

Hepatitis B vaccination and reduced risk of primary liver cancer among male adults: a cohort study in Korea

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Background Primary liver cancer is an important health problem in Korea, where hepatitis B virus (HBV) infection is prevalent. The authors conducted a prospective cohort study to evaluate the protective effect of HBV vaccination against liver cancer in adults.

Methods A total of 370 285 males aged ≥ 30 comprised the study population. They were clinically free of liver diseases, and had not been vaccinated against HBV at enrolment. The results of HBV surface antigen (HBsAg) and antibody to HBsAg (anti-HBs) marker positivity and those of the vaccination programme which took place during 1985 were used for the construction of the cohort. About 5% ($n = 18\ 914$) were HBsAg positive, 78 094 were anti-HBs positive, and 273 277 were negative for both. Among the candidates for HBV vaccination ($n = 273\ 277$), 35 934 (13.2%) people had been vaccinated against HBV during 1985. Cases of liver cancer were ascertained by record linkage and from medical records covering 1986–1989. A multivariate log-linear model was used to test statistical significance and to estimate relative risks (RR).

Results The total follow-up period was 1 404 566 person-years, with an average of 3 years and 10 months. A total of 302 incident cases were ascertained. The overall incidence rate of liver cancer was 21.7 per 100 000 person-years. With reference to the incidence level among the unvaccinated and uninfected, the RR of primary liver cancer among the chronically infected and that of the unvaccinated and infected was 18.1 (95% CI: 14.2–22.9) and 0.34 (95% CI: 0.19–0.60), respectively. The RR among the vaccinated group was 0.58 (95% CI: 0.31–1.09).

Conclusions This study suggested that artificial immunization through HBV vaccination, even in adulthood, reduces the risk of liver cancer. It might also offer a practicable means of primary prevention, especially in areas with hyperendemicity of HBV infection.

Keywords Hepatitis B virus, vaccination, prevention, primary liver cancer, cohort study

Accepted 17 July 1997

Primary liver cancer (PLCA) is an important health problem in South East Asia and sub-Saharan Africa,¹ where hepatitis B

virus (HBV) infection is prevalent. In such areas, long-standing persistent HBV infection is the main cause of PLCA, especially of hepatocellular carcinoma.² In Korea, where the prevalence of HBV infection is among the highest in the world,³ liver cancer is one of the common cancers.⁴ The point prevalence rate of HBV surface (HBs) antigenaemia was 8.0% in male adults, but only 6.2% for female adults.³ The overall prevalence of HBV infection was 61.3% in males and 52.8% in females.³ A recent study in Korea has reported that among those infected during the postnatal period, about 10–15% became chronically infected.⁵ In patients with chronic active hepatitis, 9% developed liver cirrhosis within 5 years, while 13% of patients with liver cirrhosis developed hepatocellular carcinoma within 5 years.⁶

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Hepatitis B vaccination of infants is now focused on preventing persistent infection (so-called chronic carriers),⁷ with the ultimate goal of preventing liver cancer. Direct evidence that HBV vaccination prevents hepatocarcinogenesis is, however, lacking. Several countries adopting vaccination programmes have begun research in order to seek such evidence.⁷

In Korea, plasma-derived HBV vaccines have been available for commercial use since 1983,⁸ and in the mid-1980s, vaccination against HBV infection was strongly recommended, even for adults. There were reports that naturally immunized adults, though the time when they had become immune was unclear, had a lower incidence of liver cancer than the uninfected.⁹ Those results suggested that artificial immunization through HBV vaccination even in adulthood might reduce the risk of liver cancer. The authors conducted a prospective cohort study to elucidate the protective effect of HBV vaccination against liver cancer in adults.

Materials and Methods

The results of the 1984 and 1986 biennial health examination for those insured by Korea Medical Insurance Corporation (KMIC) were used to define the study population. The KMIC, founded in 1979 by the Korean government for government employees, school teachers and their dependants, has since 1980 offered a free biennial health examination programme for those insured. In 1984, all those examined were tested for HBV surface antigen (HBsAg) by reversed passive haemagglutination (RPHA) (Hepa S-Ag Test^R, Green Cross, Seoul, Korea) and for anti-HBs by passive haemagglutination (PHA) methods (Hepa S-Ab Test^R, Green Cross, Seoul, Korea), according to the manufacturers' recommendations. In 1985, KMIC also recommended vaccination against HBV on a voluntary basis for those with negative results on both HBsAg and anti-HBs. The vaccination was three injections at 0, 1, and 6 months with the dosage of 20 µl per occasion. About 90% of the vaccine was from a domestic pharmaceutical company (HepaVax^R, Green Cross, Seoul, Korea).

A total of 370 285 males aged ≥30 comprised the study population. They were free of clinical liver diseases: their liver enzymes (sGOT and sGPT) were within normal ranges, and on physical examination by physicians in both the 1984 and 1986 health examination, they showed no clinical evidence of liver disease. They had not been vaccinated against HBV before the 1984 examination. About 5% (18 914) were HBsAg positive, 78 094 (21.1%) had natural immunity against hepatitis B (anti-HBs positive), and 273 277 (73.8%) people were candidates for HBV vaccination (both markers negative) (Table 1). Among the candidates, 35 934 (13.2%) had been vaccinated against HBV during 1985, while the others, 237 343, had not been vaccinated. Four groups of subcohort to follow-up were defined: 'the chronically infected (18 914)', 'the unvaccinated and infected (78 094)', 'the vaccinated (35 934)', and 'the unvaccinated and uninfected (237 343)'.

Probable cases of liver cancer were people who were admitted to medical institutions between 1986 and 1989 with diagnoses of either liver cancer, secondary cancer of the respiratory or digestive system, or benign tumour of other parts of the digestive system. The medical records for each probable case were abstracted by medical students or physicians who cared for

Table 1 Distribution of the cohort members by age, monthly wage, serological test result for hepatitis B virus (HBV), and HBV vaccination status at enrolment

Characteristics	No.	(%)
Age (years)		
30-34	80 808	21.9
35-39	76 299	20.6
40-44	75 973	20.5
45-49	73 069	19.7
50-54	42 172	11.4
55-59	17 071	4.6
≥60	4893	1.3
Monthly wages^a		
Lower	129 503	35.0
Middle	150 310	40.6
Upper	90 472	24.4
Serological test results for HBV		
Negative for both HBsAg and Anti-HBs	273 277	73.8
Non-vaccinee	(237 343)	(86.8)
Vaccinee	(35 934)	(13.2)
HBsAg(-) and Anti-HBs(+)	78 094	21.1
HBsAg(+) and Anti-HBs(-)	18 914	5.1

^a Lower: monthly wages <350 000 Korean won (US\$ 500) as of 1985, middle: 350 000-500 000 won, upper: >500 000 won.

the cases. The authors reviewed the abstract forms and verified the diagnosis of PLCA. In order to estimate the follow-up period, all the populations were checked to determine whether they were enlisted as beneficiaries of KMIC at the end of each of the years 1986-1989.

A multivariate log-linear model was used to adjust the effect of age and socioeconomic status as represented by monthly wage. The log-linear model also assumed a constant hazard during the 4 years.¹⁰ The GLIM package was used in a personal computer to yield relative risks (RR), 95% two-sided confidence intervals (CI) and related statistical significance ($\alpha = 0.05$, one-tailed test).¹¹

Results

The total follow-up period for all the cohort members was 1 404 566 person-years with 71 792 person-years for the chronically infected group, 297 648 for the unvaccinated and infected, 136 872 for the vaccinated, and 898 254 person-years for the unvaccinated and uninfected group. The average follow-up period (3.8 years) did not differ between groups, although older people tended to be more frequently lost to follow-up.

A total of 302 incident cases were identified during 1986-1989. The overall incidence rate of PLCA during this period was 21.7 per 100 000 person-years (Table 2). The incidence among the unvaccinated and infected, i.e. those who had natural immunity against hepatitis B (anti-HBs positive in 1984) was the lowest, 4.4, followed by that of the vaccinated 8.0 and that of the unvaccinated and uninfected, 13.7. The incidence of the chronically infected, HBsAg positives, was the highest, 215.9 per 100 000 person-years. Using the unvaccinated and uninfected group as the referent group, RR for PLCA of the chronically

Table 2 Incidence rates of primary liver cancer (PLCA) among cohort members by hepatitis B virus (HBV) serological profiles and vaccination status

Serological profiles and vaccination status	Person-years of follow-up	PLCA cases	Incidence rate	Relative risk ^a (95% CI)
HBsAg(-) and Anti-HBs(-) at 1984 health examination				
Non-vaccinee (The unvaccinated and uninfected group)	898 254	123	13.7	1.0
Vaccinee (The vaccinated group)	136 872	11	8.0	0.58 ^b (0.31-1.09)
HBsAg(-) and Anti-HBs(+) (The unvaccinated and infected group)	297 648	13	4.4	0.34 ^b (0.19-0.60)
HBsAg(+) and Anti-HBs(-) (The chronically infected group)	71 792	155	215.9	18.1 ^b (14.2-22.9)
Total	1 404 566	302	21.7	-

^a Age and monthly wages adjusted by multivariate analysis using log-linear model

^b $P < 0.05$ by Wald test (one-tailed test)

infected, the unvaccinated and infected, and the vaccinated were estimated by multivariate analysis. The RR of the chronically infected for PLCA was 18.1 (95% CI: 14.2-22.9), while the RR of the unvaccinated and infected was 0.34 (95% CI: 0.19-0.60). The incidence level among the vaccinated was lower (RR = 0.58, 95% CI: 0.31-1.09) than that among the unvaccinated and uninfected (Table 2), and on one-tailed test, the RR was significant ($P < 0.05$).

Discussion

The results suggested that immunity against HBV, whether acquired naturally or artificially (by vaccination), was associated with reduced risk of PLCA. As a large scale population study, this study has inevitable methodological limitations, however. Information on HBV markers was obtained using the RPHA and PHA methods; less accurate than radioimmunoassays.¹² The RPHA method tended to classify HBsAg positives as negatives,¹³ whereas the PHA method tended to classify anti-HBs negatives as positives.¹⁴ In this study, subjects who were misclassified as HBsAg negative or as anti-HBs positive would increase the risk of PLCA among the HBs negative or anti-HBs positive groups, respectively. That misclassification, if any, would therefore lead the RR toward unity.

Two years later, to evaluate the extent of misclassification, the authors conducted several studies based on radioimmunoassay, HBsAg, anti-HBs, and anti-HBc among the new samples taken from the subjects of the vaccinated and unvaccinated/uninfected group of this study. The proportion of anti-HBc positives was higher among the vaccinated than the unvaccinated and uninfected.^{14,15} Although specimens were collected after vaccination, the above results implied that the vaccinated before vaccination might include a far higher proportion of anti-HBc positives than the unvaccinated and uninfected. And these data suggest the protective effect of vaccination would be greater than that presented in this study.

The health behaviour of the vaccinated and the unvaccinated/uninfected might be different; this would produce bias on the protective effect of vaccination, e.g. the vaccinated had more chance of being diagnosed as suffering from PLCA. The vaccinated tended to be of higher socioeconomic status, which

might overestimate the protective effect of vaccination. In the data, however, PLCA was not associated with higher socioeconomic status, so this could reduce the above possibility.

As regards biological perspectives, the results obtained from just 4 years of follow-up might not be clear. Hepatocarcinogenesis requires several decades to develop from the HBV carrier state and several years from the subclinical stages to overt cancer.¹⁶ Even though the study population was free of liver disease at enrolment, it might include people in the pre-clinical stages of hepatocarcinogenesis, and this would not differ between the vaccinated and those not vaccinated. Nothing is known about the biological interaction of HBV vaccination in the pre-clinical stages of hepatocarcinogenesis; nevertheless the protective effect of HBV vaccination against liver cancer in adulthood can be inferred from the results, based on over one million person-years of follow-up.

Protective effects of vaccination on hepatocarcinogenesis were suggested by several researchers.¹⁷⁻¹⁹ It has been reported that HBV vaccination causes the side effect of autoimmune reactions,¹⁷ and the possibility arises that HBV vaccination, through activating a non-specific immune response, might play significant roles in the surveillance of pre-malignant cells, whether or not these transformations were caused by HBV. The mechanisms of immunological activation due to HBV injection might be related to Kupffer cells in the liver.¹⁸ Some authors have recently reported that in animal models of hepatocellular carcinomas, injection of the hepatitis virus regressed the tumours,¹⁹ which was consistent with the above possibility.

Cancer has been one of the major issues in medical research for several decades, and research focusing on aetiologies and pathogenesis has been ongoing. Some practicable approaches to the prevention of cancer have been suggested, but their feasibility has been disappointing. This study, showing the protective effect of HBV vaccination on the adult population, offers a practicable means of primary prevention, especially in areas that show hyperendemicity for liver cancer.

Acknowledgements

This study has been supported by grants from the Korea Science and Engineering Foundation (96-0701-01-01-3).

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