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# Mechanism and prediction of HCC development in HBV infection

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A B S T R A C T

Chronic hepatitis B virus (HBV) infection remains one of the leading causes of hepatocellular carcinoma (HCC) globally. Over the past few decades, the risk factors of HCC in patients with chronic hepatitis B have been well characterized, and can be divided into host and viral factors. A few groups have also derived and validated HCC prediction scores based on these risk factors. In general, the scores have high negative predictive value in identifying a low risk group who may not need HCC surveillance in the next 3–5 years. The scores have been tested originally in Asian patients, and results on their performance in the Caucasian population are conflicting. Furthermore, new research has identified genetic factors and new virological markers (e.g. hepatitis B surface antigen and core-related antigen levels) for HCC, but they are yet to be applied in routine clinical practice.



## Introduction

It is estimated that more than 240 million people have chronic hepatitis B virus (HBV) infection globally [1]. This remains one of the leading causes of hepatocellular carcinoma (HCC), especially in Asia and Africa [2]. In 2016, the World Health Organization set the ambitious goal of reducing the mortality from chronic viral hepatitis by 65% between 2015 and 2030 [3]. While universal vaccination and peripartum antiviral prophylaxis can almost eliminate mother-to-child transmission [4,5], they will have little impact on HCC and mortality in the short- and medium-term because these complications mostly occur after middle age. Instead, we have to rely on accurate risk stratification, antiviral therapy for patients in need, HCC surveillance and effective HCC treatment.

Numerous observational and mechanistic studies have identified the major risk factors of HCC in patients with chronic hepatitis B. A few groups have further combined these risk factors and derived several HCC risk scores to facilitate patient selection for HCC surveillance [6–8]. At present, all regional guidelines support 6-monthly abdominal ultrasonography for HCC surveillance for at-risk patients [9–11]. Although ultrasonography is relatively inexpensive, the procedure is labor-intensive. This can be a problem in low- and middle-income countries because of resource constraints and the number of patients. In such settings, the use of HCC risk scores may allow more efficient resource allocation.

Since this topic was last reviewed [12], there have been a number of new developments. First, while the original HCC risk scores were first developed in Asian cohorts, they were subsequently evaluated in some European and American cohorts, and a new score was derived from a European cohort (see below). Second, it is apparent that antiviral therapy reduces but does not eliminate HCC [13,14]. Antiviral therapy thus modifies the natural history of chronic hepatitis B and affects the performance of HCC risk scores. Because nowadays most at-risk patients should be on antiviral therapy, it is more important to evaluate HCC risk scores in the treated population. Better still, we may need to derive new scores based on treatment cohorts. Finally, liver fibrosis and cirrhosis are among the most important risk factors of HCC, and non-invasive tests have become the first-line assessment for fibrosis in many countries and have been incorporated into some new risk scores.

In this article, we review the mechanism of HCC development in chronic hepatitis B and highlight the important cancer risk factors. We then discuss the latest developments in HCC prediction with special emphasis on treated patients and non-invasive tests of fibrosis.

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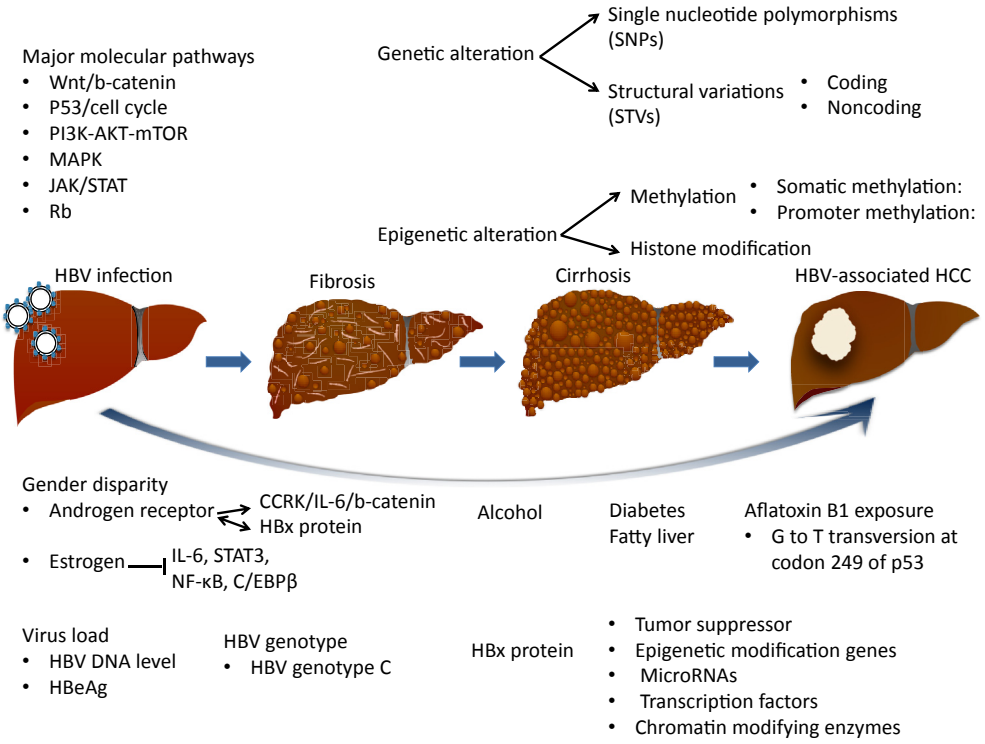


**Fig. 1.** Mechanisms of HBV-related HCC.

## Risk factors of HCC

Chronic HBV infection is a strong risk factor for HCC development (Fig. 1). HBV can promote carcinogenesis through direct or indirect mechanisms. Direct oncogenic effect includes integration of HBV DNA into the host genome, which causes chromosomal instability and numerous mutations [15], and the interaction between HBV x protein (HBx) and host proteins. The indirect effect of HBV includes chronic inflammation, oxidative stress, which contributes to the accumulation of genetic and epigenetic aberrations in liver, leading to subsequent hepatic injuries such as chronic hepatitis, fibrosis, cirrhosis, and finally tumor initiation and progression. In addition, the microenvironment of liver influenced by alcohol consumption, metabolic diseases, sex hormones, aflatoxin exposure or co-infection with HIV and/or HCV can also alter molecular pathways and thus contribute to the development of HCC [12].

### *General factors*

HBV-associated HCC is not caused by one particular driver mutation but involves several oncogenic pathways [16,17]. The most prevalent mutations are in the telomerase reverse transcriptase (TERT) promoter [16], which may lead to telomerase reactivation, allowing cells to avoid programmed cell death and acquire malignant potential. TP53 is another vital tumor suppressor gene involved in HCC development [18]. Several other somatic mutations in a number of genes in various oncogenic pathways are particularly found in HBV-associated HCC, including Wnt signaling [16], cell cycle [19,20], oxidative stress [18,21], epigenetic regulator [19], PI3K-AKT-mTOR [22,23], MAPK [22], JAK/STAT [22], and retinoblastoma pathways [20].

There is an obvious gender disparity in HBV-associated HCC, as shown by a higher incidence of HBV-associated HCC in males and postmenopausal females than other females [24–26]. It is also suggested that HBV-associated HCC is a type of hormone-responsive tumor [27]. Higher testosterone level is associated with increased HCC incidence in HBV infected male patients [28]. There seem to be a positive loop between androgen receptor (AR) and HBx. HBx increases the activity of c-Src kinase, which enhances the transcriptional activity of the AR gene, thus increases its mRNA level [29]. On the other hand, androgen-signaling pathway increases the transcription and replication of HBV genes. In addition, ligand-activated AR increases cell cycle-related kinase transcription and activates β-catenin signaling pathway, which is a classical oncogenic pathway in HCC development [30].

On the contrast, estrogen seems to protect HBV carriers from HCC development. As demonstrated by Naugler et al., estrogen inhibited MyD88-dependent interleukin-6 (IL-6) production in Kupffer cells, and ablation of IL-6 protected mice from diethylnitrosamine (DEN)-induced HCC [31]. We also found that high serum IL-6 level predates the development of HCC in chronic hepatitis B patients, and has moderate accuracy in predicting future HCC development [32]. In addition, estrogen upregulates estrogen receptor, which interacts with and alters binding of hepatocyte nuclear factor (HNF)-4α to the HBV enhancer I [33], thereby reduces IL-6 level and the activity of oncogenic nuclear factor κB (NF-κB), signal transducer and activator of transcription 3 (STAT3) and CCAAT/enhancer-binding protein β (C/EBPβ) [31,34,35].

Asians and Africans are more susceptible to HBV-associated HCC. Asians are considered high risk and Africans super high risk, but recent data suggest that the risk in Africans is probably similar [36,37]. In addition to the increased incidence of HCC, African Black and Chinese patients with HCC are often younger than their counterparts in industrialized countries [36]. It is unclear if the difference from Caucasians is due to genetic factors or the mode of HBV transmission (mother-to-child transmission versus horizontal transmission).

It has been demonstrated that alcohol consumption plays a synergistic role in the progression to HCC, with a more than 2-fold increase of the carcinogenic risk of HBV [38], mainly by accelerating the process of fibrosis and progression to cirrhosis. A prospective