*The Seoul Journal of Medicine*
*Vol. 30, No. 4: 243-248, December 1989*

# Longitudinal Study on the Negative Conversion Rate of HBsAg Among Male Adults in Korea

Byung-Joo Park[1]

*Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul 110-460, Korea*

= Abstract = The negative conversion rate of HBsAg among adult males in Korea was estimated during a two-year follow-up study on a fixed cohort of 64 HBsAg positives tested by radioimmunoassay.

The nagative conversion rate of HBsAg was 35.9% with its 95% Confidence Interval (CI) of 24.6-49.0%. The difference of rates estimated by age was not statistically significant, but the geometric mean titers of HBsAg decreased significantly by age. According to the ratio unit (RU) of HBsAg at enrollment, an inversed relationship between the ratio unit and the negative conversion rate was observed. Among in the less than 10 RU group, the negative conversion rate was 75% (95% CI: 50.6-90.4); among in the 10-49 RU group and in the larger than 50 RU group were 29.4% (95% CI: 11.4-55.9) and 11.1% (95% CI: 2.9-30.3), respectively.

Key words: ***Longitudinal study, HBsAg, Radioimmunoassay, Negative conversion rate, Male adult in Korea.***

## INTRODUCTION

The positive rates of the hepatitis B surface antigen (HBsAg) in Korea have been reported to be 6-15 % in males and 4-13% in females, which are some of the highest rates in the world (Ahn *et al.*, 1983; Kim *et al.*, 1985; Yoo *et al.*, 1988).

The chronic HBsAg carrier has serious implications with respect to both clinical and public health aspects. Carriers of the hepatitis B virus (HBV) constitute the reservoir from which the virus is spread in the community (Tanaka *et al.*, 1986). After Steiner (1960) suggested that HBV and hepatocellular carcinoma (HCC) might be causally associated, several reports supporting this suggestion have been published (Tong *et al.*, 1971; Blumberg *et al.*, 1975; Tabor *et al.*, 1977; Trichopoulos *et al.*, 1978; Kew *et al.*, 1979). Currently, HBV is regarded as one of the major causative agents of HCC. Chronic carriers of HBsAg especially are at a much higher risk of developing HCC than noncarriers (Beasley *et al.*, 1982; Feret *et al.*, 1987). Therefore, it is very important to estimate the probability of becoming a chronic HBsAg carrier after being infected with HBV and the changing pattern of HBsAg when one is identified to be HBsAg positive at a particular point in time in Korea where the incidence rate of primary liver cancer is also one of the highest in the world (Ahn *et al.*, 1989).

This study was conducted to estimate the negative conversion rate of HBsAg by age group and RIA titers at enrollment during a two-year follow-up study among male adults.

## SUBJECTS AND METHODS

### 1. Study Population

Every person insured with the Korea Medical Insurance Corporation (KMIC) has received a

Received 24/8/89; revised 24/9/89; accepted 30/9/89
[1]Author for correspondence

Table 1. Age distribution* of follow-up and drop-out subjects among actual population during two-year follow-up period

| Age Group | Follow-up | | Drop-out | | Total |
|---|---|---|---|---|---|
| | No | % | No | % | |
| 20–29 | 16 | 25.0 | 10 | 16.7 | 26 |
| 30–39 | 24 | 37.5 | 25 | 41.7 | 49 |
| 40–49 | 18 | 28.1 | 18 | 30.0 | 36 |
| 50–59 | 6 | 9.4 | 7 | 11.6 | 13 |
| Total | 64 | 100.0 | 60 | 100.0 | 124 |

*$P > 0.05$ by $\chi^2$-test

physical checkup, including a liver function test, at a designated medical institute near his office every other year since 1980. The target population were those insured people of the KMIC who were male, aged 20 and over, living in Seoul and who had no abnormal findings during the 1986 regular physical checkup. Among the target population, 1,495 people were randomly selected in June, 1986 (Yoo, 1988). A radioimmunoassay (RIA) test was performed to detect the hepatitis B surface antigen (HBsAg). According to the results, 124 people were HBsAg positive and determined to be the actual population. After two years, sixty four of those actual population were able to be followed up and re-examined HBsAg status, who became the study population, that is, the fixed cohort (Table 1).

2. Test for Hepatitis B Surface Antigen

Blood samples were collected from the study population and centrifuged at 3,000 rpm for 20 minutes. The obtained sera were refrigerated below −20°C until being tested.

Both radioimmunossay tests at enrollment and after follow-up were performed to detect HBsAg(AUSRIA®) according to the manual of Abbot Lab., U. S. A. by a well-trained medical technician at the Liver Research Institute of Seoul National University College of Medicine.

3. Data Aanlysis

**Definition of term :**

Negative conversion rate: the probability of losing HBsAg in the blood during the two-year follow-up period among HBsAg positive sitive poeple at enrollment.

**Statistical procedure :**

The negative conversion rates of HBsAg were calculated by age and RIA ratio unit at enrollment. Comparison of the rates was performed by using $\chi^2$-distribution as an asymptotic model:

$$\chi^2 = \frac{(|C - S\pi| - 1/2)^2}{S\pi(1-\pi)}$$

$\pi$ : parameter (rates among target population)
$p = C/S$ : sample estimates(rates among study population)

A comparison of RIA titers of HBsAg by age between two periods was performed by calculating the geometric mean titers(GMT) and their ratio. The statistical significance of the changes was tested with Kruskal-Wallis one-way analysis of variance at the significance level of 0.01.

## RESULTS

**Negative conversion rate of HBsAg during two years**

The negative conversion rate of HBsAg among the study population was 35.9% during the two-year follow-up period, and its 95% confidence interval was 24.6-49.0%. The rates by age group 20-29, 30-39, 40-49 and 50-59 were 37.5%(95% CI: 16.3-64.1), 37.5%(95% CI: 19.6%-59.2%), 33.3%(95% CI: 14.4-58.8) and 33.3%(95% CI: 6.0-75.9), respectively (Table 2). The negative conversion rate among those under the age of 40 was a little higher than that among those over the age of 40, but the difference was not statistically significant ($P > 0.05$ by $\chi^2$-test).

**Comparison of HBsAg titers between two years**

To elucidate the changing pattern of HBsAg titers, the geometric mean titers (GMT) were calculated by age between two periods, and the difference was tested statistically (Table 3). The difference of GMT was significantly increased with age ($P < 0.01$ by Kruskal-Wallis one-way ANOVA). The smallest decrease was observed among the 20-29 age group whose GMT was 2321.6 at enrollment and 1199.9 after follow-up. The GMT at enrollment and after follow-up were 3533.3 and 1619.7, respectively, among the 30-39 age group. And those among the 40-49 age group were 4272.7 and 1772.2, respectively. The highest decrease was observed among the 50-59 age group, 4491.8 and 963.0, respectively.

Table 2. Negative conversion rate and 95% confidence interval of HBsAg during two-year follow-up among male adults in Korea

| Age Group | No. of Follow-ups | No. of Conversions | Negative Conversion Rate(%)** | 95% C.I.* |
|---|---|---|---|---|
| 20–29 | 16 | 6 | 37.5 | 16.3–64.1 |
| 30–39 | 24 | 9 | 37.5 | 19.6–59.2 |
| 40–49 | 18 | 6 | 33.3 | 14.4–58.8 |
| 50–59 | 6 | 2 | 33.3 | 6.0–75.9 |
| Total | 64 | 23 | 35.9 | 24.6–49.0 |

*95% Confidence interval was estimated asymptotically based on $\chi^2$-distribution.
**P > 0.05 by $\chi^2$-test.

The changing pattern of GMT described by the ratios of geometric mean titers of HBsAg between the two periods showed inversed relationship with age, that is, 0.52 among the 20-29 age group, 0.46 among the 30-39 age group, 0.42 among the 40-49 age group and 0.21 among the 50-59 age group.

**Negative conversion rate of HBsAg by RIA ratio unit at enrollment**

The negative conversion rate of HBsAg among the study population varied significantly ($P < 0.01$ by $\chi^2$-test) by RIA ratio unit at enrollment and showed that the larger the RIA ratio unit at enrollment, the smaller the negative conversion rate after the two-year follow-up.

Among the study population, those whose RIA ratio unit was less than 10 at enrollment, the negative conversion rate was 75.0% with a 95% confidence interval of 50.6-90.4%. The rates of RIA ratio unit in the 10-49 age group and larger than the over-50 age group were 29.4% (95% CI: 11.4-55.9) and 11.1%(95% CI: 2.9-30.3), respectively (Table 4).

Table 3. Geometric mean titers of HBsAg by age at enrollment('86) and after follow-up('88)

| Age | No Observed | GMT* of HBsAg '86 | GMT* of HBsAg '88 | GMR** |
|---|---|---|---|---|
| 20–29 | 16 | 2321.6 | 1199.9 | 0.52 |
| 30–39 | 24 | 3533.3 | 1619.7 | 0.46 |
| 40–49 | 18 | 4272.7 | 1772.2 | 0.42 |
| 50–59 | 6 | 4491.8 | 963.0 | 0.21 |

*Ratio of geometric mean titer of HBsAg between two periods('88/'86).
**Geometric mean titer, $P < 0.05$ by Kruskal-Wallis one-way ANOVA

## DISCUSSION

The target population were the healthy insured male adults more than 20 years old, living in Seoul and a member of the Korea Medical Insurance Corporation in 1986. Probability random sampling was performed to select 1,495 representative samples. Their sera were tested for detecting HBsAg by radioimmunoassay, and 124 positives (8.7%) were identified to be the actual population. After a two-year follow-up, a recheck of HBsAg was conducted for the actual population, but only 64 people (51.6%) were able to be re-tested and became our study population. Nevertheless, the age distribution of the follow-up and drop-out population was not different significantly (Table 1, $P > 0.05$ by $\chi^2$-test) and the main reason some participants dropped out was that their workplaces were transferred to other areas during the two-years time. Therefore our results may not be biased estimates of parameters among the target population.

The test for detecting HBsAg was performed by radioimmunoassay, which has been acknowledged to have the highest sensitivity and specificity among detecting methods for serologic

Table 4. Negative conversion rate (NCR) of HBsAg during two-year follow-up period by RIA ratio unit* at enrollment

| Ratio Unit* at enrollment | No. of study population | NCR** after Follow-up | | |
|---|---|---|---|---|
| | | No. of HBsAg(+) | NCR(%)** | 95% C.I.# |
| <10 | 20 | 15 | 75.0 | 50.6–90.4 |
| 10–49 | 17 | 5 | 29.4 | 11.4–55.9 |
| 50 ≤ | 27 | 3 | 11.1 | 2.9–30.3 |

*Ratio Unit = sample cpm/cutoff value of RIA test result for HBsAg
**Negative conversion rate, $P < 0.01$ by $\chi^2$-test
#95% Confidence Interval

markers of hepatitis B virus (Park, 1987). And the same technician in the same institute has performed both tests of HBsAg at enrollment and after follow-up for the study population, which must have reduced inter-observer error and other threats to internal validity of this study (Cook & Campbell, 1979).

Because the study population of this study is a fixed cohort, that is, neither new entry nor drop-out has occurred during the follow-up period, the negative conversion rate is a cumulative incidence type of incidence rates, which means conceptually risk or probability (Kleinbaum *et al.*, 1982).

The negative conversion rates of HBsAg have been reported variously according to the study population, HBsAg detecting techniques and follow-up periods. The rates showed a parallel increasing tendency with follow-up period in several reports, that is, 3.6% during a six-months follow-up in a hyperendemic New Zealand community (Milne *et al.*, 1987), 7.8% during one year (West *et al.*, 1986), 14% during 2.1 years (Beasley *et al.*, 1982) and 26% during at least nine years (Hawkes *et al.*, 1981). But the tendency is not consistent. For example, Szmuness (1975) reported that only 7% was converted to the HBsAg negatives among HBsAg positives after longer than a four-year follow-up. The negative conversion rates in our country have been reported to be higher than those of other countries. The negative conversion rate from this study was 35.9% during the two-year follow-up period, and Kim *et al.* (1989) reported a similar rate of 38.6% during a four-year follow-up, but Moon *et al.* (1985) reported a much higher rate of. 71.4% during the two-year follow-up period. Since the overall hepatitis B virus infection rate is so high in our country compared to other countries, the higher negative conversion rate might be due to a larger proportion of persons in the early acute infection stage or latent incubation period of heptitis B virus infection among the study population (Mushahwar *et al.*, 1981). Further study to find out the factors associated with such a high negative conversion rate will be needed.

The changing pattern of geometric mean titers showed a statistically signifcant decreasing trend with age, but it could not affect the negative conversion rates themselves large enough to become significantly different by age. It's not clear whether a more rapid decrease of HBsAg titers with increasing age is due to the decrease of the chances of re-exposure to hepatitis B virus or the increase of the immune response to clear HBsAg with age, so further research to elucidate the underlying mechanism will be needed.

The negative conversion rates were significantly different according to RIA ratio unit of HBsAg at enrollment. Someone whose RIA ratio unit was detected to be under 10 in our country in 1986 has the probability of 0.75 (95% CI: 0.51-0.90) to become negative conversion of HBsAg during two years. But, the probability of negative conversion of HBsAg was markedly decreased with an increasing RIA ratio unit at enrollment, which implicates that a person with a high titer of HBsAg at a particular point in time has stong possibility of becoming a chronic carrier of HBsAg.

The main route for becoming a lifelong persis-

tent carrier is recognized to be mother-to-child transmission during perinatal period (Okada *et al.*, 1975; Tanaka *et al.*, 1986; Lok *et al.*, 1987). Because the study population of this study was adults and only one serologic marker, HBsAg, among HBV serologic markers was examined this study had limitations to estimate the exact rate of lifelong persistent carriers who became carriers in infancy, who were known to be at a high risk of developing chronic liver diseases, including hepatocellular carcinoma (Tong *et al.*, 1971, Feinman *et al.*, 1975). Therefore, further study for an extended follow-up period to estimate the rate of lifelong persistent carriers from infancy and including other HBV markers, for example, anti-HBc and HBeAg will be needed.

In conclusion, about one third among healthy adult males who are HBsAg positives at a point in time in Korea late 1980's may have the probability of negative conversion of HBsAg during two years. And the level of chronic persistent carrier rate of HBV in our country may be estimated to be two thirds of the HBsAg positive rates reported as a result of previous cross-sectional studies. The rates by age were not different significantly, but significant difference of HBsAg titers between the two periods was observed. The negative conversion rates by RIA ratio unit at enrollment were significantly different after the two-year follow-up period.

## REFERENCES


**Ahn YO, Kim CY, Lee JB, Park BJ, Kwon EH, Lee JH, Kim NK.** An epidemiologic observation on HBs antigenemia in Korean voluntary blood donors for the 6⅓ years period, 1975-1981. J. Korean Med. Assoc. 1983, 26:425-437

**Ahn YO, Park BJ, Yoo KY, Lee HS, Kim CY and Shigematsu D.** Incidence estimation of primary liver cancer among Koreans. J. Kor. Cancer 1989, 21:11-16

**Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmuness W, Chen KP.** Incidence of heptatitis B virus infections in preschool children in Taiwan. J. Infect. Dis. 1982, 146:198-204

**Blumberg BS, Larouze B, London WT, Werner B, Hesser JE, Millman I, Saimot G, Payet M.** The relation of infection with the hepatitis B agent to primary hepatic carcinoma. Am. J. Pathol. 1975, 81:669-682

**Cook TD, Campbell DT.** Quasi-Experimentation. Design & analysis issues for field settings. Houghton Mifflin Company, Boston, 1979:pp. 50-59

**Feinman SV, Cooter N, Sinclair JC, Wrobel DM, Berris B.** Clinical and epidemiological significance of the HBsAg (Australia antigen): Carrier state. Gastroenterol. 1975, 68:113-120

**Feret E, Larouze B, Diop B, Sow M, London WT, Blumberg BS.** Epidemiology of hepatitis B Virus infection in the rural community of Tip, Senegal. Am. J. Epidemiol. 1987, 125:140-149

**Hawkes RA, Boughton CR, Ferguson V, Vale TG.** The seroepidemiology of hepatitis in Papua New Guinea. Am. J. Epidemiol. 1981, 114:563-573

**Kew MC, Desmyter J, Bradburne AF, Macnab GM.** Hepatitis B virus infection in southern African blacks with hepatocellular cancer. J. Natl. Cancer Inst. 1979, 62:517-520

**Kim JS, Lee WY, Lee SW, Yoon HS, Yang SJ, Lee DH, Kim HC.** An epidemiological study on HBsAg and anti-HBs prevalence in relation to liver function tests among farmers in Korea. Korean J. Epidemiol. 1985, 7: 16-27

**Kim SI, Han KS, Cho HI, Kim HK, Kim BK, Oh YC, Cho MJ.** A follow-up study on the HBsAg and anti-HBs. J. Korean Med. Assoc. 1989, 32: 628-633

**Kleinbaum DG, Kupper LL, Morgenstern H.** Epidemiologic research. Principles and quantitative methods. Van Nostrand Reinhold Company, New York, 1982

**Lok ASF, Lai CL, Wu PC, Wong CW, Yeoh EK, Lin HJ.** Hepatitis B virus infection in Chinese families in Hong Kong. Am. J. Epidemiol. 1987, 126: 492-499

**Mile A, Allowood GK, Moyes CD, Pearce ME, Newell K.** A seroepidemiological study of the prevalence of hepatitis B infection in a hyperendemic New Zealand community. Int. J. Epidemiol. 1987, 16: 84-90

**Moon HL, Kim YS, Pio SJ, Jeong JW, Woo JY, Park DH, Kim BS, Chung WH.** Changing patterns of serologic markers in healthy HBsAg carriers. J. Korean Internal Med. 1985, 29: 505-511

**Mushahwar IK, Dientag JL, Polesky HF, McGrath LC, Deker RH, Overby LR.** Interpretation of various serological profiles of hepatitis B virus infection. Am. J. Clin. Pathol. 1981, 76: 773-777

**Okada K, Yamada T, Miyakawa Y, Mayumi M.** Hepatitis B surface antigen in the serum of infants after delivery from asymptomatic carrier mothers. J. Pediat. 1975, 87: 360-363

**Park BJ.** A study on the validity of passive hemagglutination (PHA) test for HBsAb. Kor. J. Prev. Med. 1987, 20: 114-119

**Steiner PE.** Cancer of the liver and cirrhosis in trans-Saharan Africa and the United States of America. Cancer 1960, 13: 1085-1145

**Szmuness W.** Recent advances in the epidemiology of hepatitis B. Am. J. Pathol. 1975, 81: 629-649

**Tabor E, Garetz RJ, Vogel CL.** Hepatitis B virus infec-

tion and primary hepatocellular carcinoma. JNCI 1977, 58: 1197-2000

Tanaka T, Nagai M, Yoshihara S, Imai S, Ishiguro H, Seto S, Tsukada T, Tsuda F, Miyakawa Y, Mayumi M. Changing pattern of age-specific prevalence of hepatitis B surface antigen and corresponding antibody in Japan. Am. J. Epidemiol. 1986, 124: 368-371

Tong MJ, San SH, Schaeffer BT, Chang NK, Lo KJ, Peters RL. Hepatitis-associated antigen and hepatocellular carcinoma in Taiwan. Ann. Int. Med. 1971, 75: 687-691

Trichopoulos D, Tabor E, Gerety RJ, Xirouchaki E, Sparros L, Munoz N, Linsell CA. Hepatitis B and primary hepatocellular carcinoma in a European population. Lancet 1978: 1217-1219

Yoo KY, Park BJ, Ahn YO. Seroepidemiology of hepatitis B Virus infection in healthy Korean adults in Seoul. Kor. J. Prev. Med. 1988, 21: 89-98

West SK, Lingao AL, Domingo EO, Raymundo D, Caragay B, Liver Study Group. Incidence and prevalence of hepatitis B. A community-based survey in the Philippines. Am. J. Epidemiol. 1986, 123: 681-9

= 국문초록 =

# B형간염 바이러스 표면항원(HBsAg)의 전환양상에 관한 경시적 연구

서울대학교 의과대학 예방의학교실

박 병 주

우리나라는 B형 간염 바이러스의 감염수준이 세계적으로 높을 뿐 아니라, B형 간염 바이러스가 가장 중요한 원인적 요인일 것으로 보고되고 있는 원발성 간암의 발생 수준 또한 세계적으로 높은 수준에 있음이 밝혀진 바 있다. 따라서 이러한 B형 간염과 원발성간암의 예방대책 수립을 위하여는 B형간염의 자연사에 관한 규명이 시급하며, 특히 만성 B형간염 보균자에서 간암등 만성 간질환으로의 이행위험도가 높은 것으로 보고되고 있어 B형간염 표면항원(HBsAg)의 경시적 전환양상을 파악하는 것은 매우 중요한 의미를 가진다.

우리나라 성인 남자에서의 HBsAg 전환양상을 파악하기 위하여 1986년에 의료보험관리공단 피보험자중 '86 정기건강진단 결과 이상이 없는 20세 이상의 성인 남자 1,495명을 임의 추출하여 RIA법으로 HBsAg을 검사한 결과 양성으로 판정된 124명을 잠정연구대상으로 삼았다. 2년간의 추적이 가능했던 64명의 최종연구대상의 HBsAg 양성여부를 RIA법으로 재검사하여 연령군별, 1986년 당시 HBsAg titer의 ratio unit별 음전률을 파악하였다.

2년간의 HBsAg 음전률은 35.9%(95% 신뢰구간 : 24.6-49.0%)이었으며, 연령군별로는 통계적으로 유의한 차이를 보이지 않았으나, 2년간의 HBsAg titer의 감소정도는 연령이 증가할수록 더 크게 나타났다. 1986년 당시 HBsAg의 Ratio unit별 음전률의 변화는 유의한 차이를 보였는데, Ratio unit가 10미만이었던 군에서는 2년간 75.0%(95% 신뢰구간 50.6-90.4%)이었고, 10-49인 군에서는 29.4%(95% 신뢰구간 11.4-55.9%)이었으며 50 이상이었던 군에서는 11.9%(95% 신뢰구간 2.9-30.3%)로 나타났다.