Atherosclerosis 211 (2010) 624–629

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Chronic hepatitis B infection and risk of atherosclerosis-related mortality: A 17-year follow-up study based on 22,472 residents in Taiwan

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ARTICLE INFO

Article history:
Received 20 December 2009
Received in revised form 25 February 2010
Accepted 3 March 2010
Available online 10 March 2010

Keywords:
Hepatitis B infection
Atherosclerosis-related mortality
Competing risk of liver mortality

ABSTRACT

Background: Conflicting results have been reported on the association of chronic hepatitis B infection with risks of atherosclerotic diseases previously. The present study aimed to clarify the association between HBsAg seropositivity and atherosclerosis-related/cardiovascular mortality prospectively in Taiwan, one of the most endemic areas for hepatitis B infection in the world.
Methods and results: After excluding subjects with HCV infection, we followed up a total of 22,472 subjects aged 30–65 years, consisting of 18,541 HBsAg seronegatives and 3931 seropositives, for 17 years for mortality. Cox proportional hazard models were used to estimate the hazard ratios of mortality after adjustment for traditional risk factors, glomerular filtration rates and the competing risk of liver mortality. In multivariate Cox regression analysis, taking into account liver mortality as a competing risk, the fully adjusted hazard ratios (95% CIs) of mortality from ischemic heart disease, cerebrovascular disease, atherosclerotic disease and all cardiovascular disease were 0.98 (0.82–1.17, $P=0.28$), 0.86 (0.79–1.05, $P=0.25$), 0.84 (0.72–1.06, $P=0.27$), and 0.96 (0.82–1.13, $P=0.21$) respectively for HBsAg seropositives compared with HBsAg seronegatives.
Conclusion: HBsAg seropositivity was not associated with increased mortality risks of atherosclerosis-related/cardiovascular diseases during 17-year follow-up. HBsAg seropositivity might not be a significant predictor for atherosclerosis-related/cardiovascular deaths.

1. Introduction

Cardiovascular disease is the leading cause of mortality worldwide. The current identified traditional risk factors such as hypertension, diabetes, hypercholesterolemia and smoking contribute to less than half of atherosclerotic/cardiovascular disease risk [1,2]. It appears that additional risk factors linking to atherosclerotic/cardiovascular diseases are as yet unidentified. Therefore, identification of such factors and their mechanisms of action would be essential for treatment and prevention of atherosclerotic/cardiovascular diseases from a theoretical and clinical standpoint. The concept that infections contribute to initiation and progression of atherosclerosis has been debated for many years, and continues to the present time. Several experimental and epidemiologic studies indicate a possible role for infections in the initiation and progression of atherosclerosis [3–10]. However, numerous studies presenting no association between infections and atherosclerotic diseases cast uncertainty on their roles [11–15]. Debates also surround the concept that infections can complicate the process of atherosclerosis and provoke plaque rupture leading to major adverse cardiovascular events such as acute coronary syndrome, stroke and sudden death. A large number of viruses could be associated with atherosclerosis and its complication; however the largest body of data pointed to the herpesviruses, and especially cytomegalovirus [3,4]. An association of atherosclerotic diseases with HBV (hepatitis B virus) infections is of particular interest and significance from a perspective of prevention and treatment for cardiovascular diseases. First, previous studies on the associations of HBV with atherosclerotic diseases have been reported conflicting results [7,8,10,12–17]. Resolution of these conflicting results is crucial for making clinical decisions and public health policy. Second, previous studies were mostly cross-sectional or retrospective in design and could only determine an association instead of causal temporality. Third, the existing data indicate that both viruses and bacteria can contribute to the initiation and progression of atherosclerosis; however viruses appear to more frequently than bacteria predispose to plaque rupture [3]. Forth,

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doi:10.1016/j.atherosclerosis.2010.03.008

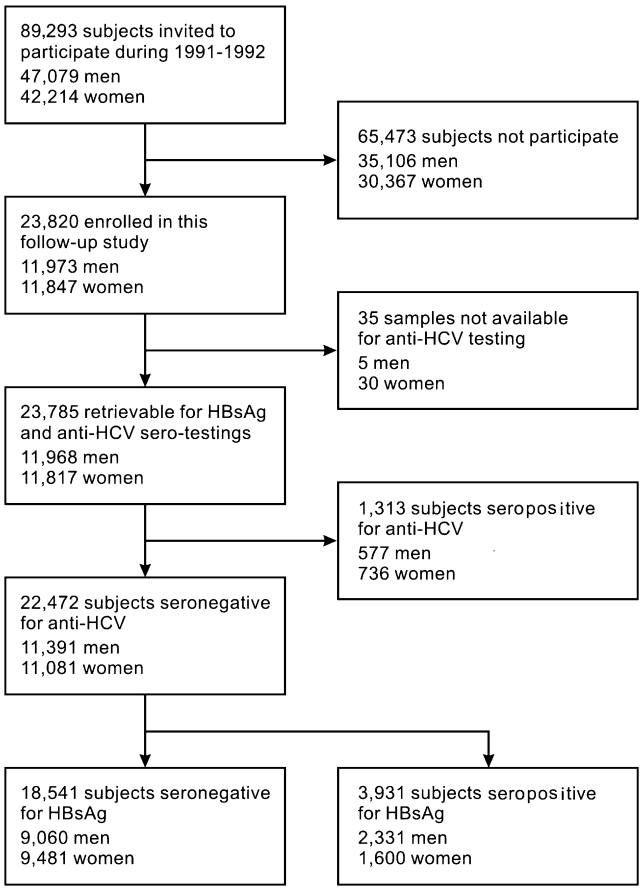

Fig. 1. Flow chart of study participants in the REVEAL-HBV study.

chronic HBV infection is a major global public health problem. Evidence of HBV infection has been identified in one third of the world population in whom there are 350–400 million carriers of HBV, causing one million deaths annually [18]. To our knowledge, there is no one study that systemically examines the mortality risks of atherosclerotic/cardiovascular diseases for chronic HBV infection prospectively in a community-based setting.

To elucidate the association between HBsAg seropositivity and mortality risks of atherosclerotic/cardiovascular diseases, we performed an unprecedented large-scale community-based prospective study of the REVEAL-HBV (Risk Evaluation of Viral Load Elevation and Associated Liver Disease and Cancer-Hepatitis B Virus) cohort in Taiwan, one of the most hyperendemic areas for hepatitis B virus infection in the world [19].

2. Methods

2.1. Design and cohort recruitment

Fig. 1 shows the flow chart of participants through the REVEAL-HBV study. The REVEAL-HBV cohort study was initially designed for a community-based cancer screening program. Since 1991, a total of 89,293 residents aged 30–65 years living in 7 townships, specifically Sanchih and Chutun located in Northern Taiwan, Kaoshu and Potzu in Southern Taiwan as well as Huhsi, Makung and Paisha in Penghu archipelagos, were invited to participate; among them 23,820 individuals agreed to participate and provided written informed consent. Demographic data on 63,454 of the 65,463 subjects (97%) not participating in the present investigation showed that they were rather comparable. Of these 23,820 participants, we excluded 1313 subjects with previous exposure to hepatitis C virus and 35 lacking adequate serum specimen for examining antibody, leaving a final study population of 22,472 subjects for further analysis. The study protocol was reviewed and approved by the Institutional Review Board of the National Taiwan University.

2.2. Determination of traditional cardiovascular risk factors

All participants were subjected to a thorough program, which included assessment of a detailed personal and family history, physical examination, determination of anthropomorphic measurements and various laboratory data. Information included socioeconomic and demographic characteristics, alcohol consumption, cigarette smoking, and a history of hypertension and diabetes. Smokers were further classified into 3 groups: never, ex-smokers and current smokers. Fasting venous blood specimens were collected for determination of total cholesterol and triglyceride levels. Glucose tolerance test was also performed. Diabetes mellitus was defined as (1) a fasting plasma glucose level ≥126 mg/dL, or (2) a 2-h glucose level ≥200 mg/dL, or (3) a history treated diabetes mellitus. Hypertension was defined as (1) an average systolic blood pressure ≥140 mm Hg, or (2) an average diastolic blood pressure ≥90 mm Hg, or (3) a history of treated hypertension.

2.3. Renal function assessment

The abbreviated Modification of Diet in Renal Disease Study formula was used to assess eGFR: estimated GFR $(\text{mL/min/1.73 m}^2) = 186 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ if female), where SCr is serum creatinine level in mg/dL, and age is in years [20,21].

2.4. Serologic determination

Serologic determination was performed as follows: HBsAg by radioimmunoassay (Abbott Laboratories, North Chicago, IL). Anti-HCV by enzyme immunoassay using second-generation commercial kits (Abbott Laboratories).

2.5. Linkage procedure and ascertainment of cause of death

In Taiwan, all deaths are registered through nationwide household registration offices. Death records are double-checked annually by registration officers. The death certificates are coded by the National Department of Health and these records has been computerized since 1971. To verify the cause of death for study participants, the death certificates were acquired through their local household registration offices. To ensure utter ascertainment of the cause of death, linkage procedure was performed with the National Death Certification Profiles from January 1, 1991, to December 31, 2007. The data linkage between the REVEAL-HBV study cohort and the National Death Certification Profiles was conducted by using the unique national identification number that is designated to every national at birth. Causes of death – classified according to the International Classification of Diseases, 9th Revision – consisted of ischemic heart disease (410–414 for ischemic heart disease, 429.2 for arteriosclerotic cardiovascular disease, and 429.7 for certain sequelae of myocardial infarction), cerebrovascular disease (430–438), expanded atherosclerotic disease (410–412 for myocardial infarction, 413 for angina pectoris, 414.0 for coronary atherosclerosis, 414.1 for aneurysm and dissection of heart, 424.1 for atherosclerotic aortic valve disease, 429.2 for arteriosclerotic cardiovascular disease, 429.7 for certain sequelae of myocardial infarction, 430–438 for cerebrovascular disease, 440 for atherosclerosis, 443.9 for peripheral arterial disease, 445 for atheroembolism, and 250 for diabetes mellitus), and all cardiovascular disease