MINI-REVIEW

Viral Hepatitis and Liver Cancer in Korea: an Epidemiological Perspective

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Abstract

In the past, hepatitis B virus (HBV) infection was endemic in the general Korean population. The association of HBV infection with the occurrence of liver cancer has been well demonstrated in several epidemiologic studies. While the mortality rates of liver cancer in Korea have decreased steadily over the last decade, the presence of hepatitis B surface antigen (HBsAg) in mothers remains high at 3-4%, and 25.5% of these HBsAg positive mothers are positive for hepatitis B e antigen (HBeAg). HBV infection caused almost a quarter of hepatocellular carcinoma (HCC) cases and one-third of deaths from HCC. These aspects of HBV infection prompted the Korean government to create a vaccination program against HBV in the early 1980s. In 1995, the Communicable Disease Prevention Act (CDPA) was reformed, and the government increased the number of HBV vaccines in the National Immunization Program (NIP), driving the vaccination rate up to 95%. In 2000, the National Health Insurance Act (NHIA) was enacted, which provided increased resources for the prevention of perinatal HBV infection. Then in 2002, the Korean government, in conjunction with the Korean Medical Association (KMA), launched an HBV perinatal transmission prevention program. The prevalence of HBsAg in children had been high (4-5%) in the early 1980s, but had dropped to below 1% in 1995, and finally reached 0.2% in 2006 after the NIP had been implemented. After the success of the NIP, Korea finally obtained its first certification of achievement from the Western Pacific Regional Office of the World Health Organization (WPRO-WHO) for reaching its goal for HBV control. An age-period-cohort analysis showed a significant reduction in the liver cancer mortality rate in children and adolescents after the NIP had been implemented. In addition to its vaccination efforts, Korea launched the National Cancer Screening Program (NCSP) for 5 leading sites of cancer, including the liver, in 1999. As a consequence of this program, the 5-year liver cancer survival rate increased from 13.2% (1996-2000) to 23.3% (2003-2008). The development of both the primary and secondary prevention for liver cancer including HBV immunization and cancer screening has been of critical importance.

Keywords: Hepatitis B - vaccination - screening - liver cancer

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Introduction

Hepatitis B (HB) is a major public health problem in some Asian and Western Pacific nations. The countries in this area have an estimated 158 million chronic carriers and approximately 300,000 deaths annually, mainly because of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Controlling the infection rate of hepatitis B virus (HBV), a public health threat, has been issued in Korea where HB surface antigen (HBsAg) positivity was relatively high up to 6.6-6.8% in early 1980s (Chae et al., 2009).

The public health burden due to cancer, including liver cancer, has also increased in Korea. Chronic infection of HBV accounts for almost two-thirds of HCC causes and similar proportion of deaths caused by HCC in Korea, where the liver was the fifth leading site of cancer, accounting for 7.9% of all cancer cases and 15.3% of all cancer deaths ranked in the second common site for the origin of cancer (Korea National Cancer Information Center, 2013). However, liver cancer incidence and mortality have been decreasing for a last decade, as have stomach cancer in men and cervical cancer in women (Jung et al., 2013) (Figure 1).

In this review, we focus on the successful implementation of strategies for HBV vaccination and the encouraging trends in the rate of HBV infection and liver cancer mortality in Korea.

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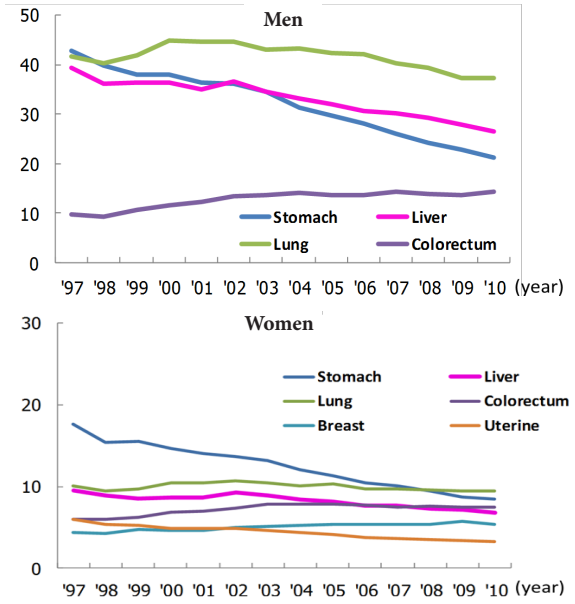

Figure 1. Cancer Mortality Trends in Korea According to Sex (per 100,000). Source: Annual report of causes of death (age-standardized rates from the Korean registration population). Statistics Korea, 2012

Hepatitis B and Liver Cancer in Korea

Viral hepatitis, especially types B and C, is known to progress to HCC. In Korea, among all HCC cases, more than two-thirds (74.2%) had positive results for HBsAg, while 8.6% had antibodies to the hepatitis C virus (anti-HCVs) in a previously conducted case-series analysis (Cheon et al., 2004). HBV is the most common infectious etiologic factor for liver cancer in Korea, followed by the hepatitis C virus (HCV). The risks in the Korean population of developing HCC from HBV or HCV infection have been reported in several case-control studies. The risk of developing HCC was 87.4 times greater among the HBsAg carriers than among the non-carriers. In addition, anti-HCV-positive subjects showed about a 30-fold increased risk of developing HCC (Shin et al., 1996). The relationship between HBV infection and the subsequent occurrence of HCC in Korea was also reported in a reconstructed cohort study in 1991 (Yoo et al., 1991). In this cohort (n=370,000), the risk for liver cancer was significantly increased (up to 5 times) in HBsAg-positive cases, regardless of positivity for anti-HBs present at the time of recruitment, compared to cases with no positivity for HBsAg or anti-HBVs. The association between HBV infection status and risk of liver cancer was also clear that the risk was reduced by about 30% among those positive for anti-HBs subjects compared with those who were susceptible to HBV, while the risk was greatest among those positive for HBsAg ($p<0.0001$).

In Korea, a key question has been what fraction of cancer incidence or deaths could be attributed to HBV and HCV infection. The population-attributable fraction (PAF) for HBV infection among infection-related cancers was 27%, while the PAF for HCV infection was only 6% of all cases and 9% of deaths (Shin et al., 2011). Considering that the PAF for all infectious agents, including Helicobacter pylori, HBV, and HCV, causing any type of cancer, reached as high as 25.1% and 25.8% for all cancer incidences and deaths in men, it was inevitable that issues concerning the prevention of HBV infection would emerge.

Prevention of Hepatitis B: Vaccination in Korea

To prevent HBV infection, an epidemiologic approach was taken, attempting to capture the characteristics of this infectious agent. The risk of becoming a chronic carrier of HBV, which is strongly associated with a progression to HCC, had been hypothesized to be based on age at infection. A stochastic analysis, performed in early 1992, showed that the force of infection by HBV was steadily decreasing with increasing age, up to approximately 20 years of age, in Korean populations (Yoo et al., 1992). The fraction of antigen positivity among persons infected by HBV was similarly decreasing with age in early childhood. These results suggested that in Korea, the majority of new HBV infections might occur in the perinatal period or early in life, and that the chronic persistency of HBV from early childhood might be causally associated with the subsequent development of liver cancer. The probability of HBV infection among neonates who were born from HBsAg-positive mothers was known to range from 10% to 20%. Furthermore, the probability of HBV infection among neonates who were born from HBeAg-positive mothers was much higher at 70-90% approximately, which was higher than that for other routes of transmission (e.g., iatrogenic, acupuncture, sexual transmission). Epidemiologic evidences suggested that the focus should ultimately move toward vaccinating children and neonates born to HBV-positive mothers.

The history of national program for vaccination in Korea is summarized in Table 1. The initial plasma-derived HBV vaccine was licensed domestically and became available in 1983. During 1984 and 1985, the government recommended that the general population be vaccinated for HBV infection. As a result, about 6 million people received an HBV vaccination. Since that time, the strategy for HBV immunization has changed in an attempt to supply the vaccine to more subjects and find more effective means of prevention. Since that initial period, tests for HBV infection have been conducted for pregnant

Table 1. A Summary of the Korean National HBV Vaccination Program

Year	Contents
1983	Plasma-derived HBV vaccine domestically licensed
1985	HBV vaccination recommended mainly to infants and children under the Communicable Disease Prevention Act (CDPA)
1987	Recombinant HBV vaccine licensed
1988	Mass HBV immunization of school-aged children implemented
1991	Universal HBV vaccination recommended by the Korean Pediatric Society (KPS)
1995	Hepatitis B legally classified as an epidemic disease National Immunization Program (NIP) for HBV introduced (vaccine given free of charge to all neonates in public health offices)
2000	Prenatal test for HBV infection supported by the National Health Insurance Act (NHIA)
2001	Hospital-based surveillance for acute HBV infection implemented
2002	The program for HBV vaccination implemented to combat vertical transmission for neonates born to HBV (+) mothers
2009	Fee coverage implemented for HBV immunization for all neonates in private health clinics

woman, and vaccination for infants had been carried out by public health centers free of charge, as a part of the Communicable Disease Prevention Act (CDPA).

Mass HBV immunization of school-aged children began when the recombinant HBV vaccines were first licensed in 1987. In 1991, the Korean Pediatric Society (KPS) included the HBV vaccine in the immunization table for neonates. When the CDPA was reformed in 1995, the government included the HBV vaccine in the National Immunization Program (NIP). HBV infection was declared one of the legal epidemic diseases, and public health offices had to provide HBV vaccines free of charge to all neonates, regardless of HBsAg positivity. This immunization, furthermore, was mandatory [Korea Centers for Disease Control and Prevention (KCDC), 2010]. In 2000, the National Health Insurance Act (NHIA) was enacted in order to prevent perinatal HBV infection. This act mandated that all costs related to antenatal screening processes, including the test for HBsAg to diagnose chronic HBV infection in pregnant women, be covered. In 2002, in conjunction with the Korean Medical Association (KMA), the Korean government launched the HBV Perinatal Transmission Prevention Program. The national program gives hepatitis B immunoglobulin (HBIG) to all neonates born to HBV-positive mothers, followed by HBV vaccination in 3 doses at 0, 1, and 6 months of age (Cho et al., 2012). The fee for antenatal care or tests for HBV has been covered by the National Health Insurance (NHI) since 2001 when the program was first initiated. In addition, private clinics have been providing the HBV vaccination free of charge to all neonates since 2009.

Successful Vaccination Strategy: Hepatitis B Infection

Since it began its effort to vaccinate all neonates against HBV infection, the Korean government has been distributing coupon booklets, which are used to pay for the cost of immunization at private obstetric clinics (Figure 2). At the time of delivery, health care personnel reminded that mothers register in the prevention program, and the registration data are sent to the national healthcare database through the health departments of cities or states. These data are used to manage on-time vaccinations and to follow up on the infants at risk for perinatal infection. The coupons are used to direct the mothers to ensure that their children receive the following services: HBIG at birth; HBV vaccine at birth and at 1 month and 6 months of age; and testing for HBsAg and anti-HBs of infants at 9-15 months of age. The mothers give the coupons to private clinics, and the private clinics submit the coupons to public health centers for reimbursement for their services (KCDC, 2010).

In December 2006, 251 public health centers and approximately 4,000 private health care providers were found to be participating in this prevention program. The proportion of the number of infants registered in the program to the estimated number of births to HBsAg-positive mothers has increased from 87.5% in 2003 to 97.1% in 2011 (Table 2) (KCDC, 2011). During the same period, 71,620 infants were estimated to be born to HBsAg-positive pregnant women (3.4% of all pregnant women), and about 65,000 of these infants were registered in the prevention program. Such a high registration rate among HBsAg-positive mothers indicates that the program has been successful, in part due to the government's recommendations for immunization and

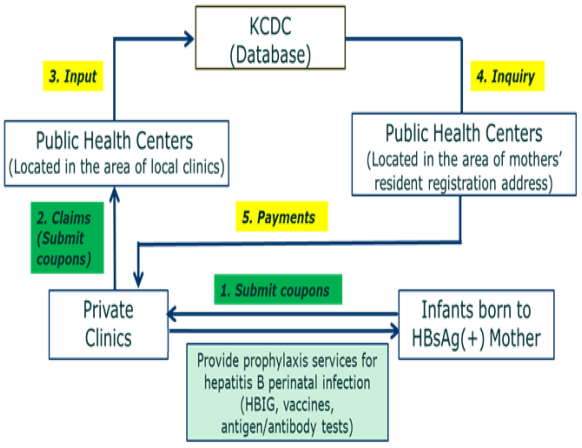

Figure 2. Korean Program for Implementing Perinatal Transmission Prevention. Source: Korea Centers for Disease Control and Prevention (2012)

Table 2. Registration of Neonates Exposed to HBV Vertical Transmission in Korea, 2002-2011

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Estimated no. of exposed*	7,857	16,678	16,074	14,791	15,237	15,783	14,909	14,235	15,045	15,045**
No. of registered	5,394	14,586	15,410	14,411	15,002	16,483	15,266	14,547	14,760	14,612
Registration rate (%)	68.70%	87.50%	95.90%	97.40%	98.50%	104.40%	102.40%	102.20%	98.10%	97.10%

*Estimated number of neonates exposed to HBV=number of neonates ×0.032 (maternal HBsAg-positive rate); **Estimated from the number of neonates in 2010; ***Sources: Korea Centers for Disease Control and Prevention (2012)

Table 3. Trends in the Prevalence of HBV Infection (HBsAg+) in Children

	Year	Age (years)	Area	No.	HBsAg Positivity	Sources
Before national immunization	1976-77	6-11	Jeonnam	1,296	4.2%	*Korean J Pediatr* 1979;22:433
	1982	8-16	Daegu	897	4.8%	*Korean J Pediatr* 1983;26:1188
After national immunization	1988	6-17	Seoul	20,540	3.2%	*Korean J Pediatr* 1995;38:1535
	1993	6-17	Seoul	27,107	2.6%	*Korean J Pediatr* 1995;38:1535
	1995	6-7	Seoul	120,106	0.8%	*Korean J Epidemiol* 1996;18:151
	2006	4-6	Nationwide	2,920	0.2%	KCDC, HepB sero-survey, 2007

coverage of the vaccination fees. Through these efforts, the rate of HBV vaccination in Korea soared to about 80% in the early years after the NIP was implemented and reached almost 90% in neonates in the early 2000s.

WHO Certification for the Achievement of Vaccination Strategy

In the 1970s and early 1980s, the prevalence of HBsAg in children was high up to 4-5% (Hong et al., 1979; Jun et al., 1983). This rate began to decrease in 1985, after the vaccination was first introduced. In 1988, the prevalence of HBsAg positivity in children was reported to be 3.2%, which decreased to 2.6% in 1993 (Sim et al., 1995). This prevalence dropped to below 1% in 1995 (Kang et al., 1996), and finally to 0.2% in 2006 (KCDC, 2009) (Table 3). A study based on the nation-wide survey (NHANES) reported that 11.7% of men and 9.5% of women in the general population of Korea had been positive for HBsAg in 1986. Current statistics clearly show a dramatic decline since then (Figure 3): the prevalence of HBsAg positivity in the general population dropped to 3.4% in men and to 2.6% in women during the last 2 decades (KCDC, 2012).

As a result of this 20-year cooperative effort, in 2007, the Western Pacific Regional Office of the World Health Organization (WPRO-WHO) granted Korea its certificate of achievement for reaching its goal for HBV control (KCDC 2008). This certification requires HBsAg-positive rates of less than 1% among children under 5 years of age and HBV vaccination coverage of over 85%. The Korean government's 3 main strategies that resulted in achieving this goal were: *i*) strengthening the NIP to reach 95% coverage for 3 doses of HBV vaccine (HepB3) at the national and metropolitan/provincial level; *ii*) preventing perinatal transmission to minimize chronic HBV infection; and *iii*) strengthening the surveillance system to monitor and evaluate the HBV control program.

In a nationwide sero-survey conducted to children aged 4-6 years who visited to public health centers, HBsAg-positive rate was measured to be 0.2%. Eventually, the result has achieved WHO's ultimate goal of HB control in its western pacific region. After all, Korea has obtained the WHO's certificate for the achievement of HB control goal in 2007 for the first time among the western pacific countries.

Liver Cancer Mortality in Korean Adolescents

HBV vaccination ultimately led to decreased liver cancer mortality rates in Korea. In order to quantitatively compare the mortality rates of liver cancer before and after the preventative program for neonates and children was implemented, the mortality rates for each year from 1991 to 2006 were analyzed using the age-period-cohort (APC) effect model (Gwack et al., 2011). This APC analysis showed a significant reduction in the liver cancer mortality rate after the implementation of the NIP (1995-2011), compared to that before (1991-1994). The relative risk for death due to liver cancer after the NIP was reported to be 0.30 from 2003 to 2006, indicating a statistically significant (70%) reduction compared to that of prior to the NIP.

This was owing to the successful vaccination strategy that focused on neonates and children who were at high risk for vertical transmission of HBV and progression to chronic HBV carriers in Korea, an endemic region for HBV where the HBV infection rate is relatively high (Seo DH et al., 2011).

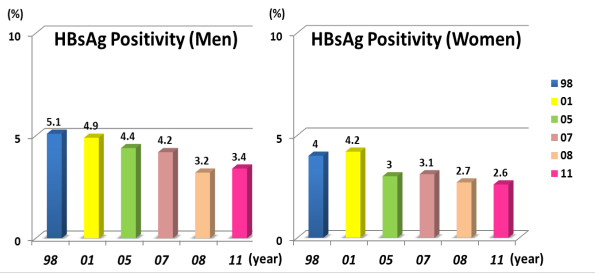

Figure 3. Trends in the Prevalence of Hepatitis B Infection (HBsAg positivity) in Korea. Source: The Korea National Health & Nutrition Examination Survey, 2012

Cancer Screening and Liver Cancer in Korea

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 its 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. It introduced the National Cancer Screening Program (NCSP) in 1999, which covers liver cancer and four other leading cancers in Korea. Under the NCSP, men and women aged over 40 years with chronic hepatitis (HBsAg- or anti-HCV-positive) and liver cirrhosis patients, regardless of HBV or HCV infection, are offered screening (Kim, 2001). To widen the coverage rate of cancer screening, clinicians are permitted to offer screening to patients with a high risk of liver cancer even if such patients are under the recommended screening age of 40 years. The NCSP liver cancer screening guidelines recommend alpha-fetoprotein (AFP) testing and abdominal ultrasonography every 6 months in the indicated population. If the patients are elderly, at high risk of liver cirrhosis progression, have risky drinking habits, or have a family history of liver cancer, computerized tomography (CT) scanning can also be performed at the discretion of their clinicians.

Table 4. International Comparison of 5-year Relative Cancer Survival Rate

	Korea (2001-2005)	USA (1996-2004)	Japan (1997-1999)	Europe (1995-1999)
Stomach	56.4	24.7	62.1	24.1
Lung	15.5	15.2	25.6	12.6
Colorectal	64.8	64.4	65.2	53.5
Liver	18.9	11.7	23.1	8.6
Thyroid	98.1	96.9	92.4	86.5
Breast	87.3	88.7	85.5	81.1
Cervix uteri	81.1	71.2	71.5	66.5
Prostate	76.9	98.9	75.5	77.0
All cancers	52.2	65.3	54.3	51.9

*Sources: Ries et al. SEER Cancer Statistics Review (1975-2005), National Cancer Institute (2008); Cancer Statistics in Japan, National Cancer Center in Japan (2008)

As a result of these efforts, the 5-year survival rate for liver cancer in Korea has greatly improved, from 13.2% in 1996-2000 to 23.3% in 2003-2008 in Korea. Partly because of such successful screening, the 5-year survival rates for stomach and liver cancer in Korea are much higher than the rate in the US, while the 5-year survival rates for colorectal and breast cancer are similar to rates in western countries (Table 4).

Conclusion

In summary, the incidence of liver cancer has continued to decrease over the last decade in Korea. The well-demonstrated association of HBV infection and the development of liver cancer led the Korean government to focus on HBV immunization, and as a result, the NIP has led to lower mortality rates due to liver cancer in Korean children and adolescents. The government combined these effective vaccination efforts with a successful national cancer screening system, creating a model for basing public health policy and law on scientific and epidemiologic evidence. This Korean strategy for liver cancer prevention offers a model for primary prevention in other countries where the prevalence of HBV infection is high.

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