RESEARCH COMMUNICATION

# Hepatitis B Vaccination and Liver Cancer Mortality Reduction in Korean Children and Adolescents

**Jin Gwack[1], Sue K Park[2,3,6], Eun-Ha Lee[4], Boyoung Park[2,3,4], Yunhee Choi[5] Keun-Young Yoo[2*]**


## Abstract

**Liver cancer is one of the three most common causes of cancer mortality in the world and it is closely related to chronic hepatitis B viral(HBV) infection in Korea. The decline of HBV prevalence for the last two decades in Korea might be partly due to the HBV vaccination which was implemented as a national program starting in 1995. The aim of this study was to assess the period effect of the national HBV vaccination on liver cancer mortality in a young population. We compared age-specific mortality rates of liver cancer before and after the national vaccination program in the Korean population under the age of 20. To reduce year-to-year fluctuations in mortality, calendar years and age groups were divided into 4-year strata and the mortality rates were calculated for each stratum. Period effects of the national vaccination program were analyzed using age-period-cohort modeling. A total of 370 liver cancer mortality cases were identified during the period from 1991 to 2006. The period effect of the national vaccination program for the period 2002-2006 had a significantly reduced liver cancer mortality rate when compared to the period 1991-1994 when the national vaccination program was not implemented (RR 0.30, 95% CI 0.21 ~ 0.44). After implementation of the national vaccination program, HBV prevalence in Korean declined from 6~8% to 2~3%. This study demonstrates that the national vaccination program has contributed to the reduction of liver cancer mortality beyond just a natural decrease in Korean children and adolescents.**


**Key words:** Liver cancer - hepatitis B - vaccination - mortality - Korea

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## Introduction

Liver cancer is one of the three most common causes of cancer mortality in the world (Ferlay et al., 2010). Since liver cancer is almost always lethal, the annual incidence and mortality rates from this tumor are equivalent (Boyle and Levin, 2008). The liver is one of the leading sites for malignant neoplasm in Korea and the rest of the world (Shin et al., 2008). Hepatitis B viral (HBV) infection is largely responsible for liver cancer in Korea (Cheon et al., 2004). Korea is one of the countries where hepatitis B virus (HBV) infection was endemic in the past; 11.7% positivity for hepatitis B surface antigen (HBsAg) in males, and 9.5% in females in 1986. However, the prevalence of HBsAg has dramatically declined during the last two decades reaching 3.3% in males and 2.7% in females in 2008 (KCDC, 2010).

HBV vaccination has been available since 1982, and it was introduced in Korea in 1985. At first, HBV vaccination was recommended mainly for government employees, soldiers, and students on a voluntary basis. The national vaccination program for infants and children was launched in 1995 after the World Health Organization recommended to countries with a HBV carrier prevalence greater than 8% to implement an immunization program. A national vaccination program against vertical transmission for neonates born to mothers with HBV began in 2002 with doses at birth, 1 month, and 6 months of age. Routine vaccination for infants can rapidly reduce the chance of transmission from mother to baby or from child to child. The decreasing trend of HBsAg positivity in Korea may be due to the HBV vaccination program as well as to improvements in the general health status along with economic growth.

*[1]Division of Epidemic Intelligence Service, Korea Centers for Disease Control and Prevention, Osong, [2]Department of Preventive Medicine, College of Medicine, [3]Cancer Research Institute, [5]Medical Research Collaborating Center, Seoul National University Hospital, [6]Department of Biomedical Science, Seoul National University Graduate School, Seoul, [4]Cancer Early Detection Branch, National Cancer Control Institute, National Cancer Center, Goyang, Korea *For correspondence: kyyoo@snu.ac.kr*

It is well known that HBV vaccination prevents the infection of HBV and lowers the HBsAg positivity rate in the population (Boyle and Levin, 2008). However, there is a limited amount of evidence indicating whether the vaccination lowers the risk of liver cancer. The effect of HBV vaccination on liver cancer incidence was first reported by Chang and colleagues in Taiwanese children in 1997. According to a recent study, the children 6 to 19 years old born after the nationwide vaccination program was launched had significantly lower incidence rates of hepatocellular carcinoma compared to those born before the program in Taiwan (Chang et al., 2009). In Korea, HBV vaccination has been associated with reduced risk of primary liver cancer among male adults (Lee et al., 1998). The aim of this study was to assess the period effect of the introduction of the national vaccination program against HBV on the decrease of liver cancer mortality in Korean children and adolescents using age-period-cohort modeling.

## Materials and Methods

We compared age-specific mortality rates of liver cancer before and after the national vaccination program in Korea. All of the mortality cases for liver cancer except for hepatoblastoma which is relatively more common in children and not associated with HBV as determined by national death certificates for children under the age of 20 for the period 1991-2006. Subjects with a C22 code except for C22.2 (hepatoblastoma) as causes of death coded by International Classification of Diseases, 10th revision (ICD-10) were classified as mortality cases of primary liver cancer.

The number of liver cancer deaths was divided by the number of the population reported by Korea National Statistical Office to calculate mortality rates. To reduce year-to-year fluctuations in mortality, calendar years and age groups were divided into 4-year strata (1991-1994, 1995-1998, 1999-2002, 2003-2006; 0-3, 4-7, 8-11, 12-15, 16-19, respectively). Liver cancer mortality rates were calculated for each.

Age, period and cohort effect parameters, the rate ratio, and 95% confidence intervals (CI) for each 4-year periods were estimated using log-linear age-period-cohort model as follows.

$$\log \lambda ijk = \mu + \alpha i + \pi j + \gamma k + \varepsilon ijk$$

The age effects were represented by $\alpha i$, the period effects by $\pi j$, and the cohort effects by $\gamma k$. The random error was represented by $\varepsilon ijk$. We fitted the models sequentially by this order: one factor age model, 2-factor age-drift, age-cohort, age-period model, and finally age-period-cohort model. The deviances of the models were compared to test the statistical significance of each factor. Since age was considered as an important predictor of liver cancer mortality among children and adolescents, a goodness of fit considering age effect will be more valuable. Therefore, we computed the adjusted RA2 which measures how much of the variability is explained by factor other than age (Holford et al., 1991). The analyses were done with the R software package 'Epi'(version 2.6), and model fitting was done with the apc.fit function (Carstensen, 2005).

## Results

A total of 370 liver cancer mortality cases under the age of 20 were identified by their national death certificates for a 16-year period (1991-2006). Table 1 shows the number of deaths and the mortality rates for liver cancer by age-period groups. The number of deaths and the mortality rates for those under the age of 20 per 100 000 continuously fell from 145 to 36 and

**Table 1. Death, Person-year and Age-specific Mortality Rates of Liver Cancer in Korea by Age-period Group (per 100,000)**

| Age group | 1991-1994 | | | 1995-1998 | | | 1999-2002 | | | 2003-2006 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | death | person -year | mortality rate | death | person -year | mortality rate | death | person -year | mortality rate | death | person -year | mortality rate |
| 0 – 3 | 25 | 26,866,710 | 0.09 | 20 | 28,366,582 | 0.07 | 16 | 25,580,071 | 0.06 | 7 | 21,011,776 | 0.03 |
| 4 – 7 | 14 | 25,941,914 | 0.05 | 11 | 26,603,203 | 0.04 | 2 | 28,200,939 | 0.01 | 4 | 25,445,063 | 0.02 |
| 8 – 11 | 9 | 31,422,955 | 0.03 | 12 | 25,753,302 | 0.05 | 4 | 26,400,503 | 0.02 | 6 | 27,885,599 | 0.0 |
| 12 – 15 | 26 | 31,450,583 | 0.08 | 37 | 31,446,265 | 0.12 | 18 | 25,639,117 | 0.07 | 6 | 26,140,238 | 0.02 |
| 16 – 19 | 72 | 33,756,768 | 0.21 | 45 | 31,318,008 | 0.14 | 23 | 31,386,316 | 0.07 | 13 | 25,629,196 | 0.0 |
| Total | 146 | 149,438,930 | 0.10 | 125 | 143,487,360 | 0.09 | 63 | 137,206,946 | 0.05 | 36 | 126,111,872 | 0.03 |

**Table 2. Summary Statistics for the Age-period-cohort Models of Liver Cancer Mortality in Korea, 1991-2006, aged 0-19**

| Model | DF | Deviance(D) | $\Delta$D | p-value for $\chi 2$ | Adjusted R2A |
|---|---|---|---|---|---|
| Age (A) | 15 | 85.6 | | | |
| Age + Drift (AD) | 14 | 24.8 | 60.8 | <0.001[a] | 0.69 |
| Age + Period (AP) | 12 | 19.0 | 66.6 | <0.001[b] | 0.72 |
| Age + Cohort (AC) | 8 | 20.5 | 65.1 | <0.001[c] | 0.55 |
| Age + Period + Cohort (APC) | 6 | 7.3 | 11.7 | 0.069[d] | 0.79 |
| | | | 13.2 | 0.001[e] | |

DF, degree of freedom; [a]A vs. AD; [b]A vs. AP; [c]A vs. AC; [d]APC vs. AP; [e]APC vs. AC

0.10 to 0.03 during the 16 year period, respectively.

Table 2 shows the goodness of fit measured by deviance for each model. Each effect of period, cohort and drift term was statistically significant after adjusting age ($p<0.001$). The addition of the period effect to an age-cohort model was statistically significant ($p=0.001$). On the other hand, the cohort effect to an age-period model wasn't significant ($p=0.069$), even though age-specific mortality rates of liver cancer decreased continuously from past to recent birth years (Figure1). Therefore, we concluded that the trend of liver cancer mortality was better represented by age-period model, in which the value of adjusted R A 2 was higher than those in age-cohort or age-drift model. The period effect of the national vaccination program for the period 1999-2002 and 2003-2006 had a significant decrease in liver cancer mortality rates (RR 0.47, 95% CI 0.35-0.64; RR 0.30, 95% CI 0.21-0.44, respectively) compared to the period 1991-1994 when the national vaccination program was not implemented (Table 3). Figure2 shows the period effect of liver cancer mortality in young Koreans. The relative risk by the period effect decreased continuously during the 16 year period from 1991 to 2006. In all period groups, the mortality rates were lowest in groups aged 4-7 or 8-11 and then increased with age (Figure 3).

**Table 3. Period Effect of the National Vaccination Program in Age-period Model**

| Period ($\pi j$) | RR | 95% confidence interval |
|---|---|---|
| 1991 – 1994 | 1.00 | |
| 1995 – 1998 | 0.89 | (0.70, 1.13) |
| 1999 – 2002 | 0.47 | (0.35, 0.64) |
| 2003 – 2006 | 0.30 | (0.21, 0.44) |

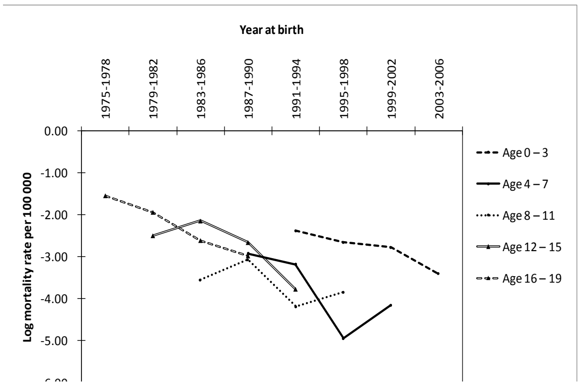


**Figure 1. Age-specific Mortality Rates of Liver Cancer in Korea by Year of Birth, 1975-2006**

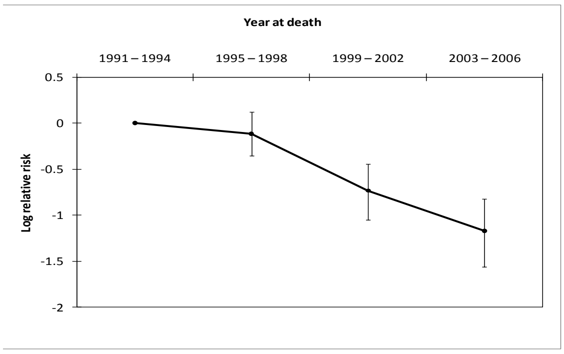


**Figure 2. Period Effects on Liver Cancer Mortality Rates in Korean Children and Adolescents**

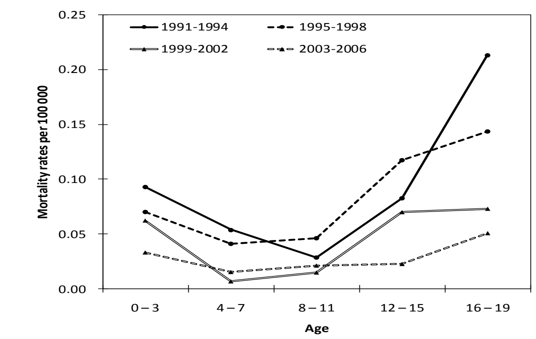


**Figure 3. Age-cohort Effects on Liver Cancer Mortality Rates in Korean Children and Adolescents**

## Discussion

This study demonstrates that the national vaccination program against HBV may have contributed to the reduction of liver cancer mortality in Korean children and adolescents. The period effect of the implementation of the national vaccination program in 1995 was significant considering for age and cohort effects. Because vaccination against HBV was recommended for all unvaccinated children as well as neonates and infants, age-period-cohort modeling was appropriate for identifying the period effect of the national vaccination program apart from the cohort effect.

The cohort effect of the national vaccination program was not significant in the present study. This could be explained by the way the program was implemented. The universal HBV vaccination program was applied to neonates, children, and adolescents at the same time, not only to certain birth cohorts. This condition might have influenced the statistical significancy of the period and cohort effect the national vaccination program.

The coverage rate of the HBV vaccination program ranged from 80% to 90% at the beginning and now the rate has reached up to 99% in infants (UNICEF and WHO, 2010). This resulted in a continuous decline in HBsAg carriers in Korean children. In the past 10 years, the HBsAg carrier rate in children has been reduced from 6~8% to 2~3%. Along with socioeconomic growth, the improvements in the general health status including nutrition and hygiene may have also contributed to the decrease of HBV infection and also the risk of liver cancer.

The effect of a national vaccination program for HBV was first evaluated in Taiwan. Chang and colleagues reported that the incidence of hepatocellular carcinoma in children aged 6 to 14 years born after the institution of a universal HBV vaccination program was significantly lower than in children born before the institution of the program (Chang et al., 1997).

Although they reported the incidence of hepatocellular carcinoma was reduced only in boys not in girls (Chang et al., 2000), Lee and colleagues confirmed a 62~70% reduction in mortality for both boys and girls with a larger number of cases later (Lee et al., 2003). And in a recent study, the authors reported the relative risk of hepatocellular carcinoma incidence was 0.31 among children aged 6-19 years in vaccinated birth cohorts compared to unvaccinated birth cohorts (Chang et al., 2009). Liver cancer is known to be related to several lifestyle factors like smoking, alcohol consumption, and ingestion of aflatoxin as well as chronic viral hepatitis. An approach to investigate the effect of the vaccination against hepatitis B on liver cancer should consider the other risk factors for a multi-factorial carcinogenesis model. But in the present study, the effects of other risk factors reflecting their lifestyle could have been minimized due to limiting the study population to children and adolescents only.

The mortality data issued by national death certificates ideally covers the entire population of Korea. It was reported that the completeness of the data reached almost 100%. However, the accuracy of the data should also be guaranteed. Jo et al.(2004) reported that the proportion of physician-issued death certificates for people age 20 and under is about 50-60% in 1990 and 90-100% in 2002. Although the proportion steadily increased for the last decade and reached almost 100%, age-specific mortality rates might have been affected because the number of mortality cases was relatively small.

The changes in factors like social and economical growth and development in hygienic and healthcare environment would also have led the changes in the trends in cancer mortality rates in Korea. However the pattern of the liver cancer mortality rates is distinct from those of other cancers. The mortality rate of liver cancer in Korea was peaked in early- and mid-90's and is decreasing slowly and steadily. Unlike this, stomach cancer mortality rate has been in decline since early-80's and lung cancer mortality rate started to drop after 2000 while that of colon cancer continued to increase. The discrepancies in changing pattern among these cancers suggest that specific factors influencing each cancer must be exiting and the national vaccination program might be one of them in regard of liver cancer.

This study is the first of its kind with age-period-cohort modeling on the evaluation of the effect of HBV vaccination on liver cancer mortality in children and adolescents. The period effect of the national vaccination program seems to lower liver cancer death in Korean children and adolescents. HBV vaccination against liver cancer control should be maintained as a national program. The change in liver cancer mortality in older ages, especially in the forties and fifties when liver cancer has a high incidence in Korea should be evaluated in further studies.

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