Short Communication

Trends in the Incidence of Hepatocellular Carcinoma in Boys and Girls in Taiwan after Large-Scale Hepatitis B Vaccination

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Abstract

In July 1984, large-scale hepatitis B vaccination of newborns began in Taiwan. Vaccination decreased the overall incidence of childhood hepatocellular carcinoma (HCC). We conducted this study to learn whether the vaccination program had the same effect on boys and girls. We collected liver carcinoma (including HCC and hepatoblastoma) deaths from 1974 to 1999 from the Taiwan Mortality Registry and the 1974–1999 population data from the Taiwan Ministry of Interior to calculate the liver carcinoma mortality rate. The populations ages 0–14 and ages 15–100 in each calendar year were treated as the study group and the reference group, respectively. We divided the 1974–1999 calendar years into 4-year strata and calculated the mortality rates of each 4-year period. We used the 1980–1983 mortality rate as the standard to calculate 4-year-interval mortality rate ratios. Vaccination effects by age and gender were estimated dividing the study and the reference groups into male and female subgroups. We used a double-comparison method to confirm the effects of hepatitis B vaccination: the mortality rate trend of the study group (ages 0–14) compared with the reference group (ages 15–100) in the same period (1984–1999), and the mortality rate trend of the study group (age 0–14) compared with itself in the pre- and postvaccination periods (1974–1983, 1984–1999). Liver carcinoma mortality decreased significantly among both males and females after 1984. In the study group, the male mortality rate decreased by up to 70%, and the female mortality rate decreased by up to 62% in the 1996–1999 interval compared with the 1980–1983 period. Both the male and the female study groups' mortality rate trends decreased from 1983 to 1999 compared with the 1974–1983 period or compared with the same period of the reference groups. Our results indicate hepatitis B vaccination decreases childhood HCC in both boys and girls.

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Introduction

Many studies support the hypothesis that chronic infection with hepatitis B virus causes HCC[2] (1–3). Before 1984, the prevalence of chronic hepatitis B infection in Taiwan was 15–20% (4); about 3 million people were chronically infected. Although such individuals may or may not have clinical symptoms of hepatitis, some develop HCC in later life. Males develop HCC more frequently than females. The male:female ratio of HCC is 2:1 in children and up to 5:1 in adults (5, 6). HCC mortality in Taiwan is high. Three thousand people died of HCC in 1983.

In July 1984, large-scale hepatitis B vaccination commenced in Taiwan. More than 300,000 newborns were vaccinated every year thereafter in this free program. The vaccination program effectively decreased chronic hepatitis B infection rates in children from 9.8% to 1.3% (7). Previously, we and other investigators reported that childhood HCC decreased after 10 years of hepatitis B vaccination (8, 9). Recently, Chang *et al.* (10), using data in the Taiwan National Cancer Registry, suggested that boys might benefit more than girls from hepatitis B vaccination in the prevention of HCC. They reported that the incidence of HCC was significantly reduced in boys born after 1984, but not in girls.

There are two sets of national health data kept by the National Health Department of Taiwan: the Cancer Registry and the Mortality Registry. In general, the Mortality Registry had more liver carcinoma cases reported than the Cancer Registry. Given that liver cancer mortality is high and 5-year survival is well below 20% in Taiwan (5, 6), surveillance of mortality rates instead of incidence rates is a reasonable alternative to investigate the effects of hepatitis B vaccination. Therefore, we used the National Mortality Registry data to ascertain the effects of hepatitis B vaccination on boys and girls.

Materials and Methods

We collected the 1974–1999 Taiwan Mortality Registry data from the Health Statistics published by the National Health Department of Taiwan. All of the cases coded "155" (liver carcinoma, which includes HCC and hepatoblastoma) according to the International Classification of Diseases were included in our study. To calculate liver carcinoma mortality rates, we also collected the Taiwanese population data, which were obtained from the annual reports on demographic statistics published by the Ministry of Interior. The population ages 0–14 in each calendar year was designated the study group, and the population ages 15–100 in each year was considered the reference group. Because the large-scale hepatitis B vaccination program of neonates began in July 1984, the percentage vaccinated in the study group (0–14 years) increased from 3.3% in 1984, to 10% in 1985, to 96.7% in 1998, and to 100% in 1999.

[2] The abbreviation used is: HCC, hepatocellular carcinoma.

Vaccinated children in the study group became predominant in the later years of the study. We reasoned that if children older than 15 years were included in the study group, the percentage vaccinated might not be sufficient to estimate an effect of the vaccination program. To reduce year-to-year fluctuations in liver carcinoma mortality, we divided the 1974–1999 calendar years into 4-year strata (1974–1975, 1976–1979, 1980–1983, 1984–1987, 1988–1991, 1992–1995, and 1996–1999) and calculated the mortality rate of each 4-year period. We used the 1980–1983 mortality rate as the standard to calculate each 4-year mortality rate ratio. Poisson regression was performed using the STATA statistics software.

We divided the study and the reference groups into male and female subgroups to evaluate the vaccination effects separately. To estimate mortality rate trends, Spearman correlations of mortality rates between 1974 and 1999 in the study and the reference groups were calculated. If hepatitis B vaccination decreased HCC incidence, then the liver carcinoma mortality rate trend of the study group (ages 0–14) should have decreased in the 1984–1999 period compared with the reference group (ages 15–100) in the same interval or compared with itself in the 1974–1983 period. This is a double-comparison method; the mortality rate trend of the study group (ages 0–14) compared with the reference group (ages 15–100) in the same period (1984–1999), and the mortality rate trend of the study group (ages 0–14) compared with itself in different periods (1974–1983, 1984–1999). The two comparisons, if they yielded similar results, would make the vaccination effects more convincing.

Results

Table 1 shows the number of liver carcinoma deaths, the population sizes, the mortality rates, and the rate ratios between 1974 and 1999 by 4-year strata in the study and the reference groups. Both male and female liver carcinoma mortality decreased significantly after 1984. In the 0–14-years-of-age (study) group, male mortality decreased by up to 70%, and female mortality decreased by up to 62% in the 1996–1999 period compared with the 1980–1983 period.

Mortality rate trends from 1974 to 1983 increased significantly in 0–14-year-old boys (Spearman's correlation coefficient = 1; $P < 0.05$) and nonsignificantly in girls (Spearman's correlation coefficient = 0.5; $P > 0.05$). The study group mortality rate trend from 1983 to 1999 decreased in boys (Spearman's correlation coefficient = −1; $P < 0.05$) and in girls (Spearman's correlation coefficient = −0.9; $P < 0.05$). On the other hand, the reference group (ages 15–100) mortality rate trend from 1974 to 1983 significantly increased in males (Spearman's correlation coefficient = 1; $P < 0.05$) and nonsignificantly in females (Spearman's correlation coefficient = 0.5; $P > 0.05$). The reference group mortality rate trend from 1983 to 1999 continued to increase in males (Spearman's correlation coefficient = 1; $P < 0.05$) and in females (Spearman's correlation coefficient = 0.9; $P < 0.05$). Therefore, both the male and the female study groups' mortality rate trends decreased from 1983 to 1999 when compared with the 1974–1983 period or compared with the same period of the reference groups. These declines in liver cancer mortality are most likely attributable to the large-scale hepatitis B vaccination program initiated in 1984.

Table 2 shows the male:female ratios of the liver carcinoma mortality rates. The male:female ratio was greater than 1.5 from 1975 to 1999 in both the study and the reference groups. In the study group, the male:female ratios trend appeared to increase from 1974 to 1983 and decrease from 1983 to 1999, but both were nonsignificant (Spearman's correlation

Table 1 Liver carcinoma mortality of the study group (0–14 years of age) and the reference group (15–100 years of age) between 1974 and 1999

Years	Male (0–14 yr)				Female (0–14 yr)				Male (15–100 yr)				Female (15–100 yr)			
	No. of deaths	Population	Mortality[a] rate	Rate[b] ratio	No. of deaths	Population	Mortality[a] rate	Rate[b] ratio	No. of deaths	Population	Mortality[a] rate	Rate[b] ratio	No. of deaths	Population	Mortality[a] rate	Rate[b] ratio
1974–75	38	5,900,065	0.64	0.63	23	5,570,060	0.41	0.87	2,982	10,734,303	27.78	0.80	880	9,505,062	9.26	0.97
1976–79	80	11,751,200	0.68	0.67	42	11,084,903	0.38	0.80	6,937	23,435,553	29.60	0.86	1,852	20,999,882	8.82	0.93
1980–83	120	11,819,258	1.02	1	53	11,130,120	0.48	1	8,962	25,957,113	34.53	1	2,244	23,598,133	9.51	1
1984–87	94	11,713,677	0.80	0.79	30	11,034,476	0.27	0.57	10,418	28,207,282	36.93	1.07	2,714	22,972,515	11.81	1.24
1988–91	78	11,395,861	0.68	0.67	23	10,699,580	0.21	0.45	11,821	30,222,588	39.11	1.13	2,944	28,160,917	10.45	1.10
1992–95	49	10,884,451	0.45	0.44	17	10,148,181	0.17	0.35	15,250	32,344,158	47.15	1.37	4,374	30,480,425	14.35	1.51
1996–99	31	10,193,769	0.30	0.30	17	9,423,797	0.18	0.38	17,717	34,430,894	51.46	1.49	5,498	32,873,288	16.72	1.76

[a] Per 100,000 population.
[b] Using 80–83 mortality rate as the standard.

Table 2 Male/Female ratios of liver carcinoma mortality rate

Year	Male:Female ratios	
	0–14 years	15–100 years
74	1.63	2.79
75–77	1.52	3.36
78–80	1.73	3.44
81–83	2.53	3.60
84–86	2.61	3.51
87–89	3.45	3.62
90–92	3.20	3.64
93–95	2.79	3.27
96–98	1.72	3.11
99	1.54	2.97

coefficients = 0.8; $P > 0.05$; and −0.42; $P > 0.05$, respectively). In the reference group, the male:female ratio trend increased significantly from 1974 to 1983 (Spearman's correlation coefficient = 1; $P < 0.05$) and decreased from 1983 to 1999 (Spearman's correlation coefficient = −0.68; $P > 0.05$).

Discussion

Most of the data in the Mortality Registry and the Cancer Registry overlap. The main differences between the Mortality Registry and the Cancer Registry are as follows: (*a*) the Mortality Registry opened earlier and has been kept on a computer file since 1971, whereas the Cancer Registry began only in 1979. Therefore, the Mortality Registry contains more information than the Cancer Registry; (*b*) the Cancer Registry had fewer reported cases in the early years than in the later period. The Cancer Registry covered about 50% of the liver cancers in 1979 and 88% in 1992, whereas the Mortality Registry did not have this problem because every death must be reported to the National Health Department of Taiwan; (*c*) the Cancer Registry contained 80% of the liver carcinoma cases in the Mortality Registry from 1979–1992; 377 liver cancer cases in the 0–15-year age group were reported in the Cancer Registry compared with 486 cases in the Mortality Registry. However, we think the Mortality Registry data still underestimates the true number of liver carcinoma cases. About 19% of the pathologically diagnosed HCC cases in the Cancer Registry are not listed in the Mortality Registry (5). Most of these cases are listed as "neoplasm of unspecified nature" (International Classification of Diseases code 239); (*d*) the accuracy of the Cancer Registry may be less than that of the Mortality Registry because Cancer Registry data are reported voluntarily by trained hospital personnel, whereas physicians are required to report Mortality Registry information. The problem common to both registries is the pathologically confirmed rate is less than 50% (5, 6). We used the Mortality Registry instead of the Cancer Registry because liver carcinoma mortality is high and the 5-year survival rate is below 20%, and these characteristics were stable through the study period. In such circumstances, incidence and mortality are nearly identical.

The proportion of non-HCC cases included in the mortality data was about 38%, with hepatoblastoma accounting for the majority (58%; Ref. 5). If hepatoblastoma mortality were decreasing significantly, the decline in liver carcinoma mortality could be attributable to a decreased death rate of hepatoblastoma. Previous studies, however, revealed that hepatoblastoma mortality was stable; the 5-year survival rates were 40% in 1976–1985 (11) and 47% in 1988–1992 (5). Therefore, the decreased liver carcinoma mortality rate that we observed is probably not attributable to decreased mortality from hepatoblastoma. Unlike the study of Chang *et al.* (10), which excluded the 0–5-year-olds, our study included this group, which also contained most of the hepatoblastoma cases. Twenty-three % of the HCC cases in the 0–15-year age group came from the 0–5-year-olds (5). Excluding the HCC cases in this age group reduces total sample size and may limit the power of statistical comparisons.

The study by Chang *et al.* (10) revealed that male:female ratios decreased steadily from 4.5 in 1981–1984 to 1.9 in 1990–1996, implying that males may benefit more than females from hepatitis B vaccination in the prevention of HCC. In our study, the male:female ratios in the study group appeared to increase from 1974 to 1983 and to decrease from 1983 to 1999, but neither trend was significant. In the 15–100-year-old reference group, the male:female ratios increased significantly from 1974 to 1983 and decreased nonsignificantly from 1983 to 1999. Therefore, the male:female ratios do not support the hypothesis that males benefit more from hepatitis B vaccination than do females in the prevention of HCC. Chang *et al.* (10) also found childhood HCC decreased significantly in males but not in females. They suggest some explanations for their observation, but they think the explanations are unlikely based on their own previous study (7). We agree, because in Taiwan, childhood HCC develops only in males and females with chronic hepatitis B infection (12), and vaccination decreased the chronic hepatitis B infection rate from 9.8% to 1.3% in both males and females (7, 10).

Why do our results differ from those of Chang *et al.*? We think the reason is the greater number of cases in our study, which makes the statistical comparisons more reliable. The number of cases since 1984 is 50% greater in our study than theirs. The dataset for Chang *et al.* consisted of 201 boys and only 70 girls. We think that if they had collected more cases, the decline in HCC incidence would have been seen in girls as well as in boys.

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