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Beasley's 1981 paper: The power of a well-designed cohort study to drive liver cancer research and prevention

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ABSTRACT

The 1981 Lancet paper by Beasley et al., "Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan" is a seminal publication that clearly demonstrated that chronic infection with hepatitis B virus (HBV), as measured by seropositivity for the hepatitis B surface antigen (HBsAg), preceded the development of hepatocellular carcinoma (HCC). In doing so, this study paved the way for liver cancer prevention efforts through the implementation of hepatitis B vaccination programs. In this commentary, we will describe the discovery of HBV, which led to the study by Beasley et al.; summarize the major findings of the Beasley paper and its implications; discuss the importance of well-designed cohort studies for prevention activities; and consider the ramifications of the Beasley study and the work that has followed since.

1. Introduction

More than 2 billion people worldwide are thought to be seropositive for past or current hepatitis B virus (HBV) infection, and over 250 million people have chronic infection [27,28]. Of those who become chronically infected, 10–25% will develop hepatocellular carcinoma (HCC) [29]. Given this prevalence and associated disease, prevention of HBV infection is a public health imperative. The identification of a link between HBV and HCC allowed the development of public health strategies that targeted HBV and prevented cancer, as well as end stage liver disease. The seminal 1981 Lancet paper by Beasley et al., "Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan" [3], provided key evidence that propelled the implementation of liver cancer prevention efforts.

In this commentary, we will describe the discovery of HBV, which led to the study by Beasley et al.; summarize the major findings of the Beasley paper and its implications; discuss the importance of well-designed cohort studies for prevention activities; and consider the ramifications of the Beasley study and the work that has followed since, including implementation of vaccination programs, natural history studies, and the need for studies of the impact of treatment in the future (Fig. 1). Throughout, we will illustrate how scientific teams subsequently addressed the implications of the Beasley paper over the course of years by systematically planning and implementing follow-up studies that could evaluate and build on those implications. This effort is particularly well-illustrated by work in Taiwan, where a national vaccination program was implemented, allowing Taiwanese investigators to be the first to show that vaccination reduces cancer risk [1,30]. Taiwanese investigators also established a cohort of individuals chronically infected with HBV to enable evaluation of the natural history of disease, impact of treatment, and strategies for screening and treatment [14].

2. Discovery of HBV

Before 1970, several studies observed that patients with "serum hepatitis" had detectable levels of "Australia antigen" or "serum hepatitis" [5–7], now known as HBV surface antigen (HBsAg) (Fig. 1). Baruch Blumberg and Harvey Alter discovered HBsAg in 1963 [5], and Chung et al. independently identified this antigen [6]. Subsequent reports implicated HBsAg in the development of viral hepatitis [31,32]. These findings inspired Irving Millman and Blumberg to devise and patent a concept to use HBsAg from human plasma to prepare a hepatitis B vaccine in 1969 [17]. This concept was groundbreaking in that it was the first time a vaccine was proposed that was not prepared from tissue culture [17]. Hilleman used the idea to develop a vaccine against HBV, which was licensed in 1976 [18], and Blumberg won the Nobel Prize in 1976 for both describing HBV and devising the novel concept of a plasma-based vaccine. In addition to Millman and Blumberg's initial technological advance through the development of a vaccine based on

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; anti-HBc, anti-hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; REVEAL-HBV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus

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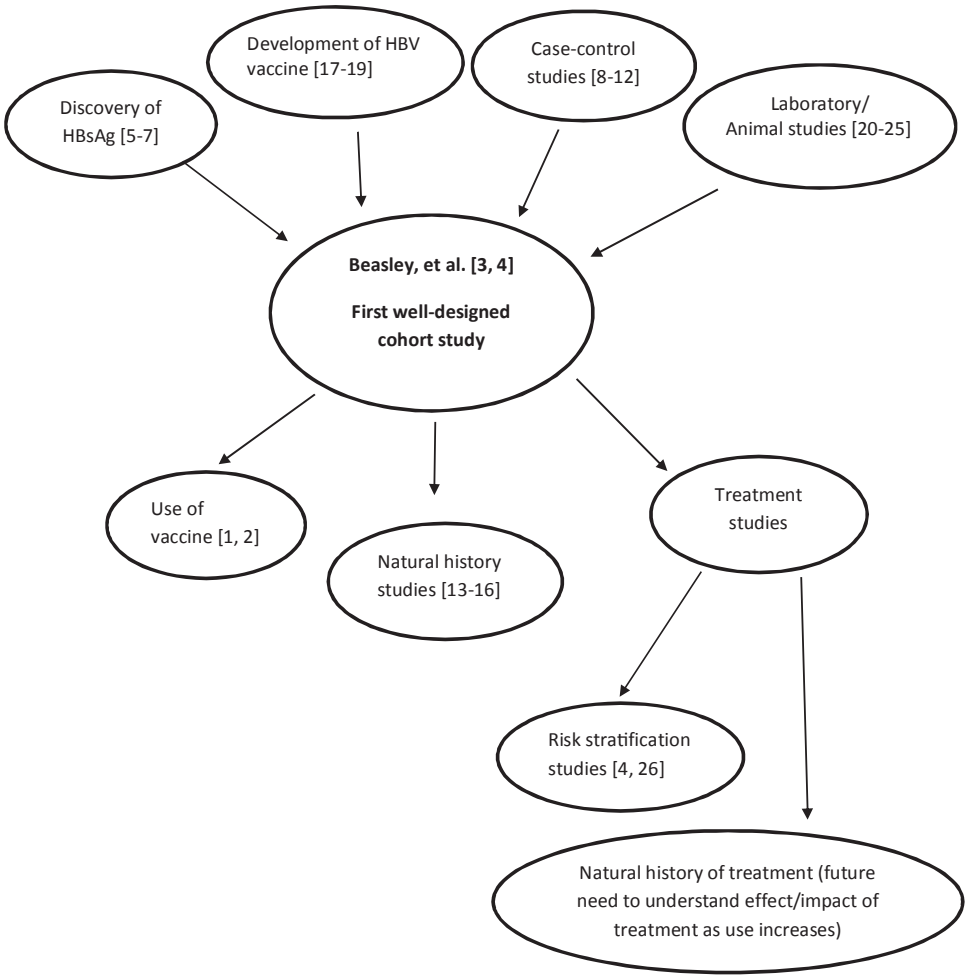

Fig. 1. Contributions to understanding of liver cancer etiology and prevention.
Abbreviations: HBsAghepatitis B surface antigen; HBVhepatitis B.

plasma-derived HBsAg rather than human tissue, mass production of the vaccine involved another innovation: development of the first genetically engineered vaccine. Charnay et al., used the recently cloned HBV genome to identify the gene that coded for HBsAg, fused the HBsAg coding sequence with the beta-galactosidase gene in bacteriophage lambda, and infected *Escherichia coli* with this bacteriophage to biosynthesize the HBsAg protein [19].

In the 1970s, laboratory and animal experiments provided evidence that HBV infection was involved in hepatocellular carcinogenesis. *In vitro* studies suggested that cell-mediated immunity was involved both in the control of HBV infection and in the generation of chronic liver damage [20,21]. Animal studies demonstrated the infectious nature of HBV, the development of liver disease and cancer after transmission of HBV, and the prevention of HBV infection after vaccination [22–25]. In addition, a number of case-control studies reported a higher prevalence of HBV antigens among patients with HCC [8–12]. One of the major limitations of the case-control design is its potential reverse causation. The exposure information is collected at disease onset; thus, whether the exposure is a cause of HCC or rather a consequence of HCC onset cannot be definitively demonstrated. For example, it could be postulated that the presence of a liver tumor might lead to a heightened immune response resulting in greater HBsAg seropositivity. Nevertheless, these previous studies laid the ground work for the Beasley paper, which is considered the final word on the association between HBV and liver cancer.

3. Seminal study by Beasley, *et al*

Beasley et al., made use of the life and health insurance system used by Chinese government employees in Taiwan to enroll 22,707 male participants and follow them for HCC (Fig. 2). They focused on men because the incidence of HCC is higher in men than women, government employees were typically male, and male employees tended to be older and to stay in service longer. Deaths were identified through health and life insurance, and the cause of death was verified through medical record review. Of the 41 deaths due to HCC, 19 had histological confirmation and the remainder had elevated serum alpha fetoprotein (AFP) levels, imaging indicative of HCC, or both. HBV markers were measured through commercial radioimmunoassay kits.

Of the 22,707 men in the cohort, 3,454 (15.2%) were HBsAg-positive, and 19,253 (84.8%) were HBsAg-negative at study entry. After an average of 3.3 years of follow-up per man, there were 307 deaths, 105 (34%) of which were among HBsAg-positive men. Of these 105 deaths, more than 50% were due to HCC (n = 40, 38.1%) or cirrhosis (n = 17, 16.2%). The incidence for HCC was 1158 per 100,000 person-years, compared to only 5 per 100,000 person-years in HBsAg-negative participants, resulting in a relative risk of 223 (95% CI: 28–1479). The magnitude of this association is quite striking for a study of cancer epidemiology, highlighting the powerful role that chronic HBV infection plays in HCC development.

This study was particularly well-considered in its design. It took advantage of an existing life and health insurance system with routine exams, as well as an existing prospective study, allowing the investigators to recruit and follow participants for HCC outcomes in a timely and efficient manner. While the study needed a large number of participants to identify a sufficient number of outcomes, the anti-hepatitis B core antigen (anti-HBc) test was too expensive to test on everyone, so the investigators tested a sample of HBsAg-seronegative men