Risk and Predictors of Mortality Associated With Chronic Hepatitis B Infection

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Background & Aims: **The study objective was to determine the risk of all-cause and cause-specific mortality as well as to examine the predictors of mortality in chronic hepatitis B infection.** ***Methods:*** **We performed a prospective cohort study of 23,820 persons (age, 30–65 y) recruited between 1991 and 1992 and followed up through 2004 from 7 townships in Taiwan. The main outcomes were all-cause and liver-related mortality rates. Mortality analyses used time-to-events methods, and survival curves were derived by the Kaplan–Meier method. Cox proportional hazard models were used to estimate multivariable-adjusted hazard ratios.** ***Results:*** **There were 1814 deaths during a mean follow-up period of 12.5 years (282,323.7 person-years of follow-up evaluation). Persons positive for hepatitis B surface antigen (HBsAg) had significantly ($P < .01$) higher adjusted hazard ratios for all causes of mortality (1.7; 95% confidence interval [CI], 1.5–1.9), liver cancer mortality (22.4; 95% CI, 15.2–32.9), and chronic liver disease and cirrhosis mortality (5.4; 95% CI, 3.5–8.4). When compared with HBsAg-negative persons, hepatitis B virus (HBV)-infected persons with HBV DNA levels less than 10^4 had a high risk of hepatocellular carcinoma mortality (4.4; 95% CI, 2.4–8.2). In HBsAg-positive persons, the mortality rate increased with cohort entry serum HBV DNA level. Liver cancer mortality ranged from 72.8 per 100,000 person-years for subjects with HBV DNA levels less than 300 copies/mL to 815.6 per 100,000 person-years for those with HBV DNA levels of 1 million copies/mL or greater. Chronic liver disease and cirrhosis deaths ranged from 9.1 to 267.4 per 100,000 person-years.** ***Conclusions:*** **Chronic HBV infection is associated with significant preventable excess mortality risk. This mortality risk is correlated strongly with the level of viral replication among other factors.**

Chronic hepatitis B (CHB) infection accounts for well over 1 million deaths each year and represents the 10th leading global cause of death.[1] Hepatitis B virus (HBV) infection accounts for the vast majority of chronic liver diseases in endemic areas such as Taiwan (75%–80%) and mainland China (73%).[2] Moreover, CHB infection accounts for 60%–80% of primary liver cancer globally, which is 1 of the 3 major causes of death in Asia, the Pacific Rim, and Africa.[1] Cirrhosis develops in approximately 20% of CHB-infected persons, and its complications, such as hepatic insufficiency and portal hypertension, contribute significantly to CHB-related morbidity and mortality.[3] Besides these well-known causes of morbidity and mortality, CHB infection also has been associated with an increased risk of lymphomas in different studies from Australia, the United Kingdom, and the United States of America.[4–6]

Several studies have addressed the mortality associated with chronic HBV infection, and survival rates for patients with CHB-related liver disease have been established from these studies.[7–9] A question still remaining is which CHB-infected patients are at greatest risk of mortality as a result of liver-related complications. There is also no information on the risk of mortality in CHB-infected patients with low viral load (HBV DNA level $< 10^4$ copies/mL) in comparison with uninfected persons.

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL)-HBV study is a large, prospective, community-based, cohort study of Taiwanese people as previously described.[10,11] For these mortality analyses, the 22,472 enrolled subjects who were known not to be hepatitis C virus (HCV) infected were studied. Data linkage to the Taiwanese national death certification system was conducted from January 1, 1991, through December 31, 2004, with a mean follow-up time of 12.5 years and 282,323.7 person-years of observation.

In these analyses, we report on the following: (1) the common causes of mortality in this cohort, (2) the difference in mortality between the CHB-infected persons and those without evidence of CHB infection, and (3) the predictors of mortality in the CHB-infected subjects.

Methods

Cohort Recruitment and Follow-up Evaluation

The REVEAL-HBV study was conducted in 7 townships in Taiwan as part of a community-based cancer screening program. Between 1991 and 1992, there were 89,293 ethnically

Abbreviations used in this paper: ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PYFU, person-years of follow-up; REVEAL, Risk Evaluation of Viral load Elevation and Associated Liver Disease/Cancer.

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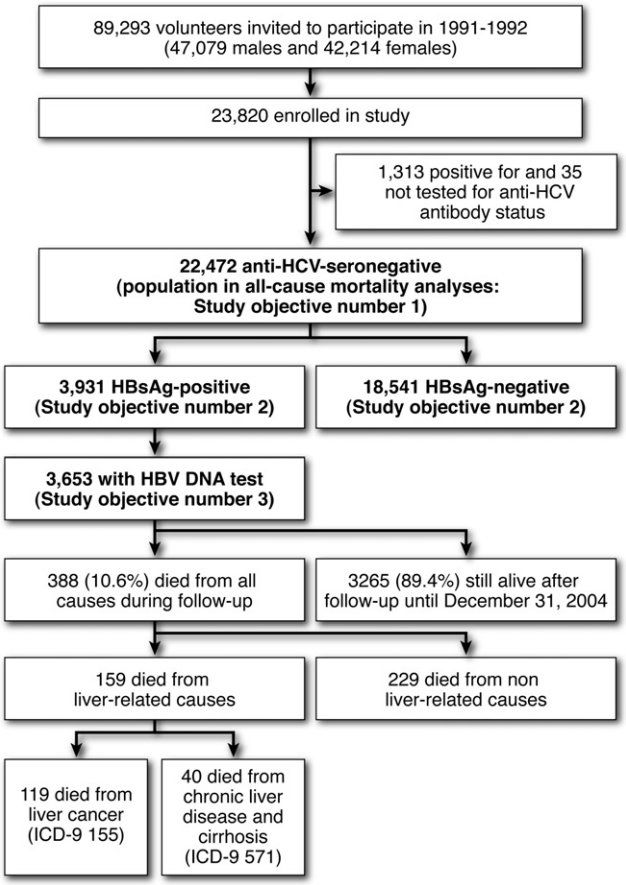

Figure 1. Study design and flow chart.

Chinese individuals aged 30–65 years who were invited to participate, and 23,820 individuals agreed and gave written informed consent. Demographic information on 63,454 of the 65,463 subjects (97%) not participating in this study show that they were quite similar except in educational level; there were more people with low-level formal education among those enrolling in the study (21% vs 6%). The gender distribution was similar (49% vs 46% women), the age distribution was slightly different (there were 29% enrolled within the 30–39 age group, vs 40% nonenrolled in the 30–39 age group), and the distribution of subjects across the townships was quite similar in both groups. Subjects enrolled in the study were interviewed by trained public health nurses, received a health examination that included abdominal ultrasonography, and had blood collected for serologic, biochemical, and HBV DNA testing. Active follow-up evaluation in hepatitis B surface antigen (HBsAg)-positive persons included planned ultrasonography every 6–12 months, and serum was collected for storage as well as additional serologic and biochemical testing. Vital status information was obtained from death certificates filed with the local household registration systems and were cross-checked with the computerized records at the National Death Certification Profiles as described later.

To ensure that subjects enrolled in the study were receiving the appropriate standard of care, subjects with evidence of a biochemical liver abnormality were sent a letter with the test results and instructed to see their physician. The study team provided assistance in securing referrals for subjects requiring assistance. In addition, anyone with suspected hepatocellular carcinoma (HCC) was referred directly by the study team to their hospital of choice. In addition, on the availability of reimbursement for HBV therapy in October of 2003, subjects meeting the established treatment guidelines were referred to the National Taiwan University Hospital for evaluation. The study protocol was reviewed and approved by the Institutional Review Board of the College of Public Health at National Taiwan University.

Table 1. Demographics of the Study Cohort

	HBsAg seronegative (n = 18,541) N (%)	HBsAg seropositive (n = 3931) N (%)	Total (n = 22,472) N (%)
Sex			
Female	9481 (51.1)	1600 (40.7)	11,081 (49.3)
Male	9060 (48.9)	2331 (59.3)	11,391 (50.7)
Age, *y*			
30–39	5297 (28.6)	1297 (33.0)	6594 (29.3)
40–49	4852 (26.2)	1091 (27.8)	5943 (26.5)
50–59	5624 (30.3)	1142 (29.1)	6766 (30.1)
60–65	2768 (14.9)	401 (10.2)	3169 (14.1)
Residential area: township (county)			
Chutung (Hsinchu)	4324 (23.3)	858 (21.8)	5182 (23.1)
Kaoshu (Pingtung)	3228 (17.4)	569 (14.5)	3797 (16.9)
Potzu (Chiayi)	2715 (14.6)	633 (16.1)	3348 (14.9)
Sanchih (Taipei)	1022 (5.5)	222 (5.7)	1244 (5.5)
Huhsi (Penghu)	1491 (8.0)	278 (7.1)	1769 (7.9)
Makung (Penghu)	5083 (27.4)	1089 (27.7)	6172 (27.5)
Paisha (Penghu)	678 (3.7)	282 (7.2)	960 (4.3)
Educational level[a]			
Uneducated	3967 (21.4)	693 (17.6)	4660 (20.8)
Primary school	7712 (41.6)	1565 (39.8)	9277 (41.3)
Junior high school	2521 (13.6)	615 (15.6)	3136 (14.0)
Senior high school	2787 (15.0)	682 (17.4)	3469 (15.4)
Vocational school	1019 (5.5)	259 (6.6)	1278 (5.7)
College or graduate school	525 (2.8)	117 (3.0)	642 (2.9)
Cigarette smoking[b]			
No	13,270 (71.7)	2647 (67.4)	15,917 (71.0)
Yes	5236 (28.3)	1281 (32.6)	6517 (29.1)
Alcohol consumption[c]			
No	16,544 (89.4)	3455 (88.1)	19,999 (89.2)
Yes	1953 (10.6)	469 (12.0)	2422 (10.8)
HBV DNA, *copies/mL*[d]			
<300		873 (23.9)	
300–999		372 (10.2)	
1000–9999		789 (21.6)	
10,000–99,999	NA	643 (17.6)	NA
100,000–999,999		349 (9.6)	
1–9.9 million		154 (4.2)	
10–99.9 million		100 (2.7)	
≥100 million		373 (10.2)	

[a]There were 10 HBsAg-negative persons whose educational level was not available.
[b]Data were not available for 38 participants.
[c]Data were not available for 51 participants.
[d]Data were not available for 278 participants.