Prevention of Hepatocellular Carcinoma by Universal Vaccination against Hepatitis B Virus: The Effect and Problems

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Abstract

Purpose: In spite of the success of hepatitis B immunization, still a significant proportion of childhood hepatocellular carcinoma (HCC) failed to be prevented by the hepatitis B immunization program. This study is aimed to investigate the problems in the HCC prevention in children.

Experimental Design: All HCC children ages 6 to 14 diagnosed between 1981 and 2000 in Taiwan were collected from two national childhood HCC registry systems. We analyzed the causes of HCC prevention failure and the risk ratio of HCC among hepatitis B carriers born before versus after the vaccination program.

Results: The incidence of HCC per 100,000 children declined from 0.54 to 0.20 in those born before versus after the vaccination program (risk ratio, 0.36). Vaccine failure (33.3-51.4%) and failure to receive hepatitis B immunoglobulin at birth (42.4-57.5%) were the main causes of HCC prevention failure. Mother-to-child transmission of hepatitis B virus infection is an important risk factor of HCC development. This is evidenced by the very high hepatitis B surface antigen seropositive rate in our HCC children (97%) and their mothers (96%). Hepatitis B carrier children born after the vaccination program had a higher risk of developing HCC than those born before the program (risk ratio, 2.3-4.5).

Conclusions: Vaccine failure and failure to receive hepatitis B immunoglobulin are the main problems preventing eradication of HCC. Hepatitis B carrier children born after the immunization program have a higher risk of developing HCC than those born before.

Hepatocellular carcinoma (HCC) is one of the most common malignancies in humans. Hepatitis B virus (HBV) is a major etiologic agent responsible for HCC (1–4). HCC occurs mainly in adults between 40 and 60 years of age with a hepatitis B surface antigen (HBsAg) seropositive rate of ~70% to 80% (5). However, in areas hyperendemic for HBV infection, HCC may also develop in children (6). In our previous study, 94% of Taiwanese children with HCC were HBsAg seropositive. It suggests a very close relationship between HBV infection and childhood HCC in Taiwan (6). HCV infection has not been related to HCC in children in the world literature and in our previous study (7).

Universal hepatitis B vaccination has effectively reduced the prevalence of HBV infection and chronic carrier rates (8). In addition, our previous study in Taiwan also showed that, according to birth cohort, the incidence of HCC in children ages between 6 and 9 years decreased from 0.52 to 0.13 per 100,000 in those born before versus after the vaccination program (9).

However, the reduction in the incidence of HCC (75%) by the universal hepatitis B vaccination program is not as effective as that in chronic HBV infection (90%). Therefore, we are curious to know whether chronic HBsAg carriers who were born after the hepatitis B immunization program have a higher risk of developing HCC than those born before the program.

Whereas we are monitoring the long-term trend of HCC in children during the 16 years after the launch of the HBV immunization program, we have accumulated more data on children in whom the vaccination program failed to prevent HCC. We try to determine the causes of HCC prevention failure in those born after the implementation of the vaccination program. These results may point the way to set better strategies toward the success of HCC prevention.

Materials and Methods

As noted in our previous study, HCC in children is diagnosed mainly in children older than 6 years. Analyses before age 6 is

difficult because most of primary hepatic malignant epithelial neoplasms are hepatoblastoma, which are not related to HBV (10, 11). In this study, we analyze all children ages 6 to 14 years who were diagnosed between July 1981 to June 2000 as having HCC to prevent the inclusion of hepatoblastoma. We need at least 6 years of follow-up after birth in all children to assure ascertainment of HCC. Thus, we include the birth cohorts from July 1984 to June 1985, the first children to experience the Taiwan HBV immunization program, through the birth cohort of July 1993 to June 1994, the last group of which there was enough follow-up time for all children in the cohort after age 6. During this time period, 35 HCC cases occurred during 17,817,510 children-years of follow-up. We set the final date of this study as June 2000 because we need adequate time for all the hospitals to report their cases and to reconfirm the accuracy of the reporting data. This study has been approved by the Review Board of the National Health Research Institute of Taiwan.

Universal immunization program for hepatitis B in Taiwan

The universal immunization program was launched in Taiwan on July 1, 1984. It covered all neonates of hepatitis B surface antigen (HBsAg) carrier mothers during its initial 2 years. It was extended to all neonates since July 1986. Gradually, the program was extended to cover all preschool children, then school children, and finally all adults (12).

Hepatitis B immunoglobulin was administered within 24 hours after birth to neonates of highly infectious mothers carrying the hepatitis B e-antigen or having a reciprocal serotiter of HBsAg >2,560 as observed in a reverse passive hemagglutination assay. All infants received four doses of plasma-derived HBV vaccines at <1 week and 1, 2, and 12 months of age until July 1992 when the vaccination schedule was changed to three doses of recombinant yeast-derived vaccine at <1 week and 1 and 6 months of age.

Childhood hepatocellular carcinoma registry systems

Two childhood HCC registry systems are used by this study to improve accuracy. The data from the two systems, including the name, ID number, birth date, gender, address, and other data, were checked, and duplicated cases were removed. Data were then merged into a final database. The capture-recapture method was used to estimate the total case number of childhood HCC.

System 1: National Cancer Registry System. Information on cases of HCC between July 1981 to June 2000 from the data bank of the National Cancer Registry System at the National Department of Health were analyzed. This registry was established in 1979. Cases of cancer in each of the 167 hospitals over 50 beds in Taiwan were enrolled in this registry. Registered data includes the patient name, gender, date of diagnosis, location of tumor, histology, hospital, and others.

System 2: Multicentric Childhood Hepatocellular Carcinoma Study Group. To ensure the accuracy of the National Cancer Registry data, we established a multicentric Childhood HCC Study Group since 1991 to register hepatomas in children diagnosed during 1981 and onward. Pediatric gastroenterologists or oncologists from 15 major hospitals, including all the 12 tertiary referral centers in Taiwan, participated in this study group. In addition to the data in the National Cancer registry, this system provided information on the age, gender, birth date, date of diagnosis, serum HBsAg, HBV immunization history, α-fetoprotein levels of the patients, treatment, outcome, and maternal serum HBsAg.

Details in children with hepatocellular carcinoma born after the universal immunization program for hepatitis B virus

To explore the possible causes of HCC prevention failure in children born after the vaccination program in Taiwan since July 1984, factors associated with the development of HCC were investigated in HCC children born after the program. These factors included serum HBsAg, histories of HBV vaccination and hepatitis B immunoglobulin injection, and maternal serum HBsAg. Detection of HBV DNA in the liver tissue was conducted by PCR in one child with negative serum HBsAg and available liver tissue.

Hepatitis B surface antigen seropositive rates in children ages 6 to 14 years old according to birth year

From the data of (*a*) the four seroepidemiologic surveys conducted in 1984 (before the implementation of the universal vaccination program), 1989, 1994, and 1999 (i.e., 5, 10, and 15 years after the launch of the program) in the same region of Taiwan (8, 13–15), and (*b*) another survey conducted in 1989 and 1993 by random sampling of children in the whole Taiwan (16), we obtained the HBsAg seropositive rates for the age according to birth years. Based on the pattern of minimal change in seroprevalence of serum HBsAg after 2 years of age, as illustrated in the 1984 survey before the vaccination program (13), we obtained the mean of the seroprevalence rates in all the surveys for children of the same birth cohort.

Incidence of hepatocellular carcinoma among hepatitis B surface antigen–positive children ages 6 to 14 years according to birth year

The HCC incidence per 100,000 HBsAg-positive children ages 6 to 14 years was calculated according to birth year by dividing the observed number of HCC children ages 6 to 14 years born during a period of time by the number of HBsAg seropositive children of the same age group and birth cohort during the same period of time.

Statistics

Poisson regression analysis, assuming the occurrence of HCC cases as rare disease, was used to calculate the relative risk of acquiring HCC in children ages 6 to 14 years in the period after the implementation of the universal HBV immunization program versus the period before the program according to birth year. We used SAS PROC GENMOD to fit the Poisson regression model to calculate the relative risk of developing HCC among hepatitis B carriers. All estimates of the 95% confidence interval were computed using profile likelihood function (17).

Results

General trend in the incidence of hepatocellular carcinoma in children. The results of the incidence of HCC in children ages 6 to 14 years by birth year are shown in Table 1. We found that the difference in the incidence of HCC between those born before and after July 1984 was substantial ($P < 0.001$). Taking those born before July 1984 as a baseline group yielded 0.36 of risk ratio for HCC in those birth cohort (July 1984-June 1994) born after the immunization program.

Characteristics of children with hepatocellular carcinoma born after the immunization program. Thirty-five children, 25 boys and 10 girls (male to female ratio, 2.5), with HCC were born

Table 1. Incidence of HCC in children of 6 to 14 years according to birth year

Birth year*	Person-years of follow-up	No. cases	Incidence (per 100,000)	RR (CI)
1966-1984	48,764,799	263	0.539×10^{-5}	1
1984-1994	17,817,510	35	0.196×10^{-5}	0.36 (0.26-0.52)

Abbreviations: RR, risk ratio; CI: confidence interval.
*Birth year was counted from July of one year to June of the next.

after July 1984 (i.e., after the implementation of the universal hepatitis B immunization program in Taiwan). Of the 25 boys, 16 (64%) were below and 9 were above 10 years of age at diagnosis. Three girls (30%) were below and seven girls were above 10 years of age at diagnosis. All 32 children with known serum levels of α-fetoprotein had an elevated level: 29 had levels >10,000 ng/mL, and the other three had a level of 6,018, 108, and 25 ng/mL, respectively. The HBsAg status was available in 33 of the 35 children.

Analysis of the causes of hepatocellular carcinoma prevention failure in 33 hepatocellular carcinoma children with known hepatitis B virus infection status. We analyzed the possible causes of HCC prevention failure in 33 HCC children who were born after the implementation of universal HBV vaccination program with available data of serum HBsAg and/or HBV DNA status by PCR. Thirty-two (97%) of the 33 were HBsAg or HBV DNA seropositive (31 with positive serum HBsAg and one with negative serum HBsAg but positive HBV DNA in the serum by PCR). The remaining one was seronegative for HBsAg and HBV DNA by PCR assay. HCC was considered as not related to HBV infection in the latter one (Fig. 1).

Among those 32 children (97.0%) with chronic HBV infection, the causes of HCC prevention failure are most likely related to HBV prevention failure. Adding together, the possible causes of HCC prevention failure in 3.0% to 6.0% may be due to no HBV vaccination, 33.3% to 51.4% due to vaccine failure, and 42.4% to 57.5% due to no hepatitis B immunoglobulin injection in spite of three or four doses of HBV vaccination.

Risks of hepatocellular carcinoma in children with chronic hepatitis B virus infection. The HBsAg seropositive rates declined from 8.7% to 10.5% in those born before the vaccination program to 0.7% to 1.7% in those born after the program. The incidences of HCC in HBsAg carrier children ages 6 to 14 years old were increased from 5.1 to 6.2 per 100,000 in those born before the program to 11.6 to 28.9 per 100,000 in those born afterward (Table 2). Using Poisson analysis, we found a higher risk for the development of HCC in children with chronic HBV infection born after the program to be statistically significant, versus those born before the program (risk ratio, 2.3-4.5).

Discussion

After long-term follow-up in Taiwan, we have confirmed the consistent decline of the incidence of childhood HCC. The HBV immunization program has been proven to be effective in preventing HBV-related HCC in children. This study revealed that the cause of HCC in 97% of HCC children born after the HBV immunization program was very likely HBV related. The success of HCC prevention is thus very much dependent on the success of the prevention of chronic HBV infection. The two most important causes of HCC

Fig. 1. Analysis of the possible causes of HCC prevention failure in 33 HCC children who were born after the implementation of universal HBV vaccination program and were with available data of serum HBsAg. Among those 32 children with chronic HBV infection, serum HBsAg was positive in 31 and negative in the remaining one (*). The latter child was found to have positive HBV DNA in the serum by PCR. The possible causes of HCC prevention failure and their related percentage were shown in square brackets. Vaccination, received three or four doses of HBV vaccination; Hx, history; ?, unknown.
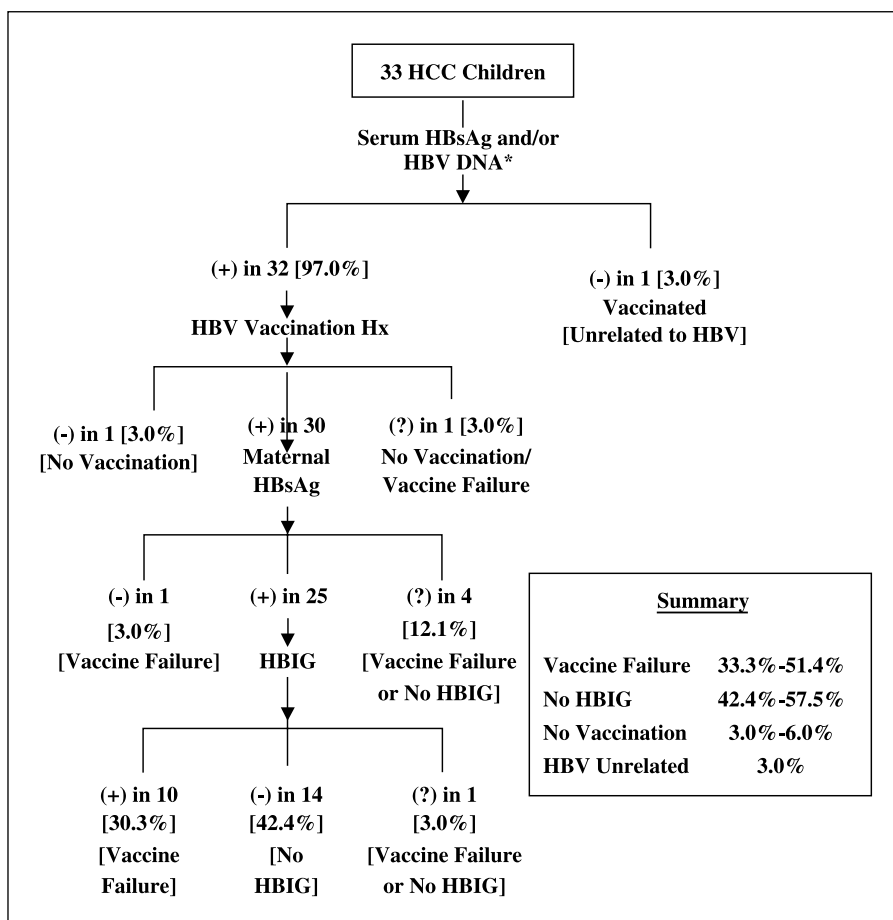
Table 2. Estimated incidence (per 100,000) of HCC among HBsAg carrier children ages 6 to 14 years according to birth year

Birth year*	Person-years at year end	Observed carrier rate (%)	Calculated no. carriers †	No. HCC	HCC in carriers ‡
1966-1984	48,764,799	8.7[§]-10.5[‖]	4,242,538-5,120,303	263	5.1-6.2
1984-1994	17,817,510	0.7[§]-1.7[‖]	124,723-302,898	35	11.6-28.1

*Birth year was counted from July of one year to June of the next year.
† Carrier rate × population of 6 to 14 years old.
‡ HCC incidence per 100,000 carriers = case no. (6-14 years) / calculated carrier no. (6-14 years old).
§Refs. (8, 13–15).
‖Ref. (16).

prevention failure were vaccine failure (33.3-51.4%) and no hepatitis B immunoglobulin injection (42.4-57.5%; Fig. 1).

It is obvious that lack of hepatitis B immunoglobulin injection in infants of highly infectious mothers is an important cause of HCC prevention failure. Adding hepatitis B immunoglobulin to HBV vaccination was reported to increase efficacy by 19% in preventing chronic HBV infection (18). Without hepatitis B immunoglobulin, they would be infected by HBV perinatally and have high risk of HCC. Hepatitis B immunoglobulin is not included as part of the universal immunization program in many areas. It is acceptable not to include hepatitis B immunoglobulin in areas with low prevalence of HBV infection or with limited budget for the vaccination program. Yet, once the universal HBV vaccination program is successfully implemented, further improvement of the efficacy and the successful prevention of HCC will be anticipated.

The birth cohort in this study is reflecting the effect of the first 10 years (1984-1994) of the HBV vaccination program in Taiwan. The coverage rate of hepatitis B immunoglobulin among the infants of high-risk mothers with positive serum hepatitis B e-antigen or reciprocal HBsAg titers >2,560 was 72% to 84% during the first 10 years of the Taiwanese HBV immunization program (11).[8]

The HBsAg carrier rate in children has been reduced from 9.8% before the HBV immunization program (1984) to 0.7% 15 years after the program (1999) in Taiwanese children (8, 13–15). Although the HBsAg seropositive rate in those born after the program has been reduced to approximately one tenth of those born before the vaccination program, the incidence of HCC in children of the same birth cohort was only reduced to 36% (Table 1). This discrepancy of the prevention efficacy may be explained by the successful prevention of horizontal transmission of HBV, whereas the maternal transmission cannot be interrupted completely by the current HBV immunization program.

Before the era of HBV immunization, ~40% of the HBsAg carriers in Taiwan were due to perinatal transmission, whereas 60% of the carriers were infected by horizontal route (18). Thus, among the 10% HBsAg carrier children in the population, ~6% were attributed to horizontal transmission and the remaining 4% were transmitted perinatally by maternal route.

The horizontal transmission can be prevented by the HBV immunization program effectively, whereas approximately a quarter (1%) of the 4% HBsAg carrier children potentially infected by their mothers may fail to respond to the hepatitis B immunization program (Table 3). The failure rate of HCC prevention ranged from 25% (9) to 36% (this study), which is very close to the failure rate of HBV prevention against maternal transmission (Table 3). Those who failed to respond to HBV immunoprophylaxis were infected mainly *in utero* or perinatally by highly infectious mothers (19).

Our study provides a strong evidence of perinatal transmission as the main route of HBV transmission in HCC children born after the universal HBV immunization era, which was not effectively eliminated by the immunization program. Another evidence supporting the better efficacy of prevention of the horizontal infection is the result of a seroepidemiologic survey conducted at 15 years after the HBV immunization program in Taiwan (8). Among the 1,357 children born after the launch of

Table 3. Comparison of the reduction of HBsAg carrier rates and incidences of childhood HCC after the universal HBV vaccination program

HBsAg carrier rates and HCC incidences in Taiwanese children	Universal HBV vaccination program	
	before	after
HBsAg carriers in the population (8, 16)	10%	1%
Percentage of HBsAg carriers in the population (8) infected by horizontal transmission	6%	0-0.1%
Percentage of HBsAg carriers in the population (8) infected by maternal transmission	4%	1%
Percentage of failure in prevention of chronic HBV infection by maternal transmission		25%
Total incidence of childhood HCC (per 10^{-5})	0.51-0.54	0.13-0.20
Percentage of failure in HCC prevention		25-36%*

*Table 1 and ref. (9).

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[8] Center for Disease Control, National Department of Health (Taiwan, ROC), unpublished data.

the HBV immunization program, 9 children were seropositive for HBsAg (8). Maternal serum HBsAg was positive in eight of nine (89%) HBsAg carrier children. These data again provide evidence to support that horizontal transmission of HBV has been prevented much more effectively than perinatal transmission by the HBV immunization program.

Further efforts to improve the hepatitis B immunoglobulin and HBV vaccine coverage rate to prevent intrauterine infection and to improve the prevention efficacy in perinatal HBV infection by highly infectious mothers are crucial for better prevention of HCC. Strategies to improve the efficacy of HBV prevention, such as developing better vaccines, the use of hepatitis B immunoglobulin in every infant of HBsAg mothers, lamivudine therapy for high-risk pregnant mothers (20), need to be further evaluated for the efficacy of HBV and HCC prevention.

In conclusion, the incidence of HCC in children has consistently declined from 6 to 16 years after the launch of the HBV immunization program in Taiwan. Vaccine failure and failure to receive hepatitis B immunoglobulin are the two most important challenges to be overcome to achieve successful HCC control. HBsAg carriers born after the HBV immunization program may have a higher risk of developing HCC than those born before the vaccination era. It is most likely due to the success in eliminating horizontal transmission and the more difficulty in eradicating perinatal transmission of HBV.

Appendix A. Taiwan Childhood Hepatoma Study Group

The members of Taiwan Childhood Hepatoma Study Group are, as follows: Tai-Tsung Chang, Kaoshiung Medical University; Jiann-Shiuh Chen, National Cheng-Kung University Hospital; Chieh-Chung Lin, Veteran General Hospital, Taichung; Fu-Chen Huang, Chang-Gung Children's Hospital, Kaoshiung; Shin-Nan Cheng, Tri-Service General Hospital; Ming-Tzong Cheng, Chang-Hua Christian Hospital; Chia-Hsian Chu, Hualien Tsu-Chi Buddhist Hospital; Su-Fen Wu, China Medical College Hospital; and Pei-Shin Chang, Taoyuan Hospital, Department of Health, Executive Yuan, Taiwan, ROC.

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