Hepatitis B Virus Genotype and Mutants: Risk Factors for Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related death behind only lung and colon cancers (1) and the principal cause of death among cirrhotic patients (2). The incidence of HCC is increasing in the United States and Europe (3). Hepatitis B virus (HBV) infection affects 400 million people worldwide and is the main risk factor for HCC in Eastern Asia and Africa (4,5). Aflatoxin B exposure further enhances the risk of tumor development in HBV-infected patients. In Western countries and in Japan, hepatitis C virus (HCV) infection, which affects approximately 170 million people worldwide, is the most prevalent risk factor for HCC (4,5). Cirrhosis is the main risk factor for HCC development and is the underlying cause of HCC in 80% of cases (4). The annual incidence of HCC is 0.4%–0.6% in HBV-infected noncirrhotic patients, 2% in HBV-infected cirrhotic patients, and 3%–8% in HCV-infected cirrhotic patients (4,5). Overall, one-third of cirrhotic patients will develop HCC during their lifetime.

Several improvements in the prevention and treatment of HCC have occurred during the last two decades. The efficacy of primary prevention through HBV vaccination was first demonstrated in Taiwan (6). The universal vaccination of infants against HBV led to a substantial decrease of the incidence in HCC. Unfortunately, this has not been the case for HCV infection, with attempts to design an effective HCV vaccine having failed so far (7). Other attempts to prevent HCC development have focused on using chemopreventive agents (eg, oltipraz) to prevent the oncogenic effects of aflatoxin, which promotes a point mutation in the *TP53* gene at codon 249. At this point, however, studies translating this strategy into effective reduction of cancer-related deaths are still needed (8). Secondary prevention may be achievable in patients with chronic HCV infection through antiviral treatments (4,9). Patients who have a sustained virological response have a decreased incidence of liver cancer. Once cirrhosis is established, however, the preventive effect of antiviral therapies for HCV is still uncertain because positive results from several studies (4,10,11) need to be confirmed in prospective controlled investigations (12).

In the West, early detection of HCC has improved as a result of the wide implementation of surveillance programs. This strategy has led to an increase in the applicability of potentially curative treatments (ie, surgery, local ablation) and, ultimately, a beneficial outcome for the patient (4). In fact, approximately one-third of patients benefit from current therapies (4,5). In addition, improvements in the outcomes of patients with HCC at later stages can be accomplished through chemoembolization (13) in intermediate-stage tumors and sorafenib, a multifunctional kinase inhibitor that blocks proliferation and neoangiogenesis, in advanced-stage tumors (14).

From a cost–benefit perspective, chemopreventive strategies should target populations that are at high risk of developing HCC. Several studies have identified HBV-related factors as key predictors of HCC development in patients with chronic HBV infection [reviewed in (15)]. For example, HBV e antigen (HBeAg) seropositivity (16), high viral load (17), and genotype C HBV (18) are independent predictors of HCC development. In addition, hepatitis B viral load correlates with the risk of progression to cirrhosis (19). Although these factors are interrelated—for instance, patients with genotype C HBV are more likely to remain HBeAg-positive than patients with genotype B HBV—each is independently associated with an increased risk of HCC development. Other genetic characteristics have recently emerged. Precore and basal core promoter (BCP) mutants are the most common naturally occurring HBV mutants. The BCP A1762T/G1764A double mutant has been reported to be associated with an increased risk of HCC development in small cohorts of patients (20,21).

In this issue of the Journal, Yang et al. (22) examined the risk of HCC associated with HBV genotypes and common variants in the precore and BCP regions in 2762 treatment-naive HBV surface antigen (HBsAg)–seropositive patients. During 33 847 person-years of follow-up, 153 HCC cases occurred. The analysis of this cohort confirmed the association of risk for cancer with age older than 60 years, male sex, presence of cirrhosis, HBV DNA level of more than 10^4 copies per milliliter, and genotype C. Subgroup analysis of patients with more than 10^4 copies of HBV DNA per milliliter revealed that the precore G1896A mutant and the BCP A1762T/G1764A double mutant were independently associated with development of HCC (adjusted hazard ratios [95% confidence interval]: 0.34 [0.21 to 0.57] and 1.73 [1.13 to 2.67], respectively).

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See "Funding" following "References."

DOI: 10.1093/jnci/djn261

The associations previously reported (20,21) between HBV mutations and HCC development suggest that genomic alterations of the virus play a role in hepatocarcinogenesis. The mechanism of action remains unclear. The BCP A1762T/G1764A double mutant has been associated with decreased T-cell responses (23) and with changes in the hepatitis B X (HBx) gene sequence. In fact, the BCP coding region overlaps the sequence that codes for the HBx protein. Hypothetically, mutations in BCP coding regions could alter the oncogenic potential of the HBx protein and thereby induce inactivation of p53-mediated apoptosis or impairment of DNA repair (24). Other changes in the BCP region have also been associated with a high risk of cancer development (25). An unexpected result of the study by Yang et al. (22) was the observation of an association between the precore G1896A mutation and a decreased risk of HCC development. The authors hypothesized that stopping HBeAg production might protect against HCC. By contrast, most of the previous studies reported that the precore G1896A mutation is associated with more active inflammation of the liver, which is associated with a higher risk of HCC.

Several mechanisms have been proposed to explain the higher incidence of HCC in patients infected with genotype C HBV vs genotype B HBV (26). It is possible that variations in viral sequence may contribute to this difference: several studies have found that subgenotype C2 is associated with a higher incidence of HCC than other subgenotypes of HBV genotype C (27,28).

One of the main challenges is to determine whether secondary prevention can be accomplished with new antiviral therapies for HBV infection. Interferon, lamivudine, adefovir dipivoxil, entecavir, and telbivudine are antiviral agents that have been approved for the treatment of chronic HBV infection (29,30). Interferon has no overall effect on preventing HCC, but there might be a beneficial effect in responders. The nucleoside analog lamivudine showed a marginally statistically significant effect in decreasing the risk of HCC development in one randomized study among patients with high HBV DNA levels and advanced fibrosis or cirrhosis (31). Other nucleoside analogs, such as entecavir (32) and telbivudine (33), have demonstrated better HBV DNA suppression than lamivudine. Large randomized controlled trials with specific end points of HCC prevention are needed to confirm the efficacy of these agents in preventing HCC development (34). These studies should stratify the patients by the main risk factors for tumor development, such as age, sex, cofactors (cigarette smoking, alcohol use), HBV DNA load, HBeAg status, and HBV genotype and by relevant mutations.

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Funding

J.M.L is Professor of Research (ICREA) and is currently supported by grants from the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (1R01DK076986-01), The Samuel Waxman Cancer Research Foundation, and the Spanish National Health Institute (SAF-2007-61898).