RESEARCH COMMUNICATION

Comparison of Incidence of Intrahepatic and Extrahepatic Cholangiocarcinoma - Focus on East and South-eastern Asia

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Abstract

Background: The term "cholangiocarcinoma" was originally used only for intrahepatic bile duct (adeno) carcinomas, but is now regarded as inclusive of intrahepatic, perihilar, and distal extrahepatic tumors of the bile ducts. A rise in incidence of intrahepatic cholangiocarcinoma has been recently reported in Western countries but comparatively little is known about recent cholangiocarcinoma incidence trends in East and South-Eastern Asia. Methods: We compared age-adjusted incidence rates of both intrahepatic and extrahepatic cholangiocarcinomas, as well as coding practices, using data from 18 cancer registries in Asia and 4 selected registries in Western countries. Intrahepatic cholangiocarcinoma incidence rates were calculated after reallocation of cases with unknown or unspecified histology among liver cancer cases. Results: Age-adjusted incidence rates of intrahepatic cholangiocarcinoma varied by more than 60-fold by region. The highest rates were found in Khon Kaen, Thailand, where 90% of liver tumors were cholangiocarcinomas. The next highest rates were found in the People's Republic of China, followed by the Republic of Korea. The highest age-adjusted incidence rate for extrahepatic cholangiocarcinoma was found in Korea. Coding practices for perihilar (Klatskin tumor) or unspecified sites of cholangiocarcinoma differed from one cancer registry to the other. The proportion of Klatskin tumors among cholangiocarcinomas was less than the one reported in clinical settings. Conclusion: Developing a consistent and uniform topographical classification for acceptable coding practice to all health professionals is necessary. In addition, epidemiological research on risk factors according to anatomical location (intrahepatic versus extrahepatic) and the macroscopic appearance and/or new histological classification of cholangiocarcinoma is also needed.

Keywords: Intrahepatic cholangiocarcinoma - extrahepatic cholangiocarcinoma - incidence - international comparison - coding practices

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Introduction

The term cholangiocarcinoma (CCA) was originally used only for intrahepatic bile duct (adeno)carcinoma, but is now regarded as inclusive of intrahepatic, perihilar, and distal extrahepatic tumors of the bile ducts (Nakeeb et al., 1996; de Groen et al., 1999; Khan et al., 2002). Since the publication of the third edition of the International Classification for Oncology (ICD-O-3) in 2000, CCA in the hilar region can also be referred to as either intrahepatic (C22.1) or extrahepatic bile duct cancer (C24.0) (Fritz et al., 2000). There are still some inconsistencies regarding the classification of cholangiocarcinoma according to anatomical distribution and clinical implications (Nakeeb et al., 1996; Sasaki et al., 1998; Hamilton and Aaltonen, 2000; Nakamura et al., 2000). Despite some overlaps in classification and common features, intrahepatic (IH) and extrahepatic (EH) cholangiocarcinoma tend to have distinct clinical and therapeutic differences, but epidemiological differences are not well-defined. In examining the epidemiology of CCA, however, it is useful to look at both IHCCA and EHCCA.

An international comparison study showed that mortality rates for IHCCA have increased since the 1970s, in contrast to a downward trend in deaths from EHCCA in most countries (Khan et al., 2002; Patel, 2002). A rise in incidence of IHCCA has also been recently observed in the United States (Patel, 2001; Shaib and El-Serag, 2004; McGlynn et al., 2006) as well as in England and Wales (West et al., 2006). However, in some regions, such as Denmark, incidence of both IHCCA and EHCCA has decreased (Jepsen et al., 2007).

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Geographical variations in CCA incidence were reported in 1993 in a paper using data from Cancer Incidence in Five Continents (CI5) Volume VI and in 2004 by another paper using data from Cancer Incidence in Five Continents (CI5) Volume VII (Parkin et al., 1993; Shaib and El-Serag, 2004). Since then, no studies have compared IHCCA and EHCCA incidence rates among different populations with more recent data. Moreover there is limited information about CCA incidence trends in Asian countries.

In the current study, in order to compare incidence rates for both IHCCA and EHCCA in East and South eastern Asia, we estimated the incidence rates using the most recent data from 18 cancer registries in Asia (11 from East and 7 from South-eastern Asia) and 4 selected registries in Western countries for comparison. We also compared estimated incidence rates from around 2000 with data from around 1985 published by Parkin et al to see changes of incidence rates (Parkin et al., 1993).

Materials and Methods

We used data submitted to the CI5 Volume 9 from 18 registries in East and South-eastern Asia and 4 selected registries in Western countries for comparison. We also included some data from registries known to have a high incidence of liver cancer in previous volumes of CI5, but not included in CI5 Volume 9. Each registry granted permission to use its data.

According to the histologically verified proportion of liver cancer cases (ICD C22), cases with unknown or unspecified histology were reallocated pro rata within each 5-year age group by sex to hepatocellular carcinoma (HCC) (ICD-O 8170-8175), CCA (all intrahepatic biliary ICD-O morphology codes 8050, 8140-8141, 8160, 8162, 8260, 8440, 8480-8500, 8570-8572), and a third group that included hepatoblastoma (8970) and sarcoma. In the practice of cancer registration, cases with the morphology code M8162/3 (Klatskin tumors) can be referred to as either IHCCA (topography C22.1) or EHCCA (C24) (Fritz et al., 2000; Wood et al., 2003; Welzel et al., 2006).

Therefore, IHCCA included cases that were coded topographically as intrahepatic bile duct cancer. Specific, age-adjusted incidence rates (standardized for the world population) were then calculated using the cases with reallocation.

EHCCAs were defined by topography code C24.0 and by morphology codes 8000, 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8161, 8162, 8260, 8310, 8480, 8490 and 8560. The proportion of cases with morphology 8000/3 varied greatly by registry (data not shown), but the numbers of cases with unspecified morphology were small, and incidence rates without correction were only slightly affected.

Results

Geographical variation in incidence rates

We found substantial geographical variability in incidence of CCA within the Asian populations for the period 1998-2002, as shown in Table 1. The highest

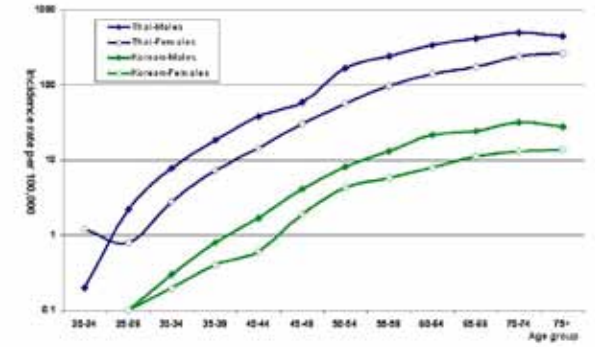

Figure 1. Age-Specific Incidence Rates of Intrahepatic Cholangiocarcinoma by Sex in Korea (1999-2002) and Khon Kaen, Thailand (1998-2002)

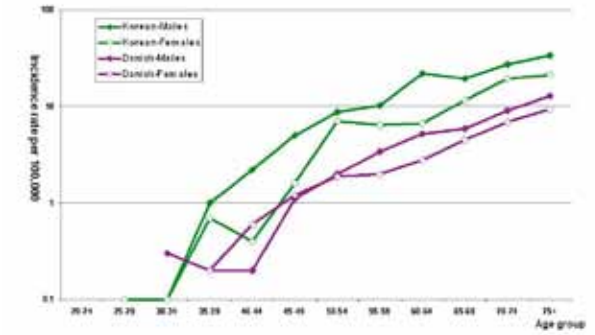

Figure 2. Age-Specific Incidence Rates of Extrahepatic Cholangiocarcinoma by Sex in Korea (1999-2002) and Denmark (1998-2002)

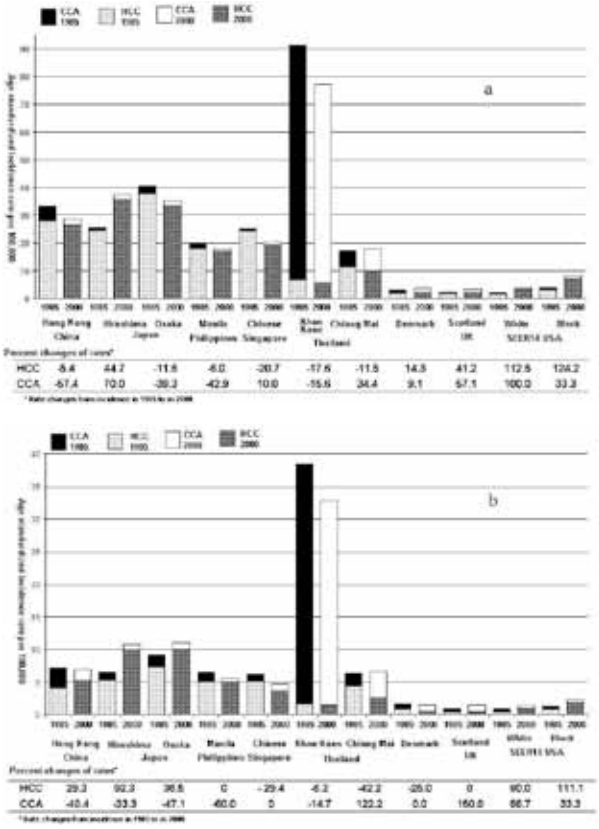

Figure 3 Comparison of Incidence Rates for Hepatocellular Carcinoma (HCC) and Cholangiocarcinoma (CCA) Between Around 1985 and 2000 in Some Selected Populations a) Males; b) Females

Table 1. Age-Standardized Incidence Rates of Liver Cancer, Hepatocellular Carcinoma and Intrahepatic and Extrahepatic Cholangiocarcinoma by Sex

Registries (data for 1998-2002)	Men				Women			
	Liver Cancer (ICD 10 C22)			Extr CCA	Liver Cancer (ICD 10 C22)			Extra CCA
	Liver all	HCC	Intra CCA	(C24.0)	Liver all	HCC	Intra CCA	(C24.0)
China, Qidong	78.2	67.0	10.3	0.0	22.8	18.0	4.6	-
China, Guangzhou	42.5	21.1	0.3	1.1	11.3	3.9	0.1	0.8
China, Hong Kong	29.5	26.4	2.3	0.3	7.3	5.3	1.7	0.2
China, Shanghai	25.9	17.0	7.4	1.4	8.3	2.7	4.9	1.4
Japan, Hiroshima (1996-2000)	39.8	35.6	1.7	2.4	11.9	10.0	0.8	1.2
Japan, Osaka	35.6	33.5	1.7	2.7	11.2	10.1	0.9	1.5
Korea KCCR (1999-2002)	44.9	38.6	5.4	3.3	12.0	9.0	2.5	1.5
Korea, Busan	49.8	43.2	5.8	4.2	14.9	11.1	3.4	2.3
Korea, Daegu	46.1	39.7	5.7	4.1	12.9	9.8	2.6	2.2
Korea, Daejeon	35.4	29.5	5.0	2.8	10.3	7.6	2.1	1.3
Philippines, Manila	21.7	17.4	1.3	0.1	7.0	5.0	0.9	0.1
Singapore, Chinese	21.3	19.2	1.1	0.4	5.0	3.6	1.1	0.3
Taiwan	52.6	46.9	4.3	0.7	20.4	15.6	3.9	0.5
Thailand, Khon Kaen	82.7	5.5	71.3	0.4	34.6	1.4	31.6	0.1
Thailand, Chiang Mai	18.4	10.0	8.2	0.4	6.7	2.6	4.0	0.2
Thailand, Bangkok	10.5	7.1	2.5	0.3	3.0	1.3	1.4	0.1
Thailand, Songkhla	8.6	6.8	1.6	0.1	1.9	1.3	0.5	0.2
Viet Nam, Hanoi	18.1	17.8	0.1	0.0	4.4	4.3	0.1	0.0
Denmark	4.0	2.4	1.2	0.7	1.9	0.6	0.9	0.5
Italy, Brescia	29.5	25.3	2.0	0.8	7.4	6.0	0.7	0.8
UK, Scotland	3.9	2.4	1.1	0.5	1.7	0.5	1.0	0.3
USA, SEER14	6.2	4.9	0.8	0.5	2.2	1.4	0.5	0.3

HCC: hepatocellular carcinoma; CCA: cholangiocarcinoma; KCCR: Korea Central Cancer Registry; SEER14: data from 14 registries in the Surveillance End Result and Epidemiology

rates of IHCCA are from Khon Kaen, Thailand (71.3 per 100,000 in men and 31.6 in women). The incidence rates in other Southeast Asian populations (Filipino, Singapore Chinese, and Vietnamese) were similar to the rates in Western populations (Denmark, Italy, Scotland, and the United States). Regional variations within Thailand and China were broad; however, variations within Japan and Korea were negligible. The proportion of IHCCA among liver cancer cases varied much more than the geographical variations of incidence rates of IHCCA. Rates for IHCCA were higher among men than women in all populations included in this study. Compared to the higher sex ratio for HCC, there were rather narrow sex ratios for CCA. Male-to-female sex ratios for IHCCA incidence were approximately two. Figure 1 showed gradual increases of age-specific incidence rates by sex with similar patterns among two registries (one is from South-eastern Asia known highest incidence rates in the world and the other is from East Asia with moderate incidence rates of IHCCA but highest rates of EHCCA).

Korea had the highest incidence rates of EHCCA. Variations in incidence rates for EHCCA were relatively small compared to IHCCA rates. A slight male preponderance was observed in all populations studied. Even though discrepancies in EHCCA incidence rates among cancer registries were not as high as those for IHCCA, incidence rates were approximately double in most age groups in Korea which had the highest rates, when compared to those for Denmark which reported the decreasing tendency (Jepsen et al., 2007) (Figure 2).

Comparison of incidence rates around 1985 and 2000

Incidence rates of liver cancer (both HCC and IHCCA) around 2000 in most Asian populations have decreased since around 1985. However increases in incidence of both HCC and IHCCA were observed in Western populations. Percent changes of incidence rates of HCC and IHCCA in most registries were much larger in men than in women except in Hong Kong and Japan where the changes were larger in women than in men. Furthermore, incidence rates of IHCCA among women in Scotland and Denmark were higher than for HCC (Figure 3).

Discussion

IHCCA is the second most common primary liver cancer and accounts for an estimated 15% of primary liver cancers worldwide (Parkin et al., 1993); however, this rate varies widely by region. We found that the ratio of IHCCA to total liver cancer in Japan, Korea, and Thailand

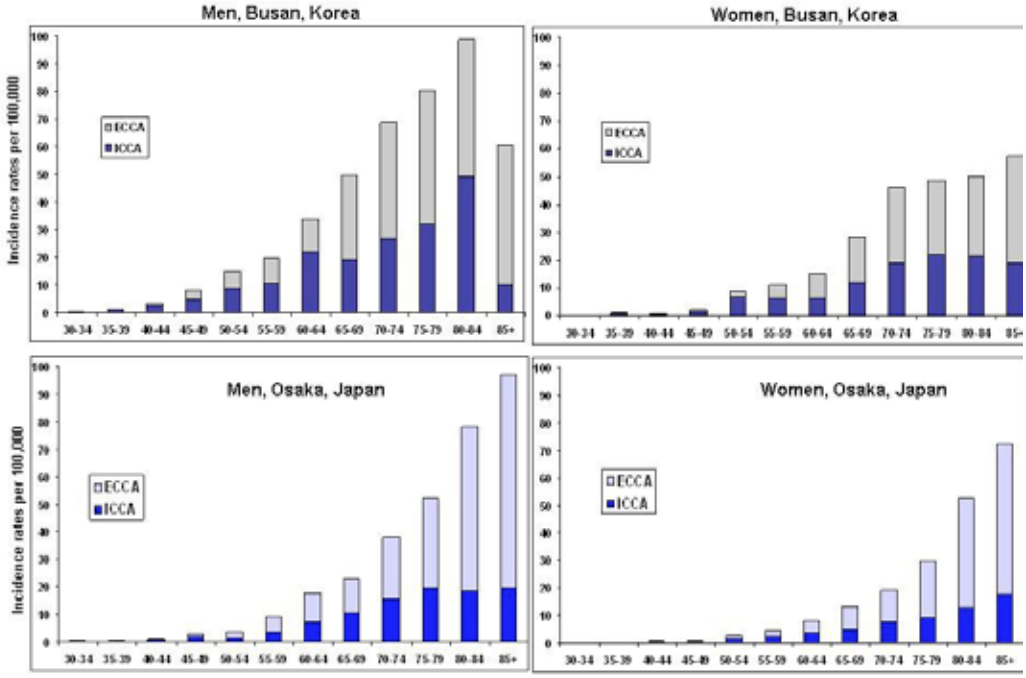

Figure 4. Age-specific Incidence Rates of Cholangiocarcinoma by Sex in Busan, Korea and Osaka, Japan (1998-2002)

were similar to those previously reported (5% in Japan (1990), 20% in Busan (Pusan), Korea (Jung et al., 1993), and 90% in Khon Kaen, Thailand (Parkin et al., 1993)). High ratios of IHCCA to liver cancer were observed in populations with low incidence of liver cancer in Denmark and Scotland. On average ratios of IHCCA to liver cancer for women were double for men in all registries included in this study, which may be due to the lower predominance of HCC in women with liver cancer.

There was little variation in international EHCCA incidence rates, with only a slight male preponderance over females reported (Fraumeni, 1975; Tominaga and Kuroishi, 1994). Incidence and mortality rates for EHCCA seem to be declining in many countries (Khan et al., 2002; Patel, 2002; Shaib and El-Serag, 2004; Khan et al., 2005), although incidence of EHCCA in both sexes was reported to have risen between 1972 and 1994 in Shanghai, China (Hsing et al., 1998).

The Japanese population had relatively higher rates of EHCCA incidence than other populations included in CI5 Volume VI (1983-1987) (Tominaga and Kuroishi, 1994). Up to the late 1990s, CCA was shadowed by the rapid increase of HCC in clinical surveys conducted biennially by the Liver Cancer Study Group of Japan (Okuda et al., 2002). A few publications have shown an increasing trend of mortality from biliary tract cancer between 1950 and 1980 in Japan (Tominaga et al., 1979; Kato et al., 1990; Tominaga and Kuroishi, 1994), and the mortality trend for IHCCA increased between 1980 and 1990 in the same country (Kato et al., 1990; Khan et al., 2002; Okuda et al., 2002). Currently, incidence rates for HCC, IHCCA and EHCCA in Japan are lower than incidence rates in Korea for liver cancer. However, further studies comparing high incidence rates among elderly men and women in Japan and Korea are needed (Figure 4).

CCA occurs with a highly varying frequency in different areas of the world. Part of the variation in incidence rates can be explained by the distribution of risk factors in different geographic regions and ethnic groups (Ben-Menachem, 2007). The overriding link between most known risk factors and CCA is chronic inflammation and chronic biliary irritation (Gores, 2003; Khan et al., 2005; Sripa and Pairojkul, 2008).

The etiology of CCA in Asian countries appears to be mostly linked to infections, especially infections with liver flukes. The mechanisms of adenocarcinoma carcinogenesis in the bile ducts caused by chronic infection with liver flukes include chronic inflammation and resulting oxidative stress (Sripa et al., 2007). The higher incidence rates found in men, and the male-to-female ratio of around 2 for both IHCCA and EHCCA, could be related to the male predominance in liver fluke infections (Dang et al., 2008; Kim et al., 2009; Lun et al., 2005; Sithithaworn and Haswell-Elkins, 2003) in Asian countries.

Established mechanistic events for Hepatitis B or C viruses in the development of CCAs consist of inflammation, liver cirrhosis, chronic hepatitis, and liver fibrosis (Bouvard et al., 2009). Significant relative risks were observed in a meta-analysis (Shin et al., 2010); however, although both viruses are classified as Group 1 Human carcinogens based on sufficient evidence in humans for HCC, the evidence in humans for CCA is limited (35). Further studies examining the role of the hepatitis viruses on the development of CCA are needed.

Apart from factors related to chronic inflammation, both IHCCA and EHCCA are well-known complications of Primary Sclerosing Cholangitis (PSC) in Western countries (de Groen et al., 1999). Approximately 90% of patients diagnosed with CCA in Western countries do not have a recognized risk factor (Ben-Menachem, 2007). Other known risk factors for CCA include obesity,

Table 2. Coding Practices for Klatskin Tumors (Hilar Cholangiocarcinoma) and Total Number of Intrahepatic and Extrahepatic Cholangiocarcinomas

Registries (data for 1998-2002)	Klatskin tumour (M 8162/3)	Total No. of Intra CCA (No. of Klatskin tumors)	Total No. of Extra CCA (No. of Klatskin tumors)	Ratio Intra vs Extra	ICD practice
China, Qidong	0	718	1	718.0	O3
China, Guangzhou	0	22	110	0.2	O2
China, Hong Kong	13	950 (6)	138 (1)	6.9	V10 & O2
China, Shanghai	0	2298	739	3.1	V9,10 & O2
Japan, Hiroshima 1996-2000	0	122	196	0.6	Other
Japan, Osaka	0	1129	1964	0.6	O2
KCCR (KCCR) 1999-2002	826	5562 (776)	4402 (46)	1.3	O3
Korea, Busan	97	572 (93)	548 (4)	1.0	O3
Korea, Daegu	75	346 (69)	334 (3)	1.0	O2
Korea, Daejeon	30	158 (29)	112 (1)	1.4	O3
Philippines, Manila	5	117 (3)	14	8.4	O3
Singapore, Chinese	1	163	54	3.0	O2
Taiwan	50	4716 (35)	789 (15)	6.0	O3
Thailand, Khon Kaen	0	3824	21	182.1	O2
Thailand, Chiang Mai	0	488	21	23.2	O2
Thailand, Bangkok	0	553	59	9.4	O2
Thailand, Songkhla	0	60	7	8.6	O2 & O3
Viet Nam, Hanoi	0	12	4	3.0	O2 & O3
Italy, Brescia	2	78 (2)	60	1.3	O2
Denmark	41	509 (41)	333	1.5	O3
UK, Scotland	20	561 (20)	223	2.5	O2
USA, SEER14	450	3630 (324)	2509 (112)	1.4	O3

ICD: International Classification of Disease; O3: ICD-Oncology-3rd edition, O2: ICD-Oncology-2nd edition, V9: ICD volume 9, V10: ICD volume 10

hepatolithiasis, and other rarer conditions (Olnes and Erlich, 2004; Shaib and El-Serag, 2004; Lazaridis and Gores, 2005; Blechacz and Gores, 2008; Khan et al., 2008). Among these risk factors, hepatolithiasis is a very uncommon disease in the West, and intra- and extrahepatic bile duct stones are much more common in Eastern Asia (Kubo et al., 1995; Su et al., 1997; Chen et al., 1999; Kim et al., 2003). Similarly, in the cholangiocarcinogenesis of other risk factors, bacterial infection and/or bile stasis related chronic cholangitis might underlie CCA development (Chen, 1999; Okuda et al., 2002; Catalano et al., 2009).

CCA may arise anywhere in the biliary tract, from small, peripheral hepatic ducts to the distal common bile duct. CCAs arising from the right and left hepatic ducts at or near their junction are called hilar CCAs (Klatskin tumors: M8162) and are defined and considered to be EHCCAs (Liver Cancer Study Group of Japan, 1997; Nakamura et al., 2000). Since the second edition of the ICD-O (ICD-O-2), which assigned Klatskin tumors the histology code 8162/3 (Percy et al., 1990), Klatskin tumors could be cross-coded either as IHCCA or EHCCA, according to ICD-O-3 (Fritz et al., 2000). From a clinical point of view, Klatskin tumors were classified as EHCCAs and represent approximately 60% of all EHCCAs (Lazaridis and Gores, 2005). In two previous studies, approximately 50% were Klatskin tumors among cases of bile duct cancer (Khan et al., 2002; DeOliveira et al., 2007). In our study, the proportions of Klatskin tumors varied greatly by region. There were no cases of Klatskin tumors in most registries in China, Japan, and Thailand. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) registries database from 1975-1999, 92% of Klatskin tumors were classified as IHCCAs (Shaib and El-Serag, 2004). However, in more recent SEER data (1998-2002), 72% of Klatskin tumors were categorized as IHCCAs. In our study, Klatskin tumours (M8162) with C221 topography that were located in an intrahepatic site were included in order to estimate the incidence rates of IHCCA in most registries with ICD-O 3 coding practice (Table 2). Variations in the proportion of IHCCA Klatskin tumors ranged from 14.0% in Korea to 0.8% in Hong Kong among registries with more than 500 IHCCA cases. Therefore, our estimated incidence rates for IHCCA for the period around 2000 in Table 1 may be over-representative or misclassified.

A final diagnosis of CCA with no anatomical site specified is uncertain, because it is not known whether these cases were coded as IHCCA or EHCCA. Coding practices for unspecified sites of CCA differed from one

Table 3. Quality Indicators of Liver Cancer (1998-2002)

Registries	Men					Women				
	Cases	MV%	DCO%	UB%	MI%	Cases	MV%	DCO%	UB%	MI%
China, Qidong*	3338	8.8	0.1	-	92.6	1016	9.7	0.1	-	92.9
China, Guangzhou	2425	29.1	-	0.1	96.9	729	20.0	-	-	96.3
China, Hong Kong	6289	58.3	3.0	-	84.9	1771	54.7	5.0	-	92.9
China, Shanghai	6001	17.8	0.5	-	73.0	2300	14.9	1.1	-	76.3
Japan, Hiroshima 1996-2000	1632	35.7	8.3	-	80.9	659	27.6	14.1	-	88.0
Japan, Osaka	13494	90.6	8.8	-	89.2	5654	89.1	10.3	-	86.9
Korea KCCR 1999-2002	40709	24.1	8.6	-	77.6	13339	23.8	10.1	-	73.9
Korea, Busan	4438	19.9	5.5	-	78.8	1582	19.7	7.6	-	74.2
Korea, Daegu	2582	30.8	6.7	0.1	76.6	869	26.9	9.9	0.1	73.6
Korea, Daejeon	990	28.0	6.5	-	79.0	339	26.3	7.4	-	71.1
Philippines, Manila	1572	25.7	-	28.2	-	569	27.6	-	26.5	-
Singapore, Chinese	1352	31.0	-	-	-	409	29.6	-	-	-
Taiwan*	30726	40.2	-	-	75.7	11436	39.1	-	-	67.5
Thailand, Khon Kaen*	2986	7.1	0.2	-	71.0	1392	7.7	0.1	-	68.2
Thailand, Chiang Mai	730	46.3	0.4	0.0	0.4	278	46.0	0.4	0.0	1.1
Thailand, Bangkok*	1392	49.4	17.4	-	-	456	50.7	12.1	-	-
Thailand, Songkhla	233	35.2	4.7	0.4	-	60	31.7	3.3	-	-
Viet Nam, Hanoi*	1037	21.2	-	-	-	283	21.9	-	-	-
Italy, Brescia	732	57.8	1.1	0.0	78.0	284	50.7	3.5	0.0	92.3
Denmark	878	83.7	1.0	5.0	87.4	540	74.6	0.7	5.4	96.3
UK, Scotland	794	51.4	0.9	2.4	90.8	512	44.9	0.6	1.6	106.2
USA, SEER14	13843	72.7	3.0	2.9	81.6	6525	70.4	4.4	3.3	98.9

KCCR: Korea Central Cancer Registry; SEER14: data from 14 registries in Surveillance, Epidemiology, and End Result; *: data were not included in CI5 IX; MV: Morphologically verified; DCO: Death certificate only; UB: Unknown basis of diagnosis; M/I: Mortality / Incidence

cancer registry to the next. Furthermore, classification-related issues, especially for EHCCA with gallbladder cancer, present difficulties for the interpretation of available data (Shaib and El-Serag, 2004). Developing a consistent and uniform topographical classification for coding practice that is acceptable to all health professionals is necessary (Okuda et al., 2002; Welzel et al., 2006; Matull et al., 2007; Esposito and Schirmacher, 2008).

The proportion of CCA cases verified microscopically has decreased substantially, presumably due to an increasing reliance on radiological imaging for diagnosis (Choi et al., 2005; DeOliveira et al., 2007). To estimate incidence rates of CCA, we reallocated cases with unspecified or unknown histology pro rata according to the histologically verified proportion. The distribution of cases with unknown or unspecified histology may not be the same as verified cases, and practices related to histological verification may also differ from region to region. Thus, estimated incidence rates in registries with a relatively low proportion of histologically verified cases of liver cancer would give a distorted estimation. However, at the time of writing, such an approach is the only feasible method of enabling an international comparison.

In the present study, we included some data from registries known to have a high incidence of liver cancer in previous volumes of CI5, but not in CI5 IX. These data did not meet our inclusion criteria (Table 3) because of a low percentage of morphologically verified liver cancers, which can be diagnosed by non-invasive tools. However, the regions covered by these East and South-eastern Asian registries are known to have high liver cancer risk, and therefore these data were included in this study.

In summary, age-adjusted incidence rates of IHCCA varied more than 60-fold by region. Changes of incidence rates of IHCCA in Asian populations are variable during the last two decades, however increases in IHCCA incidence have been observed in Western populations. Variations in incidence rates of EHCCA were relatively small compared with IHCCA incidence rates. Compared to the higher sex ratio of HCC, there were rather narrow sex ratios for CCA. A slight male preponderance was observed in all populations studied. Higher CCA incidence rates in men were attributed, in part to the higher prevalence of liver fluke infections among men in endemic areas of Asia. It is still unclear whether biliary neoplasms from different sites share common pathogenic features, even if they are linked anatomically and histopathologically (Rashid, 2002). Only a few studies have been carried out to investigate mechanisms of carcinogenesis related to CCAs according to anatomical location (Tsuda et al., 1992; Ohashi et al., 1994).

CCAs are highly fatal, but improved survival has largely been caused by developments in imaging technology, improvements in patient selection, and advances in surgical techniques (Nathan et al., 2007). To date, many molecular markers such as p53 mutation, cyclins, proliferation indices, mucins, CA19-9, c-reactive protein, and aneuploidy have been investigated for prognostic significance in relation to CCA (Briggs et al., 2009). However, from an epidemiological point of view, the role of risk factors for intrahepatic and hilar cholangiocarcinomas with Klatskin tumors coded as topographically intrahepatic have not yet been clearly elucidated. Further epidemiological research on risk factors according to anatomical location (intrahepatic versus extrahepatic cholangiocarcinoma) and according to the macroscopic appearance and/or new histological classification of CCA (Konishi et al., 2008) are needed.

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