

## RESEARCH COMMUNICATION

# Incidence of Hepatocellular Carcinoma in Children in Khon Kaen before and after National Hepatitis B Vaccine Program

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### Abstract

**Background:** Hepatitis B virus infection is one of the most important risk factors for hepatocellular carcinoma. Hepatitis B vaccination has been obligatory in the Expanded Program on Immunization (EPI) in Khon Kaen since 1990. **Objective:** To compare the incidence of hepatocellular carcinoma in children in Khon Kaen province before and after the introduction of national hepatitis B vaccination program. **Methods:** Cases of liver tumors in children under 18, diagnosed during 1985-2007, were retrieved from the population-based cancer registry of Khon Kaen. Patients were divided into 2 groups, vaccinated and non-vaccinated with hepatitis B vaccine regarding the year of birth before or after 1990. Patients with diagnosis of liver cancer from any basis of diagnosis in population-based registration, except hepatoblastoma, were included. Patients without verified histology were assumed as having hepatocellular carcinoma if the age at diagnosis was over 10. Age-standardized incidence rates (ASRs) were analyzed and expressed as numbers per 1,000,000 population. **Results:** Fifteen patients aged 13 to 18 years were included to this study. The mean and median ages at diagnosis were 15.7 and 15 years respectively. Four children had a verified histology (age 14 to 18 years, median and mean = 16). The remaining 11 patients were diagnosed based on history & physical examination, radiology and death certificate, at the aged of 13 to 18 years. The ASRs for liver cancer in children over 10 years of age of non-vaccinated and vaccinated children were 0.88 and 0.07 per million respectively ( $p = 0.039$ ). When calculated by including children at or older the 5 years of age, the ASRs for non-vaccinated and vaccinated cases were 0.97 and 0.24 per million respectively ( $p = 0.007$ ). **Conclusions:** The incidence of hepatocellular carcinoma is significantly lower in Thai children who receive hepatitis B vaccine at birth.

**Key Words:** Hepatocellular carcinoma - incidence - children - HBV vaccine

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### Introduction

Hepatocellular carcinoma is the most common liver cancer in the world. The world incidences are 14.7 and 4.92/100,000 population in males and females (Bosch et al., 1999). The incidence of hepatocellular in developed countries, 7.64 and 2.65/100,000 population in male and female, is lower than that of developing countries, 17.84 and 6.17/100,000 population in male and female (Adrian and Di Bisceglie, 2002). The incidence is especially high in Asian and Sub-Sahara regions (Bosch, 2004). In children, hepatocellular carcinoma is less common than in adults. In Thailand, the incidence of liver tumor in children under 15 years was 2.4/1,000,000. Hepatocellular carcinoma comprises 0.7% of overall childhood cancer and 25.9% of hepatic tumor (Thai Pediatric Oncology Group, 2007).

Chronic hepatitis B viral infection appears to be an important risk factor for development of hepatocellular carcinoma (IARC, 1994; Michielsen, 2005). The prevalence of hepatitis B viral infection was 65% in patients with hepatocellular carcinoma (Tangkijvanich,

1999). In Taiwan, almost all hepatocellular carcinoma patients have hepatitis B virus infection which 94% of cases caused by maternal transmission (Chang, 1998). In Thailand, 2 children diagnosed as having hepatocellular carcinoma were demonstrated to have vertical transmission of hepatitis B viral infection (Poovorawan, 1998). In general, hepatocellular carcinoma may develop 6 to 11 years after hepatitis B viral infection (Giacchino, 1991).

The prior study in Taiwan showed that adjusted mortality rate ratios of liver tumors had declined after implementation of a large-sale of hepatitis B vaccination program (Lee, 1997). In Khon Kaen, Thailand, hepatitis B vaccination was introduced as a pilot project to the Expanded Program on Immunization (EPI) for all newborns in 1990. As a result of the positive uptake, the program was then extended to cover the whole country in 1992 (Poovorawan, 2005).

In this study, we compare the incidence of childhood hepatocellular carcinoma in Khon Kaen, Thailand in children who were non-vaccinated and vaccinated against hepatitis B virus.

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## Materials and Methods

The data of the children aged below 18 who were diagnosed as having liver cancer during 1985-2007 were retrieved from data set of the population-based cancer registry of Khon Kaen Provincial Cancer Registry. Patients with specific histologically verified such as hepatoblastoma or cholangiocarcinoma were excluded. Patients with diagnosis of liver cancer from any basis of diagnosis in population-based registration were included. Patients without verified histology were assumed as having hepatocellular carcinoma if the age at diagnosis was over 10.

To look for the possibility of children residing in Khon Kaen treated in other treating institution, the data set of other Thailand cancer registries were checked additionally. The patients were divided to 2 groups by date of birth before or after 1990 which EPI with hepatitis B vaccination was implemented.

We calculate the incidence rate at different age of diagnosis. Evidently, hepatocellular carcinoma may develop 6 to 11 years after hepatitis B virus infection and the incidence of hepatocellular carcinoma is exceedingly rare in children below 10 (Litten, 2008). Moreover, the incidence of hepatoblastoma in children over 10 years appear only 0.1 per million (Bulterys et al., 1999). Therefore, we calculate the ASR of children with conceivably assumed hepatocellular carcinoma at age of 10 or above. Age-standardized incidence rate (ASR) was analyzed and expressed as a number per million (Jensen et al., 1991). The ASR is calculated by standard method (Kramarova et al., 1996). The population was adjusted according to standard world population. The child population in Khon Kaen province was provided by Khon Kaen provincial health statistics office and numbers under 18 at the middle of study period (1996) were used to calculate the ASR. We then compared ASRs of vaccinated and non-vaccinated groups.

## Results

There were 31 patients with liver cancer in children below 18 years in Khon Kaen Province during 1985 - 2007 (22 male, 9 female). There was no childhood hepatic tumor case residing in Khon Kaen treated or diagnosed in other center after checking with other registries. Seven patients who were diagnosed as having hepatoblastoma (0 - 4 years) were excluded. Four patients were histologically verified as hepatocellular carcinoma (14 - 18 years). The remaining 20 patients (0-18 years) were diagnosed as having liver cancer by death certificate only (9 cases), history and physical examination (2 cases), autopsy (no histology 1 case), imaging (8 cases). Nine patients were under 10. Therefore, the remaining 15 patients were included for calculation. Of these patients, only one child received vaccination.

Regarding the age at diagnosis, data for hepatocellular carcinomas in children above 10 are shown in Table 1 and for over 5 in Table 2. In this latter worse case scenario, we included cases with pathological verified diagnosis of

**Table 1. Incidence of Childhood Hepatocellular Carcinoma, Aged > 10 years, Khon Kaen, 1985-2007**

Groups	No.	Crude rate*	ASR*	95% CI	p-value
Overall	15	1.17	0.95	0.47-1.44	-
Non vaccination	14	1.09	0.88	0.42-1.35	0.039
Vaccination	1	0.08	0.07	-0.07-0.21	-

\*per million

**Table 2. Incidence of Childhood Hepatocellular Carcinoma, Aged > 5 years, Khon Kaen, 1985-2007**

Groups	No.	Crude rate*	ASR*	95% CI	p-value
Overall	18	1.40	1.21	0.65-1.77	-
Non vaccination	15	1.17	0.97	0.48-1.46	0.007
Vaccination	3	0.23	0.24	-0.03-0.51	-

\*per million

hepatocellular carcinoma (4 cases) and cases of hepatic tumor (non-pathological verified).

## Discussion

Primary malignant neoplasms of the liver are rare in children, comprising only 1.1% of malignancies in children younger than 20 years of age (Bulterys et al., 1999). Primary liver cancer is classified mainly to hepatoblastoma and hepatocellular carcinoma. Hepatoblastoma appears primarily in children younger than 5 years of age while hepatocellular carcinoma occurs primarily after 10 years of age. The ASRs of hepatoblastoma and hepatocellular carcinoma in Thai children 0 - 15 years in 2003 are 2 and 0.4 per million respectively (Thai Pediatric Oncology Group, 2007). These ASRs are relatively high in comparison with those of Western countries (ASRs, hepatoblastoma 1.3; hepatocellular 0.4 per million) (Bulterys et al., 1999).

Thailand is one of the countries with high incidence of hepatitis B virus infection (CDC Health Information for International Travel, 2008). The prevalence of carrier for hepatitis B virus in population was 3.4% and 0.7% prior to and after national hepatitis vaccine program. In Khon Kaen, Thailand, hepatitis B vaccination was introduced as a pilot project to the Expanded Program on Immunization (EPI) for all newborns in 1990. The program was then extended to cover the whole country in 1992 (Poovorawan, 2005).

A prior study in Taiwan showed that the adjusted mortality rate ratios of liver tumors had declined after implementation of a large-sale of hepatitis B vaccination program (Lee, 1997).

With the population-based cancer registration, we have included all of cases of childhood liver cancers in Khon Kaen province. In addition, we have also checked the possibility of cases that might have been treated or diagnosed in other referral centers. This study reveals that the ASR in vaccination group is significantly lower than non vaccination group. This is the first study in Thailand demonstrating the role of hepatitis B vaccine lowering the incidence of hepatocellular carcinoma in children below 18 years of age. However, the follow-up period is still too short to demonstrate the effect of the incidence of hepatocellular carcinoma in adult. A

prolonged follow-up period by mean of cancer registration is needed.

Regarding the limitation of diagnosis verification in population-based registration data, the cases with varied basis of diagnosis with childhood liver cancer are included in this study. Interestingly, the age at diagnosis are clearly divided to 2 extreme age groups, younger than 5 and older than 10. Evidently, hepatocellular carcinoma may develop 6 to 11 years after hepatitis B virus infection and the incidence of hepatocellular carcinoma is exceedingly rare in children below 10 years (Giacchino, 1991; Litte, 2008). Moreover, the incidence of hepatoblastoma in children over 10 years appear only 0.1 per million (Bulterys et al., 1999). Therefore, the ASR for hepatocellular carcinoma is calculated by using the cut-point at 10 years of patient age.

The overall ASR for hepatocellular carcinoma in Khon Kaen during 1985 to 2007 is higher than that of Thailand incidence (0.95 vs 0.26 per million) (Thai Pediatric Oncology Group, 2007). The incidence of hepatocellular carcinoma is significantly lower in the vaccinated group (0.07 vs 0.88 per million) if ASR is calculated by including only patients older than 10 years at diagnosis. If the ASR is calculated by including the children aged above 5, the difference of incidence among the vaccinated and non-vaccinated group is more strongly significant (0.24 vs 0.97 per million).

In conclusion, the incidence of hepatocellular carcinoma is significantly lower in children who received hepatitis B vaccine at birth. Hepatitis B virus infection is not the only known risk factor for developing hepatocellular carcinoma. Other factors are toxin, metabolic disease, cirrhosis due to any causes and others. The serology of viral response is not known in cases of both vaccinated and non-vaccinated groups in this study. In the future study, virology study should be done. In addition, the effect of hepatitis B vaccination against liver cancer incidence in adult should be reassessed in the prolonged period of follow-up by using data of the population-based cancer registration.

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