

Decreased Incidence of Hepatocellular Carcinoma in Hepatitis B Vaccinees: A 20-Year Follow-up Study

Mei-Hwei Chang, San-Lin You, Chien-Jen Chen, Chun-Jen Liu, Chuan-Mo Lee, Shi-Ming Lin, Heng-Cheng Chu, Tzee-Chung Wu, Sheng-Shun Yang, Hsu-Sung Kuo, Ding-Shinn Chen, the Taiwan Hepatoma Study Group

- Background** Hepatitis B virus (HBV) infection is a major cause of hepatocellular carcinoma. This population-based study aimed to investigate whether prevention of hepatocellular carcinoma by the universal Taiwanese HBV vaccine program, launched in July 1984, has extended beyond childhood and to identify the predictors of hepatocellular carcinoma for vaccinated birth cohorts.
- Methods** Data on 1958 patients with hepatocellular carcinoma who were aged 6–29 years at diagnosis in Taiwan between 1983 and 2004 were collected from two national hepatocellular carcinoma registries. Age- and sex-specific incidence among vaccinated and unvaccinated birth cohorts were analyzed by using Poisson regression models. All statistical tests were two-sided. Records of 64 hepatocellular carcinoma patients and 5524435 HBV vaccinees who were born after the initiation of the vaccination program were compared for HBV immunization characteristics during infancy and prenatal maternal hepatitis B surface antigen (HBsAg) and e antigen (HBeAg) serostatus.
- Results** Hepatocellular carcinoma incidence was statistically significantly lower among children aged 6–19 years in vaccinated compared with unvaccinated birth cohorts (64 hepatocellular cancers among vaccinees in 37709304 person-years vs 444 cancers in unvaccinated subjects in 78496406 person-years, showing an age- and sex-adjusted relative risk of 0.31, $P < .001$, for persons vaccinated at birth). The risk of developing hepatocellular carcinoma for vaccinated cohorts was statistically significantly associated with incomplete HBV vaccination (for those who received fewer than three doses of HBV vaccine, odds ratio [OR] = 4.32, 95% confidence interval [CI] = 2.34 to 7.91); with prenatal maternal HBsAg seropositivity (OR = 29.50, 95% CI = 13.98 to 62.60); with prenatal maternal HBeAg seropositivity (with administration of hepatitis B immunoglobulin at birth, OR = 5.13, 95% CI = 2.24 to 11.71; and without it, OR = 9.43, 95% CI = 3.54 to 25.11).
- Conclusion** The prevention of hepatocellular carcinoma by this HBV vaccine extends from childhood to early adulthood. Failure to prevent hepatocellular carcinoma results mostly from unsuccessful control of HBV infection by highly infectious mothers.

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Hepatocellular carcinoma is one of the most common cancers in humans, and hepatitis B virus (HBV) is its most important etiologic agent (1–3). Approximately 60%–80% of adult hepatocellular carcinoma patients are seropositive for the hepatitis B surface antigen (HBsAg) in areas in which HBV is endemic (4,5). In such areas, hepatocellular carcinoma may also develop in children (6). Our earlier study demonstrated nearly 100% HBsAg seropositivity among children with hepatocellular carcinoma and integration of HBV DNA into the host genome in their tumor tissue. These findings suggested a close relationship between HBV infection and childhood hepatocellular cancer in Taiwan (6,7).

A universal HBV immunization program was launched more than two decades ago in Taiwan in July 1984 (8). The prevalence of chronic HBV infection and the incidence of hepatocellular carcinoma in Taiwanese children have been substantially reduced since the inception of this program (9–11). Because hepatocellular carcinoma develops most frequently in persons aged

Affiliations of authors: Department of Pediatrics (M-HC) and Graduate Institute of Clinical Medicine (C-JL, D-SC), College of Medicine, and Graduate Institute of Epidemiology (S-LY, C-JC), College of Public Health, National Taiwan University, Taipei, Taiwan; Genomics Research Center, Academia Sinica, Taipei, Taiwan (S-LY, C-JC); Division of Hepatogastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, College of Medicine, Chang Gung University, Kaohsiung, Taiwan (C-ML); Liver Research Unit, Chang Gung University and Hospital, Linkou, Taiwan (S-ML); Division of Gastroenterology, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan (H-CC); Division of Gastroenterology, Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan (T-CW); Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan (S-SY); Department of Health, Center for Disease Control, Taipei, Taiwan (H-SK).

Correspondence to: Mei-Hwei Chang, MD, Department of Pediatrics, National Taiwan University Hospital, Chung-Shan S. Road, Taipei, Taiwan (e-mail: changmh@ntu.edu.tw).

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40 years or older (12), it is crucial to evaluate whether the cancer-preventing effect of HBV vaccination extends beyond childhood. Also, although the childhood vaccination program has been successful in preventing childhood hepatocellular carcinoma, some children in Taiwan remain affected by hepatocellular carcinoma (10,11).

The specific aims of this study were 1) to assess the ability of the universal vaccination program to prevent the incidence of hepatocellular carcinoma in children and adolescents who were 6–19 years old and had been vaccinated at birth and 2) to identify predictors of hepatocellular carcinoma risk in vaccinated cohorts. It was hoped that the results might enable us to understand the problems that hinder successful hepatocellular carcinoma control within a hepatitis B vaccination program and might therefore help improve the efficacy of the program.

Subjects and Methods

Universal Hepatitis B Immunization Program in Taiwan

During its first 2 years (July 1, 1984, to June 30, 1986), the Taiwan hepatitis B immunization program covered only infants born to mothers who were HBsAg carriers. It was extended to all infants younger than 12 months in 1986, to all children aged 1–4 years in 1987, to all children aged 5–9 years in 1988–1990, to all children and adolescents aged 10–19 years in 1989–1991, and to adults 20 years and older in 1990–1993 (8).

In the initial stage of the program, hepatitis B immunoglobulin (HBIG) was administered within 24 hours after birth to neonates of highly infectious mothers carrying the hepatitis B e antigen (HBeAg). Children of mothers with an HBsAg serotiter greater than a dilution of 1:2560 by the reverse passive hemagglutination assay were also given the HBIG within 24 hours after birth because the HBeAg assay was not available in remote areas. All infants received four doses of plasma-derived HBV vaccine when they were younger than 1 week and at 1, 2, and 12 months of age until November 1, 1992. At that time, the vaccination schedule was changed for new participants to three doses of recombinant yeast-derived vaccine, given to infants at less than 1 week, 1 month, and 6 months of age. This vaccination program had a high national coverage rate, with 92.8% of the accumulated total of vaccinated infants having received three or more doses during July 1, 1984, to December 31, 2002.

Ascertainment of Hepatocellular Carcinoma Incidence

Among both vaccinated and unvaccinated birth cohorts, the diagnostic criterion for hepatocellular carcinoma was either 1) histologically proven hepatocellular carcinoma or 2) a liver tumor detected by an imaging study in a patient with an elevated α -fetoprotein level (>400 ng/mL). Patients with elevated α -fetoprotein levels due to severe hepatitis, pregnancy, or germ cell tumors were excluded. The diagnostic criteria for hepatocellular carcinoma did not change during the study period. Pediatric hepatocellular carcinoma is diagnosed mainly in children older than 6 years, and hepatoblastoma is mostly diagnosed in children younger than 6 years (13,14). Therefore, children younger than 6 years were excluded to avoid the inclusion of hepatoblastoma.

CONTEXT AND CAVEATS

Prior knowledge

A universal hepatitis B virus vaccination program was initiated in July 1984 in Taiwan. Vaccinated children have been followed through adolescence to adulthood to determine the effectiveness of the vaccine in prevention of hepatocellular carcinoma.

Study design

Incidence of hepatocellular carcinoma in Taiwan from 1983 to 2004 was ascertained from two national cancer registries, and age- and sex-specific incidence were compared among vaccinated and unvaccinated birth cohorts with regression models. Characteristics of the 64 children who were vaccinated and developed hepatocellular carcinoma were also analyzed.

Contribution

Incidence of hepatocellular carcinoma was statistically significantly reduced among individuals who were aged 6–19 years in postvaccine vs prevaccine birth cohorts. Vaccinated individuals who still developed this cancer were likely to have been insufficiently dosed or to have been born to hepatitis B virus-seropositive mothers.

Implications

Properly administered, the effectiveness of the hepatitis B virus vaccine appears to extend into early adulthood.

Limitations

This study did not examine other possible risk factors for the development of hepatocellular carcinoma.

From the Editors

National Cancer Registry System

Taiwan has a population of 23 million, with a low migration rate, modest difference in socioeconomic development between city and township, convenient transportation, and an excellent health-care system even in remote areas. Nearly all cancer patients in Taiwan are diagnosed and treated in hospitals with 50 or more beds. In 1979, the Taiwanese Department of Health launched a cancer registry system based on the *International Classification of Diseases for Oncology* system. Hospitals with 50 or more beds are obligated to report cancer cases. This registry system is considered to be a relatively complete and accurate system, with the unregistered rate estimated to be as low as 3.8% based on the patient death certificates in 2001–2005 (15).

Information on hepatocellular carcinoma cases diagnosed between July 1, 1983, and June 30, 2004, was obtained from the national cancer registry system. Registry data included identification information, sex, date of birth, date of diagnosis, anatomical site of the tumor, histological diagnosis, and treatments. The yearly histological confirmation rate ranged from 80% to 85% for all registered cancers.

Taiwan Hepatoma Study Group Registry System

A multicentered registry system, the Taiwan Hepatoma Study Group, was established in 2004 to extend the epidemiological evaluation of the changing incidence of hepatocellular carcinoma before and after the HBV vaccination program by collecting data

about both children and young adults (6–29 years of age). Participants included adult and pediatric hepatologists, gastroenterologists, and oncologists from 19 medical centers and 25 regional and local hospitals. In this registry system, identification information, sex, date of birth, date of diagnosis, HBsAg and anti-hepatitis C virus (HCV) serostatus, serum α -fetoprotein level, image and histological diagnosis, maternal HBV markers, HBV immunization history, treatment, and outcome for hepatocellular carcinoma were recorded.

Corroboration and Ascertainment of the Data Collected From the Two Registry Systems

Vaccinated and unvaccinated birth cohorts were divided with respect to July 1, 1984, the launch time of the vaccination program. Persons born on or after July 1, 1984, were classified as vaccinated and those born before July 1, 1984, were classified as unvaccinated. Data from the two hepatocellular carcinoma registry systems were merged into a final database, with a total of 1958 hepatocellular carcinoma patients diagnosed between July 1, 1983, and June 30, 2004. They included 508 patients aged 6–19 years (444 unvaccinated and 64 vaccinated birth cohorts) and 1450 patients aged 20–29 years (all unvaccinated birth cohorts) at diagnosis for comparison. Among all 1958 hepatocellular carcinoma patients, 1712 patients were ascertained through the national cancer registry system and 1151 patients by the Taiwan Hepatoma Study Group. All patients were double-checked in both registries, and 905 duplicated patient records were identified and merged.

National Household Registry System and the Person-Years of the General Population Under Observation

By law, all birth, death, migration, and marriage events for every person in Taiwan are registered in the National Household Registry System. This registry has been continuously updated, resulting in reliable demographic data since 1905, and the Ministry of the Interior has regulated the procedures used for household registration statistics since 1973. This system was almost complete (99.3%) according to the year 2000 census in Taiwan (16), so its data are very representative of the population that each hepatocellular carcinoma patient came from. In this study, the number of person-years for those aged 6–29 years in the general population in birth cohorts from 1953 to 1998 was calculated from data in this registry.

HBV Serostatus and HBV Immunization Data

Prenatal maternal HBsAg and HBeAg serostatus of all pregnant women, the HBV vaccination dose for all infants in Taiwan, and HBIG injection time in infants of HBeAg-seropositive mothers were registered in the HBV immunization data bank of the Taiwan Center for Disease Control since the launch of the HBV vaccination program. The person-years specific for HBV markers in all pregnant mothers and the immunization records of all infants born in Taiwan during July 1984 to June 2004 were derived from this data bank.

HBsAg serostatus at the onset of hepatocellular carcinoma, history of immunization with HBIG and/or the HBV vaccine, and prenatal maternal HBsAg and HBeAg serostatus of all hepatocellular carcinoma patients born after July 1984 were retrieved either from

the Taiwan Center for Disease Control HBV immunization data bank or from the medical records in the reporting hospitals of the Taiwan Hepatoma Study Groups, whereas the HBsAg seroprevalence rate of the entire population was estimated from our previous study (17). Records of 64 hepatocellular carcinoma patients and 5 524 435 HBV vaccinees who were born after the initiation of the vaccination program were compared for HBV immunization characteristics during infancy and for prenatal maternal HBsAg and HBeAg serostatus.

Statistical Methods and Data Analysis

The hepatocellular carcinoma incidence rates per 100 000 person-years were derived by dividing the numbers of hepatocellular carcinoma patients by the person-years of the general population under observation for groups stratified by age at diagnosis, birth year, sex, maternal HBV markers, or infant immunization status. The general population was defined as the birth cohort-specific population of Taiwan according to the National Household Registry System.

The preventive effect of the HBV vaccination program on hepatocellular carcinoma incidence rates was analyzed by using Poisson regression analysis, assuming that the occurrence of hepatocellular carcinoma in young people was a rare event (18). The SAS procedure “Proc GENMOD” was used to estimate multivariable-adjusted relative risk (RR) with 95% confidence intervals (CIs).

The relative risks of developing hepatocellular carcinoma for each age group were derived by comparing hepatocellular carcinoma incidence rates of vaccinated with those of unvaccinated birth cohorts. Poisson regression analysis of hepatocellular carcinoma incidence rates was carried out to estimate multivariable-adjusted rate ratios with 95% confidence intervals for categories specified by age, sex, and birth year. The age groups were categorized for every 5 years, and the birth cohorts were categorized into two groups based on birth dates before or after July 1, 1984, when the universal HBV vaccination program was launched.

The odds ratios (ORs) with 95% confidence intervals for various hepatocellular carcinoma risk predictors including HBV immunization history, HBsAg serostatus, and maternal HBsAg and HBeAg serostatus were estimated by comparison of the number of hepatocellular carcinoma patients vs the entire vaccinated population and calculated using the profile likelihood function. Statistical significance was defined as *P* less than .05 by two-tailed tests. SAS software (version 8.01; SAS Institute Inc, Cary, NC) was used for all analyses.

The research protocol was approved by the Institutional Review Boards of the National Taiwan University Hospital and the Ethical Committee of the Bureau of the Health Promotion, Department of Health, Republic of China.

Results

Incidence Rates of Hepatocellular Carcinoma in Unvaccinated Birth Cohorts

Between July 1, 1983, and June 30, 2004, 1894 people were diagnosed with hepatocellular carcinoma who were born before July 1,

Table 1. Age-specific incidence rates for hepatocellular carcinomas (HCCs) diagnosed between July 1, 1983, and June 30, 2004, in birth cohorts born before the Taiwanese universal hepatitis B virus vaccination program, launched in July 1, 1984*

Age at diagnosis, y	Birth year	Person-years of the general population	HCC			
			No. of HCCs	Incidence rate (per 100 000 person-years)	Rate ratio (95% CI)	P
6–9	July 1973 to June 1984	15 040 548	74	0.49	1.00 (referent)	
10–14	July 1968 to June 1984	27 008 617	152	0.56	1.14 (0.87 to 1.51)	.34
15–19	July 1963 to June 1984	36 447 239	218	0.60	1.22 (0.93 to 1.58)	.14
20–24	July 1958 to June 1984	43 919 201	471	1.07	2.18 (1.71 to 2.79)	<.001
25–29	July 1953 to June 1979	43 009 757	979	2.28	4.63 (3.65 to 5.86)	<.001
Total			1894			<.001

* Rate ratios with 95% CIs and *P* values were estimated by Poisson regression analysis. All statistical analyses were two-sided. CI = confidence interval.

1984, when the Taiwan universal HBV vaccination program was launched. Of these, 74 children aged 6–9 years were diagnosed, that is, 0.49 patients per 100 000 person-years, and progressively, greater numbers of individuals were diagnosed at ages 10–14, 15–19, 20–24, or 25–29 years, with 2.28 patients per 100 000 person-years, or more than four times as many hepatocellular carcinoma patients in the oldest age group (Table 1). The age trend of increase in hepatocellular carcinoma incidence rates with increasing age was highly statistically significant ($P < .001$ based on test for trend) in those aged 20 years or older but not in those younger than 20 years.

Hepatocellular Carcinoma Incidence Rates in Vaccinated vs Unvaccinated Birth Cohorts

We also tabulated the hepatocellular carcinoma incidence rates for persons who were diagnosed at similar ages during 1983–2004 but who were born before vs after the implementation of the universal HBV vaccination program (Table 2). The hepatocellular carcinoma incidence rates per 100 000 person-years for age groups of 6–9, 10–14, and 15–19 years decreased to 0.15, 0.19, and 0.16 patients per 100 000 person-years, respectively, for the vaccinated cohorts. No difference in hepatocellular carcinoma incidence was observed in those born between July 1979 and June 1984 for whom

the primary HBV vaccination was given during later childhood. The age-specific incidence rates of hepatocellular carcinoma were statistically significantly ($P < .001$) lower in vaccinated compared with unvaccinated birth cohorts: 64 hepatocellular cancers among 37 709 304 person-years vs 444 cancers in 78 496 406 person-years. The relative risk of hepatocellular cancer in vaccinated persons compared with unvaccinated persons ranged from 0.31 to 0.38 (Table 2).

Difference in Hepatocellular Carcinoma Incidence by Sex

We also tabulated the incidence rates of hepatocellular carcinoma by sex in the following age groups: 6–9, 10–14, and 15–19 years. Hepatocellular carcinoma incidence predominated among boys in all age and birth year groups (Table 3). The most remarkable difference in incidence by sex was found in children aged 6–9 years, among whom the male to female ratio was especially high. Vaccinated cohorts had lower hepatocellular carcinoma incidence rates than unvaccinated cohorts in all groups defined by age and sex.

Multivariable Regression Analysis of Hepatocellular Carcinoma Incidence

Relative risks of developing hepatocellular carcinoma in vaccinated vs nonvaccinated birth cohorts were then calculated using

Table 2. Incidence rates of hepatocellular carcinoma (HCC) diagnosed in 1983–2004 among children who were 6–9, 10–14, or 15–19 years old and born before or after the launch of the Taiwanese universal hepatitis B virus (HBV) vaccination program in July 1, 1984*

Age at diagnosis, y	Birth year	Person-years	HCC			
			No. of HCCs	Incidence rate (per 100 000 person-years)	Rate ratio (95% CI)	P
6–9	July 1973 to June 1979	7 028 287	36	0.51	1 (referent)	
	July 1979 to June 1984	8 012 261	38	0.47	0.93 (0.59 to 1.46)	.74
	July 1984 to June 1998	17 010 463†	26†	0.15	0.30 (0.18 to 0.42)	<.001
10–14	July 1968 to June 1979	17 025 965	102	0.60	1 (referent)	
	July 1979 to June 1984	9 982 652	50	0.50	0.84 (0.60 to 1.17)	.29
	July 1984 to June 1994	14 395 987†	28†	0.19	0.32 (0.21 to 0.49)	<.001
15–19	July 1963 to June 1979	26 506 175	138	0.52	1 (referent)	
	July 1979 to June 1984	9 941 064	80	0.80	1.55 (1.17 to 2.04)	.001
	July 1984 to June 1989	6 302 890†	10†	0.16	0.30 (0.16 to 0.58)	<.001

* Rate ratios with 95% CIs and *P* values were estimated by Poisson regression analysis. All statistical tests were two-sided. CI = confidence interval.

† Only 64 children with HCC were aged 6–19 years and born after the initiation of HBV vaccination program.

Table 3. Comparison of incidence rates of hepatocellular carcinoma (HCC) during July 1983 to June 2004 between boys and girls by age among birth cohorts born before vs after the national hepatitis B virus vaccination program*

Age at diagnosis, y	Birth year	Male			Female			Male to female rate ratio (95% CI)	P
		Person-years	No. of HCCs	Incidence rate (per 100 000 person-years)	Person-years	No. of HCCs	Incidence rate (per 100 000 person-years)		
6–9	1973–1984	7 743 549	63	0.81	7 296 999	11	0.15	5.40 (2.84 to 10.24)	<.001
	1984–1998	9 003 355	21	0.24	8 007 108	5	0.06	3.74 (1.41 to 9.91)	.008
10–14	1968–1984	13 894 862	103	0.74	13 113 755	49	0.37	1.98 (1.41 to 2.79)	<.001
	1984–1994	7 478 178	18	0.23	6 917 809	10	0.14	1.67 (0.77 to 3.61)	.196
15–19	1963–1984	18 703 552	156	0.83	17 743 687	62	0.35	2.38 (1.78 to 3.20)	<.001
	1984–1989	3 253 139	7	0.22	3 049 751	3	0.10	2.19 (0.57 to 8.46)	.256

* Rate ratios with 95% CIs and *P* values were estimated by Poisson regression analysis. All statistical tests were two-sided. CI = confidence interval.

Poisson regression analysis adjusted for birth cohort, age at diagnosis, and sex. The vaccinated birth cohorts had a statistically significantly lower hepatocellular carcinoma incidence rate than the unvaccinated birth cohorts, with an adjusted relative risk of 0.31 (95% CI = 0.24 to 0.41, *P* < .001) (Table 4). Boys had a statistically significantly higher incidence of hepatocellular carcinoma than girls (adjusted RR = 2.50, 95% CI = 2.04 to 3.01, *P* < .001).

HBsAg and Anti-HCV Serostatus

We also examined the characteristics of persons who were vaccinated against HBV and developed hepatocarcinoma to determine why they remained at risk (see Supplementary Table 1, available online). Among 64 hepatocellular carcinoma patients born after July 1, 1984, 59 had data available concerning HBsAg serostatus at the time of hepatocellular carcinoma diagnosis. The HBsAg seropositivity rate (56 of 59 [94.9%]) was statistically significantly higher than that (219 of 17 637 [1.2%]) of an age-matched control from a community survey in Taiwan (*P* < .001) (16), suggesting that incidence of hepatocellular carcinoma among HBV vaccinees is associated with HBV infection. None of the remaining three HBsAg-seronegative hepatocellular carcinoma patients were anti-HCV positive.

Because anti-HCV testing was available widely in Taiwan after July 1, 1992, only those hepatocellular carcinoma patients who were diagnosed after that date were analyzed for anti-HCV data. All of the 23 vaccinated children aged 6–19 years who had hepatocellular carcinoma and who were tested for HCV status were anti-HCV seronegative.

Prenatal Maternal HBsAg and HBeAg Serostatus

We also investigated whether children who were diagnosed with hepatocellular carcinoma after the initiation of the vaccine program might have HBsAg- or HBeAg-seropositive mothers (Table 5). Children whose mothers were seropositive for HBsAg and who were exposed perinatally (44 hepatocellular carcinoma patients and 729 420 persons in the entire vaccinated population) had a higher risk of developing hepatocellular carcinoma than those with HBsAg-seronegative mothers (eight hepatocellular carcinoma patients and 3 656 182 persons in the entire vaccinated population) (OR = 29.50, 95% CI = 13.98 to 62.60, *P* < .001).

HBV Immunization History

We also checked to determine whether those who developed hepatocellular carcinoma in the vaccine era had been properly dosed and immunized (Table 5). Those with incomplete HBV vaccination, that is, fewer than three doses of HBV vaccine (14 hepatocellular carcinoma patients and 395 976 persons in the entire vaccinated population), had a higher risk of developing hepatocellular carcinoma than those with complete HBV vaccination (42 hepatocellular carcinoma patients and 5 128 459 persons in the entire vaccinated population) (OR = 4.32, 95% CI = 2.34 to 7.91, *P* < .001).

Among the 35 children with hepatocellular carcinoma whose mothers had known prenatal HBsAg and HBeAg status, 27 hepatocellular carcinoma patients with HBeAg-seropositive mothers should have received HBIG at birth in addition to three or more doses of HBV vaccine according to our protocol. We found that 19 of these 27 patients with highly infectious mothers

Table 4. Multivariable-adjusted relative risk of developing hepatocellular carcinoma (HCC) between July 1983 and June 2004 in birth cohorts born before vs after the national hepatitis B virus vaccination program*

Variable	Group	Person-years	No. of HCCs	RR (95% CI)	P
Birth cohort	Nonvaccinated	78 496 404	444	1.00 (referent)	
	Vaccinated	37 709 340	64	0.31 (0.24 to 0.41)	<.001
Age, y	6–9	32 051 011	100	1.00 (referent)	
	10–14	41 404 604	180	1.18 (0.92 to 1.51)	.183
	15–19	42 750 129	228	1.26 (0.99 to 1.60)	.065
Sex	Female	56 129 109	140	1.00 (referent)	
	Male	60 076 635	368	2.50 (2.04 to 3.01)	<.001

* Rate ratio with 95% CIs and *P* values were estimated by Poisson regression analysis. All statistical tests are two-sided. CI = confidence interval; RR = relative risk.

Table 5. Influence of prenatal maternal exposure and hepatitis B virus (HBV) immunization history during infancy on risk of hepatocellular carcinoma (HCC) among patients vs those in the general population who were 6–19 years old during July 1983 and June 2004*[§]

Risk factor	No. of HCC patients (%)*	Persons in the entire vaccinated population*†	OR (95% CI)	P
Prenatal maternal HBsAg‡	Known maternal HBsAg (n = 52)			
HBsAg seronegative	8	3656182	1.00 (referent)	
HBsAg seropositive	44	729420	29.5 (13.98 to 62.60)	<.001
HBV vaccination status	HBsAg seropositive patients (n = 56)			
Vaccination ≥3 doses	42	5128459	1.00 (referent)	
Vaccination <3 doses	14	395976	4.32 (2.34 to 7.91)	<.001
Maternal HBsAg and HBeAg status and patient's HBIG immunization status	Known maternal HBeAg in HBsAg seropositive patients (n = 35)			
HBsAg seropositive and HBeAg seronegative and HBIG seronegative	8	464763	1.00 (referent)	
HBsAg seropositive and HBeAg seropositive and HBIG seropositive	19	215343	5.13 (2.24 to 11.71)	<.001
HBsAg seropositive and HBeAg seropositive and HBIG seronegative	8	49314	9.43 (3.54 to 25.11)	<.001

* Data on HBV vaccination history and HBIG immunization during infancy and prenatal maternal HBsAg and HBeAg serostatus among the birth cohorts from July 1984 to June 2004 were obtained from the Taiwan Center for Disease Control HBV Immunization data bank. CI = confidence interval; HBeAg = hepatitis B e antigen; HBIG = hepatitis B immunoglobulin; HBsAg = hepatitis B surface antigen; OR = odds ratio.

† Persons from entire vaccinated population in Taiwan of the same birth cohorts and specified HBV immunization history or prenatal maternal HBV serostatus as the HCC patients to serve as a control for comparison.

‡ Prenatal maternal screening rate was 79% in Taiwan.

§ Data were analyzed by logistic regression; P values were two-sided.

were completely immunized with HBIG injection at birth and three or more doses of HBV vaccine, but they were still at a higher risk of developing hepatocellular carcinoma than those with HBsAg seropositive and HBeAg seronegative mothers (OR = 5.13, 95% CI = 2.24 to 11.7) (19 of 215 343 vs eight of 464 763, $P < .001$) (Table 5). They were vaccine failure patients. The remaining eight of the 27 high-risk patients did not receive HBIG injection at birth, leading to an even higher risk of developing hepatocellular carcinoma (OR = 9.43, 95% CI = 3.54 to 25.11) (eight of 49 314 vs eight of 464 763, $P < .001$) (Table 5). None of the nine hepatocellular carcinoma patients with unknown prenatal maternal HBeAg serostatus received HBIG injection.

Comparison of the Effect of Recombinant vs Plasma-Derived Vaccine

Recombinant HBV vaccine was used since November 1992, so we also compared hepatocellular carcinoma incidences in the birth cohorts of vaccinated children born in July 1984 to October 1992 vs November 1992 to June 2004 by multivariable regression analysis.

Hepatocellular carcinoma incidence rates were statistically significantly lower in the birth cohorts of 1992–2004, to whom the recombinant vaccine was given (Table 6). However, the reduced incidence of hepatocellular carcinoma in post-1992 birth cohorts might also be attributed to the higher rate of HBIG injection at birth in the 1992–2004 birth cohorts (85.3%) compared with that in the children from 1984 to 1992 with prenatal HBeAg seropositive and HBsAg seropositive mothers (77.6%).

Discussion

In this study, we provided new evidence that the incidence rate of hepatocellular carcinoma in children 6–19 years of age was statistically significantly reduced for those born after the initiation of the vaccination program. These data suggest that the effectiveness of the universal HBV immunization program to prevent hepatocellular carcinoma has extended beyond childhood and into young adulthood over the past two decades. This study provides evidence of effective long-term cancer prevention

Table 6. Multivariable-adjusted relative risk of developing hepatocellular carcinoma (HCC) in children who received recombinant vaccine (born in November 1992 to June 2004) vs those who received plasma-derived vaccine (born in July 1984 to October 1992) of the hepatitis B virus–vaccinated cohort*

Variable	Vaccine group	Person-years	No. of HCCs	RR (95% CI)	P
Vaccine	Plasma vaccine	15768508	32	1.00 (referent)	
	Recombinant vaccine	8101136	7	0.43 (0.19 to 0.97)	.04
Age, y	6–9	17010463	26	1.00 (referent)	
	10–11†	6859181	13	1.12 (0.58 to 2.20)	.73
Sex	Female	11300232	11	1.00 (referent)	
	Male	12569412	28	2.32 (1.16 to 4.66)	.01

* Relative risks were estimated by multivariate Poisson regression analysis. All statistical tests were two-sided. CI = confidence interval; RR = relative risk.

† Only children of 6–11 years old were analyzed because those born after July 1992 were younger than 12 years up to June 2004.

by vaccination and supports the conclusion that the HBV vaccine is a good cancer-preventive vaccine.

Effective strategies to enhance the efficacy of hepatocellular carcinoma prevention by HBV immunization can be substantiated only after understanding the causes of prevention failure. Chronic HBV infection is a strong risk factor for hepatocellular carcinoma development among those born after the implementation of the vaccination program. Most (95%) vaccinated hepatocellular carcinoma patients aged 6–19 years were HBsAg seropositive. The success of the hepatocellular carcinoma prevention depends mainly on the eradication of chronic HBV infection.

These data revealed that prenatal maternal HBsAg status is the key factor affecting chronic HBV infection and hence hepatocellular carcinoma development. Vaccine failure and poor compliance with the HBV immunization protocol are the two most important causes of failure to block HBV transmission to children from high-risk mothers, which leads to hepatocellular carcinoma prevention failure.

In this study, at least one-half of the children with hepatocellular carcinoma received complete immunoprophylaxis but were not protected from chronic HBV infection and hepatocellular carcinoma. Vaccine failure is a problem leading to prevention failure of hepatocellular carcinoma. With intrauterine HBV infection as an example, it occurred in approximately 2.4% of the infants of HBeAg-seropositive HBsAg carrier mothers (19). Maternal transmission of HBV could not be eradicated by the current HBV immunization program. Further efforts to completely interrupt maternal transmission are crucial in eradicating HBV-related hepatocellular carcinoma.

Those who received incomplete HBV vaccination (ie, fewer than three doses of the vaccine) during infancy and infants of HBeAg- and HBsAg-seropositive mothers with no HBIG at birth had higher risk of developing hepatocellular carcinoma (Table 5). Approximately 30% of children with hepatocellular carcinoma born to HBeAg-seropositive HBsAg carrier mothers did not receive HBIG at birth. Improvements of the HBIG injection rate within 24 hours after birth in infants of high-risk mothers should be implemented.

Hepatitis B vaccine was introduced throughout 164 World Health Organization member states by the end of 2006 (World Health Organization Department of Immunization, Vaccines and Biologicals data; 2007 global summary) (<http://www.who.int/immunization/documents/en/>). Global coverage was estimated at 60% and varied from 86% in the United States to 28% in Southeast Asia. We must enhance the HBV vaccine coverage rate worldwide, give HBIG to infants of high-risk mothers, and set strategies to combat vaccine failure for the success of global hepatocellular carcinoma control.

In spite of the important role of HBV infection in hepatocellular carcinoma among children and adolescents, HBV may not be its only etiologic factor. This study did not investigate the role of other possible risk factors for hepatocellular carcinoma reported in adults. We therefore have some reservations in concluding that HBV vaccination is the only factor contributing to the reduction of hepatocellular carcinoma. Although HCV infection may also contribute to hepatic tumorigenesis (20), we did not find sufficient evidence in this study or in earlier data (21) to support HCV as an

important etiologic agent in hepatocellular carcinoma among children and adolescents. Smoking, alcohol consumption, and aflatoxin exposures have also been reported as risk factors (22–24). However, prevalence of smoking and alcohol consumption in adolescents increased only in recent years in Taiwan (25). Furthermore, the relatively higher male predominance in the 6- to 9-year age group than in the 10- to 19-year age group suggests that hepatocellular carcinoma occurs before adolescence and cannot be explained by smoking or alcohol consumption. Low prevalence of aflatoxin-related mutations at codon 249 of the tumor suppressor gene *TP53* in hepatocellular carcinoma patients in Taiwan implies that aflatoxin is not an important etiologic agent (26).

This study has limitations in that the role of host factors, such as genetic polymorphisms, were not studied, which could influence the interpretation of the data. Yet, most of the host factors that predispose one to hepatocellular carcinoma are still unclear and remain to be identified. The HBV variants or genotypes among our hepatocellular carcinoma patients also need to be further elucidated.

In conclusion, HBV vaccination has proven to be good at preventing hepatocellular carcinoma both in children and in young adults two decades after the initiation of the Taiwan HBV immunization program. In those cases in which the HBV vaccine did not prevent hepatocellular cancer, the most common cause appears to have been failure to control perinatal HBV infection by highly infectious mothers. Because we observed a trend of increased hepatocellular carcinoma incidence among subjects who were aged 20 years or older in this study, we anticipate that continued work will be necessary to further establish the efficacy of the vaccine in preventing hepatocellular carcinoma among adults.

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In addition to the authors, members of the Taiwan Hepatoma Study Group include the following persons:

Tsang-Eng Wang, MD, Department of Internal Medicine, Mackay Memorial Hospital, Taipei; Der-Cheng Liang, MD, Department of Pediatrics, Mackay Memorial Hospital, Taipei; Man-San Kong, MD, Department of Pediatrics, Chang Gung Memorial Hospital, Linkou; Yao-Jong Yang, MD, Department of Pediatrics, College of Medicine, National Cheng-Kung University, Tainan; Gin-Ho Lo, MD, Division of Gastroenterology, Department of Internal Medicine, Veteran General Hospital, Kaohsiung; Shu-Fen Wu, MD, Department of Pediatrics, China Medical University Hospital, Taichung; Maw-Soan Soon, MD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Changhua Christian Hospital, Changhua; Wan-Long Chuang, MD, Department of Internal Medicine, Kaohsiung Medical University, Kaohsiung; Tai-Tsung Chang, MD, Department of Pediatrics, Kaohsiung Medical University, Kaohsiung; Chi-Chieh Yang, MD, Digestive Disease Center, Changhua Show-Chwan Memorial Hospital, Changhua; Ching-Yih Lin, MD, Division of Gastroenterology, Department of Internal Medicine, Chi-Mei Medical Center, Tainan; Bor-Wen Chen, MD, Department of Pediatrics, Koo Foundation Sun Yat-Sen Cancer Center, Taipei; Po-Ming Wang, MD, Department of Radiation Oncology, Cheng-Ching Hospital, Taichung; Rong-Nan Chien, MD, Liver Research Unit, Chang Gung Memorial Hospital and University, Keelung; Chia-Hsiang Chu, MD, Department of Pediatrics, Buddhist Tzu-Chi General Hospital, Hualien; Li-Ying Liao, MD, Department of Internal Medicine, Taipei City Hospital–Ren Ai Branch, Taipei; Fu-Cheng Huang, MD, Department of Pediatrics, Chang Gung University, College of Medicine, Kaohsiung; Ehr-Hsin Tsai, MD, Department of Internal Medicine, Tzu-Yuan Hospital, Yunlin; Chien-Sen Tseng, MD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yuan’s General Hospital, Kaohsiung; Kuo-Ching Yang, MD, Division of Gastroenterology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei; Lien-Ray Mo, MD, Department of Gastroenterology, Tainan Municipal Hospital, Tainan; Yeong-Shan Cheng, MD, Department of Gastroenterology, Wang-Fang Hospital, Taipei Medical University, Taipei; Chang-Hua Chou, MD, Department of Internal Medicine, Sin-Lau Hospital, Tainan; Sin-Nan Chien, MD, Department of Pediatrics, Tri-Service General Hospital, Taipei, Taiwan.

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