Hepatitis B Vaccination and Hepatocellular Carcinoma Rates in Boys and Girls

Mei-Hwei Chang, MD
Wen-Yi Shau, MD, PhD
Chien-Jen Chen, ScD
Tzee-Chung Wu, MD
Man-Shan Kong
Dor-Cherng Liang, MD
Hsu-Mei Hsu, MPH
Hong-Yuan Hsu, MD, PhD
Ding-Shinn Chen, MD
for the Taiwan Childhood Hepatoma Study Group

Hepatocellular carcinoma (HCC) occurs mainly in adults 40 to 60 years of age.1 However, in areas hyperendemic for hepatitis B virus (HBV) infection, HCC may develop in children.2 We have found a nearly 100% hepatitis B surface antigen seropositivity rate in Taiwanese children with HCC, indicating an intimate relationship between HBV and childhood HCC.2 In 1984, a hepatitis B vaccination program was launched and has effectively reduced the prevalence of HBV infection, chronic HBV infection rate,3 and incidence of HCC in children in Taiwan.4

A male predominance of HCC has long been observed.5,6 The mechanism is unknown, but a tumorigenic effect of androgens has been suggested.7 We found a male-female ratio of 3.4:1 in children with HCC,8 which is similar to that in adults. Since the influence of hormones in children is much less than that in adults, investigating HCC in children may facilitate understanding of the mechanism of HCC. We therefore studied children with HCC by sex before and after the implementation of the HBV vaccination program.

METHODS

Subjects
A vaccination program was implemented in Taiwan in July 1984.9 Hepatitis B immunoglobulin was given to neonates of highly infectious mothers carrying hepatitis B e antigen. All infants received 3 or 4 doses of HBV vaccine.

According to our previous observation, HCC in children was diagnosed mainly in those older than 6 years,2 while hepatoblastoma was diagnosed in younger children.10 In this study, we included children 6 to 14 years of age with liver cancer to preclude the inclusion of hepatoblastoma.

Context Hepatocellular carcinoma (HCC) has a male predominance and is closely related to hepatitis B virus (HBV) infection. Hepatitis B virus vaccination was launched in 1984 in Taiwan for neonates of mothers carrying hepatitis B e antigen, resulting in a decreased incidence of HCC in children. The effect on boys vs girls is not known.

Objective To evaluate the association between a HBV vaccination program with incidence of childhood HCC by sex.

Design and Setting Analysis of data collected from Taiwan’s National Cancer Registry System and the Taiwan Childhood Hepatoma Study Group between 1981 and 1996.

Participants Children aged 6 to 14 years who were diagnosed as having HCC (201 boys and 70 girls).

Main Outcome Measure Incidence of HCC in boys and girls before and after implementation of the vaccination program.

Results The boy-girl incidence ratio decreased steadily from 4.5 in 1981-1984 (before the program’s introduction) to 1.9 in 1990-1996 (6-12 years after the vaccination program was launched). The incidence of HCC in boys born after 1984 was significantly reduced in comparison with those born before 1978 (relative risk [RR], 0.72; P = .002). No significant decrease in HCC incidence was observed in girls born in the same periods (RR, 0.77; P = .20). The incidence of HCC in boys remained stable with increasing age, while an increase of HCC incidence with age in girls was observed. These age and sex effects remained the same regardless of birth before or after the vaccination program.

Conclusion Our results suggest that boys may benefit more from HBV vaccination than girls in the prevention of HCC.
The study population was stratified both by age at diagnosis and the year of birth. Children with HCC who were older than 6 years on July 1, 1984, when the HBV vaccination program was launched, were born before July 1978. Children born before 1978 and after 1984 were the respective cohorts without and with the effect of HBV vaccination. Children born between 1978 and 1984 were born during the transition to full implementation of the HBV vaccination program. They might have received HBV vaccination beyond infancy.

Age-specific and birth-year–specific incidences of HCC were calculated for boys and girls. Relative incidences of HCC among children divided into groups by age, birth cohort, and sex were analyzed using Poisson regression. The modification of age effect on HCC incidence by sex was statistically tested by cross production of age and sex variables (the interaction term) and expressed in separate models when the age trends were significantly different between female and male.

The relative risk (RR) of HCC in boys born between 1978 and 1984 declined significantly in comparison with those born before 1978 (RR, 0.83; P = .02); the trend of decrease in the RR of HCC was even more evident in those born after 1984 when compared with those born before 1978 (RR, 0.72; P = .002) (Table 2). However, the trend of decline in girls was not significant for the birth cohort born between 1978 and 1983 vs those born before 1978 (RR, 1.02; P = .90) or for those born after 1984 vs those born before 1978 (RR, 0.77; P = .20).

The age trend of HCC risk was significantly modified by sex. The risk of HCC in boys remained constant from age 6 to 14 years, while the risk of HCC in girls, though lower than in boys, increased significantly with age. In separate models, there was no significant age trend for boys (RR, 0.97; 95% CI, 0.92-1.03; P = .33), while the incidence of HCC in girls increased significantly by 1.15 times for each year increment of age (RR, 1.15; 95% CI, 1.04-1.28; P = .007). The age effect in boys and girls was the same before and after vaccination (Figure).

### Table 1. Incidence of Hepatocellular Carcinoma in Boys and Girls Aged 6 to 14 Years in Taiwan, 1981-1996

<table>
<thead>
<tr>
<th>Year of Diagnosis*</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Population</td>
</tr>
<tr>
<td>1981-1984</td>
<td>56</td>
<td>5 182 103</td>
</tr>
<tr>
<td>1984-1990</td>
<td>94</td>
<td>10 753 818</td>
</tr>
<tr>
<td>1990-1996</td>
<td>51</td>
<td>10 396 566</td>
</tr>
</tbody>
</table>

†Number per 100 000 population.

### Table 2. Effect of Birth Year on the Development of Childhood Hepatocellular Carcinoma by Sex*

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Boys RR (95% CI)</th>
<th>P Value</th>
<th>Girls RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966-1977</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>1978-1983</td>
<td>0.83 (0.71-0.96)</td>
<td>.02</td>
<td>1.02 (0.79-1.30)</td>
<td>.90</td>
</tr>
<tr>
<td>1984-1989</td>
<td>0.72 (0.59-0.80)</td>
<td>.002</td>
<td>0.77 (0.52-1.15)</td>
<td>.20</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.

**RESULTS**

A consistent predominance of HCC in boys was found throughout the observation period. The incidence of childhood HCC declined gradually in boys during 1981-1996, while the incidence in girls remained stable (Table 1). Although the trend of the predominance in boys remained, the boy/girl ratio of the incidence of HCC declined gradually with time from 4.5 for years of diagnosis 1981-1984 to 1.9 for years of diagnosis 1990-1996.

**COMMENT**

In the present study, we observed a predominance of HCC in boys both before and after the HBV vaccination pro-
The incidence of HCC in boys born after July 1978 was significantly lower than in those born before July 1978 ($P=.001$). The incidence of HCC in boys 6 to 14 years did not change regardless of the birth year, suggesting that the age effect on the incidence of HCC was not prominent in boys. The incidence of HCC in girls aged 6 to 14 years increased with age, regardless of the birth year. The incidence of HCC in girls did not change in different birth cohorts.

This predominance cannot be explained by the effect of sex hormones, as in adults. Tumor suppression gene regulation, the metabolism of carcinogens, or genetic alterations have been proposed to differ between men and women and need further study. This predominance decreased after the vaccination program because the incidence of HCC decreased significantly in boys but not in girls. Why the vaccination program seems to have had more of an effect on boys remains unclear. The low incidence of HCC in girls may render the statistical comparison of the incidences difficult. It is possible that the vaccination program seems to have had a more significant effect on boys than in girls, but seems unlikely that case finding for such a serious disease would differ between boys and girls or change over time.

A seroepidemiologic study in Taipei conducted in both 1984 and 1994 in children showed no or a slight predominance in boys in the incidence of HBV infection. In contrast, the remarkable predominance of HCC in boys suggests that factor(s) in addition to chronic HBV infection may contribute to hepatocarcinogenesis in males, particularly the early occurrence in prepubertal males.

**REFERENCES**


