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HEPATITIS B VIRUS GENOTYPES AND THE RISK OF DEVELOPING HEPATOCELLULAR CARCINOMA

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Abstract
Hepatitis B is a viral infectious disease that affects the liver and can occur in acute or chronic forms. According to WHO estimates, in 2022 there were 254 million people worldwide living with chronic hepatitis B, with approximately 1.2 million new infections occurring each year. Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver, resulting from malignant transformation of hepatocytes. It is estimated that in 2022 about 1.1 million people died from hepatitis, mainly due to liver cirrhosis and hepatocellular carcinoma (primary liver cancer).

Keywords: Malignancy, hepatocellular carcinoma, univariate analysis, chronic hepatitis B, case-control, HBsAg.

Introduction

Most retrospective and case–control studies have shown that patients infected with HBV genotype C experience more severe liver disease, including cirrhosis and hepatocellular carcinoma (HCC), than patients with genotype B. A community-based prospective study of 2,762 HBV carriers in Taiwan found that genotype C was associated with an increased risk of HCC compared with genotype B, with an adjusted hazard ratio of 2.35 (95% CI: 1.68–3.30; $P < 0.001$).

In another study of 4,841 HBV-infected men in Taiwan, Yu et al. found that viral load was higher among patients with genotype C compared with those with genotype B. Furthermore, patients with genotype C who also had a very high viral load had a 26-fold higher likelihood of developing HCC than patients with other genotypes or those with low/undetectable viral load. Our recent inpatient cohort study of 2,688 Taiwanese HBsAg-positive patients without signs of cirrhosis, followed for a mean of 14.7 years, also showed that annual incidence of HCC was higher in patients with genotype C than in those with genotype B by univariate analysis. These data support the concept that genotype C correlates with increased risk of HCC. Interestingly, several reports indicate that genotype B is associated with HCC occurring at a younger age, whereas genotype C is associated with HCC at older ages.

HBV genotype also affects clinical and pathological features of patients with resectable HCC. In Taiwan, among 193 HBV-related HCC patients who underwent surgery, patients with genotype B had a higher frequency of solitary tumors (94% vs. 86%, $P = 0.048$), but more satellite nodules (22% vs. 12%, $P = 0.05$) compared with patients with genotype C (Chen et al., 2004; Lin et al., 2007). Wu et al. (2009) also reported that hepatic inflammatory activity was higher in genotype C patients than in genotype B patients ($P = 0.023$). A larger proportion of genotype C patients tended to have higher viral loads (>10^6 copies/mL) compared with genotype B patients (52.3% vs. 37.6%, $P = 0.067$).

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These differences may influence recurrence rates and prognosis in patients with HBV genotypes B and C.

Compared with primary genotypes, the clinical significance of HBV subtypes is less well studied. One study examined subtype distribution among 296 patients with HBV-associated HCC collected from different regions of Japan (Orito et al., 2005). The study found subtype B2 in 4.4% of patients, subtype B1 in 7.4%, and genotype C in 86.5% of cases. Notably, in the Tohoku region and Okinawa, subtype B2, subtype B1, and genotype C were present in 6.7%, 40%, and 48.9% of patients respectively, compared with 4%, 1.6%, and 93.2% in other regions of Japan. These data suggest that subtype B1 may have a more benign course than subtype B2.

A study of 242 HBsAg-positive patients in Taiwan did not find significant differences in the distribution of genotype C subtypes among patients at different stages of liver disease. This suggests that subtypes of genotype C have minimal influence on progression of chronic hepatitis B in Taiwan. However, another study in Hong Kong of 1,006 chronic hepatitis B patients with a mean follow-up of 7.7 years showed that subtype C2 had the highest risk of HCC (OR: 2.75; 95% CI: 1.66–4.56; $P < 0.0001$), while subtype C1 had an intermediate risk (OR: 1.70; 95% CI: 1.09–2.64; $P = 0.020$) compared with genotype B (Chan et al., 2008). Additionally, multiple mutations in genotype C4 have been associated with faster progression of liver disease and increased risk of HCC in the indigenous population of Australia (Littlejohn et al., 2014). Genotypes B2 and C4 have been shown to be recombinant with other genotypes and may play significant roles in the natural history and pathogenesis of disease. Further studies across different regions with detailed strain characterization are required to confirm links between HBV subtypes and HCC risk.

Although studies examining the association between HBV genotypes and HCC risk are limited, HCC appears to be more frequent among patients infected with genotypes D and F than among those infected with genotype A (Thakur et al., 2002; Livingston et al., 2007). In a prospective study of indigenous HBV carriers in Alaska, the risk of HCC was significantly higher among persons infected with genotype F compared with genotypes A–D ($P < 0.001$; OR: 7.73; 95% CI: 3.69–16.4; $P < 0.001$) (Livingston et al., 2007).

Among the various naturally occurring HBV mutants, several mutations in the X gene of the HBV genome are frequently detected in patients with HCC. These mutants may play an important role in HCC development, as shown by multiple studies.

Several studies have shown that the 3′ end of the X gene is often deleted in HCC cells. This deletion leads to formation of a carboxy-terminal truncated HBx protein. Subsequent studies reported that this truncated protein is present in about 80% of HCC tissues. It is believed that this truncated protein may contribute to hepatocarcinogenesis by promoting cell proliferation and inhibiting apoptosis.

A cohort study of HBV carriers infected with genotypes B and C found that genotype C had a higher prevalence of the BCP A1762T/G1764A variant than genotype B. This was confirmed in two additional studies. A long-term follow-up study of 1,526 patients found that presence of these variants was associated with increased risk of HCC. A meta-analysis also showed that these variants are a significant predictor of HCC development with a pooled odds ratio of 3.79. Recently, BCP A1762T/G1764A variants were shown to correlate with liver cirrhosis in Taiwanese patients with genotypes B and C. These variants serve as independent risk factors for cirrhosis (OR: 4.26; 95% CI: 1.32–13.77), as demonstrated by quantitative pyrosequencing analysis. The risk of cirrhosis was

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higher in patients with BCP A1762T/G1764A levels ≥45% compared to <45% (adjusted OR 2.81; 95% CI: 1.40–5.67; P = 0.004).

Furthermore, the BCP A1762T/G1764A variants affect carboxy-terminal codons 130 and 131 of the X protein due to the overlapping nature of the HBV genome. This may lead to amino acid changes in HBx that increase fibrogenic activity and contribute to hepatocarcinogenesis.

Mutations in enhancer II (C1653T) and other parts of the basal core promoter (T1753V) have been linked to HCC development. A Hong Kong study showed that patients with the C1653T mutation had a significantly higher risk of HCC compared with patients without it (OR: 2.43; 95% CI: 1.08–5.54; P = 0.028). Another study in Taiwan showed that patients with T1753V had a significantly increased risk of HCC (OR: 2.43; 95% CI: 1.33–4.44; P = 0.028) compared with patients without this mutation.

Previous reports also indicated that deletions in the pre-S gene are strongly associated with development of liver cirrhosis and HCC (Chen et al., 2007; Lin et al., 2007c; Fang et al., 2008). The proposed mechanism is that endoplasmic reticulum stress from pre-S accumulation causes oxidative DNA damage; thus, pre-S deletion variants may lead to host genome mutagenesis, promoting hepatocarcinogenesis (Hsieh et al., 2004).

In our case–control study, we found that presence of pre-S deletions was an independent risk factor for HCC (odds ratio [OR]: 3.72; 95% confidence interval [CI]: 1.44–9.65; P = 0.007). Moreover, the frequency of pre-S deletions was significantly higher among genotype C patients compared with genotype B patients (Lin et al., 2007c). A meta-analysis also confirmed that the pooled OR for HCC with pre-S deletions was 3.77 (95% CI: 2.57–5.52). Notably, the OR for pre-S deletions in genotype C patients was higher than in genotype B patients, as reported by Liu et al. (2009b). In our previous study, we mapped the pre-S region and found that all deletion areas contained T- and B-cell epitopes. Most of these regions had lost one or more functional sites, including the human serum albumin-binding site and nucleocapsid-binding site. Thus, pre-S mutations may lead to impaired immunity against HBV, contributing to hepatocyte injury and hepatocarcinogenesis. Odds ratios for HCC in HBV carriers with mutations in the core-promoter and pre-S regions are shown in Figure 2. Further research showed that combination of pre-S deletions and core-promoter mutations is closely associated with disease progression and HCC development (Chen et al., 2006, 2007; Yuen et al., 2008; Liu et al., 2009b).

In addition to potential hepatocarcinogenesis, HBV variants also affect postoperative prognosis of HCC patients. In a study of 185 liver specimens taken from the non-tumorous portion of surgically resected HBV-associated HCC tissues, presence of the BCP mutation independently predicted disease-free survival (adjusted OR: 2.075; 95% CI: 1.203–3.579). Moreover, short (<100 bp) pre-S deletions were significantly associated with lower disease-free survival (P = 0.005) (Yeh et al., 2010).

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