Cigarette Smoking, Alcohol Drinking, Hepatitis B, and Risk for Hepatocellular Carcinoma in Korea

Sun Ha Jee, Heechoul Ohrr, Jae Woong Sull, Jonathan M. Samet

Background: **Liver cancer is one of the most common cancers worldwide, particularly in Asia and Africa, where infectious hepatitis and aflatoxin exposures are common. We conducted a prospective cohort study of liver cancer in Korea to assess the independent effects and interactions of smoking, alcohol consumption, and hepatitis B on risk of mortality from hepatocellular carcinoma.** ***Methods:*** **From a total of 1 283 112 men and women free of cancer at baseline, 3807 died from liver cancer during follow-up from 1993 to 2002. All participants reported their smoking and alcohol consumption, and hepatitis B surface antigen (HBsAg) status was documented for 47.2% of the participants. Relative risk and 95% confidence intervals (CIs) of mortality from hepatocellular carcinoma were calculated using proportional hazards models adjusted for age, alcohol drinking, diabetes, and HBsAg status.** ***Results:*** **Current smoking was associated with increased risk of mortality from hepatocellular carcinoma in men (RR = 1.4; 95% CI = 1.3 to 1.6) but not women (RR = 1.1; CI = 0.8 to1.7). The relative risk of mortality from hepatocellular carcinoma for male HBsAg carriers was 24.3 (95% CI = 21.9 to 26.9) times that in HBsAg-negative males; the relative risk for HBsAg-positive women was 54.4 (95% CI = 24.8 to119.5). Heavy alcohol drinking was associated with hepatocellular carcinoma mortality risk in the subgroup of men who were tested for HBsAg (RR =1.5; 95% CI = 1.2 to 2.0). There was no interaction among smoking, alcohol drinking, and HBsAg in terms of hepatocellular carcinoma mortality.** ***Conclusion:*** **Cigarette smoking, heavy alcohol consumption, and HBsAg were independently associated with increased risk of mortality from hepatocellular carcinoma but did not interact synergistically. The relatively higher increase in mortality from hepatocellular carcinoma in HBsAg-seropositive women compared with men merits further research. [J Natl Cancer Inst 2004;96:1851–5]**

Liver cancer is one of the most common cancers worldwide. It is particularly widespread in Asia and Africa, where infectious hepatitis and aflatoxin exposures are common. Established causal risk factors include hepatitis B infection, dietary aflatoxin exposure, chronic alcohol consumption, hepatic cirrhosis, and cigarette smoking, the last of which was recently classified as causal by the International Agency for Research on Cancer (IARC) *(1).* Although many epidemiologic studies have addressed these and other risk factors, there has been limited exploration of the combined effects of these exposures, reflecting the limitations posed by the study population size and the exposure data available in the studies carried out to date. Synergism among common factors such as hepatitis B infection, smoking, and alcohol consumption would have substantial public health and clinical relevance because it would place some individuals at extremely high risk. To date, some studies have provided findings on synergism, but a recent review on smoking and other factors carried out by the IARC found the evidence to be inconclusive *(1).*

We have conducted a prospective cohort study of the causes of cancer in a cohort of Koreans (the Korean Cancer Prevention Study) insured by the National Health Insurance Corporation *(2).* The cohort is large, numbering more than 1.3 million; information on smoking and alcohol use is available for all participants, and information on hepatitis B surface antigen (HBsAg) is available for approximately half. Follow-up, accomplished through record linkage at the national level, is complete, except for emigrants. In this article, we describe risk for hepatocellular carcinoma in relation to smoking, alcohol use, and HBsAg during 10 years of follow-up, over which there were 3807 deaths from hepatocellular carcinoma.

Subjects and Methods

Study Participants

The Korean Cancer Prevention Study is a prospective cohort study that was designed to assess risk factors for mortality, incidence, and hospital admission from cancer, with a follow-up of 10 years. Information concerning the development of this cohort from participants in the Korea Medical Insurance Corporation has been provided elsewhere *(2).* In brief, the cohort was composed of government employees, teachers, and their dependents who were insured by the Korea Medical Insurance Corporation from 1992 through 1995, had at least one medical examination, and completed a questionnaire during that time. All insured workers are required to participate in biennial medical examinations. In 1992, 94% of the insured workers completed the biennial examinations, and 95% completed the biennial examinations in 1994; 37% (1993) and 24% (1995) of the insured workers' dependents completed biennial medical examinations.

The Korean Cancer Prevention Study cohort includes 1 329 525 Koreans (846 907 men and 482 618 women) from 30 to 95 years of age who met the above selection criteria. Of the study participants, 784 870 (59.0%) were enrolled in 1992, 367 903 (27.7%) in 1993, 98 417 (7.4%) in 1994, and 78 335

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(5.9%) in 1995. Of the 1 329 525 participants, 3719 who reported a history of any form of cancer at enrollment and 1483 who died from cancer before the start of follow-up were excluded. We further excluded the following numbers of participants because of missing information: 9619 on alcohol drinking, 17 108 on fasting serum glucose level, and 14 484 on weight or height. The final sample size was 1 283 112. Of these participants, data on HBsAg status were available for 605 844 (47.2%).

Data Collection

The biennial examinations followed a standard procedure and were conducted by medical staff at local hospitals. On the 1992, 1993, 1994, and 1995 questionnaires, participants were asked to describe their smoking habits, along with other health habits, including alcohol consumption. The completed questionnaires were reviewed by trained staff and then entered into a database. The data were checked further during analysis.

Based on questionnaire responses at the baseline examination, participants were classified as "current smokers" if they reported smoking currently for at least 1 year, "never smokers" if they had never smoked, and "ex-smokers" if they had smoked but quit.

Alcohol consumption per day was categorized as follows: not drinking (0 g), light drinking (1–24.9 g), moderate drinking (25–49.9 g), heavy drinking (50–99 g), and very heavy drinking (99.9 g or more). Total daily alcohol consumption was expressed as number of glasses per week in relation to Korea's most popular alcoholic beverage, "Soju." One glass of Soju contains about 12 g of ethanol.

Obesity was also examined as a risk factor. We used the World Health Organization standard body mass index (BMI) cutpoints for Asians: <18.5, 18.5–22.9, 23.0–24.9, and ≥ 25.0 kg/m^2) *(3)*.

Fasting serum glucose; liver enzymes, including alanine aminotransferase and aspartate aminotransferase; and HBsAg were detected in serum using enzymatic assays (Boehringer Mannheim, Germany) on a Hitachi 737 autoanalyzer. Serum HBsAg was tested by radioimmunoassay or reverse passive hemagglutination in hospital laboratories (Ausria II, Abbott, North Chicago, IL, USA) *(4)*.

The median follow-up period was 10 years, from January 1, 1993, to December 31, 2002. The exact dates of completion of the survey form were not recorded. Consequently, follow-up accrual began on January 1 of the calendar year following the year in which the survey form was completed. Persons who completed a survey but died in the same calendar year were excluded.

Because the study involved routinely collected medical data, it was not necessary to obtain individual participant consent. The study was approved by the Institutional Review Boards of Yonsei University and the Johns Hopkins Bloomberg School of Public Health.

Cancer Outcomes

The principal outcome variable was mortality from hepatocellular carcinoma. Mortality outcomes were ascertained from death certificates. A computerized search of death certificate data from the National Statistical Office in Korea was performed using the unique identification number assigned at birth. Causes of death were assigned at the hospitals by trained abstractors. The analysis is limited to those deaths assigned to C22.0, primary hepatocellular carcinoma, in the 10th revision of the International Classification of Diseases *(5)*. We excluded all other cancers coded to liver and intrahepatic bile ducts (C22.1–C22.9).

Statistical Analysis

Age-adjusted death rates were calculated for each category of smoking, drinking, and HBsAg carrier status and were directly standardized to the age distribution of the Korean national population in 1995. We also used Cox proportional hazards modeling to compute relative risks (RR) and 95% confidence intervals (CIs) and to adjust for other potential risk factors *(6)*. The proportionality assumption was verified by inspection of hazard plots. Because liver cancer incidence varies steeply with age, we used linear and quadratic trends for age. Indicator variables were used for smoking and alcohol use. To calculate the population-attributable risk for HBsAg positivity, cigarette smoking, any alcohol use, and the presence of diabetes mellitus, we used Levin's formula *(7)* with generalization to the two strata of smoking status *(8)*. We used the adjusted relative risk values to calculate population-attributable risk. All statistical tests were two-sided, and statistical significance was determined at $P<.05$.

Results

The population was mostly middle-aged, with approximately twice as many men as women (Table 1). The population had a low BMI on average, with 23.9% of men and 26.9% of women at ≥ 25 kg/m^2 and 0.8% of men and 2.5% of women >30 kg/m^2. Both smoking and alcohol use were substantially more common in men than in women. At baseline, 9.4% of 478 189 men and 6.5% of 127 655 women for whom HBsAg status was available. Most of the cohort was followed for at least 9 years. A total of 3807 deaths were coded as primary carcinoma of the liver for the follow-up period of 1993–2002.

Table 1. Baseline characteristics of men and women in the Korean Cancer Prevention Study, 1992–1995

Characteristic*	Men (n = 823 158)	Women (n = 459 954)
Age, y	45.2 ± 11.1	49.5 ± 12.1
Body mass index, kg/m^2	23.2 ± 2.6	23.2 ± 3.3
Fasting serum glucose, mg/dL	92.8 ± 25.1	90.6 ± 24.3
Alcohol consumption, g/day	17.2 ± 32.2	0.2 ± 1.9
Alanine aminotransferase, U/L	26.5 ± 17.3	22.4 ± 9.7
Aspartate aminotransferase, U/L	26.1 ± 21.6	19.3 ± 11.8
Conditions, %		
HBsAg positive†	9.4	6.5
Diabetes‡	5.0	4.4
Any alcohol use	76.3	14.2
Smoking status		
Never smokers	20.8	93.8
Ex smoker	20.7	2.1
Current smokers	58.5	4.1
Liver dysfunction§	27.5	14.1

*Data are means ± standard deviation or percentage.

†The data on hepatitis B surface antigen (HBsAg) are from 478 189 men and 127 655 women.

‡Defined as fasting blood glucose value of at least 126 mg/dL.

§Alanine aminotransferase >30 U/L or aspartate aminotransferase >35 U/L.

Risk Factors for Hepatocellular Carcinoma

Table 2 shows the age-adjusted rates and the relative risk of hepatocellular carcinoma death in men in relation to smoking, alcohol use, diabetes, and HBsAg status. The findings show that smoking was associated with an increased risk of hepatocellular carcinoma, particularly among current smokers. Considering current smokers only, we examined dose-response relationships with number of cigarettes smoked per day and number of years of smoking. The relative risk for hepatocellular carcinoma did not increase with amount of smoking. However, for duration of smoking, with 1–9 years as the reference category, statistically significant increases were evident for smokers of 20–29 years (RR = 1.4; 95% CI = 1.1 to 1.7) and ≥30 years (RR = 1.4; 95% CI = 1.1 to 1.8); this pattern was unchanged with stratification by HBsAg status. Relative risk increased with increasing alcohol consumption. For example, compared with never smokers who were nondrinkers, the relative risk of hepatocellular carcinoma for current smokers who smoked for ≥30 years and drank 100 g/day of alcohol was estimated to be 2.5 (95% CI = 1.3 to 3.5). Risk was also higher among HBsAg-positive participants, among whom the relative risk of hepatocellular carcinoma was 24.3 (95% CI = 21.9 to 26.9) compared with HBsAg-negative participants. When HBsAg status was adjusted for in the Cox model, the relative risks associated with smoking and alcohol consumption did not change. BMI was not associated with risk (data not shown).

Data were available for fewer women, and the analyses that were carried out for men could therefore not be fully replicated (Table 3). Smoking and alcohol consumption were associated with increased relative risk of hepatocellular carcinoma in women, but the estimates had wide confidence intervals. Being HBsAg positive was strongly associated with risk for hepatocellular carcinoma in women, with an estimated effect much higher than that for men (RR = 54.4; 95% CI = 24.8 to 119.5). The interaction of sex with HBsAg status in determining hepatocellular carcinoma risk was statistically significant ($P = .01$).

We explored patterns of effect modification among smoking, alcohol use, and HBsAg status using the Cox proportional hazards model in men. Table 4 shows the age- and diabetes-adjusted relative risk estimates for the strata defined by pairs of three variables: HBsAg status, smoking, and alcohol intake. For smoking and HBsAg, the pattern of relative risk estimates suggested a possibly multiplicative or greater combined effect; the interaction between HBsAg and alcohol was possibly additive. The interaction between smoking and HBsAg was positive but not statistically significantly elevated. That is, risk of hepatocellular carcinoma was similar in smokers only, drinkers only, and in smokers and drinkers. We also found no evidence for interaction of diabetes with HBsAg, smoking, and alcohol use (data not shown).

We further explored the independent and joint effects of smoking and alcohol consumption on risk of hepatocellular carcinoma mortality with stratification by HBsAg status. No statistically significant interaction among the factors was observed (Fig. 1). We estimated the population-attributable risks due to HBsAg positivity, cigarette smoking, and any alcohol use as 66.7% (95% CI = 64.4% to 69.1%), 25.1% (95% CI = 18.0% to 31.9%), and 4.6% (95% CI = 0% to 10.9%), respectively.

Discussion

In this large prospective cohort study of Korean men and women, we found that cigarette smoking, alcohol drinking, and HBsAg seropositivity were independent risk factors for hepatocellular carcinoma in both men and women. No interaction among these three risk factors was observed.

Smoking has been extensively investigated as a risk factor for hepatocellular carcinoma *(1)* and a range of associations, from no association to relative risk estimates of ≥2, has been observed. However, the IARC recently classified smoking as a cause of hepatocellular carcinoma *(1)* based on the carcinogenic potential of several compounds in tobacco smoke and the role that the liver plays in the metabolism of these compounds *(9)*, a

Table 2. Age-adjusted mortality rates per 100 000 and relative risks of mortality from hepatocellular carcinoma in men in the Korean Cancer Prevention Study (1993–2002)*

Characteristic	All†			Subjects with HBsAg data‡		
	No.	Rate	RR (95% CI)	No.	Rate	RR (95% CI)
Smoking						
Never smoker	557	32.8	1.0 (referent)	387	48.8	1.0 (referent)
Ex-smoker	840	52.4	1.2 (1.1–1.4)	515	54.3	1.1 (1.0 to 1.3)
Current smoker	1944	43.4	1.4 (1.3–1.6)	1354	54.4	1.5 (1.3 to 1.7)
Alcohol intake, g						
0	1074	48.1	1.0 (referent)	683	63.9	1.0 (referent)
1–24.9	1704	38.3	1.0 (0.9 to 1.1)	1076	46.0	1.0 (0.9 to 1.1)
25–49.9	324	48.1	1.0 (0.9 to 1.2)	279	65.2	1.1 (0.9 to 1.3)
50–99.9	170	46.3	1.1 (0.9 to 1.4)	153	64.2	1.2 (1.0 to 1.5)
≥100	69	51.0	1.4 (1.0 to 1.8)	65	70.0	1.5 (1.2 to 2.0)
Diabetes§						
No	2960	37.3	1.0 (referent)	2006	47.1	1.0 (referent)
Yes	381	62.2	1.7 (1.5 to 2.0)	250	82.3	1.9 (1.6 to 2.2)
HBsAg						
Negative				734	21.8	1.0 (referent)
Positive				1522	405.2	24.3 (21.9 to 26.9)

*Risk ratios (RRs) and 95% confidence intervals (CIs) from multivariable Cox proportional models.

†Adjusted for age, age squared, smoking, alcohol use, and diabetes.

‡Adjusted for variables in "All" and includes hepatitis B surface antigen (HBsAg), which was measured in 478 189 men and 127 655 women.

§The referent category is a fasting serum glucose level of <126 mg/dL; diabetes is defined as a fasting serum glucose level of ≥126 mg/dL and/or medication.

Table 3. Age-adjusted mortality rates and relative risks of mortality from hepatocellular carcinoma in women in the Korean Cancer Prevention Study (1993–2002)*

Characteristic	All†			Subjects with HBsAg data‡		
	No.	Rate	RR (95% CI)	No.	Rate	RR (95% CI)
Smoking						
Never smoker	399	9.1	1.0 (referent)	45	4.8	1.0 (referent)
Ex-smoker	27	14.3	1.3 (0.8 to 2.1)	1	12.8	NE
Current smoker	40	8.5	1.1 (0.8 to 1.7)	0	0	NE
Alcohol intake						
Nondrinker	397	7.8	1.0 (referent)	36	4.5	1.0 (referent)
Ever drinker	69	8.8	1.2 (0.9 to 1.5)	10	6.1	2.0 (0.9 to 4.5)
Diabetes§						
No	425	9.1	1.0 (referent)	44	4.7	1.0 (referent)
Yes	41	11.0	1.7 (1.2 to 2.6)	2	8.6	NE
HBsAg						
Negative				9	1.2	1.0 (referent)
Positive				37	58.4	54.4 (24.9 to 119.5)

*Risk ratio (RRs) and 95% confidence intervals (CIs) from multivariable Cox proportional models.

†Adjusted for age, age squared, smoking, alcohol use, and diabetes.

‡Adjusted for variables in "All" and hepatitis B surface antigen (HBsAg), which was measured in 478 189 men and 127 655 women. NE = not estimated due to the low number of participants in this group.

§The referent category is a fasting serum glucose level <126 mg/dL; diabetes is defined as a fasting serum glucose level ≥126 mg/dL and/or medication.

systematic review of the epidemiologic evidence, and a determination that the association of smoking with hepatocellular carcinoma could not be explained by confounding from alcohol consumption or hepatitis B *(1)*. Our results are consistent with a causal role of cigarette smoking in the etiology of hepatocellular carcinoma. We estimated that 25% of cancer diagnoses were attributable to smoking.

We readily confirmed the very strong association of hepatitis B on hepatocellular carcinoma risk *(10)*. The magnitude of the increased risk was similar to that seen in other studies, and we observed a statistically significantly greater risk in women than in men. Previously, only one study reported a difference by sex in risk of hepatocellular carcinoma associated with hepatitis B. This study, a cohort study in China, reported that the relative risk for hepatocellular carcinoma in women was nearly twice that in men, although the interaction with sex was not statistically significant ($P = .11$) *(11)*. We documented a similar magnitude of risk by sex. Given the lack of interaction of hepatitis B seropositivity with other risk factors that are more frequent in males, particularly alcohol consumption and smoking, future research into the mechanism by which hepatitis B increases mortality from hepatocellular carcinoma might be directed at hormonal or other factors associated with sex.

Our results also indicate that heavy alcohol consumption increases the risk for liver cancer. This observed association is in agreement with those of most recent studies on this topic *(12–16)*.

Our study has several potential limitations that arise primarily from the use of data collected as part of an insurance plan. The questionnaires provide self-reported smoking and alcohol use information without validation. In addition, death certificate attribution of cause of death to hepatocellular carcinoma is subject to misclassification *(17)* with the potential for miscoding metastatic tumors to the liver as primary cancers of the liver. Although false-positives undoubtedly occur with this classification method, we do not think that our findings can be explained by inadequate specificity of death certificate classification, because we would anticipate a general bias toward the null from misclassification unless it were differential by exposure.

Table 4. Relative risk of mortality from hepatocellular carcinoma among men in the Korean Cancer Prevention Study (1993–2002)*

Variable 1	Variable 2	Person-years	No.	RR (95% CI)
HBsAg	Smoking status			
Negative	Never smoker	846 937	136	1.0 (referent)
Negative	Ever smoker	3368 042	604	1.1 (0.9 to 1.4)
Positive	Never smoker	92 132	256	18.8 (14.7 to 24.0)
Positive	Ever smoker	345 114	1284	29.0 (23.7 to 35.4)
HBsAg	Alcohol intake			
Negative	0–24.9 g/day	3274 530	570	1.0 (referent)
Negative	≥25 g/day	958 448	170	1.2 (1.0 to 1.4)
Positive	0–24.9 g/day	346 988	1210	24.6 (21.9 to 27.7)
Positive	≥25 g/day	90 258	330	27.7 (23.7 to 32.4)
Alcohol intake	Smoking status			
0–24.9 g/day	Never smoker	831 143	336	1.0 (referent)
0–24.9 g/day	Ever smoker	2790 375	1,440	1.5 (1.3 to 1.7)
≥25 g/day	Never smoker	125 926	56	1.5 (1.1 to 2.0)
≥25 g/day	Ever smoker	922 781	444	1.6 (1.4 to 1.9)

*Risk ratio (RRs) and 95% confidence intervals (CIs) from multivariable Cox proportional models after adjusting for age, smoking, alcohol intake, hepatitis B antigen (HBsAg), and diabetes.

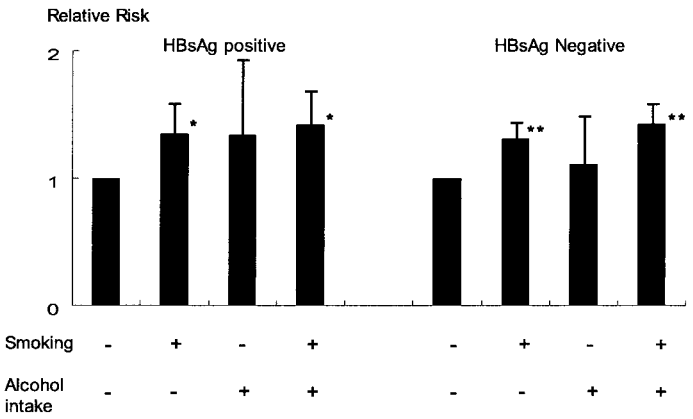

Fig. 1. Relative risk for liver cancer death by smoking and alcohol intake stratified by hepatitis B surface antigen (HBsAg) status. Smoking is classified as "–" for never smoker and "+" for smoker; alcohol intake as "–" for non-drinker or <25 g /day and "+" for >25g/day. Bars represent median and upper 95% confidence intervals. *P* values were calculated using Cox proportional models and were two-sided; * indicates $P = .0011$ and $P = .0017$; ** indicates $P < .001$ compared with those who reported not drinking or smoking.

To gain some insight into the potential degree of misclassification, we examined the proportion of incident liver cancer case patients who died and had their deaths coded to primary liver cancer during the follow-up interval. For those 2449 patients with incident cancer diagnosed through 1997, 73% died and had their death coded to primary liver cancer by the end of follow-up in 2002. Independent cancer registry data show 5-year survival of 10.5% for incident liver cancer *(18)*. Given this high mortality rate and the high rate of coding of death in incident liver cancer cases to liver cancer in our data, we consider that misclassification of outcome is not an issue in interpreting our findings.

In addition, our study cohort is not representative of all Koreans because it includes employed persons and their families and, consequently, may under-represent heavy users of alcohol and tobacco. However, follow-up should be almost complete because of our use of record linkage with unique personal identifiers to national databases; thus, any loss to follow-up should not introduce bias.

This study also had several strengths. A particular strength was the large number of participants, which allowed for the exploration of interactions among these well-established risk factors. The array of interactions has been addressed in a number of previously published studies, without consistent findings for effect modification among these agents. In its most recent review, the IARC Working Group *(1)* did not find strong evidence that the risk of hepatocellular carcinoma due to smoking was modified by either alcohol consumption or hepatitis. However, risk modification was not assessed formally in most of the studies, and power for assessing effect modification was limited for most of them. Evidence for synergism between smoking and alcohol has been noted in several case–control studies *(19,20)*. For smoking and hepatitis, synergism was found in two case–control studies *(20,21)*, but two prospective cohort studies *(11,22)* did not find a synergistic interaction. The same two prospective cohort studies *(11,22)* reported that there was no interaction between alcohol consumption and hepatitis B in hepatocellular carcinoma risk. Interpretation of these findings from a small number of studies needs to be guarded, given their methodologic limitations. Our study provides further evidence against interaction of smoking with alcohol consumption, smoking with hepatitis B, and alcohol with hepatitis B in determining risk for hepatocellular carcinoma.

Hepatocellular carcinoma has a well-established suite of environmental risk factors, both infectious and noninfectious. Exposures to these risk factors vary around the world, but exposure to each of the key risk factors can potentially be controlled and the majority of hepatocellular carcinoma deaths avoided. Our analyses of Koreans show the potential for prevention and the need to implement strong prevention programs: the multivariable adjusted population-attributable risks for hepatitis B (66.7%) and smoking (25.1%) accounted for most cases, and we found little indication of a joint contribution. In Korea, relatively high rates of the major known risk factors for hepatocellular carcinoma mortality—HBsAg seropositivity, cigarette smoking, and alcohol drinking—exist, emphasizing the need for mass immunization against hepatitis B virus and antismoking and antidrinking programs. Since 1995, the Korean government has carried out a program of vaccination against hepatitis B, and the prevalence of HBsAg seropositivity is now falling *(23)*.

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NOTES

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