Published in final edited form as:

Dig Dis Sci. 2014 December ; 59(12): 3103–3110. doi:10.1007/s10620-014-3276-2.

Secular Trends in the Incidence of Cholangiocarcinoma in the USA and the Impact of Misclassification

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Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Conflict of interest No conflicts of interest exist for Drs. Tyson, Ilyas, Duan, Green, Younes, El-Serag, or Davila.

Abstract

Background and Aims—It has been reported that the incidence of intrahepatic cholangiocarcinoma (ICC) has increased in the USA, while extrahepatic cholangiocarcinoma (ECC) has decreased or remained stable. However, neither the recent trends nor the effects of the misclassification of Klatskin tumors are known.

Methods—Using the Surveillance, Epidemiology, and End Results program databases, we calculated the average annual age-adjusted incidence rates (AA-IRs) of ICC and ECC in 4-year time periods (1992–1995, 1996–1999, 2000–2003, 2004–2007). These AA-IRs were calculated with misclassified as well as correctly classified Klatskin tumors. AA-IRs were also calculated based on age, sex, and race. Multivariable Poisson regression models were used to evaluate the secular trends of ICC and ECC.

Results—The AA-IR of ICC was 0.92 in 1992–1995 and 0.93 in 2004–2007, while the AA-IR of ECC increased from 0.70 in 1992–1995 to 0.95 in 2004–2007. There was no significant trend in AA-IR of ICC ($p = 0.07$), while there was a significant increase in ECC across the 4-year time periods ($p < 0.001$). Klatskin tumors comprised 6.7 % of CCs with approximately 90 and 45 % misclassified as ICC during 1992–2000 and 2001–2007, respectively. Adjusted Poisson models showed no significant differences in the temporal trend of ICC or ECC due to misclassification of Klatskin tumors.

Conclusions—The incidence of ICC has remained stable between 1992 and 2007 with only slight fluctuations, while the incidence of ECC has been increasing. Misclassification of Klatskin tumors does not appear to play a significant role in the trends of CCs.

Keywords

Epidemiology; Liver cancer; Misclassification; Bile duct cancer

Introduction

Cholangiocarcinoma (CC) is the second most common primary hepatic malignancy [1–4]. CC has been conventionally classified by location as intrahepatic (ICC), hilar, or extrahepatic (ECC) [1, 4, 5]. The distinction between ICC, hilar, and ECC has become increasingly important as the epidemiological (i.e., incidence and risk factors) and clinical (e.g., prognosis and treatment) features associated with each site may be different [2, 4, 5]. Over the past few decades, it has been reported in several regions around the world that the incidence of ICC has been increasing while that of ECC has been stable or decreasing [6, 7]. Khan et al. described secular trends of ICC and ECC in several developed countries (USA, England and Wales, Scotland, France, Italy, Japan, and Australia) from 1979 to 1998 using the World Health Organization (WHO) mortality database. The age-standardized mortality rates for ICC increased in both sexes in all of these countries, except for Japanese women where the rates remained stable, whereas the mortality rates for ECC decreased in the USA, England, and Wales, increased in Italy and Japan, and remained stable in France [8]. In the USA from the 1970s–1990s, the estimated annual percentage change in mortality for ICC was about +8 %, while ECC was about –2.5 % [6, 7].

Population-based data on CC in the USA have been reported from the cancer registries of the Surveillance, Epidemiology, and End Results (SEER) program, and have generally indicated a significant threefold to fivefold increase in ICC and a decline in ECC across nine SEER registries [3, 9]. In a study by Patel et al., the age-adjusted incidence of ICC increased from 0.13 per 100,000 persons in 1973 to 0.67 per 100,000 in 1997 [9]. Subsequently, Shaib et al. [3] reported the age-adjusted incidence of ICC increased from 0.32 per 100,000 persons during 1975–1979 to 0.85 per 100,000 during 1995–1999, and ECC incidence decreased from 1.08 per 100,000 in 1979 to 0.82 per 100,000 in 1998. No study has examined the secular trends of ICC or ECC incidence in the USA since 2000.

It is unclear whether the reported trends represent a true increase in ICC and decrease in ECC in the USA and worldwide. Changes in the International Classification of Diseases for Oncology (ICD-O) coding practices, the potential for misclassification of CCs by pathologists and cancer registries, and the use of overly inclusive or highly variable ICD-O coding schemes to identify ICC and ECC in published studies may have contributed to at least some of these observed trends. Hilar CCs also known as Klatskin tumors involving the bifurcation of the hepatic ducts are a subtype of ECC [2, 5]. These Klatskin tumors could be assigned to ICC or ECC based on differing versions of the ICD-O coding scheme. Welzel et al. [10] found that misclassification of Klatskin tumors as ICC in SEER during 1992–2000 accounted for a 13 % over-reporting of ICC and a 15 % under-reporting of ECC. A recent publication by Khan et al. [8] suggested that misclassification as well as under coding of Klatskin tumors in England and Wales may have impacted the incidence trends of both ICC and ECC. Therefore, further investigation of CC trends accounting for changes in the classification of Klatskin tumors is warranted.

Using data from 13 SEER registries, we examined the secular trends of ICC and ECC in the USA and further explored the effect of misclassification of Klatskin tumors on these trends.

Methods

We used data from 13 SEER registries (Connecticut, Atlanta, rural Georgia, Detroit, Iowa, New Mexico, Hawaii, Seattle, Utah, Alaska, Los Angeles, San Francisco-Oakland, San Jose) to identify ICC and ECC cases diagnosed between 1992 and 2007. We chose 1992 as a starting point because it is the first year when Klatskin tumors could be identified by a unique ICD-O histology code. In Version 1 of the ICD-O (1973–1991), Klatskin tumor was not given a unique histology code, and therefore, it could have been classified as ICC or ECC by topography code. In Version 2 of the ICD-O (1992–2000), Klatskin tumor was given a unique histology code that could be linked to ICC but not ECC topography code. Finally, in Version 3 of the ICD-O (2001 to present), the histology code for Klatskin tumor could be linked to either ICC or ECC topography codes. The ICD-O histology and topography codes used to identify cases of ICC and ECC were determined in consultation with study pathologists and literature review [3, 10, 11]. ICC was defined by topography code C22.0 with histology codes 8140, 8160, 8161, 8162, 8480, 8481, 8500 or topography code C22.1 with histology codes 8000, 8010, 8020, 8140, 8160, 8161, 8162, 8480, 8481, and 8500. ECC was defined by topography code C24.0 and histology codes 8000, 8010, 8140, 8160, 8161, 8480, 8481, 8490, 8260, 8500. The histology code for Klatskin tumor is

8162 [12, 13]. Since this code could be referenced to either the ICC (C22) or ECC (C24) topography code, it was used to identify cases of Klatskin tumors in either category. All patients with CC diagnosed by positive histology, cytology, microscopic confirmation, direct visualization, or radiology were included in our study cohort.

Age-adjusted and age-specific incidence rates were calculated for ICC and ECC per 100,000 persons in the underlying population. The US census from 2000 was used as the standard population for calculating the age-adjusted rates. All rates were presented as the average annual age-adjusted rate (AA-IR) within successive 4-year time periods (1992–1995, 1996–1999, 2000–2003, 2004–2007). Incidence rates for ICC and ECC were calculated for several groups based on age (<50, 50–64, 65–74, 75), sex, and race (White, Black, Asian) groups. The SEER regions were also grouped into Central (Detroit, Iowa, and New Mexico), East (Connecticut, Atlanta, and rural Georgia), and West (Hawaii, Seattle, Utah, Alaska, Los Angeles, San Francisco-Oakland, San Jose).

AA-IRs were initially calculated separately for ICC, ECC, and Klatskin tumors. We then calculated rates for ICC and ECC using the original SEER classification scheme where Klatskin tumors (histology code 8162) can be included under ICC (topography code C22) or ECC (topography code C24). Misclassified Klatskin tumors were defined as having an ICC topography code with a Klatskin histology code. The effect of misclassification was evaluated by reclassifying all Klatskin tumors initially categorized as ICC to ECC. For the AA-IRs and Poisson models (ICC and ECC) with misclassified Klatskin tumors, the original SEER classification of Klatskin tumors is used where some Klatskin tumors are misclassified as ICC and others are correctly classified as ECC. For the AA-IRs and Poisson models (ICC and ECC) with reclassified Klatskin tumors, the misclassified Klatskin tumors as ICC were identified and reclassified under ECC. Poisson regression with misclassification and reclassification of Klatskin tumors was conducted to examine the association between the 4-year time periods and the incidence of ICC or ECC while adjusting for age, sex, race, and SEER region. The linear trend over time periods was tested in the models. All statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

We identified 9,840 CC cases during 1992–2007. Approximately 54 % were classified as ICC ($n = 5,359$) and 46 % were classified as ECC ($n = 4,481$). Klatskin tumors with histology code 8162 comprised 662 (6.7 %) of all CC cases. Approximately 73 % (480/662) of Klatskin tumors were misclassified as ICC. Most misclassification (361/480, 75 %) occurred during 1992–2000 when Version 2 of the ICD-O was in effect. The misclassified proportion of Klatskin tumors dropped to 45 % (119 of 263) during the period 2001–2007 with Version 3 of the ICD-O, compared to 90 % (361 of 399) during 1992–2000.

Incidence Rates of ICC and ECC by Time Period

Temporal trends in the average annual AA-IR of ICC, ECC, and Klatskin tumors are presented in Table 1. A significant increase in the average AA-IRs for ICC and ECC were observed over time, while a significant decline in Klatskin tumors was observed. The average AA-IR for ICC and ECC with misclassified and reclassified Klatskin tumors in

successive 4-year time periods is shown in Table 2. For ICC with misclassified Klatskin tumors, the annual AA-IR during 1992–1995 was 0.92 (95 % CI 0.89–0.94) per 100,000 persons, increased during 1996–1999 to 1.09 (95 % CI 1.07–1.12), and returned to baseline (1992–1995) levels during 2000–2003 and 2004–2007. The trend in ICC incidence rates with reclassified Klatskin tumors, both 4-year time periods and annually, was slightly different from the trend of ICC with misclassification (Table 2; Fig. 1). Although the AA-IR increased significantly from 1992–1995 to 1996–1999, then decreased during 2000–2003, there was a significant increase during 2004–2007. There was no significant linear trend in incidence rates in the successive 4-year time periods for either ICC with misclassified or reclassified Klatskin tumors (*p* values 0.07 and 0.48, respectively).

For ECC with misclassified Klatskin tumors, the annual AA-IR during 1992–1995 was 0.70 (95 % CI 0.68–0.72), remained stable during 1996–1999, and increased significantly during 2000–2003 (0.87; 95 % CI 0.85–0.90) and 2004–2007 (0.95; 95 % CI 0.92–0.97). There was a 36 % increase in the incidence of ECC from 1992–1995 to 2004–2007. A similar pattern was observed for ECC with reclassified Klatskin tumors, for both 4-year time periods and annually, as shown in Table 2 and Fig. 1. There was a significant linear trend in incidence rates in the successive 4-year time periods of ECC with misclassified and reclassified Klatskin tumors, *p* values <0.001.

Incidence Rates of ICC and ECC Based on Age by Time Period

The secular trends of age-specific incidence rates of ICC and ECC are shown in Fig. 2. Both ICC and ECC incidence rates were higher with increasing age. However, there were no significant secular trends in age-specific ICC incidence rates except for a decrease in ICC incidence in patients ≥75 years between 1996–1999 and 2000–2003, from 7.88 (95 % CI 7.27–8.52) to 5.57 (95 % CI 5.08–6.10). For ECC (with misclassified Klatskin tumors), there were significantly increased age-specific incidence rates among those 65–74 (+40 %) and ≥75 years (+42 %) between 1992–1995 and 2004–2007.

Incidence Rates of ICC and ECC Based on Sex and Race by Time Period

The secular trends of sex- and race-specific AA-IRs of ICC and ECC are shown in Table 3. The age-adjusted incidence rates of ICC were significantly higher in males than females and in Asians than Whites or Blacks across all time periods. The ICC incidence rates in males increased significantly from 1992–1995 to 1996–1999, but then decreased significantly from 1996–1999 to 2000–2003 and remained constant throughout the remainder of the study period. A similar trend was observed in females with significantly increased rates from 1992–1995 to 1996–1999 and a significant decrease from 1996–1999 to 2000–2003, but females had a significant increase again in 2004–2007. Comparing 2004–2007 to 1992–1995, the incidence of ICC among females increased by 11 % whereas the incidence among males decreased by 8 %. Among Whites and Asians, there was an increase in ICC incidence rates from 1992–1995 to 1996–1999 with a subsequent decrease in incidence in 2000–2003 (Table 3).

The age-adjusted incidence rates of ECC (with misclassified Klatskin tumors) were significantly higher in males than females and in Asians than Whites or Blacks across all

time periods (Table 3). There were statistically significant increases in the age-adjusted incidence rates of ECC from 1992–1995 to 2004–2007 for males (+32 %), females (+36 %), Whites (+31 %), Blacks (+65 %), and Asians (+37 %; Table 3).

Multivariable Analysis of Predictors of ICC and ECC

In the multivariable Poisson regression model for ICC with misclassified Klatskin tumors, the incidence rate ratio (IRR) of ICC increased by approximately 18 % during 1996–1999 compared to 1992–1995 ($p < 0.0001$); however, there were no significant differences in the IRRs during 2000–2003 or 2004–2007 compared with 1992–1995. In the ICC model with reclassified Klatskin tumors, a similar trend was observed during 1996–1999 and 2000–2003; however, a 9 % increase in the IRR was observed in 2004–2007 compared with 1992–1995 ($p = 0.03$). In the ICC models with misclassified and reclassified Klatskin tumors, older age (> 50 years), Asian race, and male sex were associated with an increased risk for ICC, while Black race was associated with a lower risk for ICC (Table 4).

In the multivariable Poisson regression model for ECC with misclassified Klatskin tumors, there was a 22 and 32 % increased risk for ECC during 2000–2003 and 2004–2007 compared with 1992–1995 ($p < 0.0001$; Table 4). With reclassified Klatskin tumors, there were 14 and 19 % increases during the same time periods. In the ECC models with misclassified and reclassified Klatskin tumors, older age (> 50 years), Asian race, and male sex were associated with an increased risk for ECC (Table 5).

Discussion

Our study investigated the secular trends in the incidence of ICC and ECC in the USA during 1992–2007 and the potential impact of Klatskin tumor misclassification on these trends. We found significant increase in the incidence of ICC occurring prior to 2000, a decrease in 2000–2003, and an increase in 2004–2007 amounting to an overall relatively stable trend. In contrast, we observed the incidence of ECC to be relatively stable prior to 2000, followed by steady increases thereafter. Although misclassification of Klatskin tumors decreases after 2000 from 90 to 45 %, this was not a major factor in the secular trends of CC because of the low number of Klatskin tumors (7 % of all CC cases) and the largely similar ICC and ECC incidence trends regardless of how Klatskin tumors were classified.

Our data support the previously reported increasing incidence of ICC and the stable incidence of ECC prior to 2000. However, by extending our study period to 2007, we show a reversal in these trends. Our findings are different from those of a recent study from England and Wales that examined rates from 1990 to 2008, and observed an increasing incidence of ICC and decreasing incidence in ECC even after reclassifying Klatskin tumors [14]. The role of Klatskin tumor classification on the observed differences in trends between the countries is unclear; while only 7 % of CC was documented as Klatskin tumors in the USA and less than 1 % in England and Wales [14], the validity and completeness of diagnostic methods and hence the true number of Klatskin tumors is unknown. A survey of cancer registries in England and Wales showed that if CCs are not specifically coded as Klatskin tumors and left as general CC, they are likely to be inappropriately coded as ICC, making it difficult to account for all Klatskin tumors [14].

Contrary to data from other world regions [6–8, 14], there appears to be an increase in the incidence of ECC in the USA. We found that older age, Asian race, and male sex were associated with a significant increase in risk for ECC (as well as ICC). The relative increase between 1992 and 2007 in ECC was highest among Blacks (65 %) compared to other races (~32–37 %). There was a relative decrease in ICC between 1992 and 2007 among men (–8 %) with an increase among women (+11 %). The reason for these observed trends is unclear. The established risk factors for ECC include parasitic infections, biliary duct cysts, hepatolithiasis, and primary sclerosing cholangitis and probable risk factors include diabetes and heavy alcohol consumption [4]. HCV and cirrhosis have been associated with ICC, but not ECC [4]. The distribution of these factors among cases of ECC and ICC is not known and needs to be examined.

To accurately monitor future trends in ICC and ECC, it is imperative that the international community obtain consensus on classifying CCs and develop a standardized coding scheme. Variation in the incidence of ICC and ECC observed among studies could reflect differences in classifying and coding ICC and ECC [3, 14–19]. Revising ICD-O codes to include specific diagnostic and histology codes that clearly differentiate between ECC and ICC should be considered.

In this updated review of the incidence rates of ICC and ECC between 1992 and 2007 in the USA, we found that the incidence of ICC is fluctuating, but largely stable and ECC increasing slightly. Measurable misclassification of Klat-skin tumors did not completely account for the observed trends in incidence. We recommend greater focus on the consistency and accuracy of diagnosing CC and its subtypes so that correct incidence rates can be monitored and compared.

Acknowledgments

This work is partly funded by NIH Grant T32 DK083266-01A1, NIH Grant R01-CA-125487, NIH/National Institute of Diabetes and Digestive and Kidney Disease, Center Grant P30 DK56338 and the VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (#CIN 13-413).

Abbreviations

CC	Cholangiocarcinoma
ICC	Intrahepatic cholangiocarcinoma
ECC	Extrahepatic cholangiocarcinoma
WHO	World Health Organization
SEER	Surveillance, Epidemiology, and End Results
ICD-O	International Classification of Diseases for Oncology
AA-IR	Age-adjusted incidence rate

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Fig. 1. Age-adjusted incidence rate of ICC and ECC from 1992 to 2007 including ICD-O Versions 2 (1992–2000) and 3 (2001–2007); **a** with misclassified Klatskin tumors, **b** with reclassified Klatskin tumors

Fig. 2. Age-specific incidence rates of **a** ICC and **b** ECC by time period; original SEER classification

Table 1

Temporal trends in the average annual age-adjusted incidence rates of ICC, ECC, and Klatskin tumors

	ICC <i>n</i> = 4,891	ECC <i>n</i> = 4,287	Klatskin <i>n</i> = 662
1992–1995 (<i>n</i> = 2,027)	0.80 (0.78–0.83)	0.68 (0.66–0.71)	0.12 (0.12–0.14)
1996–1999 (<i>n</i> = 2,379)	0.97 (0.94–0.99)	0.67 (0.64–0.69)	0.14 (0.13–0.15)
2000–2003 (<i>n</i> = 2,553)	0.83 (0.81–0.85)	0.82 (0.80–0.85)	0.13 (0.12–0.14)
2004–2007 (<i>n</i> = 2,881)	0.89 (0.87–0.91)	0.89 (0.87–0.91)	0.09 (0.08–0.10)

Table 2

Average annual age-adjusted incidence rates of ICC and ECC with misclassification and reclassification of Klatskin tumors

Time period	<u>AA-IR (95 % CI) (with misclassification)</u>		<u>AA-IR (95 % CI) (with reclassification)</u>	
	ICC <i>n</i> = 5,359	ECC <i>n</i> = 4,481	ICC <i>n</i> = 4,879	ECC <i>n</i> = 4,961
1992–1995 (<i>n</i> = 2,027)	0.92 (0.89–0.94)	0.70 (0.68–0.72)	0.80 (0.78–0.83)	0.82 (0.79–0.84)
1996–1999 (<i>n</i> = 2,379)	1.09 (1.07–1.12)	0.68 (0.66–0.71)	0.97 (0.94–0.99)	0.81 (0.79–0.84)
2000–2003 (<i>n</i> = 2,553)	0.91 (0.89–0.94)	0.87 (0.85–0.90)	0.84 (0.81–0.86)	0.95 (0.92–0.97)
2004–2007 (<i>n</i> = 2,881)	0.93 (0.90–0.95)	0.95 (0.92–0.97)	0.89 (0.87–0.91)	0.99 (0.96–1.01)

Table 3

Average annual age-adjusted incidence rates of (A) ICC and (B) ECC per 100,000 based on sex and race by time period; original SEER classification

Time period	Gender AA-IR (95 % CI)		Race AA-IR (95 % CI)		
	Male	Female	White	Black	Asian
(A) ICC					
1992–1995 (<i>n</i> = 1,153)	1.18 (1.13–1.22)	0.73 (0.70–0.76)	0.87 (0.84–0.90)	0.70 (0.62–0.78)	1.47 (1.35–1.59)
1996–1999 (<i>n</i> = 1,466)	1.35 (1.30–1.39)	0.90 (0.87–0.94)	1.06 (1.03–1.09)	0.84 (0.75–0.92)	1.57 (1.45–1.68)
2000–2003 (<i>n</i> = 1,309)	1.14 (1.10–1.18)	0.74 (0.71–0.77)	0.87 (0.85–0.90)	0.75 (0.68–0.83)	1.33 (1.24–1.43)
2004–2007 (<i>n</i> = 1,431)	1.09 (1.05–1.13)	0.81 (0.78–0.84)	0.87 (0.84–0.89)	0.77 (0.69–0.84)	1.45 (1.36–1.54)
(B) ECC					
1992–1995 (<i>n</i> = 874)	0.87 (0.83–0.91)	0.59 (0.56–0.61)	0.67 (0.64–0.69)	0.52 (0.45–0.59)	1.09 (0.99–1.19)
1996–1999 (<i>n</i> = 913)	0.85 (0.81–0.89)	0.56 (0.54–0.59)	0.68 (0.66–0.71)	0.57 (0.50–0.64)	0.80 (0.72–0.88)
2000–2003 (<i>n</i> = 1,244)	1.11 (1.07–1.15)	0.70 (0.67–0.73)	0.81 (0.79–0.84)	0.74 (0.66–0.82)	1.41 (1.31–1.50)
2004–2007 (<i>n</i> = 1,450)	1.15 (1.11–1.20)	0.80 (0.77–0.83)	0.88 (0.85–0.90)	0.86 (0.79–0.94)	1.49 (1.40–1.58)

Table 4

Poisson regression model of ICC with risk ratios for both the models with misclassification and reclassification of Klatskin tumors

	RR (model with misclassification)	<i>p</i> value	RR (model with reclassification)	<i>p</i> value
Predictors ^a				
1992–1995	Reference		Reference	
1996–1999	1.18	< 0.0001	1.19	< 0.0001
2000–2003	0.98	0.68	1.03	0.49
2004–2007	1.00	0.93	1.09	0.03
Age				
< 50	Reference		Reference	
50–64	12.54	< 0.0001	12.20	< 0.0001
65–74	33.48	< 0.0001	32.07	< 0.0001
75	52.35	< 0.0001	48.53	< 0.0001
Race				
White	Reference		Reference	
Black	0.85	0.004	0.87	0.02
Asian	1.63	< 0.0001	1.66	< 0.0001
Sex				
Female	Reference		Reference	
Male	1.48	< 0.0001	1.45	< 0.0001

^a Adjusted for SEER regions

Table 5

Poisson regression model of ECC with risk ratios for both the models with misclassification and reclassification of Klatkskin tumors

	RR (model with misclassification)	<i>p</i> value	RR (model with reclassification)	<i>p</i> value
Predictors^a				
1992–1995	Reference		Reference	
1996–1999	0.97	0.50	1.00	0.91
2000–2003	1.22	< 0.0001	1.14	0.001
2004–2007	1.32	< 0.0001	1.19	< 0.0001
Age				
< 50	Reference		Reference	
50–64	16.42	< 0.0001	16.56	< 0.0001
65–74	51.41	< 0.0001	51.82	< 0.0001
75	97.24	< 0.0001	99.41	< 0.0001
Race				
White	Reference		Reference	
Black	0.96	0.46	0.92	0.12
Asian	1.68	< 0.0001	1.65	< 0.0001
Sex				
Female	Reference		Reference	
Male	1.48	< 0.0001	1.5	< 0.0001

^a Adjusted for SEER regions