HBV Infection and Hepatocellular Carcinoma

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KEYWORDS

• Hepatitis B • Hepatocellular carcinoma • Interferon • Nucleos(t)ide analogues
• Surveillance

KEY POINTS

- Safe and effective sterilizing vaccine against hepatitis B virus (HBV) has already been proved to actively antagonize hepatocellular carcinoma (HCC) in the juvenile population of endemic regions.
- Another preventive measure against HCC is screening/surveillance of patients with HBV with abdominal ultrasonography, which aims to improve HCC treatment through early diagnosis, the only practical approach to reduce liver-related mortality.
- It is still unclear whether permanent suppression of HBV by nucleos(t)ide analogs may also translate into a reduced risk of HCC in carriers, while preventing liver-related death from clinical decompensation.

INTRODUCTION

After the discovery of the serologic marker of the hepatitis B virus (HBV) in 1967, a wealth of epidemiologic data began to accumulate that progressively highlighted the role of HBV in hepatocellular carcinoma (HCC) worldwide. However, it was not until 1981, long before the basic mechanisms of HBV-related carcinogenesis could be fully elucidated by molecular studies of cell biology, that HBV was unequivocally linked to HCC through the landmark study by Palmer Beasley in Taiwan.[1] After prospective follow-up of more than 19,000 male state employees who were covered by a nationwide program of medical care and had their health status records traceable to death, it was found that virtually every case of HCC occurred in chronic carriers of HBV in whom the relative risk of developing HCC was ultimately greater than 200-fold that in uninfected controls. Since a similar link between HBV and HCC was subsequently demonstrated in the black population in South Africa, another endemic area for liver tumors, it was clear that HCC in those geographic areas could only be efficiently

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fought by interrupting the perinatal transmission of HBV, which was the dominant modality of infection in the general population. The advent of a safe and effective sterilizing vaccine served the purpose, allowing us to dream about the possible eradication of hepatitis B. The battle started in Taiwan with a vaccination campaign for neonates of infected mothers, a program that was subsequently extended to mass vaccination of all neonates. As a result, the rates of chronic hepatitis B among teens decreased remarkably (from 10% to less than 1%) leading to a 50% drop in the rates of mortality from HCC in the same population.[2] Although the battle to prevent HBV-related HCC is running successfully to the point that more than 320 million neonates have been targeted thus far, substantial improvements have also been made in the management of patients who already have HCC, since standardization of the policies for the diagnosis and treatment of the tumor and the underlying hepatitis B. Currently, the guidelines for the management of HCC have been updated and optimized as a result of multidisciplinary contributions from experts in the scientific communities in the United States, Europe, and Asia Pacific to generate recommendations based on evidence and with the aim of developing cost-effective personalized therapies.[3–5]

EPIDEMIOLOGY

HBV is the dominant risk factor for HCC, which represents more than 90% of all liver cancers and each year accounts for 749,000 new cases and 692,000 HCC-related deaths.[6] Because of geographic variations in the incidence of hepatitis B, the fraction of HCC attributable to HBV varies significantly in various continents, representing less than 20% of all cases of HCC in the United States and up to 65% in China and Far East; Europe is divided into a low risk (18%) area (west and north Europe) and a high risk (51%) area (east and south Europe). However, the role of HBV in HCC may be greater than that depicted by seroepidemiologic studies, as suggested by the existence of hepatitis B surface antigen (HBsAg) seronegative individuals who may harbor subclinical infection with HBV in the liver as both free and integrated forms of HBV-DNA (**Fig. 1**).[7,8] Although the potential of occult infection to spread to the uninfected population is questioned, there is circumstantial evidence that occult HBV infection may have clinical consequences because it may cause deterioration of preexisting liver disease and reactivate to severe hepatitis B after exposure to immunosuppressive regimens.[9] As the pattern of HBV infection is changing as a result of the mass vaccination of newborns and risk groups against HBV, a decline in the infection rates among the general population has been demonstrated in endemic areas, whereas the spread of HBV is on the increase in research-rich countries like the United States and northern Europe as a consequence of increased population exposure to parenteral risks.[10]

RISK FACTORS

Virus-related, host-related, dietary, and lifestyle factors are associated with an increased risk of HCC in patients who are chronically infected by HBV. Increasing age and male gender, both reflecting increased exposure to HBV, have long been known to enhance the risk for HCC. More recently, evidence has emerged that gender disparity in HCC risk may also reflect protection against this tumor by estrogen via a complex path involving hepatocyte nuclear factor-4α.[11] Hepatitis severity and coinfection with such hepatropic viruses as hepatitis D virus and hepatitis C virus (HCV), or human immunodeficiency virus have been found to boost the HCC risk during chronic infection with HBV. Alcohol abuse, which itself is a relevant risk factor for