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Risk factors for intra- and extrahepatic cholangiocarcinoma in the United States: a population based case-control study

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Abstract

Background & Aims—Intrahepatic and extrahepatic cholangiocarcinomas are rare and highly malignant cancers of the bile duct. While the incidence of extrahepatic cholangiocarcinoma (ECC) has remained constant, the incidence of intrahepatic cholangiocarcinoma (ICC) has increased in the United States. As the etiology of both tumors is poorly understood, a population-based case-control study was conducted to examine the association of ECC and ICC with pre-existing medical conditions.

Methods—Medical conditions among 535 ICC patients, 549 ECC patients (diagnosed 1993-1999) and 102,782 cancer-free controls were identified using the Surveillance, Epidemiology and End Results-Medicare databases. Logistic regression analysis was used to calculate adjusted odds ratios.

Results—In addition to established risk factors (choledochal cysts, cholangitis, inflammatory bowel disease), several other conditions were significantly associated with ECC and ICC: biliary cirrhosis (ECC, ICC: p=0.0001), cholelithiasis (ECC, ICC: p=<0.0001), alcoholic liver disease (ECC p<0.0001; ICC p=0.01), nonspecific cirrhosis (ECC, ICC: p<0.0001), diabetes (ECC, ICC: p=<0.0001), thyrotoxicosis (ECC p=0.006; ICC p=0.04) and chronic pancreatitis (ECC, ICC: p=<0.0001). Conditions only associated with ICC were obesity (ECC p=0.75; ICC p<0.01), chronic non-alcoholic liver disease (ECC p<0.08; ICC p=0.02), hepatitis C virus infection (ECC p<0.67; ICC p=0.01) and smoking (ECC p=0.07, ICC p=0.04).

Conclusions—Several novel associations with ECC and ICC were identified. HCV infection, chronic non-alcoholic liver disease and obesity, all of which are increasing in incidence, and smoking were associated only with ICC, suggesting that these conditions may explain the divergent incidence trends of the tumors.

Cholangiocarcinomas are highly fatal tumors of the bile duct that are anatomically classified as intrahepatic (ICC) or extrahepatic according to their location with respect to the liver.[1, 2] In low incidence areas such as the United States, risk factors for the tumors are poorly characterized.

Despite differences in clinical and pathological presentation, both ICC and ECC have been associated with pre-existing medical conditions such as Caroli disease, primary sclerosing

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cholangitis and inflammatory bowel disease.[3-6] Liver flukes and Thorotrast exposure have also been associated with both tumors. Recent evidence suggests, however, that the etiopathogenesis of ECC and ICC may differ. For example, it has been reported that ICC and hepatocellular carcinoma (HCC) may arise from common progenitor cells, particularly in patients with chronic liver disease.[7, 8] In support of this hypothesis are the similar, increasing, temporal incidence trends in HCC and ICC in the United States.[9] Rates of ECC, by contrast, have remained constant.[10] In addition, a recent study reported that ICC may be associated with hepatitis C virus infection (HCV), alcoholic liver disease and diabetes,[11] conditions that are also related to HCC.[12] It is unclear, however, whether these conditions are also associated with ECC.

To date, no studies have investigated risk factors for cholangiocarcinoma by anatomical site. Therefore, it was the goal of this study to extend our previous investigation[13] of ICC risk factors in order to examine the association between pre-existing medical conditions and development of ECC and ICC.

Materials and Methods

Data Source

The data for this study were obtained from the Surveillance, Epidemiology, and End Results (SEER)-Medicare databases which link cancer registry data and Medicare enrollment and claims files. The National Cancer Institute's SEER Program is an ongoing, contract-supported effort that collects information on cancer incidence and survival in the United States.[14] During the study period, 1993-1999, SEER included eleven population-based cancer registries in 5 states and 6 metropolitan areas (Connecticut, Hawaii, Iowa, New Mexico, Utah and Atlanta, Detroit, Los Angeles, San Francisco/Oakland, San Jose, Seattle), covering approximately 14% of the US population. Information on patient demographics, tumor site, morphology, and stage at diagnosis, treatment, and follow-up information are obtained by SEER registries from hospital and outpatient records. The quality and completeness of the data are ascertained in yearly studies. The population covered by SEER registries is comparable to the US population in educational levels and measures of poverty, however, it is more urban and has a higher proportion of foreign-born persons. During the study period, the classification of malignancies was based on the International Classification of Diseases for Oncology, Version 2 (ICD-O2).[15]

Medicare, administered by the Centers for Medicare & Medicaid Services (CMS), is the primary health insurer for 97% of the US population aged 65 years and older. Medicare also covers patients under age 65 with certain disabilities, and people of all ages with end-stage renal disease. Approximately 99% of Medicare beneficiaries receive part A benefits (Hospital Insurance) and approximately 95% subscribe to part B benefits (Medical Insurance), covering outpatient hospital care and physicians' visits.[16] Data on Medicare claims are available for Medicare parts A and B. These files contain dates of service, ICD 9th revision, clinical modification (ICD-9-CM) diagnosis codes and Current Procedural Terminology (CPT, Version 4) codes for all billed claims.

Details on the SEER-Medicare databases, first linked in 1991, have been described previously.[17] Briefly, SEER registries provide individual identifiers for all persons in their files. The identifiers are matched to the identifiers contained in the Medicare master enrollment file. For each of the linkages, 93 percent of persons age 65 and older in the SEER files have been matched to the Medicare enrollment file.

Study Population

All patients age 65 years of age and older who were diagnosed with ECC or ICC between 1993 and 1999 in the SEER11 registries were eligible for study inclusion. The identification of cases followed the histologic classification suggested by the World Health Organization.[18] ECCs were defined by topography code C24.0 (extrahepatic bile duct) and morphology codes 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8161, 8260, 8310, 8480, 8490, 8560 and 8162. ICCs were identified by topography code C22.0 (liver) and morphology codes 8160 and 8161, or by topography code C22.1 (intrahepatic bile duct) and morphology codes 8010, 8020, 8140, 8160, and 8161. Only patients enrolled in Medicare Parts A and B for at least 3 years before diagnosis of ECC or ICC were eligible for inclusion to insure adequate time for prior diagnoses to be recorded. This criterion resulted in a minimum age of 68 years of the study participants.

Patient exclusion criteria included: 1) patients younger than age 65 years at diagnoses of ICC or ECC, 2) persons enrolled in Medicare because of disabilities or end-stage renal disease, 3) patients with unspecified diagnostic confirmation of ICC or ECC, 4) patients with ICC or ECC identified solely by autopsy or death certificate, 5) patients enrolled in a health maintenance organization (HMO) during the study period as Medicare HMO plans are not required to submit individual claims to the Centers for Medicare and Medicaid Services,[19] 6) patients with prior diagnoses of stomach, colon, lung, pancreatic, breast, or rectal cancers.

Individuals with no prior cancer diagnoses were selected as controls from a 5% random sample of Medicare-enrolled beneficiaries who resided in the geographic regions of the SEER11 registries. Control selection was based on the same inclusion/exclusion criteria as used for case selection.

Risk Factor Assessment

Selected medical conditions were identified on the basis of Medicare part A or B claims for the 3 years preceding the diagnosis of ECC or ICC. Controls were assigned a pseudo-diagnosis date using a random number generator. Cases and controls were matched on the year of search for risk factors to minimize possible diagnostic trends. Risk factors for ICC or ECC were categorized into five diagnostic groups based on ICD-9 or CPT- codes.[20] In addition to the main analysis, two sensitivity analyses were performed to examine the stability of the results. The first excluded medical condition diagnosed in the year preceding the cancer diagnosis in order to investigate the impact of possible diagnostic detection bias. The second sensitivity analysis excluded all ECC or ICC cases without strong diagnostic confirmation.

The biliary tract conditions and operations group included choledochal cysts (ICD-9 code 751.69), cholangitis (ICD-9 codes 575.8 and 576.1), biliary cirrhosis (ICD-9 code 571.6), cholelithiasis (ICD-9 code 574), choledocholithiasis (ICD-9 code 574.5), cholecystitis (ICD-9 codes 575.0, 575.11, 575.12), cholecystectomy (CPT-4 code 51), and liver flukes (ICD-9 codes 121.0, 121.11, 121.3). As primary sclerosing cholangitis does not have a separate ICD code it could only be examined as part of the cholangitis group.

The **chronic liver disease group** included hemochromatosis (ICD-9 code 275.0), alcoholic liver disease, nonspecific cirrhosis and chronic non-alcoholic liver disease. Alcoholic liver disease was defined as the presence of alcoholic fatty liver disease (ICD-9 code 571.0), alcoholic hepatitis (ICD-9 code 571.1), alcoholic cirrhosis of the liver (ICD-9 code 571.2), alcoholic liver damage (ICD-9 code 571.3), or cirrhosis (ICD-9 codes 571.5, 571.6) in the presence of alcoholism (ICD-9 codes 291, 303, 305.0). Nonspecific cirrhosis was defined as the presence of cirrhosis (ICD-9 codes 571.5, 571.6) without HCV, HBV, or alcoholic liver disease. Chronic non-alcoholic liver disease was defined by ICD-9 code 571.8. HCV was defined by ICD-9 codes 070.41, 070.44, 070.51, 070.54 and 070.7.

The **endocrine disorders** group included type II diabetes mellitus (ICD-9 code 250) and thyrotoxicosis (ICD-9 codes 242.0). The **digestive disorders group** included duodenal ulcer (ICD-9 code 532), chronic pancreatitis (ICD-9 code 577.1), and the inflammatory bowel diseases: ulcerative colitis (ICD-9 codes 556, 556.9, 556.1, 556.2, 556.3, 556.5, 556.6, and 557.0) and Crohn's disease (ICD-9 codes 555). The **miscellaneous conditions group** was composed of smoking (ICD-9 code V15.82) and obesity (ICD-9 codes 278.00, 278.01, 278.02, V77.8)

Statistical Analysis

Covariates included age, race, geographic region, and state buy-in status. Race was classified as white, black, Hispanic, Asian, and other. Geographic region was categorized according to the SEER11 registries. The Medicare state buy-in variable indicates whether a third-party pays a beneficiary's Medicare premiums, and was thus used as an indicator of lower socioeconomic status.

Demographic features and pre-existing medical conditions were compared between cases and controls using t- tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Logistic regression, adjusted for age, sex, race, geographic region, and state buy-in status, was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to examine the associations. Wald χ^2 tests were used to determine the significance of variables in the logistic regressions. Tests of statistical significance and confidence intervals were two-sided; $p<0.05$ was considered statistically significant. Statistical analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Between 1993 and 1999, 2091 cholangiocarcinomas (ICC: n=1989, 52.2%; ECC: n=1002, 47.9%) were diagnosed in the SEER11 registries. Of these, 549 (54.8%) ECC and 535 (49.1%) ICC patients met the study inclusion criteria. 453 ECC and 554 ICC patients were excluded for the following reasons: 177 ECC and 177 ICC patients were enrolled in Medicare for less then three years before the tumor diagnosis, 213 ECC and 248 ICC patients were not enrolled in both Medicare parts A and B or were part of a HMO, 41 ECC patients and 103 ICC patients were missing information on diagnostic confirmation, 4 ECC and 6 ICC cases were reported solely by autopsy or death certificate and 18 ECC and 17 ICC patients had prior diagnoses of stomach, colon, lung, pancreatic, breast or rectal cancer. Three ICC patients were excluded due to imprecise date of cancer diagnosis. Of 341,032 possible controls with no prior diagnosis of cancer, 102,782 met the inclusion criteria. Exclusions included 98,690 persons with less then three years of continuous enrollment in Medicare, 137,079 persons who were not enrolled in both Medicare parts A and B or were enrolled in an HMO and 2481 persons who relocated outside a SEER11 registry area during the study period.

The demographic characteristics of the study population are summarized in Table 1. The mean age of the ECC and ICC cases was greater than that of controls ($p<0.0001$), however, the mean age of the ECC and ICC cases did not differ ($p = 0.56$). Compared to controls, both sets of cases had a significantly greater proportion of males ($p<0.0001$). A comparison of ECC to ICC cases, however, found no significant difference in gender ($p=0.33$).

The great majority of all participants were white, but there were significant differences in the distribution of other races/ethnicities (ECC vs. controls, $p<0.0001$; ICC vs. controls, $p<0.0001$; ICC vs. ECC, $p=0.04$). Geographic location also differed among all three groups (ECC vs. controls, $p<0.03$; ICC vs. controls, $p<0.02$; ICC vs. ECC, $p=0.04$), although there was no difference in dual enrollment status (Table 1).

Table 2 displays the frequency of pre-existing medical conditions grouped under five headings.

Biliary tract conditions and operations

All bile duct conditions and operations except liver flukes were significantly more prevalent among the cases than the controls. The prevalence of liver fluke infestation was uniformly low among all participants (0 among cases; 4 among controls).

Chronic liver diseases

Alcoholic liver disease and nonspecific cirrhosis were significantly more common among both ECC and ICC cases than controls. In contrast, hemochromatosis (p=0.05), chronic non-alcoholic liver disease (p=0.03) and HCV infection (p=0.03) were significantly more prevalent only among the ICC cases.

Endocrine disorders

Type II diabetes was significantly more common among both ECC and ICC cases than controls (p=<0.0001). The prevalence of thyrotoxicosis was significantly higher only among the ECC cases (p=.04).

Digestive disorders

Inflammatory bowel disease (IBD) was significantly higher among both ICC and ECC cases than controls (p = .04 and p<.0001, respectively). However, when IBD was categorized into its components, Crohn's disease was significantly more common only among the ECC cases (p=0.02), while ulcerative colitis was significantly more common only among the ICC cases (p<0.0001). Duodenal ulcer and chronic pancreatitis were both significantly more common in ECC and ICC cases compared to controls.

Miscellaneous risk factors

Cigarette smoking was significantly more common among both ECC and ICC cases than the controls. There was no significant difference however, in the prevalence of obesity among the groups

Table 3 presents the results of the multivariate analysis, adjusted for demographic characteristics (sex, age, and race) and socioeconomic (state buy-in) status. Most conditions that were associated with ECC and/or ICC in the univariate analysis remained significant in the multivariate analysis. There were no changes among the biliary tract conditions. Among the liver diseases, non-alcoholic liver disease and HCV remained significantly associated with ICC, but the hemochromatosis association became of borderline significance.

The multivariate analysis confirmed the significant association between diabetes and both ECC and ICC. In addition, thyrotoxicosis became significantly associated with ICC (p=0.04) and remained associated with ECC (p=0.006). Among the digestive disorders, duodenal ulcer, and chronic pancreatitis remained significantly associated with both ECC and ICC. Inflammatory bowel disease also remained significantly associated, with Crohn's disease overrepresented among ECC and ICC cases, and ulcerative colitis overrepresented only among ICC patients. Among the miscellaneous conditions, smoking remained significantly associated with ICC (p=0.04) and obesity became significantly associated with ICC (p=0.01).

In the first sensitivity analysis, ECC or ICC cases without strong diagnostic confirmation, i.e. cases without positive histology or cytology, were excluded. Eighty-five percent of the ECC cases and 70% of the ICC cases had tissue confirmation. No changes in the reported associations were found (data not shown). In the second sensitivity analysis, all pre-existing

medical condition diagnosed ≤1 year prior to the cancer diagnoses were excluded. Cholangitis, cholelithiasis, choledocholithiasis, nonspecific cirrhosis, diabetes mellitus, and thyrotoxicosis remained significantly associated with ECC and ICC, while inflammatory bowel disease remained significantly associated with ICC (data not show).

Discussion

In this first-ever U.S. population-based study to examine risk factors for cholangiocarcinoma by anatomical site, several medical conditions were significantly related to both ECC and ICC. These conditions include biliary cirrhosis, cholelithiasis and choledocholithiasis, cholecystitis and cholecystectomy, alcoholic liver disease, liver cirrhosis, type II diabetes, thyrotoxicosis, chronic pancreatitis and possibly duodenal ulcer disease. In addition, HCV infection, obesity, chronic non-alcoholic liver disease, and smoking were significantly more common among ICC, but not ECC, patients. As HCV infection, obesity, and chronic non-alcoholic liver disease are increasing in the US,[21-23] these conditions may be contributing to the divergent trends in ECC and ICC and may also explain similar trends in ICC and HCC.[24]

Among the biliary tract conditions examined, both cholangitis (most likely primary sclerosing cholangitis, PSC) and primary biliary cirrhosis (PBC) were significantly associated with ICC and ECC. PSC and PBC are autoimmune-mediated cholangiopathies[25-27] associated with the chronic destruction of bile ducts, but the pathogenesis and pattern of bile duct involvement differ considerably. PSC involves the intra- and extrahepatic biliary tree, is associated with inflammatory bowel disease and is a known risk factor for cholangiocarcinoma.[28] Although PSC-related cancers are reported to peak in the 4th or 5th decade,[29, 30] the association between PSC and cholangiocarcinoma was also observed the current study's elderly population. In contrast, PBC which occurs in the small intralobular bile ducts, has not previously been associated with cholangiocarcinoma.[31] Chronic inflammation and cholestasis, as well as chronic liver damage, are associated with risk of malignant biliary transformation,[32] suggesting that an association between PBC and ICC is biologically plausible. However, reasons for the association between PBC and ECC are less clear. The small numbers of PBC and absence of information on diagnostic confirmation suggest that the reported association should be confirmed in other studies. It should also be noted that although the ICD-9 code for biliary cirrhosis refers to primary biliary cirrhosis, it is possible that some secondary biliary cirrhosis diagnoses were included.

As anticipated, Crohn's disease and ulcerative colitis were more prevalent among the cases than the controls. Although ulcerative colitis was only significantly associated with ICC, the relationship with ECC was in the predicted direction and may not have attained significance due to small numbers.

Biliary tract stone disease (cholelithiasis, and choledocholithiasis), as well as possible surrogates for symptomatic lithiasis, cholecystitis and cholecystectomy, were significantly more prevalent in cases than controls. Hepatolithiasis, although uncommon in the West, is endemic in some parts of Asia and has consistently been associated with ICC because of inflammation and epithelial proliferation.[33] In parallel, extrahepatic lithiasis may promote chronic inflammatory changes in the extrahepatic bile ducts and thereby increase ECC risk. Reasons why extrahepatic biliary lithiasis would increase the risk for ICC are less clear. However, this association was also reported by a recent ICC case-control study in Denmark.[34] Extrahepatic lithiasis may be associated with cholestasis. It is also possible that the increased ICC risk may result from factors that favor the development of biliary lithiasis itself, such as altered bile composition or conditions associated with metabolic syndrome.

Cholecystectomy has been previously reported to be associated with decreased risk for ECC.[35] In the ICC study in Denmark, however, cholecystectomy was associated with a non-significant increased risk.[36] In the current study, cholecystectomy was more frequent in both ECC and ICC cases than in controls. It should be noted, however, that the majority (85% for ECC and 91% for ICC) of surgical procedures were performed in the year prior to tumor diagnosis, indicating that cholecystectomy may be due to the disease process itself. It is also possible that some patients underwent cholecystectomy for presumed cholecystitis when the symptoms were a result of the underlying cancer.

Chronic liver diseases such as alcoholic liver disease and cirrhosis were significantly associated with ICC, as they were in the previously reported ICC study in Denmark.[37] Both alcoholic liver disease and cirrhosis are well established risk factors for HCC.[38, 39] Conceivably, alcohol may be related to ICC in a similar way, particularly as there is evidence that both types of primary liver cancers arise from common progenitor cells that may give rise to tumors with hepatocellular or cholangiocellular phenotypes.[40] Alcoholic liver disease was also significantly associated with ECC, consistent with a previous study that reported alcohol consumption was a risk factor for ECC among PSC patients (N. Chalasani, personal communication).[41]

Obesity and non-alcoholic liver disease were significantly associated with ICC but not ECC. In recent years, obesity and non-alcoholic fatty liver disease (NAFLD) have received increasing attention as NAFLD may act as a co-factor in HCV- and alcohol-related liver disease.[42-47] In addition, non-alcoholic steatohepatitis (NASH) represents an independent risk factor for the development of liver fibrosis, cirrhosis, and ultimately HCC.[48, 49] In the current study, the same constellation of conditions was associated with ICC. If the associations are confirmed, there are possible public health consequences as recent studies suggest that hepatic steatosis may be present in up to one third of the population,[50, 51] and NASH may be present in 2-5%. The current study also found that diabetes was significantly associated with ECC and ICC. Although elevated insulin and glucose levels may directly stimulate fibrogenesis and release of connective tissue growth factors and favor inflammatory changes,[52-54] the interplay of the components of the metabolic syndrome (obesity, hyperlipidemia, NAFLD, diabetes) is complex, and requires further study to investigate the independent contributions of each factor.

In the current study, HCV infection was associated with ICC, as previously reported[11], but not ECC. Recent studies from Korea, Japan and Italy have also reported an association between HCV and cholangiocarcinoma.[55-57] In support of these findings, HCV RNA has been isolated from cholangiocarcinoma tissue[58] and HCV has been shown to cause bile duct epithelial cell injury.[59] Similar to HCV related-HCC, the increased risk of ICC in patients with HCV may result from HCV-associated chronic liver damage.

The current study found a significant association between hyperthyroidism and ICC and ECC, in line with a previous study that reported a higher prevalence of thyroid diseases in cholangiocarcinoma patients.[60] Restriction of analyses to patients with autoimmune thyroiditis (Grave's disease) found an increased risk for cholangiocarcinoma, however the association did not attain statistical significance. The association of hypermetabolic state in hyperthyroidism and oxidative tissue injury been summarized in a recent review.[61] Elevated thyroxine (T4) and triiodothyronine (T3) levels were reported to alter hepatic lipid peroxidation, promote protein oxidation, and radical oxygen species induced-DNA damage, which may explain the increased risk of cholangiocarcinoma in thyrotoxicosis patients.

Duodenal ulcer disease, which may be a surrogate for Helicobacter pylori (H. pylori) infection and chronic pancreatitis, was significantly more common among ECC and ICC cases than controls. H. pylori, a major cause of duodenal ulcer disease, is classified as a group 1 carcinogen

by the International Agency for Research on Cancer.[62] Several studies have also proposed an association between H. pylori and cholangiocarcinoma[63-65] though the association remains controversial. Therefore, these findings should be interpreted cautiously, as ECC patients, in particular, frequently undergo endoscopy for diagnosis and palliative stent implantation, favoring the possibility of diagnostic bias.

In the current study, chronic pancreatitis was significantly associated with both ECC and ICC. Several mechanisms, including chronic inflammatory changes, could explain the association. In addition, chronic pancreatitis is often associated with obstructive cholestasis favoring malignant transformation through compression of the intrapancreatic portion of the common bile duct.[66] However, confounding by alcoholism, a major risk factor for chronic pancreatitis, cannot be excluded.[67] As previously reported,[68] cigarette smoking was significantly associated with ICC. Consistent with previous reports, there was no association with smoking and ECC.[69]

The current study was large and multiethnic but had several potential limitations. As the study only included patients of age 68 and older, the findings may not be generalizable to younger patients. In the SEER registries, however, the median age at diagnosis of both tumors is between 70 and 74 years, thus the study population is representative of the high-risk groups for these tumors. Completeness and accuracy of the Medicare data are not well reported. To minimize the possibility of missing diagnoses, however, analyses were restricted to patients with at least 3 years of continuous enrollment in Medicare. Furthermore, patients who were enrolled in Medicare HMO plans were excluded, as the HMOs have differing claims submission requirements.[70] The possibility of diagnostic bias cannot be excluded as persons with serious medical conditions are more likely to undergo testing and thus have more diagnoses than other persons. In the case of a biliary tumor such as ECC or ICC, individuals are likely to undergo endoscopy and to be tested for hepatitis virus infections.

Although the current study of almost 1100 cholangiocarcinoma patients was quite large, the small numbers of some pre-existing medical conditions merit caution in drawing strong conclusions. In addition, the exclusion of diagnoses that were made at least 1 year prior to cancer diagnosis likely affected the power to detect significant associations. Finally, as Medicare data are collected for billing, rather than research, purposes, the prevalences of smoking and obesity were almost certainly underrepresented. The current manuscript includes these variables, nevertheless, as a possible means of stimulating hypotheses in these areas.

Important strengths of this study are related to the source of the data, as well as the case and control definitions. SEER has a 98% case ascertainment rate and data quality that has been well-demonstrated. The use of Medicare Parts A and B data rather than personal interview to determine pre-existing medical conditions likely avoided recall bias, while the matching of cases and controls on the search for risk factors minimized the possibility of differing testing and diagnostic trends.

In summary, ICC and ECC share some common risk factors, which include choledochal cysts, cholangitis, ulcerative colitis, biliary tract stone disease, cirrhosis, alcoholic liver disease as surrogate for alcohol consumption, type II diabetes, thyrotoxicosis, and pancreatitis, and possibly duodenal ulcer disease. As chronic non-alcoholic liver disease, obesity and HCV infection were associated with ICC and are increasing in incidence, they may explain the divergent trends in ICC and ECC rates.

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Table 1

Demographic characteristics of the study participants

	ECC cases (n=549)		ECC vs. controls p value	ICC cases (n=535)		ICC vs. controls p value	Controls (n=102,782)		ICC vs. ECC p value
	n	%		n	%		n	%	
Mean age in yrs (s.d.)	78.7	6.9	<0.001	79	6.4	<0.001	77.1	6.8	0.6
Sex			<0.001			<0.001			0.3
Female	269	49.0		278	52.0		65,639	63.9	
Male	280	51.0		257	48.0		37,143	36.1	
Race/ethnicity			<0.001			<0.001			0.04
White	468	85.3		448	83.7		87,569	85.2	
Black	26	4.7		25	4.7		6,746	6.6	
Hispanic	11	2.0		5	0.9		2,116	2.1	
Asian	12	2.2		29	5.4		3,589	3.5	
Other	32	5.8		28	5.2		2,762	2.7	
Geographic location			0.03			0.02			0.04
Atlanta	28	5.1		30	5.6		6,567	6.4	
Utah	22	4.0		19	3.6		5,047	4.9	
Connecticut	75	13.7		77	14.4		14,254	13.9	
Detroit	118	21.5		78	14.6		16,199	15.8	
Hawaii	16	2.9		23	4.3		2,812	2.7	
Iowa	87	15.9		78	14.6		14,287	13.9	
Los Angeles	76	13.8		76	14.2		15,855	15.4	
New Mexico	24	4.4		14	2.6		5,238	5.1	
San Francisco	31	5.7		46	8.6		7,670	7.5	
San Jose	21	3.8		23	4.3		4,572	4.5	
Seattle	51	9.3		71	13.3		10,281	10.0	
Dual Enrollment[1]			0.2			0.5			0.7
Ever	90	16.4		83	15.5		14,809	14.4	

[1] state buy-in status

Table 2

Comparison of pre-existing medical conditions among ECC cases, ICC cases and controls[1]

	ECC Cases (n=549)			ICC Cases (n=535)			Controls (n=102,782)	
	n	%	p value	n	%	p value	n	%
Biliary tract conditions and operations								
Cholecochal cysts	27	4.9	<0.001	21	3.9	<0.001	108	0.1
Cholangitis	50	9.1	<0.001	67	12.5	<0.001	201	0.2
Biliary cirrhosis	<5	<0.9	0.003	5	0.9	<0.001	53	0.1
Cholelithiasis	202	36.8	<0.001	172	32.1	<0.001	4,273	4.2
Choledocholithiasis	87	15.8	<0.001	59	11	<0.001	543	0.5
Cholecystitis	42	7.7	<0.001	29	5.4	<0.001	973	0.9
Cholecystectomy	87	15.8	<0.001	41	7.7	<0.001	1,649	1.6
Liver flukes	-	-	-	-	-	-	-	-
Chronic liver diseases								
Alcoholic liver disease	8	1.5	<0.001	5	0.9	0.008	310	0.3
Nonspecified cirrhosis	10	1.8	<0.001	17	3.2	<0.001	359	0.3
Hemochromatosis	<5	<0.9	0.25	<5	<0.9	0.05	282	0.3
Chronic non-alcoholic liver disease	<5	<0.9	0.08	5	0.9	0.03	353	0.3
HCV infection	<5	<0.9	0.36	<5	<0.9	0.03	142	0.1
Endocrine Disorders								
Diabetes mellitus type II	165	30.1	<0.001	177	33.1	<0.001	22,764	22.1
Thyrotoxicosis	30	5.5	0.04	27	5	0.12	3,864	3.8
Digestive disorders								
Inflammatory Bowel Disease	10	1.8	0.03	18	3.4	<0.001	936	0.9
Crohn's Disease	6	1.1	0.02	5	0.9	0.06	419	0.4
Ulcerative Colitis	5	0.9	0.11	13	2.4	<0.001	595	0.6
Duodenal ulcer	20	3.6	0.001	34	6.4	<0.001	1,836	1.8
Chronic pancreatitis	13	2.4	<0.001	8	1.5	<0.001	272	0.3
Miscellaneous conditions								
Smoking	12	2.2	0.03	12	2.2	0.02	1,212	1.2
Obesity	16	2.9	0.79	23	4.3	0.12	3,201	3.1

[1] Cells sizes less than five are suppressed according to the SEER-Medicare data use agreement

[2] Fisher's Exact test used to compute p value where n<5

Table 3

Multiple logistic regression analysis examining the association between selected medical conditions and ECC or ICC, adjusted for age, gender, race, geographic location, and state buy-in status

	ECC Cases (n=549)			ICC Cases (n=535)		
	OR	95% Confidence Interval	p-value	OR	95% Confidence Interval	p-value
Bile duct diseases						
Cholecochal cysts	47.1	30.4-73.2	<0.001	36.9	22.7 - 59.7	<0.001
Cholangitis	45.7	32.9-63.6	<0.001	64.2	47.7 - 86.5	<0.001
Biliary cirrhosis	11.8	3.7-38.2	<0.001	19.8	7.8 - 49.9	<0.001
Cholelithiasis	11.0	9.1-13.2	<0.001	13.5	11.3 - 16.1	<0.001
Choledocholithiasis	34.0	26.6-43.6	<0.001	22.5	16.9 - 30.0	<0.001
Cholecystitis	5.9	4.0-8.6	<0.001	8.5	6.1 - 11.7	<0.001
Cholecystectomy	12.0	9.5-15.3	<0.001	5.4	3.9 - 7.5	<0.001
Liver Flukes	-	-	-	-	-	-
Chronic liver diseases						
Alcoholic liver disease	4.5	2.2-9.1	<0.001	3.1	1.3 - 7.5	0.01
Nonspecified cirrhosis	5.4	2.9-10.2	<0.001	10.0	6.1 - 16.4	<0.001
Hemochromatosis	1.3	0.3-5.2	0.73	2.6	1.0 - 7.0	0.06
Non-alcoholic liver disease	2.4	0.9-6.5	0.08	3.0	1.2 - 7.3	0.02
HCV infection	1.5	0.2-11.0	0.67	4.4	1.4 - 14.0	0.01
Endocrine disorders						
Diabetes mellitus type II	1.5	1.3-1.8	<0.001	1.8	1.5 - 2.1	<0.001
Thyrotoxicosis	1.7	1.2-2.4	0.006	1.5	1.0 - 2.2	0.04
Digestive disorders						
IBD	2.1	1.1-4.0	0.02	4.0	2.5 - 6.4	<0.001
Crohn's Disease	2.8	1.3-6.4	0.01	2.4	1.0 - 5.9	0.05
Ulcerative Colitis	1.7	0.7-4.0	0.27	4.5	2.6 - 7.9	<0.001
Duodenal ulcer	1.9	1.2-3.0	0.005	3.4	2.4 - 4.8	<0.001
Chronic pancreatitis	9.3	5.30-16.46	<0.001	5.9	2.9 - 12.0	<0.001
Miscellaneous conditions						
Smoking	1.7	1.0-3.0	0.07	1.8	1.0 - 3.2	0.04
Obesity	1.1	0.7-1.8	0.71	1.7	1.1 - 2.6	0.01