

# Descriptive Epidemiology of Cholangiocarcinoma and Clonorchiasis in Korea

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In 2009, infection with the liver fluke *Clonorchis sinensis* (*C. sinensis*) was classified as “carcinogenic to humans” (Group 1) based on its involvement in the etiology of cholangiocarcinoma by the International Agency for Research on Cancer. However, little is known about the descriptive epidemiology of cholangiocarcinoma in Korea. We examined incidence trends of intrahepatic and extrahepatic cholangiocarcinomas, using data from the Korea National Cancer Incidence database for 1999–2005. The prevalence of *C. sinensis* infection was estimated from a recent population-based survey in rural endemic areas. Cholangiocarcinoma incidence rates are currently rising, even while primary liver cancer incidence rates are decreasing. Annual percent changes in cholangiocarcinoma incidence rates were 8% for males and 11% in females. Known areas of *C. sinensis* endemicity showed high incidence rates of cholangiocarcinoma. The positivity of *C. sinensis* eggs in stool samples from endemic areas was more than 25% of adults tested during 2005–2008. From a meta-analysis, the summary odds ratio for cholangiocarcinoma due to *C. sinensis* infection was 4.7 (95% confidence interval: 2.2–9.8). Approximately 10% of cholangiocarcinomas in Korea were caused by chronic *C. sinensis* infections. More specific policies, including health education and an extensive effort for early detection in endemic areas, are needed.

**Key Words:** cholangiocarcinoma, *Clonorchis sinensis*, Korea

## INTRODUCTION

The two liver flukes *Clonorchis sinensis* (*C. sinensis*) and *Opisthorchis viverrini* (*O. viverrini*) are members of the Opisthorchiidae family (1). These species are considered to be of major social and economic relevance for both humans and animals in Asian countries including China, Korea, Vietnam, Laos, and Thailand (2). In 1994, infection with *O. viverrini* was classified by the International Agency for Research on Cancer (IARC) as “carcinogenic to humans” (Group 1) based on its involvement in the etiology of cholangiocarcinoma (CCA). Alternatively, infection with *C. sinensis* was classified as “probably carcinogenic to humans” (Group 2A) because there was only limited evidence for the carcinogenicity of this worm in humans (3).

In Volume 100B from February of 2009, the IARC Monograph Working Group reassessed the carcinogenicity of infection with liver flukes by applying a comprehensive review of all of the available published literature (4). Prevalence of infection with *C. sinensis* was shown to correlate with the incidence of CCA (5), and several case-control studies showed a high risk for this cancer (6–8).

Therefore, infections with *O. viverrini* and *C. sinensis* are now

both classified in Group 1 by the IARC, based on “sufficient evidence in humans” for CCA.

Beginning in the 1970’s, several papers reported a high correlation between CCA and clonorchiasis in the southern part of the Korean Peninsula (9, 10).

However, little is known about the existing distribution and trend of incidence, and related risk factors of CCA in Korea, a nation where *C. sinensis* infection is highly prevalent.

In the present paper, incidence rates of CCA and the prevalence of infection with *C. sinensis* are described in an attempt to evaluate the burden of CCA related to infection with *C. sinensis* in Korea.

## MATERIALS AND METHODS

### Incidence of CCA

We extracted intrahepatic CCA cases (International Classification of Disease (ICD) 10 code C22.1 (11), ICD-Oncology (ICD-O) (12) code 8160, including adenocarcinoma (ICD-O codes 8140, 8161, 8260, 8440, 8480, and 8560), duct carcinoma (ICD-O code 8500), and Klatskin tumor (ICD-O codes 8162), and extrahepatic CCA: ICD 10 code C24.0) from the Korea National Can-

cer Incidence Database (KNCIDB). We examined all of the records of CCA reported from 1999 through 2005. Next, we computed the age-standardized incidence rates per 100,000 person-years on the basis of the world standard population. To compare changes in incidence between 1999 and 2005, we calculated the estimated annual percentage change (EAPC). Incidence rates were separately analyzed by sex and region for two calendar periods (1999-2002 and 2003-2005) because Korean national incidence rates in Cancer Incidence in Five Continents volume 9 published by IARC covered the 1999-2002 period and the incidence rates for 2003-2005 were published in 2009 (13, 14).

#### Prevalence of *C. sinensis* infection from 2005-2008

During 2005-2008, a total of 4,234 subjects (age range: 30-89; mean age: 59.9 yr) were recruited as a part of population-based cohort construction in areas of Haman and Sanchong in Gyeongsangnam-do which was known endemic of *C. sinensis*; from the basin of the Nakdong River. A trained research assistant interviewed each participant about the demographic characteristics, alcohol drinking and tobacco smoking habits, dietary habits including raw fresh-water fish, and disease history. Stool samples were also collected for laboratory examination. Additionally, informed consent was obtained from all participants, and the study protocol was approved by the National Cancer Center of Korea.

Stool samples were examined using the formalin-ether sedimentation method to identify the presence of *C. sinensis* eggs. Also, data from national surveys of intestinal parasites from 1971 (1st report) to 2004 (7th report) were used for an estimation of the population-attributable fraction.

#### Summary risk of *C. sinensis* infection with CCA and population attributable fraction calculation

Using published data from cross-sectional (9, 10) and case-control studies (6-8) of CCA with *C. sinensis* infection, meta-analysis was performed to estimate the risk of CCA. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated on the basis of both fixed- and random-effect models. Heterogeneity analysis was then carried out to verify if there was a significant difference between studies. The Stata version 10.0 (Stata-Corp, TX, USA) and Comprehensive Meta-Analysis version 2 (Biostat, NJ, USA) software programs were used for the meta-analysis. Using the formula below, the attributable fraction was estimated using information about the prevalence of *C. sinensis* infection in 1981 (15) and relative risk estimates from meta-analysis. The calculated attributable fraction was applied to the number of incidence cases of CCA in 2005 in consideration of the latency period.

Population-attributable fraction=

$$\frac{C. \text{sinensis prevalence} \times (\text{summary odds ratio} - 1)}{C. \text{sinensis prevalence} \times (\text{summary odds ratio} - 1) + 1} \times 100$$

## RESULTS

#### Incidence of intrahepatic CCA

Since 1999, the annual average incidence of primary liver cancer was 10,500 cases for males and 3,500 cases for females. In addition, a decreasing trend was observed, with an EAPC of approximately -2%. Intrahepatic CCA accounted for approximately 10% of liver cancers (8.8% for males and 10.6% for females) and this proportion increased by year, with levels of 11.6% for males and 22.7% for females in 2005. Intrahepatic CCA rates increased gradually from 2001 (with EAPCs of 7.9% and 10.6% for males and females, respectively); however, the extrahepatic CCA rates were stable during the same period (Table 1). There were approximately 2.5- to 3.0-fold variations by region, with Gyeongsangnam-do having the highest incidence rates for males (Table 2). The increase in the incidence of female cases (168.6%) was higher than that seen for males (149.7%) in recent years (2003-2005) compared to the earlier years examined (1999-2002). Very sharp increases in cases involving both males and females age 50 and over were observed during the time period of 2003 through 2005 (Fig. 1).

#### Prevalence of *C. sinensis* infection in the Gyeongsangnam-do area in 2005-2008

Overall *C. sinensis* egg positivity in stool was measured at 28.2% (27.6% in 2005; 34.5% in 2006; 25.4% in 2007; 21.7% in 2008) among adults ages 30 and over (the age-standardized prevalence rates were 35.0% and 20.8% for males and females, respec-

**Table 1.** Number of cases and age-standardized incidence rates of liver cancer (C22), intrahepatic cholangiocarcinoma (C22.1), and extrahepatic cholangiocarcinoma (C24.0) in Korea, 1999-2005

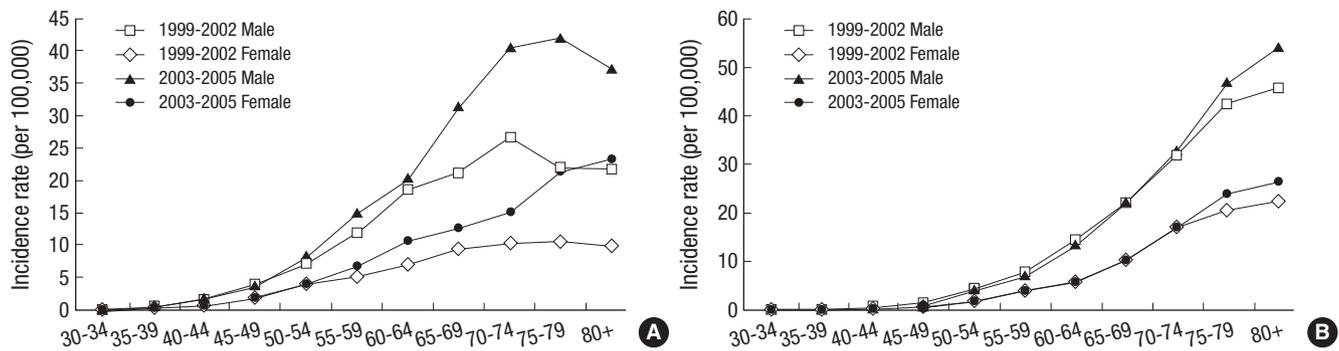
Year	Sex Site	Male			Female		
		Liver C22	ICCA C22.1	ECCA C24.0	Liver C22	ICCA C22.1	ECCA C24.0
		Cases (ASR)	Cases (ASR)	Cases (ASR)	Cases (ASR)	Cases (ASR)	Cases (ASR)
1999		10,027 (46.8)	733 (3.6)	683 (3.6)	3,259 (12.3)	367 (1.4)	443 (1.6)
2000		9,898 (44.7)	648 (3.1)	652 (3.3)	3,228 (11.8)	403 (1.5)	477 (1.6)
2001		10,433 (45.1)	770 (3.5)	737 (3.6)	3,435 (12.2)	389 (1.4)	506 (1.7)
2002		10,490 (43.9)	906 (3.9)	712 (3.3)	3,471 (11.8)	536 (1.8)	496 (1.6)
2003		10,586 (42.3)	961 (4.1)	752 (3.4)	3,501 (11.5)	617 (2.0)	568 (1.7)
2004		10,880 (42.0)	1,164 (4.8)	856 (3.7)	3,542 (11.2)	699 (2.2)	586 (1.7)
2005		11,264 (42.0)	1,307 (5.2)	859 (3.6)	3,643 (11.1)	828 (2.5)	612 (1.7)
Total (average)		10,511 (43.7)	927 (4.1)	750 (3.5)	3,440 (11.7)	548 (1.8)	527 (1.7)
APC %		-1.8	7.9	0.3	-1.7	10.6	1.3
Proportion			8.8%			15.9%	

ASR, age-standardized incidence rates; APC, annual percent change; ICCA, intrahepatic cholangiocarcinoma; ECCA, extrahepatic cholangiocarcinoma.

**Table 2.** Age-standardized incidence rates of cholangiocarcinoma (CCA) by region in Korea over two time periods: 1999-2002 and 2003-2005

Regions	Intrahepatic CCA				Extrahepatic CCA			
	Male		Female		Male		Female	
	99-02	03-05	99-02	03-05	99-02	03-05	99-02	03-05
Overall	3.5	4.7	1.5	2.2	3.5	3.5	1.6	1.7
Seoul	2.6	3.6	1.4	2.0	2.6	2.9	1.4	1.4
Busan	3.5	5.3	1.9	2.6	4.0	4.1	2.4	2.2
Daegu	4.5	5.7	1.7	2.5	4.8	4.0	2.2	2.3
Incheon	3.5	3.6	1.5	2.1	3.1	3.2	1.3	2.0
Gwangju	4.3	6.7	1.4	2.4	4.6	6.0	1.8	2.4
Daejeon	3.3	4.6	1.2	1.8	2.9	3.6	1.5	2.0
Ulsan	5.1	5.4	1.6	2.3	4.5	3.1	1.7	2.0
Gyeonggi-do	2.8	3.5	1.4	1.8	2.9	2.9	1.4	1.3
Gangwon-do	2.0	2.9	0.9	1.7	3.0	2.5	1.0	1.2
Chungcheongbuk-do	3.7	4.5	1.6	2.4	2.5	2.9	1.4	1.9
Chungcheongnam-do	3.1	4.1	1.6	1.8	2.9	2.9	1.2	1.2
Jeollabuk-do	5.3	6.0	1.6	2.1	4.0	3.7	1.8	1.6
Jeollanam-do	3.2	5.8	1.8	2.6	3.8	4.3	1.8	2.3
Gyeongsangbuk-do	3.7	5.7	1.3	2.5	4.3	4.4	1.8	1.6
Gyeongsangnam-do	7.2	8.5	2.1	3.0	4.8	5.3	1.9	2.4
Jeju-do	3.1	5.0	2.0	3.2	4.4	3.1	2.5	1.6

National Cancer Incidence Database, Korea Central Cancer Registry, National Cancer Center, Korea.



**Fig. 1.** Age specific incidence rates of cholangiocarcinoma by sex for 1999-2000 and 2003-2005. (A) Intrahepatic, (B) Extrahepatic.

**Table 3.** Prevalence of *Clonorchis sinensis* among residents in the endemic area, Gyeongsangnam-do: 2005-2008

Age group	Total		Male		Female	
	No. examined	Egg pos. (%)	No. examined	Egg pos. (%)	No. examined	Egg pos. (%)
30-39	174	28 (16.1)	51	11 (21.6)	123	17 (13.8)
40-49	489	168 (34.4)	202	93 (46.0)	287	75 (26.1)
50-59	1,037	315 (30.4)	447	174 (38.9)	590	141 (23.9)
60-69	1,632	463 (28.4)	588	223 (37.9)	1,044	240 (23.0)
70+	902	218 (24.2)	374	119 (31.8)	528	99 (18.8)
Total	4,234	1,192 (28.2)	1,662	620 (37.3)	2,572	572 (22.2)
Age-standardized proportion (95% CI)*	26.3 (23.9-28.8)		35.0 (34.9-35.1)		20.8 (20.7-20.9)	

\*Age-standardized proportion to the population in Kyeongsang Nam-do in 2005.

tively). A higher prevalence was observed in the 40- to 59-yr-old age group in both males and females (Table 3).

**Risk estimates for CCA according to *C. sinensis* infection status and population-attributable fraction based on Korean studies**

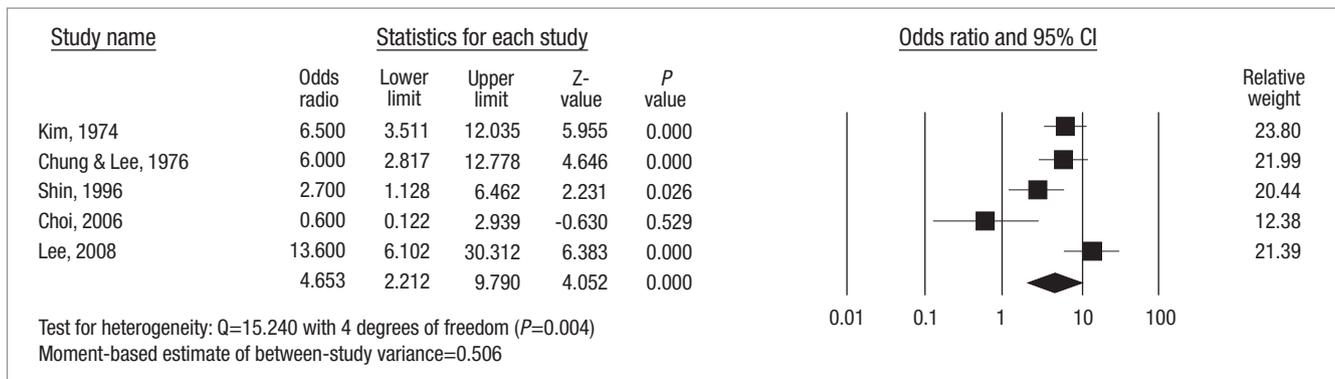
Table 4, Fig. 2 illustrate the risk estimates for CCA according to

*C. sinensis* infection status. The overall odds ratio for CCA due to *C. sinensis* infection was 4.7 (95% CI: 2.2-9.8). In 2005, 9.5% of CCA cases were attributable to infection with *C. sinensis* (12.2% for males, 5.5% for females) (Table 5). In the endemic areas, the population-attributable fraction was much higher, at levels of 27.9% and 16.2% for males and females, respectively.

**Table 4.** Summary of study characteristics for cholangiocarcinoma according to *Clonorchis sinensis* infection status in Korea

Reference	Study design and place	Case		Control		Characteristics
		N	<i>C. sinensis</i> positive	N	<i>C. sinensis</i> positive	
Kim, 1974 (9)	Cross-sectional study, Seoul National University Hospital, Seoul and Pusan (Busan) Gospel Hospital, Busan, 1961-1972	54	21	1,348	120	Cases: CCA Control: HCC cases Crude OR
Chung & Lee, 1976 (10)	Cross-sectional study, Pusan National University Hospital, Busan, 1964-1974	36	19	559	88	Cases: CCA Frequency matched control from the patients admitted in the study hospital with no liver cancer Crude OR
Shin, 1996 (6)	Hospital based case-control study Pusan (Busan) Paik Hospital, Busan, 1990-1993	36	12	350	44	Cases: CCA Adjusted OR
Choi, 2006 (7)	Hospital based case-control study Samsung Medical Center, Seoul, 2003-2004	164	25	164	11	Cases: Intrahepatic, hilar, extrahepatic CCA Adjusted OR
Lee, 2008 (8)	Hospital based case-control study Asan Medical Center, Seoul, 2000-2004	622	26	2,488	9	Cases: Intrahepatic CCA Adjusted OR

CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; OR, odds-ratio.



**Fig. 2.** Risk estimates for cholangiocarcinoma according to *Clonorchis sinensis* infection status.

**Table 5.** *Clonorchis sinensis* infection-attributable cholangiocarcinoma in Korea, 2005

Sex	No. of CCA cases	Prevalence of <i>C. sinensis</i>	Population Attributable Fraction to <i>C. sinensis</i> (%)	
			Application for overall cases in 2005	Nationwide % in 1981*
Male	2,166		3.8	12.2
Female	1,440		1.6	5.5
Both sex	3,606			9.5
	Application for cases <sup>†</sup> in Gyeongsang-nam-do in 2005		% in Gyeongsang-nam-do, 1981 <sup>†</sup>	
Male	250		10.6	27.9
Female	161		5.3	16.2
Both sex	411			22.6

\**C. sinensis* prevalence in 1981 (Total=2.6%, M=3.8%, F=1.6%) (Ref [15]); <sup>†</sup>cases with patients age 30 or over; <sup>‡</sup>% among patients age 30 or over. (Source: Prevalence of intestinal parasitic infections in Korea: the 3rd report. The Ministry of Health and Social Affairs. The Korea Association of Parasite Eradication. 1981). CCA, cholangiocarcinoma.

**DISCUSSION**

The age-standardized incidence rates of intrahepatic CCA in Ko-

rea were 4.1 per 100,000 males and 1.8 per 100,000 females, respectively, from 1999 to 2005 and these are between two and four times higher than those in the United States (e.g., in the 1996-2000 period, White males, 0.92/100,000; Black males, 0.93/100,000; White females, 0.57/100,000; Black females, 0.39/100,000) (16) and England and Wales (e.g., in the 1999-2001 period, males, 1.33/100,000; females, 1.06/100,000) (17). Increases in intrahepatic CCA were observed in our study, correlating well with studies conducted in the United States, England, and Wales (16, 17). The reasons for increases in CCA incidence are not clear. Some part of this increase may be attributed to changes in the coding system, from ICD-O-2 to ICD-O-3, but these changes were not drastic (18). More rapid increases among the elderly might be attributed to complete and accurate cancer registration (14). The CCA incidence was higher in males than in females but the increase in CCA incidence was bigger in females than in males. This might be caused that the greater percent change due to relatively small numbers of CCA case in females than in males. It needs further studies.

Since 1971, national surveys of intestinal parasitic infections have monitored the overall prevalence of *C. sinensis* in Korea

(15). Areas heavily endemic for clonorchiasis in Korea are scattered throughout the country, with the most extensive and intensive endemic regions found mainly along the Nakdong River and the lower reaches of the rivers located in Gyeongsangnam-do (19). The infection status of *C. sinensis* has shown little change over 25 yr, despite the development of effective antihelminthics such as praziquantel. The repeated consumption of fresh-water fish is one of the main contributing factors for the high prevalence of clonorchiasis, even after intervention with praziquantel (5).

In an ecological study conducted during 2000-2004 in Korea, *C. sinensis* prevalence (2.1% in Chuncheon, 7.8% in Chungju, and 31.3% in Haman) correlated strongly with CCA incidence rates (0.3, 1.8, and 5.5 per 100,000 persons, respectively) (5).

In Korea, the national liver cancer surveillance program for high-risk patients began in 2002 and is comprised of carriers of hepatitis B virus or C virus. Any individuals with current or prior *C. sinensis* infection are also part of the high-risk group for the contraction of primary liver cancer in areas endemic for *C. sinensis*. Therefore, these high-risk individuals should be included in the surveillance program.

Apart from clonorchiasis, a main risk factor of CCA, the other known risk factors include chronic infection with hepatitis B and C viruses (HBV and HCV), liver cirrhosis, chronic non-alcoholic liver disease, obesity and hepatolithiasis (4, 20, 21). A possible association between HBV and HCV-known to cause hepatocellular carcinoma- and CCA was reported by IARC as there is only limited human evidence (4). Both intrahepatic CCA and extrahepatic CCA are well-known complications of Primary Sclerosing Cholangitis (PSC) in Western countries (22).

Among these risk factors, hepatolithiasis is a very uncommon disease in the West, in contrast, intra- and extrahepatic bile duct stones are much more common in Eastern Asia (23). Hepatolithiasis is strongly associated with CCA with proportions varying from 10% in Japan, 35% in Korea to more than 60% in Taiwan (China) (24-26).

In conclusion, approximately 10% of CCA cases are estimated due to infection with *C. sinensis* (12% for males, 6% for females). In contrast, *C. sinensis* infection causes a quarter of CCA cases in the endemic area. Even though the control of *C. sinensis* is successful due to very effective chemotherapy using praziquantel, CCA risk has been continuously increasing, particularly in areas hyper-endemic for *C. sinensis* infection. A more straightforward policy for the prevention of *C. sinensis* infestation that includes health education to avoid repeated consumption of raw fresh-water fish and an extensive effort for early detection targeting those who are currently or have been infected with *C. sinensis* in endemic areas is strongly needed.

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