RESEARCH COMMUNICATION

Trends in Liver Cancer Incidence between 1985 and 2009, Khon Kaen, Thailand: Cholangiocarcinoma

Supot Kamsa-ard[1*], Surapon Wiangnon[2], Krittika Suwanrungruang[1], Supannee Promthet[3], Narong Khuntikeo[4], Siriporn Kamsa-ard[5], Suwannee Mahaweerawat[6]

Abstract

Background: The Khon Kaen Cancer Registry (KKCR), having both hospital and population-based registration, was established in 1984 at the Faculty of Medicine, Khon Kaen University. Liver cancer is the most frequent malignancy among Thais from northeastern Thailand, but there has hitherto been no assessment of trends over time. Objective: To perform a statistical assessment of the incidence trends between 1985 and 2009 of liver cancer, specifically focusing on cholangiocarcinoma (CHCA). Methods: Cases of CHCA, registered between 1985 and 2009, were retrieved from the KKCR and all those with a specific ICD-O-3rd diagnosis with a coding of C22.1, C24.0, C24.8 and C24.9 were selected. Incidence trends were calculated using the generalized linear model method (GLM), which generates incidence rate based logarithms. Jointpoint analysis was used to identify the best fitting model. Results: Of the 18,589 cases of liver cancer 42% (7,859) were hepatocellular carcinoma and 58% (10,731) were CHCA. Among persons with CHCA, males were affected two times more frequently than females. Three-quarters of the cases were between 55 and 69 years of age. Morphology verified through a cytological or histological examination of tissue from the primary site (%MV) was only 10.8 % (1,141). The respective overall Age Standardized Rate (ASR) for CHCA from 1985 to 2009 was 16.8 to 62.0 per 100,000 among males and 4.8 to 25.6 per 100,000 among females. The respective, overall, ASR of CHCA among males vs. females was 44.3 per 100,000 (95% CI: 38.9 to 49.7) vs. 17.6 (95% CI: 14.5 to 20.7). Among males vs. females, the respective incidence from 1990 to 2009 has been significantly decreasing by –0.7% per year (annual percent change, APC: –0.7%, 95%CI: –2.1% to +0.8%) vs. –0.4% per year (APC: –0.4%, 95% CI: –2.1% to +1.4%). Conclusions: The rate increase in the first 5 to 6 years may be due to improved completeness of the registry, since in the subsequent 10 to 12 years there is a rather stable rate. It may be, however, that the recent decline in incidence represents a real fall in risk.

Keywords: Cancer registry data - cholangiocarcinoma - incidence rate - time trends - Khon Kaen, Thailand

Asian Pacific J Cancer Prev, **12**, 2209-2213

Introduction

The rates of liver cancer in Thailand are among the highest in the world, particularly in the northeastern region where it is an endemic disease. In Thailand, The estimated age-standardized incidence rate (ASR) among males in this region (especially in Khon Kean province) is between 78.4 and 94.8 per 100,000 vs. 32.7 and 39.4 per 100,000 among females. The most common type of pathology is CHCA (viz., between 82.0 and 89.0 of the liver cancers in Khon Kaen province) (Vatanasapt et al., 1993; Deerasamee et al., 1999; Sriplung et al., 2003; Khuhaprema et al., 2007; 2010).The overall mortality rate for all sites of cancer, from a 2009 report, was 104.6 per 100 000 per year among males, 72.6 per 100 000 per year among females, and 88.3 per 100 000 per year among both males and females. By comparison, the rate of liver cancer and intrahepatic bile duct was 31.1 per 100,000 per year among males, 12.3 among females, and 21.6 among both males and females (Ministry of Public Health, 2009).

Recent data from the Srinagarind Hospital-based tumor registry revealed that the number of new cases of liver cancer and cholangiocarcinoma in 2009 was 1,027 cases; the first ranked among males and the third ranked among females. The respective number of cases of liver cancers and cholangiocarcinomas among males vs. females was 742 and 285. The male to female ratio was 2.4:1. Regarding the quality of the data, we found that histology had been verified in only 12.7% (Cancer unit, 2010).

The Khon Kaen Cancer Registry (KKCR) was established in 1984 at the Faculty of Medicine and Srinagarind Hospital, Khon Kaen University. It therefore comprises both hospital and population-based

[1]Cancer Unit, [2]Department of Pediatrics, [5]Department of Surgery, [6]Medical Record Section, Faculty of Medicine, [3]Department of Epidemiology, [4]Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand
**For correspondence: surapon@kku.ac.th*

registrations. Despite its longstanding operation, no information on trends has been produced on liver cancer in Khon Kaen which is an endemic disease.

Materials and Methods

Objective

To assess the incidence trends for liver cancer (specifically for cholangiocarcinoma) in Khon Kaen between 1985 and 2009.

Case definitions

All cholangiocarcinoma cases (CHCA) lived in Khon Kaen province and were registered between January 1, 1985 and December 31, 2009. CHCA is an ICD-O-3rd diagnosis and we only selected the CHCAs with specific coding C22.1, C24.0, C24.8, and C24.9 (excluding C24.1, Ampulla of Vater) (Fritz et al., 2000).

Registry procedure

The data for Khon Kaen residents diagnosed with cancer at Srinagarind Hospital were extracted from the Hospital-based cancer registry and medical records registered at other hospitals throughout the province were reviewed by staff from the Khon Kaen Cancer Unit. Death certificates were linked to the Bureau of Policy and Strategy, Ministry of Public Health (http://bps.ops.moph.go.th/). To prevent duplication, all of the data were reviewed and checked with existing registry files before data entry. All of the data are therefore verified, checked for duplication, coded and entered into the CanReg4 software. (http://www.iacr.com.fr/).

The ASR uses population counts by age and sex for its denominator. These demographic data were sourced from official annual publications from the Prime Minister's Office. These show that the population in Khon Kaen province was stable vis-à-vis migrational in- and outflows, which leaves vital statistics as the primary reason for any trends in population. (Prime Minister's Office, 2007)

Outcome measurement

The incidence for cholangiocarcinoma (CHCA) is based on logarithms and the denominator derived from each year's population estimates (Table 1).

Data collection

The data on cancer patients was collected by both active and passive methods from a university hospital (Srinagarind Hospital), a regional hospital (Khon Kaen Provincial Hospital), an army hospital, two private hospitals and 24 community hospitals. The registrars visited all of the registered sites in a regular schedule. The medical charts of patients diagnosed as having cancer were reviewed and registered by registry personnel. Any questionable cases were traced to the original source(s) of information for clarification. Multiple primary cases were checked by physicians using their original records and with any other physicians concerned.

Death certificates with a mention of cancer were collected from the population statistics from the Office of the Ministry of Interior. The registrars reviewed these sources to notify and recheck with health personnel in each area. At present the vital status of all registered cases is regularly updated by checking personal identification number of patients with the population statistics from the Office of the Ministry of Interior.

Statistical methods

Percentages were used to describe the proportion by sex, basis of diagnosis, stage at diagnosis, and histological grading. The mean and standard deviation were used to describe age at diagnosis. The Age Standardized Rate (ASR) and 95% confidence interval (95% CI) were used to describe the incidence rates of Cholangiocarcinoma (CHCA) (Jensen et al., 1991). The Jointpoint regression program (version 3.4.4 April 2010) was used to identify points where a significant change in the linear slope of the trends occurred, the corresponding p-value and the 95% Confidence Interval of the Annual Percent Change (APC). (Kim et al., 2000; National Cancer Institute, 2003)

Results

Demographic characteristics of cholangiocarcinomas

Overall, the study included 10,730 cases of cholangiocarcinoma from 1985 to 2009. The median number of new diagnosed cases was 430 per year (Min: 101 cases, Max: 673 cases). According to time period, from 1985 to 1997 and 1998 to 2009. The male to female ratio were 2.4 to 1, 2.1 to 1 (see Tablew 1). The age group with the largest number of cases were between 55 and 64, between 60 and 69 years of age. The basis for diagnosis was mostly by endoscopic and radiologic evidence while morphological verification (i.e., based on either cytological or histological examination of tissue from the primary site, %MV) were the basis for 13.3% (545), 9.0% (596) . As for the stage of disease, the largest single group (21.2%,874), 22.1(1,457) were late stage (i.e., Stages III and IV), respectively. For the histological grading, the common histology were unknown, while they were well differentiated in a few in both periods 1985 to 1997 and 1998 to 2009. The number of cases by period and sex, between 1985 and 2009, was two times greater among males than females.

Age-standardized incidence rates

The respective, age-standardized rate per 100 000 (ASR) for CHCA for (a) men (b) women and (c) men and women between 1985 and 2009 ranged from (a) 16.8 to 62.0 (b) 4.9 to 25.6 and (c) 10.5 to 42.5. Thus, the overall ASR per 100 000 was 44.3 for males (95% CI: 38.9 to 49.7), 17.6 for females (95% CI: 14.5 to 20.7) and 30.1 for males and females (95% CI: 25.6 to 34.5) (Figure 1).

Trends in incidence of cholangiocarcinomas

For an analysis of the trends in the incidence of CHCA, we excluded the period of diagnosis between 1985 and 1989 because during that time the registries were in their opening stages and the data were incomplete; thereby making the ASR unreliable.

For the period 1990 to 2009, the Jointpoint regression and age-period-cohort models were used to determine the

Table 1. Baseline Demographics and Clinical Characteristics of Cholangiocarcinomas in Khon Kaen

Characteristics		1985 to 1997		1998 to 2009	
Sex	Males	2,911	70.7	4,508	68.2
	Females	1,209	29.3	2,102	31.8
Male to female ratio		2.4 : 1		2.1 : 1	
Age at diagnosis, years of age					
	15-19	-	-	3	0.1
	20-24	6	0.2	3	0.1
	25-29	11	0.3	9	0.1
	30-34	47	1.1	41	0.6
	35-39	117	2.8	100	1.5
	40-44	218	5.3	238	3.6
	45-49	414	10.1	395	6.0
	50-54	582	14.1	748	11.3
	55-59	729	17.7	948	14.3
	60-64	742	18.0	1,140	17.3
	65-69	556	13.5	1,161	17.6
	70-74	378	9.2	900	13.6
	75+	320	7.8	924	14.0
Mean (SD)		58.9 (11.1)		62.6 (11.1)	
Median (Min: Max)		59.0 (22.1)		63.0 (18.0)	
Basis of diagnosis					
Death Certificate Only		20	0.5	345	5.2
History & Physical		795	19.3	189	2.9
Endoscopy & radiology		2,551	61.9	4,784	72.4
Surgery & autopsy		206	5.0	173	2.6
Specific tests		3	0.1	523	7.9
Cytology or hematology		5	0.1	15	0.2
Histology of metastasis		3	0.1	88	1.3
Histology of primary		534	13.0	493	7.5
Autopsy with histology		3	0.1	-	-
Stage at diagnosis					
	Stage I	4	0.1	7	0.1
	Stage II	2	0.1	16	0.2
	Stage III	7	0.2	26	0.4
	Stage IV	867	21.0	1,431	21.7
	Unknown	3,240	78.6	5,097	77.5
Histology grading					
Well differentiated		2	0.1	139	2.1
Moderately differentiated		-	-	40	0.6
Poorly differentiated		-	-	30	0.5
Undifferentiated		-	-	6	0.1
Unknown		4,118	99.9	6,395	96.7

incidence trends and to identify the best model. These analyses revealed that the incidence had been significantly decreasing by (a) –0.70% per year among males (Annual Percent Change, APC: –0.70%, 95% CI: –2.1% to +0.8%) (b) –0.40% per year among females (APC: –0.40, 95% CI:

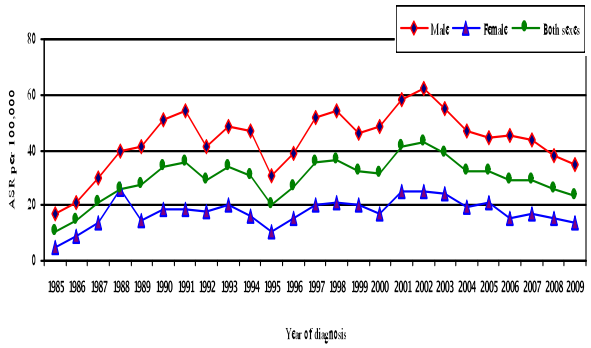

Figure 1. Incidence rates (per 100 000 per year) of Cholangiocarcinomas by Sex in Khon Kaen, 1985-2009

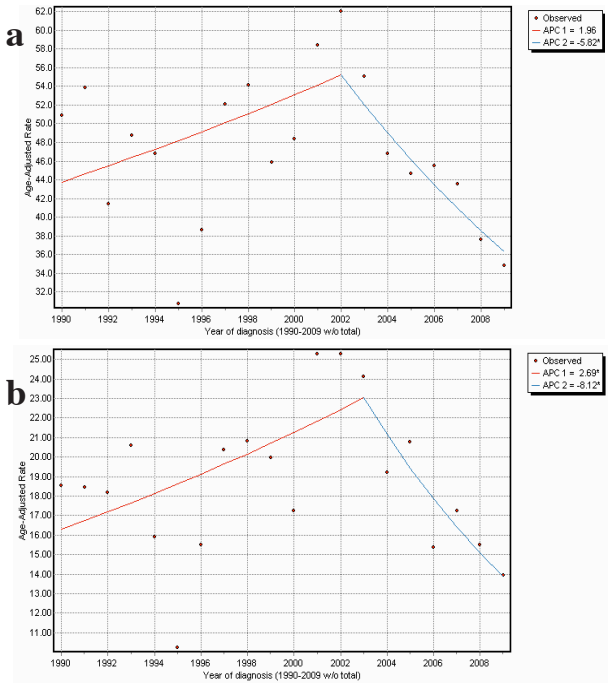

Figure 2. Joinpoint Trends in Age-adjusted Rates per 100,000 for Cholangiocarcinoma in Khon Kaen between 1990 & 2003 and 2003 & 2009. a) Males; b) females

–2.1% to +1.4%).) and (c) –0.61 per year among males and females APC: = –0.61, 95% CI: –2.1% to 0.9%). According to the Jointpoint analysis of years, the annual respective percent change (APC) in the incidence rates between 1990 and 2002, 2002 and 2009 among males was +2.0 percent per year (APC1: +2.0%, 95% CI: -0.5% to 4.4%), APC2 = –5.8%, 95% CI: –10.4% to –1.0%). In females the respective APC between 1990 and 2003 and 2003 and 2009 was +2.7 percent per year (APC1: +2.7%, 95% CI: 0.1% to 5.4%), APC2 = –8.1%, 95% CI: –14.6% to –1.1%). For both males and females the respective APC between 1990 and 2003 and 2003 and 2009 was +1.9 percent per year (APC1: +1.9%, 95% CI: +0.3% to +4.2%), APC2: –7.5%, 95% CI: –13.5% to –1.0%) (Figure 2).

Discussion

This is the first analysis of time trends in liver cancer incidence in Khon Kaen, Thailand. According to all the histological types of primary cancer of the liver (i.e., hepatocellular carcinoma (HCC) and cholangiocarcinoma (CHCA), our data showed statistically significant decreasing trends in the incidence of liver cancer in Khon Kaen between 1985 and 2009, in both males and females. Overall, the ASR per 100 000 for liver cancer was 79.4 for males and 32.0 for females. The results of the current study are similar to the 78.4 to 94.8 per 100 000 among males and the 32.7 to 39.4 per 100 000 among females, reported in the cancer incidence data from the Volumes on Cancer in Thailand (1989-1991, 1992-1994, 1995-1997, 1998-2000 and 2001-2003) (Vatanasapt et al., 1993, Deerasamee et al., 1999, Sriplung et al., 2003, Khuhaprema et al., 2007, Khuhaprema et al., 2010). By comparison, a study from Sa Kaeo province in eastern

Thailand showed that trends in liver cancer—according to death certificates between 1993-2003 and hospital records (between 1999-2003)—had risen from 6.5 to 34.2 among both males and females (Amon et al., 2005). The lower rate in Khon Kaen province may be due to differences in the way of describing (artifacts): for example, the degree of disease burden, etiology, and especially the host factors like age (Sripa, 2005). We compared the time trends of age-standardize incidence rates of liver cancer in East Asia, Europe and the USA, from Cancer Incidence in Five Continents Vol. IV-VIII and found a much higher rate in northeastern Thailand (i.e., 50.0 per 100 000 among males and 15.0 per 100 000 among females) (Qiu et al., 2007).

For Cholangiocarcinoma (CHCA), the incidence rate increased in the first 5 to 6 years (i.e., between 1985 and 1991) but this may be due to improved data collection methods and thus the completeness of the registries (Figure 1). In addition, ultrasound screening alone was not sufficiently sensitive for detection of CHCA. Since only 0.5% had suspected CHCA, further investigation(s) were needed to confirm any diagnosis (Mairiang et al., 2006). By way of confirmation, in the following 10 to 12 years (i.e., between 1992 and 2003) the rate was rather stable. The recent decline in incidence may, therefore, represent a real falling risk.

From 1990 to 2009, overall the trends shows a slight decrease, possibly due to preventive strategies in Khon Kaen, which is an endemic area for liver fluke infestations, as it is too difficult to break the cycle of infection caused by centuries old, culturally-ingrained eating patterns (Parkin et al., 1993), and re-infection by Opisthorchis viverrini (Upatham et al., 1988). As is well-known, there is a strong association between CHCA and infection with the liver flukes, both Clonorchis sinensis and O. viverrini. (Elkins et al., 1990; Srivatanakul et al., 1991; Mairiang et al., 1992). Very importantly, the WHO has now declared (in 2011) that *O. viverrin*i is a verified biological carcinogen (Sripa, 2011).

The incidence of CHCA over the past ten years has remained virtually unchanged despite the fact that it has been over twenty years since the study by Thammavit (1978) suggested nitrosamine as an initiator and liver flukes as the promoter and almost ten years since the anti-Opisthorchiasis drug (Praziquantel) was approved for wide-scale treatment. A dramatic shift in trends will take time since it probably takes thirty years to transform opisthorchiasis to CHCA (Vatanasapt et al., 1993; 1995).

Regarding data quality in the Khon Kaen Cancer Registry (KKCR), four dimensions are considered when evaluating the quality of data (Bray, 2009) and they are: comparability, validity, timeliness and completeness. How does the KKCR rate? Firstly, comparability: KKCR uses the international standard for classification and coding of new cases. This includes the definitions of incidence, the rules of recording and reporting of multiple primary cancers (Fritz et al., 2000; IACR, Lyon 2004). Secondly, validity: A synonym for validity is accuracy. We reviewed the histological verification and death certificates only (DCO) and found the percentage of morphologically-verified (%MV) cases was very low for liver cancer in Khon Kean province (males=7.9%; females=8.4%). It is common for patients to come to the hospital at a late stage when there is really only palliative care (Cancer Unit, 2010), as it is frequently too late for surgical resection or chemotherapy. Strangely, according to DCOs, this reason was given for a very low proportion of cases (males=3.3%; females=3.8%) (Khuhaprema et al., 2010). For a greater level of confidence, we used the IARC-Check for validity as well as checking the internal consistency between variables (Ferlay et al, 2005). Thirdly, timeliness: We have no formal guidelines for timeliness at present. The issues of prime concern include: data collection, data processing, statistical analysis/synthesis and reporting reliable and complete data. Lastly, completeness: We used the capture-recapture methodology to obtain a quantitative evaluation of the degree of completeness of the registry (Parkin, 2009) and the result was that the estimated completeness of cancer registration in Khon Kaen province was high (99.7 %; 95%: CI: 99.5% to 99.8%) (Suwanrungruang et al., 2011). By comparison, the same analysis of an African cancer registry for adults 15 and over revealed that the overall completeness of registration of diagnosed cancer cases was 89.6% (95%: CI: 87.0% to 91.7%) (Parkin et al., 2001).

In conclusion, the registry documents that CHCA with an ICD-O 3rd for C22.1, C24.0, C24.8, and C24.9 had an average declining trend among males and females of 0.7 and 0.4 percent per year, respectively. The rate increase seen in the KKCR in its first 5 to 6 years of operation may be due to improving thoroughness in data collection and completeness of the registries; especially since over the following 10 to 12 years CHCA rates were rather stable. Most importantly, we documented a decline in incidence in recent years which may represent a real falling risk.

Acknowledgements

We thank the Faculty of Medicine for financial support, The International Association of Cancer Registries (IACR) for the poster presented at the 32nd IACR meeting in Yokohama Japan, October 12-14, 2010, the Khon Kaen University Cancer Unit staff for their careful data collection and management, and Mr. Bryan Roderick Hamman and Mrs. Janice Loewen-Hamman for assistance with the English-language presentation of the manuscript.

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