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Ten-Year Changes in the Hepatitis B Prevalence in the Birth Cohorts in Korea

Results From Nationally Representative Cross-Sectional Surveys

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Abstract: To compare the prevalence of hepatitis B virus (HBV) infection over a 10-year period in terms of population-level trends, we established hypothetical birth cohorts that represented each 10-year interval age group.

We used data from the Korean National Health and Nutrition Examination Surveys conducted between 1998 to 2001 and 2008 to 2011. Trends in the HBV infection were calculated using data from individuals aged 20 to 59 years in 1998 to 2001 and those aged 30 to 69 years in 2008 to 2011.

In 2008 to 2011, the prevalence of HBV infection, as measured using serum HBV surface antigen (HBsAg) seroprevalence, among participants aged 30 to 69 years was 4.2% (95% CI=3.7–4.7%), which represents a 1.3% absolute change and 20% change in prevalence ratio, which was significant compared with the prevalence among those aged 20 to 59 years in 1998 to 2001 (5.5%, 95% CI=4.7–6.3%). The prevalence of HBV infection decreased most in the lowest income group, with marginal significance in males ($P=0.06$) and significance in females ($P=0.03$). In terms of education, females with at least a high school education showed a significant decrease ($P=0.03$).

Using a birth cohort approach, the prognosis for HBV infection in terms of death or hospitalization, or resolution upon antiviral treatment of their HBV infections, identified by a decrease in the HBsAg seroprevalence was worse in the lower income group and in females with higher education. We postulate that these socioeconomic inequalities were caused by alcohol consumption, disparities in liver cancer surveillance, and access to antiviral treatment because of cost and reimbursement guidelines.

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Abbreviations: anti-HBc = hepatitis B core antibodies, CI = confidence interval, HBeAg = hepatitis B e antigens, HBsAg = HBV surface antigen, HBV = hepatitis B virus, IFN-a = interferon alfa, KNHANES = Korean National Health and Nutrition Examination Surveys.

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INTRODUCTION

Liver cancer is the sixth most common cancer and third leading cause of cancer-related deaths worldwide. The burden of liver cancer is heavier in less-developed countries, primarily in Eastern Asia,¹ and the major risk factor for liver cancer or hepatocellular carcinoma is chronic hepatitis B virus (HBV) infection. Indeed, HBV infection is responsible for most cases of liver cancer in developing countries, accounting for 75% to 80% of these cases in Asian countries.^{2,3}

Although both the incidence and mortality rates have decreased since the 1990s, liver cancer ranks fifth in terms of cancer incidence and second in terms of cancer-related deaths in the Republic of Korea and has remained a major burden.⁴ Indeed, HBV infection accounts for nearly 70% of hepatocellular carcinoma cases in Korea.⁵ The risk of developing liver diseases, including cirrhosis and cancer, increases in chronic HBV carriers, but their natural history is variable and influenced not only by individual characteristics, such as age, sex, or serum hepatitis B e antigens (HBeAgs), but also by disease management.⁶ For example, antiviral treatments such as interferon alfa (IFN-a), lamivudine, and adefovir dipivoxil are available for chronic HBV carriers to prevent the development of liver diseases that influence morbidity and mortality.⁷

Descriptive studies of trends in the prevalence of HBV infection are needed to understand the control of HBV infection. For younger populations, the decrement in HBV prevalence can be explained by the prevention of vertical transmission or HBV vaccination in early childhood,⁸ given that the majority of infections in endemic areas, such as Asian countries, are transmitted from an infected mother to her child, either at birth or during early childhood.⁹ However, there might be a different explanation for the decrement or increment in adults. The increments in HBV prevalence in an adult population might be attributable to horizontal transmission, such as sexual or other personal contact between infected people or via injection,^{10,11} although this is uncommon.¹⁰ Therefore, the prevalence of HBV infection should be described separately for pediatric and adult groups, and the trends in specific birth cohorts are needed to understand the management of HBV carriers. However, studies have examined only trends in entire populations using a cross-sectional approach that measures the relevant variables at certain time points and that attributes decreasing trends to vaccination programs.^{11–14}

Therefore, using nationally representative cross-sectional surveys conducted at 10-year intervals, we established a hypothetical birth cohort representing each 10-year interval age group and conducted a trend study to compare the prevalence of HBV infection over a 10-year period to examine the management of HBV carriers in terms of population-level trends. To assess the disparities in the management of HBV carriers in the Republic of Korea, we also compared the

prevalence of HBV carriers according to socioeconomic status, such as education and income, which might affect the management of HBV carriers, including their access to and compliance with therapeutic agents and regimens.

METHODS

Study Population

The temporal trends in the prevalence of HBV infection according to sex, age, income, and education were derived from the Korean National Health and Nutrition Examination Surveys (KNHANES), a series of cross-sectional, population-based, and nationally representative surveys that provide representative estimates of the prevalence of health conditions and the nutritional status of the Korean population. KNHANES is conducted by the Korea Centers for Disease Control and Prevention and comprises 5 surveys: I (1998), II (2001), III (2005), IV (2007–2009), and V (2010–2012). A complex, stratified, multistage cluster probability sampling of the noninstitutionalized Korean population was used. KNHANES includes a questionnaire on health behaviors, a health examination performed at a mobile examination center, and a nutrition survey using a food-frequency questionnaire. Details of the survey are described in full elsewhere.^{15,16}

Our analysis relied on data collected from KNHANES I and II (1998 and 2001) and parts of IV and V (2008 and 2011) from members of the same age group separated by a 10-year interval. Individual HBV infection status was determined according to the serum HBV surface antigen (HBsAg) status measured using an electrochemiluminescence immunoassay, while hepatitis B core antibodies (anti-HBc) and hepatitis B surface antibodies (anti-HBs) were not analyzed. Our sample included individuals aged 20 to 59 years who participated in KNHANES I and II and those aged 30 to 69 years who participated in KNHANES 2008 and 2011 who had complete HBsAg results. The KNHANES data are available publicly.¹⁷ The study protocol was approved by the Institutional Review Board of the Korean Centers for Disease Control and Prevention, and all participants provided written informed consent. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Statistical Analysis

All analyses incorporated sampling weights, stratification, and clustering to adjust for selection and nonresponse bias. Trends in the prevalence of HBV infection in the age groups under examination between 1998 to 2001 and 2008 to 2011 were calculated based on data from individuals aged 20 to 59 years at the time of KNHANES I and II and those aged 30 to 69 years at the time of KNHANES 2008 and 2011, considering a 10-year age increment in the birth cohort. We also compared the prevalence rates in the same 10-year interval birth cohort groups. For example, those in their 20s in 1998 to 2001 were compared with those in their 30s in 2008 to 2011, and those aged 50 to 59 in 1998 to 2001 were compared with those aged 60 to 69 in 2008 to 2011. Absolute changes between 1998 to 2001 and 2008 to 2011 were calculated by subtracting the HBV prevalence in 1998 to 2001 from that in 2008 to 2011, and the percentage ratio changes were calculated by dividing the absolute change by the prevalence in 1998 to 2001. We performed bootstrapping (using 1000 bootstrap samples) to obtain

95% confidence intervals (CIs) of the absolute changes and prevalence ratios.

Income and education levels were used to define socioeconomic status. Income was categorized into 4 levels by dividing the household income by the square root of the number of household members. Education was categorized into 2 levels: high school or less for males and middle school or less for females (I) and college or higher for males and high school or higher for females (II). The prevalence of HBV was compared according to socioeconomic status within the birth cohort for a 10-year interval, and absolute changes, prevalence ratios, and their 95% CI were also calculated.

In addition, the trend in the prevalence of current alcohol consumption (defined by consumption of even a single drink in the previous year) was calculated in terms of sex, gender-specific household income, and gender-specific educational level. Alcohol consumption is another principal cause of liver cancer in Asia, acting multiplicatively with HBV infection in HBV carriers¹⁸ among HBV carriers.

RESULTS

Table 1 shows the basic characteristics of the hypothetical birth cohort in 1998 to 2001 with those of the cohort in 2008 to 2011.

In 2008 to 2011, the prevalence of HBV infection, as measured by the serum HBsAg seroprevalence, among participants 30 to 69 years of age was 4.2% (95% CI = 3.7–4.7%), which represents a 1.3% decrease compared with the prevalence among those 20 to 59 years of age in 1998 to 2001 (5.5%, 95%

TABLE 1. Characteristics of Birth Cohort Between 1998 to 2001 and 2008 to 2011

Age	1998–2001 (20–59 Years Old)		2008–2011 (30–69 Years Old)	
	N	%* (95% CI)	N	%* (95% CI)
Total				
20–29	2573	20.2 (18.7–21.7)	—	—
30–39	3611	30.6 (28.4–32.7)	1425	23.4 (21.7–25.0)
40–49	3135	29.7 (27.8–31.6)	2474	27.1 (25.5–28.6)
50–59	2194	19.5 (17.9–21.2)	2363	27.9 (26.5–29.3)
60–69	—	—	2289	21.7 (20.4–22.9)
Total	11513		8551	
Male				
20–29	1117	20.6 (18.7–22.5)	—	—
30–39	1639	29.7 (27.1–32.4)	594	23.9 (21.8–26.1)
40–49	1454	29.5 (27.3–31.6)	1032	27.1 (25.2–29.0)
50–59	1003	20.2 (18.3–22.1)	1034	27.9 (26.0–29.8)
60–69	—	—	988	21.1 (19.6–22.6)
Total	5213		3648	
Female				
20–29	1456	20.0 (18.1–21.8)	—	—
30–39	1972	31.1 (28.8–33.5)	831	22.8 (20.9–24.7)
40–49	1681	29.8 (27.7–32.0)	1442	27.0 (25.2–28.8)
50–59	1191	19.1 (17.1–21.1)	1329	27.9 (26.3–29.6)
60–69	—	—	1301	22.2 (20.9–23.6)
Total	6300		4903	

CI = confidence interval.

* Weighted percent.

CI = 4.7–6.3%). Therefore, the prevalence of HBV infection in the population aged 20 to 59 in 1998 to 2001 decreased significantly, by 1.3% absolutely and by 20% in terms of the prevalence ratio over 10 years. The degree of the decrease as measured by the prevalence ratio was 20% in males and 30% in females, and both were significant (Table 2).

When we compared each age group over the 10-year period, the prevalence of HBV infection decreased in all age groups. The greatest decreases in prevalence between 1998 to 2001 and 2008 to 2011 occurred in males aged 20 to 29 and females aged 40 to 49 years in 1998 to 2001, but statistical significance was observed only in females aged 40 to 49 years in 1998 to 2001 in terms of both the absolute change and prevalence ratio during the 10 years (Table 2).

Table 3 presents the trends in the prevalence of HBV infection according to sex, income, and education. The prevalence of HBV infection decreased in all of the sex-income groups, except in males with level II and III incomes, who showed a slight increment without significance. Among males, the prevalence of HBV infection decreased most in the lowest income group, with marginal significance (Table 3; *P*-value 0.08 for male and 0.07 for female). The prevalence of HBV infection decreased in the women with the highest income level (Table 3; *P*-value 0.04), and females in their 40s in 1998 to 2001 with higher income levels (level III–IV) showed significant decreases over the 10-year period (Supplementary Appendix Table 1).

In terms of gender-specific educational level, the prevalence of HBV infection decreased in all sex-education groups, except in males with a higher education level (level II). Females with higher education (level II) showed a significant decrease (Table 3; *P*-value 0.03), especially in the 40- to 49-year age group in 1998 to 2001, over 10 years (Supplementary Appendix Table 2). In males, those with a lower

education level and 50 to 59 years of age in 1998 to 2001 showed a significant decrement.

DISCUSSION

To our knowledge, this is the first study using a hypothetical birth cohort to compare the changes in the prevalence of HBV infection over a 10-year period (between 1998–2001 and 2008–2011) at the population level. We also assessed the disparities in the management of HBV carriers by examining the different patterns of the changes in seroprevalence according to socioeconomic status.

The results demonstrated an overall decrease in the seroprevalence of HBsAg in the Republic of Korea by 20% as a prevalence ratio (–1.3% absolute change) in the birth cohort over 10 years. However, the changes in the prevalence pattern differed according to socioeconomic status. The decrease was most pronounced in males and females with the lowest incomes and in females with the highest income or higher education status.

Several studies have found a decreased prevalence of HBV infection, especially in young people, since the introduction of HBV vaccination programs.^{11–13,19} One study suggested that the decreased HBsAg seroprevalence in adults is due to reduced horizontal transmission, safer injection practices, and HBV vaccination of high-risk groups.¹¹ Using a cross-sectional approach, these explanations might be acceptable. With a birth cohort approach using nationally representative noninstitutionalized samples, however, the decrement in the HBsAg seroprevalence might be explained by death or hospitalization due to the deterioration of chronic HBV infection, seroclearance upon antiviral treatment of their HBV infections, or resolution of acute infection; albeit, we did not consider the latter because it is rare in Asian populations.¹² Therefore, our results suggest

TABLE 2. Prevalence of HBsAg-Positive Status by Birth Cohort Between 1998–2001 and 2008–2011

Age*	1998–2001	2008–2011	Absolute Change		Prevalence Ratio	
	Rate (95% CI)	Rate (95% CI)	Difference (95% CI)	<i>P</i> -Value	Ratio (95% CI)	<i>P</i> -Value
Total						
20–29	4.9 (3.4, 6.5)	3.5 (2.6, 4.4)	–1.4 (–3.3, 0.1)	0.10	0.7 (0.5, 1.0)	0.09
30–39	5.2 (4.0, 6.4)	4.8 (3.7, 5.8)	–0.5 (–1.9, 0.9)	0.53	0.9 (0.7, 1.2)	0.54
40–49	6.5 (4.9, 8.0)	4.7 (3.7, 5.8)	–1.8 (–3.7, 0.2)	0.07	0.7 (0.5, 1.0)	0.06
50–59	5.0 (3.5, 6.4)	3.7 (2.7, 4.6)	–1.3 (–3.1, 0.4)	0.14	0.7 (0.5, 1.1)	0.13
Total	5.5 (4.7, 6.3)	4.2 (3.7, 4.7)	–1.3 (–2.3, –0.4)	0.01	0.8 (0.6, 0.9)	0.01
Male						
20–29	5.7 (3.1, 8.2)	3.7 (2.5, 5.0)	–1.9 (–4.9, 0.8)	0.18	0.7 (0.4, 1.2)	0.15
30–39	6.1 (4.2, 8.0)	5.3 (3.7, 7.0)	–0.7 (–3.0, 1.6)	0.55	0.9 (0.6, 1.4)	0.56
40–49	6.1 (4.1, 8.0)	6.0 (4.2, 7.9)	0.0 (–2.6, 2.5)	0.99	1.0 (0.6, 1.5)	0.99
50–59	5.2 (3.2, 7.2)	3.7 (2.2, 5.2)	–1.5 (–4.3, 1.2)	0.30	0.7 (0.4, 1.3)	0.29
Total	5.8 (4.7, 6.9)	4.8 (4.0, 5.6)	–1.0 (–2.3, 0.3)	0.13	0.8 (0.6, 1.0)	0.12
Female						
20–29	4.4 (2.4, 6.3)	3.3 (2.2, 4.4)	–1.1 (–3.0, 0.9)	0.29	0.8 (0.5, 1.3)	0.29
30–39	4.6 (3.2, 6.0)	4.1 (2.9, 5.4)	–0.5 (–2.5, 1.3)	0.62	0.9 (0.6, 1.4)	0.62
40–49	6.8 (4.4, 9.2)	3.4 (2.1, 4.7)	–3.4 (–6.3, –0.8)	0.02	0.5 (0.3, 0.8)	0.01
50–59	4.7 (2.7, 6.8)	3.6 (2.4, 4.8)	–1.1 (–3.5, 1.0)	0.32	0.8 (0.5, 1.3)	0.31
Total	5.2 (4.2, 6.3)	3.6 (3.0, 4.2)	–1.6 (–2.9, –0.4)	0.01	0.7 (0.5, 0.9)	0.01

CI = confidence interval.

* Age in 1998 to 2001. In 2008 to 2011, the age was 10 years greater than that in 1998 to 2001.

TABLE 3. Prevalence Rates (%) of HBsAg-Positive Status by Income, Education Level, and Sex by Birth Cohort Between 1998 to 2001 and 2008 to 2011

Level	1998–2001	2008–2011	Absolute Change		Prevalence Ratio	
	Rate (95% CI)	Rate (95% CI)	Difference (95% CI)	P-Value	Ratio (95% CI)	P-Value
Male						
Income level I	6.8 (3.8, 9.9)	3.7 (1.9, 5.5)	−3.1 (−6.6, 0.3)	0.08	0.5 (0.3, 1.1)	0.08
Income level II	5.1 (3.1, 7.1)	5.2 (3.5, 6.9)	0.1 (−2.6, 2.7)	0.96	1.0 (0.5, 1.8)	0.96
Income level III	5.1 (3.3, 7.0)	4.6 (3.2, 5.9)	−0.6 (−3.1, 1.7)	0.64	0.9 (0.6, 1.4)	0.62
Income level IV	5.8 (3.8, 7.8)	4.7 (3.3, 6.1)	−1.1 (−3.7, 1.2)	0.39	0.8 (0.5, 1.3)	0.40
Education level I	6.5 (5.1, 8.0)	5.3 (3.3, 7.3)	−1.2 (−3.7, 1.1)	0.31	0.8 (0.5, 1.2)	0.37
Education level II	4.7 (3.2, 6.1)	4.8 (3.8, 5.7)	0.1 (−1.6, 1.6)	0.92	1.0 (0.6, 1.5)	0.92
Female						
Income level I	4.3 (2.6, 6.1)	2.2 (1.2, 3.2)	−2.1 (−4.5, 0.2)	0.07	0.5 (0.2, 1.1)	0.06
Income level II	4.5 (3.0, 6.0)	4.2 (2.9, 5.4)	−0.3 (−2.5, 1.6)	0.76	0.9 (0.5, 1.5)	0.77
Income level III	5.4 (3.2, 7.6)	3.7 (2.5, 4.9)	−1.7 (−4.1, 0.5)	0.14	0.7 (0.4, 1.1)	0.12
Income level IV	6.4 (4.0, 8.9)	3.8 (2.5, 5.0)	−2.7 (−5.5, −0.4)	0.04	0.6 (0.3, 0.9)	0.03
Education level I	5.8 (4.1, 7.6)	4.7 (2.8, 6.6)	−1.2 (−3.0, 5.7)	0.61	0.8 (0.5, 2.33959)	0.95
Education level II	5.0 (3.7, 6.2)	3.5 (2.9, 4.1)	−1.5 (−3.0, −0.2)	0.04	0.7 (0.5, 0.9)	0.03

CI = confidence interval.

that almost 20% of adult HBV carriers aged 20 to 59 years died or were admitted to the hospital over the 10-year period for treatment of sequelae of HBV infection. This is because the 10-year survival rate of chronic HBV carriers is 89%, and primary liver cancer developed in 12% of carriers in a prospective Korean study.⁸ Alternatively, adult carriers achieved seroclearance upon antiviral treatment of their HBV infections.

The prognosis for HBV infection which was assessed by a decrease in the prevalence of HBsAg seroprevalence in a birth cohort over time was affected by socioeconomic status based on income and education levels. The substantial decrease in the lowest income group might be explained by 2 possibilities. First, although antiviral treatment options are important for preventing the development of HBV infection-related sequelae,⁷ a lower income might prevent access to such treatments. In Asian countries, expense is one of the main barriers to HBV antiviral drug treatment for patients with chronic infection.²⁰ Korea provides national health insurance coverage for the entire population, but there are limitations to the reimbursement for antiviral therapy in terms of the selection, duration, and doses of agents and how to respond to the development of resistance.²¹ Therefore, the cost of antiviral drugs remains an obstacle for optimal treatment in lower income group. Second, surveillance of individuals at high-risk is important for effective management, and the Korean government provides abdominal ultrasonography combined with alpha-fetoprotein measurement for groups at high risk of liver cancer, such as chronic HBV carriers.²² However, the compliance rate for liver cancer screening was lower in HBV carriers with lower household income compared with higher income levels, indicating significant inequalities according to income level,²³ and this might contribute to worse consequences for HBV infection.

Females with the highest income and education levels exhibited significant decreases in HBV seroprevalence. This may be associated with resolution of infection upon antiviral therapy. Such females would experience few limitations in terms of access to antiviral treatment or reductions in alcohol

consumption, which plays an important role in the development of chronic HBV-related complications.^{24–26} In females with the highest income or higher education background, the current alcohol drinking rate doubled significantly in 10 years (Figure 1). This suggests that the higher death or hospitalization rates identified by a decrease in HBsAg seroprevalence in this group were attributed to increased alcohol consumption.

We investigated changes in the seroprevalence of HBV infection in a hypothetical birth cohort, in addition to separate 10-year interval age groups. Our approach differs from those of earlier Korean studies using KNHANES data to evaluate longitudinal trends in the entire population.^{11,14} Although we did not follow-up individuals in our hypothetical birth cohort, this nationally representative cohort contained subjects aged 20 to 59 years at the time of the 1998 to 2001 KNHANES who were thus 30 to 69 years of age at the time of the 2008 to 2011 KNHANES. Thus, we employed a cohort approach by comparing data from subjects aged 20 to 29 years at the time of the 1998 to 2001 KNHANES with those of subjects aged 30 to 39 years at the time of the 2008 to 2011 KNHANES. Unlike previous Korean studies that attributed the downward trend in HBsAg-positivity to vaccination,^{11,14} we consider that the explanation is a combination of death and complete recovery of patients with HBV infection.

Several limitations should also be mentioned. Since the total anti-HBc and immunoglobulin M anti-HBc were not measured in the KNHANES, only current HBV infections could be examined, and thus we do not know whether the HBsAg-positive status reflected an acute or chronic infection. However, most HBV infections in Korea spread via vertical transmission,²⁷ and it is likely that individuals who were HBsAg-positive after 20 years of age were infected with HBV during infancy or in early childhood. In addition, the HBeAg level, which is a good indicator of the effectiveness of anti-hepatitis B therapy, infectiveness,⁶ and hepatitis C or hepatitis D coinfection (which may influence the HBsAg level²⁸), was not measured in KNHANES subjects. Thus, we encountered a limitation when seeking to estimate the burden of hepatitis B

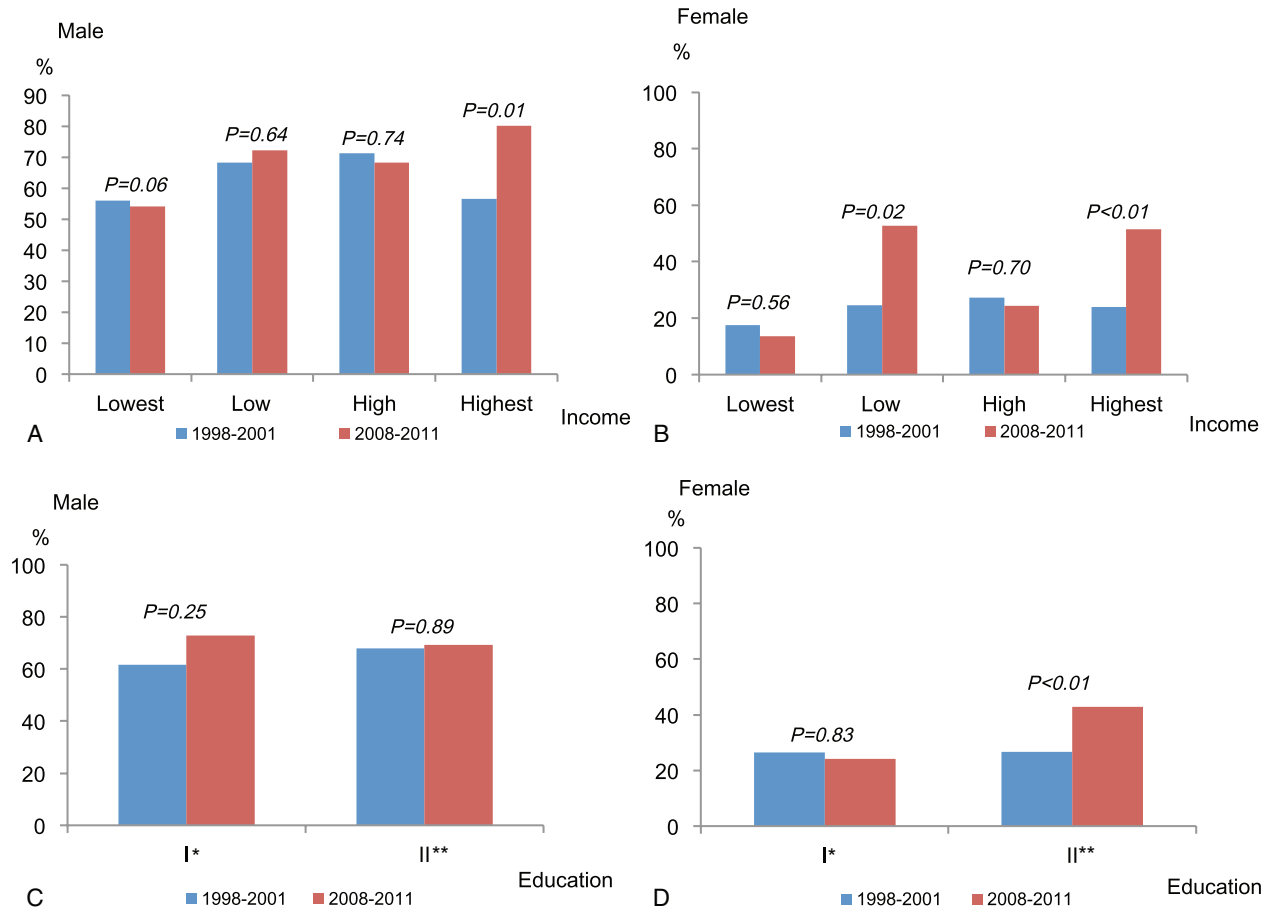


FIGURE 1. Current alcohol drinking rates (%) among HBsAg-positive individuals by income, education, and sex between 1998 to 2001 and 2008 to 2011. $P < 0.05$ indicates significant differences between 1998 to 2001 and 2008 to 2011. *For males, high school or less; for females, middle school or less. **For males, college or more; for females, high school or more.

infection. Second, other variables might explain the differences in HBV prevalence according to socioeconomic status, but we focused on alcohol consumption. Third, due to the limited sample size, the 95% CIs of the results were wide, especially for females with a lower education level; however, since the KNHANES used a sufficient sample size to produce nationally representative estimates, the number of HBsAg carriers itself was already small in Korea. Fourth, we did not include participants aged <20 or >60 years at the time of the 1998 to 2001 KNHANES, although it is important to evaluate the impact of interventions treating HBV infections in such subjects. This was because the teenagers were undergoing compulsory education, and the sample sizes of those aged >60 years in the follow-up hypothetical cohort (subjects of the 2008–2011 KNHANES) were small.

Interventions targeting high-risk groups, such as HBV carriers, are important for preventing the morbidity and mortality related to liver disease. These interventions should include primary prevention, such as lifestyle modifications; secondary prevention, such as liver cancer surveillance; and tertiary prevention, such as adequate antiviral treatment. This study found socioeconomic inequalities in the prognosis of HBV infection and postulated that these inequalities were caused by alcohol consumption, disparities in liver cancer surveillance, and access to antiviral treatment based on cost and reimbursement guidelines. Additional studies on the

reasons for these inequalities are needed to develop public health interventions for specific populations and to reduce the disease burden related to liver disease as a sequelae of HBV infection.

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