RESEARCH COMMUNICATION

Trends in Incidence of Hepatocellular Carcinoma, 1990 - 2009, Khon Kaen, Thailand

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Abstract

Background: Liver cancer is the most frequent cancer among Thais especially people in northeastern Thailand, but there has as yet been no assessment of trend. The data of all cancers in Khon Kaen can be retrieved from data base of the Khon Kaen Cancer Registry (KKCR) which was established in 1984. Objective: To assess the incidence trend of hepatocellular carcinoma in Khon Kaen, Thailand, between 1990 and 2009. Methods: Population-based cases of liver cancer registered between 1985 and 2009 were retrieved from the KKCR data base and cases with diagnosis of hepatocellular carcinoma (HCC) with the coding C22.0 according to ICD-O were selected. Incidence trends were calculated using the Jointpoint analysis. Results: There were 7,859 cases of HCC during the study period. Males were affected two times more frequently than females. The most common age group of cases was 50 and 69 years (60.3%). Most patients were diagnosed based on radiology imaging (40.6%) while the morphology verification was 7%. The age-standardized rates (ASR) were 13.1 to 49.8 per 100,000 among males and 4.8 to 38.4 per 100,000 among females depending on year of diagnosis since 1985. Remarkably, the ASRs were clearly low during first few years of starting the registration. The overall ASRs of HCC were 30.3 per 100,000 in males (95% CI: 25.9 to 34.6) and 13.1 per 100,000 (95% CI: 10.4 to 15.8) in females. During 1990-2009, the trends in incidences have been decreasing significantly with the annual percent change (APC) of 6.2% per year (95% CI: –7.6 to –4.8) in males and by 6.5% per year in females (95% CI: –8.4 to –4.9). Conclusions: The incidence trends have been decreasing in both sexes. The recent decline in incidence may represent a falling risk.

Keywords: Population-based - hepatocellular carcinoma - incidence trends - Khon Kaen

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Introduction

Liver cancer has the highest rate in Thailand in both male and female which age standardized rate (ASR) of 38.6 and 14.6 per 100,000, respectively. The incidence is particularly high in Khon Kaen with the ASR 87.7 in male and 36.3 per 100,000 in female (Khuhaprema et al., 2010). Unlike the other part of Thailand, cholangiocarcinoma (CHCA) is far more common than hepatocellular carcinoma (HCC) in this region with the ratio of approximately 8:1 (Khuhaprema et al., 2010). Liver fluke, which is endemic in the northeast, is a common risk for developing CHCA while hepatitis virus, alcohol, aflatoxin and others are for HCC (Yu et al., 2004; IARC, 2011).

To reduce the viral hepatitis infection in population, universal hepatitis B vaccination has implemented in Khon Kaen since 1990 according to expanded program on immunization with current coverage of more than 98% (Ministry of Health, 2009). Hepatitis B vaccination has been reported to reduce the incidence of hepatocellular carcinoma (Chang et al., 1997; Lee, 1997; Bah et al., 2001).

Khon Kaen is located in the northeast of Thailand. The Khon Kaen Cancer Registry (KKCR) was established in 1984. It provides the data of prolonged cancer registration. Despite its longstanding operation, no information on trend has been produced on liver cancer until recently for cholangiocelluar carcinoma (Kamsa-ard et al., 2011). The present paper focuses on the situation regarding HCC.

Materials and Methods

All liver cancer cases with the code of C22.0 according to International Classification of Disease for Oncology (WHO, 2000) were selected from population-based data set of KKCR. These cases were diagnosed as having HCC during January 1985 to December 2009. The data for Khon Kaen residents diagnosed with cancer collected from all health centers and institutions throughout the province were extracted, reviewed and registered by KKCR staff. The registrars visit all registered sites by regular schedule. Any questionable cases are traced to the original source of

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information for clarification. Multiple primary cases are checked by physicians using their original records and with any other physicians concerned. The vital status of registered cases has been regularly updated by checking with the population statistics of the office of the Ministry of Interior using personal identification number. Death notifications by cancer cause were linked with the data set of the Bureau of policy and strategy, Ministry of public health (http://bps.opsmoph.go.th). To prevent the duplication, all data were reviewed and checked with existing registry files before data entry. All the data are verified, checked for duplication coded and entered into the CanReg4 software (http://www.iacr.com.fr/). As for population denominators, the demographic data were available from official sources on a yearly basis (Prime ministry's office, 2007).

Statistical methods

Percentages were used to describe the proportion of gender, basis of diagnosis, stage at diagnosis, and histology grading. The mean with standard deviation were used to describe age at diagnosis. The age standardized rate and 95% confidence interval (95% CI) were used to describe the incidence rates (Jensen, 1991). The Joinpoint regression program version 3.4.4 is used to identify points where a significant change in the linear slope of the trend occurred (National Cancer Institute, 2003). During the first few years of the beginning of the registry, the number of case was lower and then came to plateau thereafter. Therefore, time trends were assessed by 2 periods, 1990-2002 and 2002-2009.

Results

The study comprised 7,859 cases of hepatocellular carcinoma. The median number of cases was 317 per year (107 - 488). The number of case was lower during the fist few years of starting registration. Male to female ratio was 2.1:1. The most common age group of cases was 50 and 69 years (60.3%). The majority of case was diagnosed by mean of endoscopy and radiology (63.5%) while the morphology verification obtained only 7%. The basis of diagnosis by death certificate only (DCO) was 6.4% for the whole period. The DCO declined to 2.5% during 1998-2009. Staging was not known in majority of the cases. However, at least one fifth of patients presented at advanced stage (III and IV; 23%).

The age standardized rate (ASR) for HCC between 1985 and 2009 were 13.1 to 49.8 per 100,000 among males, 4.8 to 38.4 per 100,000 among females, and 8.9 to 35.7 per 100,000 for both males and females. The overall ASRs were 30.3 per 100,000 in male (95% CI: 25.9 to 34.6), 13.1(95% CI: 10.4 to 15.8) in females, and 21.2 (95% CI: 17.6 to 24.9) for both sexes (Figure 1).

Trends in incidence of HCC

The incidence has been decreasing significantly from 1990 to 2009 by 6.2% per year in male (APC: -6.2%, 95% CI: -7.6 to -4.8) while it has been decreasing significantly by 6.5% per year in female (APC: -6.5%, 95% CI: -8.4 to -4.9), and also decreasing significantly by 6.3 % per year in both sexes (APC: -6.3%, 95% CI: -7.8 to -4.8).

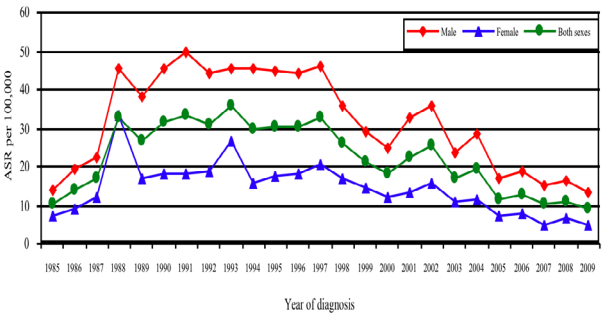

Figure 1. Incidence Rates (per 100,000 per year) of Hepatocellular Carcinoma by Gender over Time in Khon Kaen, 1985-2009

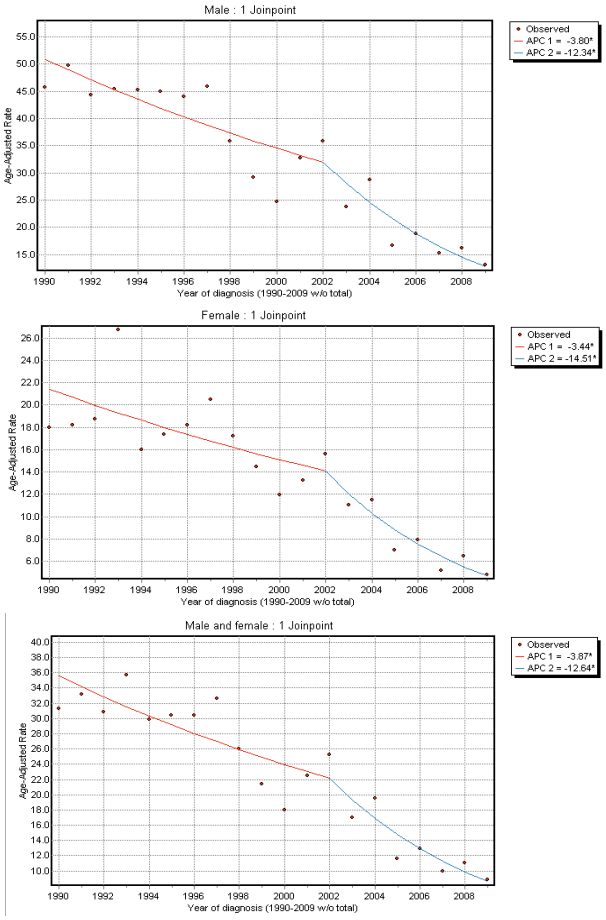

Figure 2. Trends in ASR per 100,000 for Hepatocellular Carcinoma in Khon Kaen, 1990- 2002 and 2003-2009. a) Males; b) Females; c) Both

According to the period, the annual percent change (APC) in the incidence rates in male between 1990-2002 was -3.8% (95% CI: -6.0 to -1.6) and 2003-2009 was -12.3% (95% CI: -17.5 to -6.9) (Figure 2). The APC in female during 1990-2002 was -3.4% (95% CI: -6.3 to -0.4) and during 2003-2009 was -14.5% (95%CI: -21.3 to -7.1.) . The APC in both sexes between 1990-2002 was -3.9% (95% CI: -6.1 to -1.6) and between 2003-2009 was -12.2% (95% CI: -18.1 to -6.9).

Discussion

This is the first analysis of time trend in incidence of hepatocellular carcinoma (HCC) in Thailand by using

data from Khon Kaen cancer registry during 1990-2009. Our data showed statistically significant decreasing time trend in the incidence of HCC in Khon Kaen in both males and females. The rates of decreasing time trend are more rapidly during the latter period (2003-9). The previous report of time trend of liver cancer from a province of Sakaeo, Thailand was limited to the data of death certificate and hospital record (Amon, 2005).

In this population-based registration data, HCC and cholangiocarcinoma (CHCA) were diagnosed mainly by imaging method together with tumor marker, alfa feto-protein (AFP). At least one fifth of patients presented at advanced stage (23%). According to the medical practice in those advanced cases, operations were performed in limited indicative candidates and thus, the histology was obtained in limited number (7%). However, ultrasonography and computer tomography have been reported to confirm the diagnosis of HCC and CHCA sensitively (Mairiang et al., 2006). In addition, AFP is also helpful to differentiate HCC and CHCA since it basically increases in patient with HCC. The diagnosis of HCC in this study was in acceptable limit (6.4%).

The incidences of liver cancer in Thailand and in Khon Kaen in male and female were 87.7 and 36.3 per 100,000, respectively. Among the liver cancers in Khon Kaen, CHCA is far more common than HCC which 10% has been proven to be HCC (Khuhaprema et al., 2010). CHCA is known to have a strong association with infection with the liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini* (Elkins et al., 1990; Parkin et al., 1993; Sripa and Srivatanakul, 2008) while the risk factors for development of HCC are hepatitis virus, alcohol, aflatoxin (Srivatanakul et al., 1991; Yu et al., 2004; IARC, 2011). Heavy alcohol consumption may have synergism for carcinogenesis of HCC. Alcohol consumption in Thailand is increasing recently (National News Bureau of Thailand, 2009). The direct measurement of aflatoxin-albumin in sera from human subject in Thailand suggested that aflatoxin intake was relatively low (Wild, 1992). In Thailand, universal vaccination against hepatitis B virus has been implemented for all newborns in national expanded program on immunization since 1992 but it was earlier implemented as a pilot project in Khon Kaen since 1990. Currently, the vaccination coverage is more than 98% (Ministry of Health, 2009). The prevalence of carrier for hepatitis B virus in population was 7-8% (Thongcharoen et al., 1976) prior and 0.7% after novel universal hepatitis B vaccination strategy (Chongsrisawat, 2006). In Khon Kaen, the incidence of HCC has been shown lower significantly in children who received hepatitis B vaccine at birth compared to those non-vaccinated at birth (Wichajarn et al., 2008). Similarly, in Gambia and Taiwan the data indicated that immunization of children under 1 year against hepatitis B could reduce the incidence of HCC (Chang et al. 1997; Lee, 1997; Bah et al., 2001). In our study, the trends of incidence were declining rapidly especially in the late of study period. This may indicate the preventable efficacy of the immunization against hepatitis B infection. In addition, the public hygiene was improved with the time. The infection from other hepatitis viruses was also reportedly decreased (Ratanasuwan et al., 2004).

In comparison to trends of incidence of CHCA in Khon Kaen, they remain stable throughout the period (Kamsa-ard, 2011). It's a probability from ineffective preventive strategies in Khon Kaen which is an endemic area for liver fluke, *Clonorchis sinensis* and *Opisthorchis viverrini*. It appears difficult to get rid of the cycle of infection in practice (Sripa and Srivatanakul, 2008).

Among the risk factors for hepatocellular carcinoma, hepatitis B infection is currently the only controllable factor. Other preventive strategies should be implemented to the community.

In conclusion, the incidence trends have been declining similarly in both sexes which are more rapidly after 2000. The recent decline in incidence may represent a falling risk especially hepatitis B virus infection. Long term study by using registration data will help to demonstrate this trend in incidence of hepatocellular carcinoma.

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