.487
Male	70	50.4	22	55.0	48	48.5	
Female	69	49.6	18	45.0	51	51.5	
Age at diagnosis							.475
20–39	12	8.6	3	7.5	9	9.1	
40–59	67	48.2	22	55.0	45	45.5	
60–69	40	28.8	8	20.0	32	32.3	
≥70	20	14.4	7	17.5	13	13.1	
Race/Ethnicity							
Hispanic/Latino	86	61.9	20	50.0	66	66.7	.173
Black/African American	27	19.4	11	27.5	16	16.2	
White/Caucasian	14	10.1	5	12.5	9	9.1	
Asian/Middle Eastern[b]	12	8.6	4	10.0	8	8.1	
Nativity (N= 128, 29, 99)							.014
Born in the U.S.	50	36.0	17	42.5	33	33.3	
Born outside the U.S.	78	56.1	12	30.0	66	66.7	
Stage (N= 121, 32, 82)							.485
1	7	5.0	1	2.5	6	6.1	
2	15	10.8	3	7.5	12	12.1	
3	6	4.3	3	7.5	3	3.0	
4	83	59.7	22	55.0	61	61.2	
Anatomic location							.311
Intrahepatic	89	64.0	23	57.5	66	66.7	
Extrahepatic	50	36.0	17	42.5	33	33.3	

[a]Unknowns not included.
[b]Asians and Middle Eastern.

2012–2017). Among patients diagnosed at stage 4, 60% were Hispanic in 2005–2011 and 66% were Hispanic in 2012–2017.

Table 2 shows the RR of various factors for cholangiocarcinoma in the 2 time periods. In 2012–2017, the RR of cholangiocarcinoma among Hispanic individuals was 1.2 times the risk compared with other race/ethnicity individuals (95% confidence interval [CI]: 1.0, 1.6). Also in 2012–2017, the risk of cholangiocarcinoma diagnosed among those born outside the U.S. was 1.3 times the risk compared with people who were born in the U.S. (95% CI: 1.1, 1.6). In the latter time period, the risk of cholangiocarcinoma was significantly higher among those who had diabetes (RR: 1.4; 95% CI: 1.1, 1.5) as well as those who were overweight/obese (RR: 1.2; 95% CI: 1.1, 1.6). In the earlier time period, the risk of cholangiocarcinoma was higher among those who had hepatitis B (RR: 2.1; 95% CI: 1.0, 4.7) and hepatitis C (RR: 1.9; 95% CI: 1.1, 3.2).

Overall, the incidence rate for cholangiocarcinoma increased from 1.2 to 2.4 per 100,000 person-years between the 2 time periods (incidence rate ratio: 2.1, *P*-value <.005) and the incidence rate ratio was higher specifically for intrahepatic cholangiocarcinoma cases (Table 3). The intrahepatic cholangiocarcinoma incidence rate increased from 0.6 to 1.5 per 100,000 person-years (incidence rate ratio: 2.6, *P*-value <.005), and the extrahepatic cholangiocarcinoma incidence rate increased from 0.6 to 0.9 per 100,000 person-years (incidence rate ratio: 1.5, *P*-value = .10). Hispanics had the highest rate of incidence increase (rate ratio: 2.8, *P*-value <.005) compared with other race/ethnicity groups. Among age groups, individuals aged 40–59 years and 60–69 years had the highest rate of incidence increase (incidence rate ratio: 2.0, *P*-value = .009 and incidence rate ratio: 2.8, *P*-value = .004, respectively) compared with other age groups. Between males and females, males had the highest rate of incidence increase (incidence rate ratio: 2.4, *P*-value <.005).

Discussion

Several important observations emerged from the current study. We found that overall cholangiocarcinoma incidence increased among our underserved cohort. Similar to prior studies,[3,4,10,11] we found that there was a disproportionately greater increase in incidence of intrahepatic cholangiocarcinoma than that in extrahepatic cholangiocarcinoma. The overall risk of cholangiocarcinoma was higher in the later time period for Hispanic individuals, those born outside the U.S., and those with diabetes mellitus and who were overweight or obese. Hispanic individuals

Table 2. Relative Risk of Various Factors for Cholangiocarcinoma Diagnosed in 2005–2011 and 2012–2017[a]

	2005–2011		2012–2017	
	N = 40		N = 99	
Characteristic	Relative risk	95% CI	Relative risk	95% CI
Race/ethnicity				
Hispanic/Latino	0.6	(0.4, 1.0)	1.2	(1.0, 1.6)
Black/African American	1.6	(1.0, 2.7)	1.0	(0.6, 1.1)
White/Caucasian	1.3	(0.6, 2.7)	1.0	(0.6, 1.3)
Asian/Middle Eastern	1.2	(0.5, 2.7)	1.0	(0.6, 1.4)
Nativity				
Born outside the U.S.	0.5	(0.2, 0.9)	1.3	(1.1, 1.6)
Comorbidities				
Hepatitis B infection	2.1	(1.0, 4.7)	0.6	(0.2, 1.6)
Hepatitis C infection	1.9	(1.1 ,3.2)	0.7	(0.5, 1.1)
Cirrhosis	1.3	(0.7, 2.5)	0.9	(0.6, 1.2)
Diabetes mellitus	0.4	(0.2, 1.0)	1.4	(1.1, 1.5)
Heavy alcohol use	1.6	(1.0, 2.7)	0.8	(0.6, 1.1)
Tobacco use	1.5	(1.0, 2.4)	0.9	(0.7, 1.1)
Overweight/obese	0.5	(0.3, 1.0)	1.2	(1.1, 1.6)

[a]Unknowns not included.

were disproportionately affected by the increase in cholangiocarcinoma incidence (87% from 1.5 to 2.8 cases per 100,000/y between 2005 and 2017). Those aged between 40 and 59 years and 60 and 69 years also had a significant increase in incidence. Males had a higher incidence rate ratio than females. Our findings add to nationwide data that demonstrate increased incidence among Hispanic and younger populations,[3,8,9,11,12] causing concern for widening health disparities.

Increasing incidence among Hispanic populations is particularly worrisome as prior research has shown poorer outcomes for Hispanics with cholangiocarcinoma. A previous study notes higher mortality among Hispanic patients with intrahepatic cholangiocarcinoma,[8] echoing the numerous health disparities faced by Hispanic subpopulations.[18] Our cohort was comprised of patients seen at a county-funded hospital and who often lack health insurance.[13] Another study reported that Hispanic patients diagnosed with cholangiocarcinoma who lacked health insurance had decreased odds of receiving chemotherapy and surgery.[19] Increased time between diagnosis and treatment of cholangiocarcinoma has also been noted among Hispanic patients and patients who are uninsured.[20] Lower income has been associated with worse survival among individuals with intrahepatic cholangiocarcinoma, both nationally and in Texas.[20,21] Strategies aimed at improving access to care

Table 3. Incidence Rate Ratios of Cholangiocarcinoma Among Ethnic, Age, and Gender Groups Across Two Time Periods[a]

	Incidence rates per 100,000			
Characteristic	2005–2011	2012–2017	Incidence rate ratio (95% CI)	*P* value
Overall	1.2	2.4	2.1 (1.5, 3.0)	<.005
Intrahepatic	0.6	1.5	2.6 (1.6, 4.1)	<.005
Extrahepatic	0.6	0.9	1.5 (0.9, 2.5)	.101
Race				
Hispanics	1.5	2.8	2.5 (1.6, 4.0)	<.005
Blacks	1.6	2.0	1.3 (0.6, 2.6)	.545
White	0.3	0.4	1.4 (0.5, 3.5)	.531
Age, y				
20–39	0.2	0.7	2.7 (0.7, 10.0)	.101
40–59	1.9	4.5	2.0 (1.2, 3.0)	.009
60–69	3.2	9.0	2.8 (1.3, 5.8)	.004
>70	4.8	5.5	1.2 (0.5, 2.6)	.719
Gender				
Male	1.1	2.5	2.4 (1.5, 3.9)	<.005
Female	1.2	2.3	1.8 (1.1, 2.9)	.013

[a]Unknowns not included.

and thus more prompt diagnoses and treatment may mitigate mortality among vulnerable populations.

Increased immigration from Central America may be contributing to our findings of increased incidence and RR of cholangiocarcinoma among Hispanic individuals. Those born outside the U.S. had an increased RR of 1.3 compared with those born in the U.S. for having cholangiocarcinoma in the latter time period. A majority of patients in our cohort were born in Mexico. In Houston, there has been increasing immigration from Mexico, Central America, and South America.[22] It has been found that intrahepatic cholangiocarcinoma is diagnosed at advanced stages in Mexico[23]; however, few studies have investigated rising incidence of cholangiocarcinoma in these areas. It is possible that individuals from these areas have an increased risk of cholangiocarcinoma or that having immigrated to the U.S. causes increased risk. Further research is necessary to elucidate genetic, cultural, or environmental factors among various Hispanic subpopulations that may lead to higher risk for cholangiocarcinoma.

Prior studies have found that diabetes mellitus and obesity are associated with an increased risk for cholangiocarcinoma.[5,6] In our cohort within the later time period, those with diabetes mellitus had a significantly higher RR of 1.4 and those who were overweight/obese had a significantly higher RR of 1.2 compared to other comorbidities. It is known that the prevalence of diabetes mellitus and obesity has been increasing over time, and particularly among the 40- to 59-year age group.[24] Hispanic individuals have a higher prevalence of diabetes mellitus and a slightly higher mean BMI than the national average.[25] It is unclear whether diabetes may be a confounding factor among those who are overweight or obese. Our findings identify that risk factors for cholangiocarcinoma include common health problems such as diabetes and obesity. Many of these comorbidities can be mitigated with improved preventative health to reduce the risk of developing cholangiocarcinoma.

Compared with national and state data, our cohort was diagnosed at relatively younger ages and at later stages. The median age at diagnosis was 57 years for intrahepatic and extrahepatic cholangiocarcinoma, compared with 67 years for intrahepatic cholangiocarcinoma and 72 years for extrahepatic cholangiocarcinoma cases nationally.[3] Furthermore, 73% with intrahepatic cholangiocarcinoma and 48% with extrahepatic cholangiocarcinoma were diagnosed at stage III or stage IV disease, compared with 69% for intrahepatic cholangiocarcinoma and 46% for extrahepatic cholangiocarcinoma nationally.[3] It is known that diagnosis at later stage of disease is associated with worse prognosis.[9] However, it is unclear why our cohort was diagnosed at younger ages and later stages than the national average. Our cohort may have also been burdened by multiple comorbidities for cholangiocarcinoma, leading to earlier disease development. Additionally, our cohort consists of a large majority of uninsured patients who may have presented late in their disease progression. This further highlights the importance of identifying factors that may increase risk for cholangiocarcinoma.

Our findings are not generalizable to populations that are not predominately urban, low income, and Hispanic. One of the shortcomings of our study is that our cohort received care at a single healthcare system. However, our findings are valuable for understanding trends in cholangiocarcinoma within Harris County and likely echo findings of other urban, county hospital systems. An additional limitation is that we were not able to perform multivariable logistic regression to identify risk factors and confounders of cholangiocarcinoma. It is also not possible to attribute causative effects of the current studied comorbidities in the development of cholangiocarcinoma. Some of these risk factors may be equally likely to be present in patients with other biliary diseases or those with other types of malignancy. Another limitation of our study is the size difference between our 2 time periods, as this may have limited our ability to detect statistical significance in changes of incidence and comorbidities over time. Additionally, Hispanic populations are diverse and further research on cholangiocarcinoma incidence should focus on Hispanic subgroups. Finally, we did not subdivide incidence and comorbidities by site or histology of cholangiocarcinoma beyond intrahepatic and extrahepatic and thus may have missed trends by cholangiocarcinoma classification.

We report that cholangiocarcinoma incidence is increasing over time and among Hispanic, male, and middle-aged individuals. These results are reflective of increasing cholangiocarcinoma incidence rates in the U.S. Diabetes mellitus and obesity in turn may be contributing factors to these increasing rates. Our findings are useful for elucidating trends in incidence and comorbidities of a relatively rare malignancy within Houston, Harris County and across cities with similar demographics. Further investigation should be directed at understanding the epidemiology and risk factors of this high-mortality cancer to mitigate health disparities among high-risk populations such as individuals who are Hispanic and those with diabetes mellitus or obesity.

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Authors' Contributions:
Disha Kumar contributed to investigation, data analysis, and manuscript writing and editing. Varun Bansal contributed to investigation and manuscript writing and editing. Syed A. Raza contributed to data analysis, methodology, and manuscript writing and editing. Aaron P. Thrift contributed to data analysis, methodology, and manuscript editing. Hoda M. Malaty continued to interpretation of results and manuscript editing. Robert J. Sealock contributed to study design, data curation, investigation, and manuscript editing. All authors approve of the final manuscript. The study sponsor did not directly contribute to study design, collection, analysis, or interpretation of data except by supporting Syed A. Raza.

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data, analytic methods, and study materials will not be made available to other researchers.