RESEARCH ARTICLE

Age-Period-Cohort Analysis of Liver Cancer Mortality in Korea

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Abstract

Background: Liver cancer is one of the most common causes of death in the world. In Korea, hepatitis B virus (HBV) is a major risk factor for liver cancer but infection rates have been declining since the implementation of the national vaccination program. In this study, we examined the secular trends in liver cancer mortality to distinguish the effects of age, time period, and birth cohort. Materials and Methods: Data for the annual number of liver cancer deaths in Korean adults (30 years and older) were obtained from the Korean Statistical Information Service for the period from 1984-2013. Joinpoint regression analysis was used to study the shapes of and to detect the changes in mortality trends. Also, an age-period-cohort model was designed to study the effect of each age, period, and birth cohort on liver cancer mortality. Results: For both men and women, the age-standardized mortality rate for liver cancer increased from 1984 to 1993 and decreased thereafter. The highest liver cancer mortality rate has shifted to an older age group in recent years. Within the same birth cohort group, the mortality rate of older age groups has been higher than in the younger age groups. Age-period-cohort analysis showed an association with a high mortality rate in the older age group and in recent years, whereas a decreasing mortality rate were observed in the younger birth cohort. Conclusions: This study confirmed a decreasing trend in liver cancer mortality among Korean men and women after 1993. The trends in mortality rate may be mainly attributed to cohort effects.

Keywords: Liver cancer - mortality - trends - age - time period - birth cohort - Korea

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Introduction

Liver cancer is the second most common cause of death from cancer worldwide (Ferlay et al., 2013). In Korea, it is the sixth most common type of cancer overall, and the fifth most common cancer in men (Jung et al., 2015).

Hepatitis B virus (HBV) is the leading cause of acute hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) in South East Asia, China, and sub-Saharan Africa (WHO, 2009). HBV infection has decreased in the Korean population since the advent of vaccination programs. However, such programs were only compulsory for newborn infants and adolescents, while vaccination for adults were on a voluntary basis. Therefore, the decrease is limited to the younger population, and viral persistence remains in the middle-aged and older populations (Kim et al., 2013).

The mortality rates in Asian countries (Japan and Korea) are 5-10 times higher than those in Western countries (the USA, the UK and France). Japan showed a decreasing trend after several peaks, indicating a cohort effect. Korea had a comparatively high mortality rate a decade ago, but the rate appeared to be decreasing steadily. However, in the USA and the UK, constant increasing trends were observed, though the mortality in the young generation is decreasing in the USA (Matsuda and Saika, 2012).

Due to the high fatality of liver cancer (the overall ratio of mortality to incidence is 0.95) and the relative lack of variability in survival in different world regions, the geographical patterns in mortality closely follow those in incidence (Ferlay et al., 2013). The incidence rates for developing liver cancer for Eastern Asian areas in 2012 were 31.9 for men and 10.2 for women. According to the Korean National Cancer Center, the incidence rates for men and women were 35.2 and 9.7, respectively, for the same period.

Recent developments in age-period-cohort (APC) analysis have emphasized a critical role in studying health outcomes (Yang, 2008; Reither et al., 2009). APC analysis distinguishes three types of time-related variations in disease trends of interest. The age effect represents the different risks associated with different age groups. The period effect represents variations over time in vital rates simultaneously associated with different age groups. The cohort effect describes changes in rates across groups of individuals born during the same period-that is, for successive age groups in successive time periods (Yang et al., 2004). Several studies have been conducted to examine birth cohort effects on liver cancer incidence and mortality

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rates in Canada (Jiang et al., 2011), Italy (Dal Maso et al., 2008), France (Benhamiche et al., 1998), Spain (Morales et al., 1993), China (Wang et al., 2014) and Taiwan (Tzeng and Lee, 2015).

Gwack et al. assessed the period effect of the national HBV vaccination on liver cancer mortality in a young population (Gwack et al., 2011). They compared age-specific mortality rates of liver cancer before and after the national vaccination program in the Korean population under the age of 20.

However, there is no study assessing the trend of liver cancer mortality among Korean adults, who comprise the majority in the number of deaths due to liver cancer. Therefore, the aim of this study was to examine secular trends in liver cancer mortality and distinguish the effects of age, time period, and birth cohort on the trends in liver cancer mortality from 1984 to 2013 in Korea.

Materials and Methods

Data for analyzing liver cancer mortality were obtained from the Korean Statistical Information Service, for the period from 1984-2013 (Statistics Korea, 2013). The annual number of liver cancer deaths and population was abstracted and truncated to subjects older than 30 years, due to a small number of deaths among the younger population. The classification of liver cancer was defined as C22 from the 10th revision of the International Classification of Diseases (ICD-10) (Fritz et al., 2000). The obtained data were arranged into six 5-year periods (1984-88 to 2009-13), eleven 5-year age groups (30-34 to 80+), and fourteen 5-year cohorts for further analyses. From the data, we computed age-standardized mortality rates (ASMRs) per 100,000 person-years. The direct method based on Segi's world standard population data was used for standardization (Ahmad et al., 2001). ASMRs matrices of men and women were created for each period and age group.

In order to study the shapes of and detect changes in the mortality trends, joinpoint analyses were performed. The permutation procedure in joinpoint regression is a powerful tool for determining the number of change-points and estimating their locations (Kim et al., 2000). We determined the number of breakpoints, denoted as joinpoints, and estimated the parameters using Joinpoint Regression Program 4.1.1.3. For joinpoint analysis, we used the log-linear model under the Poisson assumption. Since we could not assume constant variance for our model, heteroscedasticity had to be handled using weighted least squares. The results of joinpoint regression are presented in the form of annual percent changes (APC) in liver cancer mortality trends.

We could visually check the effect of the period, cohort and age on liver cancer mortality rate by exploratory data analysis. Also, an APC model was created to study the effect of each age, period, and birth cohort on liver cancer mortality. A log-linear model was used under the assumption that the response variable, the mortality of liver cancer, follows a Poisson distribution. We obtained our model as follows, where denotes age, period and cohort effect, respectively.

To handle the identification problem that occurs due to the linear dependency among age, period and cohort, the intrinsic estimator (IE) method proposed by Yang et al. was used (Yang et al., 2004). We generated various models using different combinations of independent variables. For these models, deviances and Akaike Information Criterions (AIC) were computed and compared to evaluate each model's goodness-of-fit and to check the significance of each factor.

Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA), Stata 12.0 (Statacorp, College Station, TX, USA) and Joinpoint Regression Program 4.1.1.3 (National Cancer Institute).

Results

Table 1 presents the rates for age-specific mortality from liver cancer in Korean men and women. The liver cancer mortality rates continuously increased as age increased for women but not for men.

Table 2 shows the significant changes in the linear trends. The liver cancer mortality rate for men increased significantly until 1992-1993 [APC: 1.9 (95%CI, 1.1 to 2.7)] and showed a decline in successive periods of 1993-2007 [APC: -2.7 (95%CI, -3.0 to -2.3)] and 2007-2013 [APC: -4.2 (95%CI, -5.3 to -3.0)]. Similarly, in women, the liver cancer mortality rate showed a significant increase from 1984 to 1992 [APC: 1.6 (95%CI, 0.1 to 3.1)] and successively decreased through 1992-2005 [-2.1 (95%CI, -2.8 to -1.5)] and 2005-2013 [-3.6 (95%CI, -4.8 to -2.5)].

The age-specific liver cancer mortality rates in various time periods are depicted in Figure. 1a and 1b.

Table 1. Age-specific mortality rate for liver cancer in Korea, 1984-2013 (100,000)

	Period of Death					
Age	84-88	89-93	94-98	99-03	04-08	09-13
Men						
30-34	7.0	6.0	4.0	3.2	2.2	1.6
35-39	19.6	17.8	12.7	9.9	6.0	5.0
40-44	43.6	40.9	34.0	26.0	20.2	13.4
45-49	76.7	78.7	64.5	51.8	43.3	31.1
50-54	111.0	120.2	106.3	89.2	72.0	54.9
55-59	143.1	152.5	142.9	123.8	103.5	78.1
60-64	164.9	177.5	173.3	149.2	127.9	102.8
65-69	169.6	203.1	196.2	176.7	156.5	127.6
70-74	147.9	193.5	231.3	203.5	187.9	170.9
75-79	140.2	177.7	219.0	225.4	216.7	203.0
80+	147.0	154.1	183.4	206.4	224.3	238.4
Women						
30-34	2.6	2.0	1.0	0.0	0.7	0.7
35-39	5.4	4.3	2.0	2.0	1.6	1.0
40-44	10.4	7.7	5.0	3.9	2.9	2.3
45-49	17.6	15.9	11.4	8.1	6.7	4.7
50-54	25.3	25.0	19.6	15.9	12.5	0.0
55-59	31.7	34.3	30.5	25.7	19.7	13.0
60-64	38.1	44.7	40.9	36.2	32.6	24.5
65-69	45.1	53.5	54.0	49.8	46.1	38.3
70-74	45.8	59.9	70.5	65.1	59.8	54.6
75-79	44.4	60.0	73.9	76.5	77.5	74.3
80+	56.0	62.5	72.2	77.6	84.4	90.9

Table 2. Joinpoint Analysis for the Trends in Mortality of Liver Cancer by sex

	ASR*		Joinpoint analysis†					
	Years		Trend 1		Trend 2		Trend 3	
	1984	2013	Years	APC	Years	APC	Years	APC
Overall	48.5	31.3	1984 to 1993	1.6 (0.7 to 2.5)	1993 to 2007	-2.5 (-2.9 to -2.1)	2007 to 2013	-4.0 (-5.2 to -2.7)
Men	82.7	51.9	1984 to 1993	1.9 (1.1 to 2.7)	1993 to 2007	-2.7 (-3.0 to -2.3)	2007 to 2013	-4.2 (-5.3 to -3.0)
Women	20.5	13.7	1984 to 1992	1.6 (0.1 to 3.1)	1992 to 2005	-2.1 (-2.8 to -1.5)	2005 to 2013	-3.6 (-4.8 to -2.5)

ASR=Age-standardized mortality rate for a given year; APC=Annual percent change (95% confidence interval), *Age standardized incidence rate was calculated per 100,000 people for a given year and Segi's world standard population is used for age-standardization, †Joinpoint regression analysis was conducted to determine whether trends in incidence of liver cancer had changed significantly relative to sex from 1984–2013

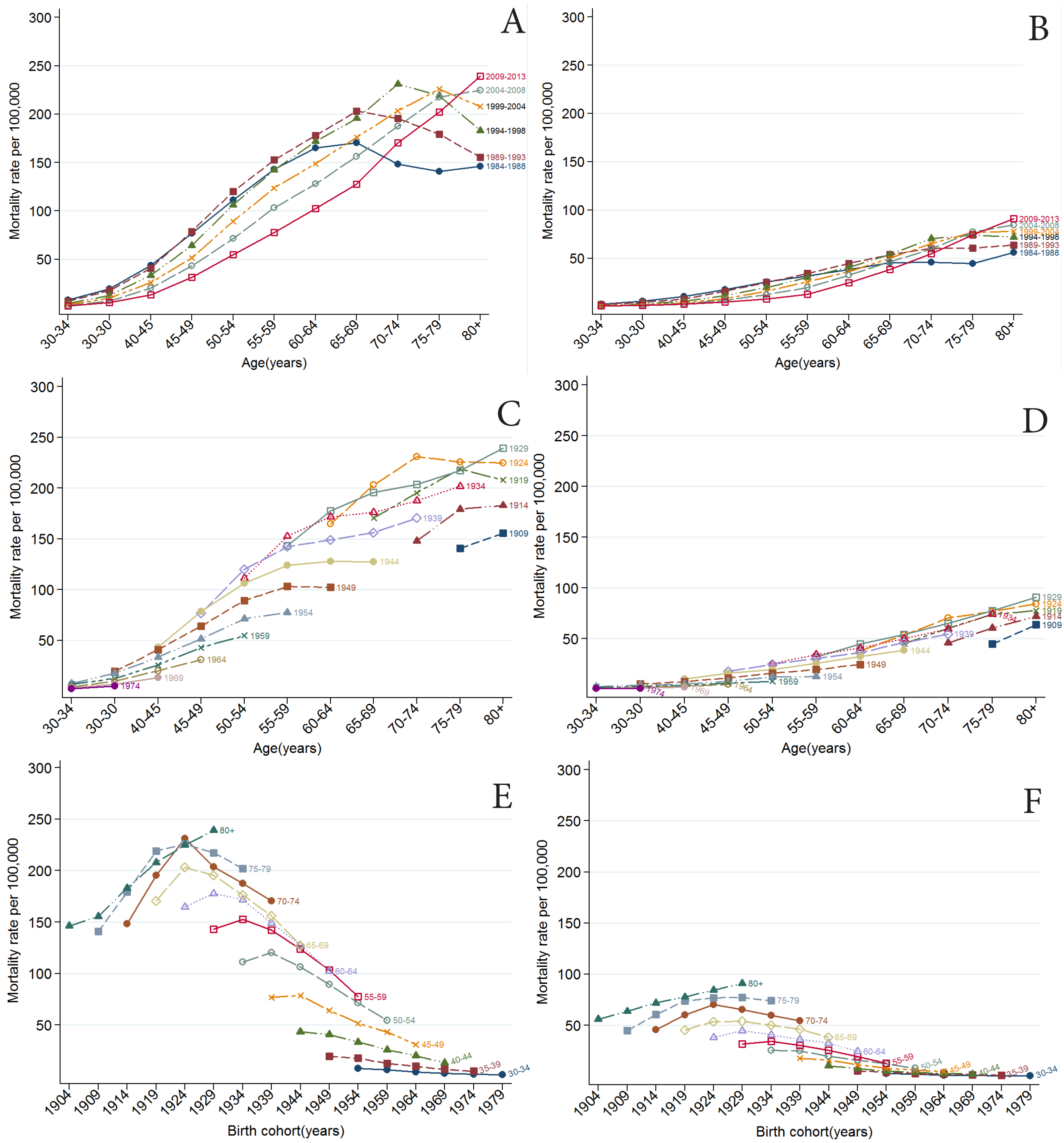

Figure 1. Age-period-cohort effect of age-specific mortality caused by colorectal cancer from 1984-2013 for males and females; Age-specific mortality rate by period in men (a) and women (b), Age-specific mortality rate by birth cohort in men (c) and women (d), and birth cohort-specific mortality rate by age in men (e) and women (f)

The increase in mortality associated with aging was more rapid among men than among women. Within the same period group, the rate in older age groups was higher than in younger age groups in recent years. However, the peak

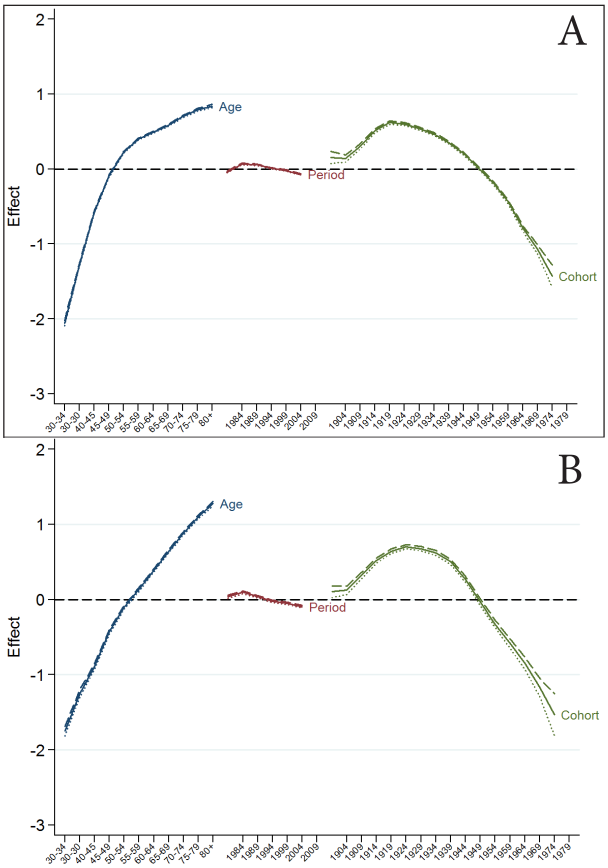

Figure 2. Age-period-cohort analysis of colorectal cancer in Korean men (a) and women (b)

Table 3. Goodness of Fit of Age-Period-cohort Model Assessment for Liver Cancer Mortality Rates in Korea, 1984-2013

Model	AIC	DEV	d.f.	ΔDEV	Δd.f.
Men					
APC	13.0	158.4	36	Ref	Ref
AC	18.6	535.4	40	377.0	4
AP	87.9	5134.4	50	4976.0	14
PC	192.2	12006.0	45	11847.6	9
Age	226.0	14254.5	55	14096.1	19
Women					
APC	10.7	89.2	36	Ref	Ref
AC	11.3	136.0	40	46.8	4
AP	63.8	3619.0	50	3529.7	14
PC	17.4	546.8	45	457.6	9
Age	86.8	5149.0	55	5059.8	19

AIC: akaike information criterion; DEV: deviance; d.f.: degree of freedom; APC: full age-period-cohort model using intrinsic estimator model; AC: age/cohort model; AP: age/period model; PC: period/cohort model; Age: age model

for the liver cancer mortality rate shifted to an older age group in recent years.

The age-specific rates in various birth cohorts are depicted in Figure. 1c and 1d. Within the same birth cohort group, the liver cancer mortality rate for older age groups was higher than for younger age groups.

Figure. 1e and 1f also show that liver cancer mortality rates in birth cohorts born after 1924 decreased consecutively within the same age groups; however, birth cohort-specific liver cancer mortality rates stabilized slightly in younger birth cohorts within the same age groups.

Table 3 presents the goodness-of-fit for the age-period-cohort models. Considering the lowest value of AIC, the age-period-cohort model using the intrinsic model seems to be the best fitted model to account for the trend in liver cancer mortality among both men and women.

The estimates obtained from the best fitted age-period-cohort model are presented in Figure 2. The liver cancer mortality rate increased rapidly in women within all age groups, whereas the increasing trends slowed among men older than 50 years old. The period effects decreased slightly since 1984-1989 among both men and women. The cohort effects peaked in the birth cohort born in 1919-1924, then leveled off and significantly decreased in younger generations. This indicates a contribution from the cohort effect to the decrease in the linear trend of liver cancer mortality.

Discussion

In our age-period-cohort analysis of liver cancer mortality among Korean men and women from 1984 to 2013, the decreasing rate of liver cancer mortality can be explained predominantly by both age and birth cohort effect: the risk of liver cancer death increased steadily until the 1924 birth cohort, and decreased among Koreans born after 1924.

In Korea, the seropositivity of HBsAg in this study increased with age from 20 to 40 years old, and then decreased thereafter, which is comparable to other reports (Chae et al., 2009; Kim et al., 2009; Lee et al., 2013). The reasons for decreasing seroprevalence in those over age 50 may be related to the natural loss of HBsAg and death from liver diseases such as cirrhosis or hepatocellular carcinoma (Lee et al., 2011).

According to a recent report (Kim et al., 2013) based on data from The Korea National Health and Nutrition Examination Survey (KNHANES), the HBsAg-positive population markedly declined in younger age groups over the study period (1998 to 2010). Among teenagers (10 to 19 years), prevalence decreased, from 2.2% in 1998 to 0.12% in 2010 ($p<0.0001$). Among subjects aged 20 to 39 years, the prevalence of HBsAg carriers decreased significantly (5.48% to 2.34% in the 20s and 6.15% to 3.85% in the 30s). Among subjects aged 40 to 49 years, the presence of HBsAg carriers also decreased (5.43% in 1998 and 3.71% in 2010). However, among subjects aged 50 years or older, HBsAg seropositivity did not decrease throughout the study period.

Gwack et al. demonstrated 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 following the implementation of the national vaccination program in 1995 was significant after accounting 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 independent of the cohort effect.

HBV infection has decreased in the Korean population since the advent of vaccination programs. However, the decrease is limited to the younger population, and viral persistence remains in the middle-aged and older population. In fact, a total of 375 liver cancer mortality cases from the younger population were identified during the period from 1991 to 2006 while a total of 167,162 liver cancer mortality cases from the middle-aged and older population were identified during the same period (Statistics Korea, 2013).

HBsAg seroprevalence has been reduced by half during the past 30 years, probably due to the combined effect of vaccination and antiviral therapy (Lee et al., 2013). The HBV vaccine response has been superior in females compared to males (Fang et al., 1994; Zeeshan et al., 2007), and this result was compatible with previous studies in Korea (Park et al., 2003; Kim et al., 2009). That is one of reasons why the mortality rate from liver cancer is lower in females in the present study.

The population-based national survey (KNHANES) revealed a decreased prevalence of HBV infection in the general Korean population over the last decade. The decrease in HBsAg carriers was more prominent in the younger population. Universal vaccination programs have contributed to the marked decline of HBV infection in subjects younger than 20 years (2.2% to 0.12%). A similar decline in HBV infection rates was reported in Taiwan following its newborn vaccination program (Lin et al., 2003).

Unsurprisingly, the prevalence of HBsAg positivity has remained unchanged in middle-aged and elderly populations. Although HBsAg-positive rates tend to decrease with aging due to a natural loss of HBsAg [14], the overall trends in HBV infection were unaffected. This suggests that the risk for HBV-related cirrhosis or HCC in the elderly population may not decrease for some time. Recent national cancer statistics have confirmed that the incidence of HCC in Korea has not declined in the elderly population: 13,126 in 2000 and 15,936 in 2009 (Jung et al., 2012).

In our study, the mortality from HCC still remained high in the older population and even increased in the population aged 80 years or older. Therefore, effective surveillance strategies to detect HBV infection in the general adult population are still required for the middle-aged and older population.

Screening programs to detect HBV infection in the general adult population should therefore be maintained. Screening, defining high-risk subjects, and providing optimal antiviral treatment are also important to reduce mortality and morbidity from chronic HBV infection (Kim et al., 2013).

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. Future attempts 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.

The strength of our study is that 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. reported that the proportion of physician-issued death certificates for people aged 20 and under was about 50-60% in 1990 and 90-100% in 2002 (Jo et al., 2004). 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 successful changes in the rates of liver cancer mortality in Korea were not solely due to Korea's HBV vaccination efforts, but also depended on the country's 10-year plan for cancer control, implemented by the government in 1996. Because HCC has such a poor prognosis and lacks effective therapies, the Korean government recognized the need to develop screening programs (Yeo et al., 2013). It introduced the National Cancer Screening Program (NCSP) in 1999, which covers liver cancer and four other leading cancers in Korea.

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 adults. HBV vaccination against liver cancer control should be maintained as a national program. The change in liver cancer mortality in older ages groups, especially in the forties and fifties when liver cancer has a high incidence in Korea should be evaluated in further studies.

In conclusion, our study showed a decreasing trend in liver cancer mortality among Korean men and women after 1993. The mortality rate trends can be mainly attributed to cohort effects.

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