

HEPATITIS B VIRUS: THE MAJOR ETIOLOGY OF HEPATOCELLULAR CARCINOMA

ABSTRACT

Approximately two billion people are infected with hepatitis B (HBV) worldwide. Infection due to the virus can be influenced by many factors such as host immune status, age at infection, and level of viral replication. Majority of patients do recover from acute form of the infection; however, around 10% of the newly infected, 70–80% of which occur in the perinatal period, progress to chronic disease state and are at great risk of developing complications. Although the mechanisms by which chronic hepatitis B viral infection results in hepatocellular carcinoma (HCC) are unclear, there is good evidence to suggest that the virus itself exerts a direct hepatocarcinogenic effect. With an estimated 85% worldwide cases of HCC attributed to HBV, the virus is said to be the third leading cause of cancer deaths. Despite the discoveries in cancer biology of physiological and pathological factors in relation to prognosis, HCC remains a fatal disease due to late diagnosis. The proportion is lower in developed countries (around 40%) than developing countries (around 85%) where the endemic high prevalence of HBV strongly predisposes to the development of chronic liver disease and subsequent progression to hepatocellular carcinoma. Better approaches to universal HBV vaccination and identification and treatment of chronic hepatitis B are needed to allow for the application of the many advances that have been made in the understanding, prevention, and treatment of hepatocellular carcinoma.

Key words: tumor, cirrhosis, HBV protein, HBV DNA, hepatocyte, chronic hepatitis B

INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that there are more than 350 million HBV carriers in the world, of whom roughly one million die annually from HBV-related liver diseases. The implementation of effective vaccination programs in many countries has resulted in a significant decrease in the incidence of acute hepatitis B. Nevertheless, hepatitis B remains an important cause of morbidity and mortality (1).

HBV causes both acute and chronic infection in humans with varying clinical manifestations (2). During the acute phase, manifestations range from subclinical or anicteric hepatitis to icteric hepatitis and, in some cases, fulminant hepatitis, while in the chronic phase, manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Extrahepatic manifestations, including serum sickness, polyarteritis nodosa, and essential mixed cryoglobulinemia, membranous glomerulonephritis, and aplastic anemia can also occur with both acute and chronic infections (3; 4).

Hepatocellular carcinoma (HCC), characterized by rapid tumor growth and a high propensity of vascular invasion, is one of the most common malignancies, ranking fifth in frequency among all malignancies in the world (5). Around 85% of worldwide cases can be attributed to chronic infection with HBV, suggesting that chronic hepatitis B is a major risk factor for development of the disease considered to be the third most common cause of death from cancer worldwide (6; 7). In addition chronic hepatitis infection could cause cirrhosis with global incidence of 57% estimated to be due to infection with HBV (8). Cirrhosis could be present in 80–90% of patients with hepatitis B-related HCC, but there is also evidence that HBV infection could directly damage DNA in liver cells, potentially leading to cancer when cirrhosis is not present (9). Due to differences in the prevalence of viral hepatitis, the incidence of HCC in low and middle income countries is considered to be much higher with about 85% of cases, than in high income countries with 40% (10; 11).

Increasing evidence points out to two major HBV-specific mechanisms that contribute to the development of HCC. The first is the integration of the viral genome into the host chromosome resulting in loss of tumor suppressor gene functions, and/or activation of tumor-promoting genes. The second mechanism involves the expression of trans-activating factors derived from the HBV genome, which have the potential to influence intracellular signal transduction pathways and alter host gene expression (12).

HBV can be transmitted through percutaneous or mucosal exposure to infected blood or other body fluids. The transmission has been observed with numerous forms of human contact including perinatal/mother-to-child; household (nonsexual); sexual; needle-sharing; and occupational/health-care-related. The highest concentrations of infectious HBV are found in blood and serum. However, other body fluids, such as semen and saliva could also be infectious.

Persons with chronic HBV infection are the major reservoir for transmission, although any person testing positive for hepatitis B surface antigen (HBsAg) is potentially infectious to both household and sexual contacts (13).

HBV is a partially double stranded DNA virus belonging to the Hepadnavirus family. The viral genome is a circular DNA molecule of 3.2 kb organized in a compact manner with four partially-overlapping open reading frames (ORF) including surface (S), core (C), polymerase (P) and X genes. These viral genes can be translated to different viral proteins from four major transcripts, such as surface antigen (HBsAg), e antigen (HBeAg) and core antigen (HBcAg). The host immune system produces corresponding antibodies against these viral proteins, including anti-HBs, anti-HBe and anti-HBc. These antigens and antibodies lay the basis for serological diagnosis of HBV infection (2). HBV shows a high degree of species specificity and infects only humans and higher primates. Other members of the Hepadnavirus family, namely the duck hepatitis virus, woodchuck hepatitis virus and ground squirrel hepatitis virus, are also species-specific (14).

HBV is divided into four major serotypes (adr, adw, ayr, ayw) as a result of antigenic epitopes present on its envelope proteins and based on a nucleotide divergence in the entire viral genome, the virus has been established and classified into eight genotypes (A to H) with a characteristic geographic distribution. The accumulated evidences suggest that the genotypes have an impact on the natural course of chronic HBV infection with differences in the severity of underlying liver disease or treatment response (15).

Strategies to limit the impact of HCC include primary prevention against new cases of viral hepatitis, secondary prevention in susceptible individuals, and early detection. Universal hepatitis B vaccination has resulted in dramatic reduction in cases of chronic hepatitis B and HCC in children and adolescents. In addition, randomized controlled trials and meta-analysis has shown that successful treatment of chronic hepatitis B can reduce the risk of HCC and cirrhotic complications (11).

BRIEF HISTORICAL BACKGROUND

An aetiological association between cirrhosis and HCC was suspected as early as the beginning of the 20th Century (16). By the 1950s it was realized that it was posthepatitic cirrhosis that was most closely linked to tumour formation (17; 18). Following the introduction of serological tests for HBV in the late 1960s it soon became evident that chronic HBV infection was a major risk

factor for the development of HCC. Refinements of molecular techniques for identifying viral DNA, availability of HCC cell lines harbouring integrated HBV DNA, and a variety of animal models, either infected with viruses belonging to the same family as HBV (the *hepadnaviridae*) or transgenically propagated with specific HBV genes, has made it possible to investigate in depth the role of chronic HBV in the pathogenesis of HCC (19).

MECHANISM OF HCC INDUCTION BY HBV

Multifactorial mechanisms contribute to the development of hepatocellular carcinoma (HCC) in chronic HBV infection. Both viral and host factors including genetic alterations induced by viral DNA integration, expression of oncogenic viral proteins and chronic immune-mediated hepatitis have been implicated as contributing factors (20).

Chronic inflammation and cirrhosis

A potential element of HBV-related hepatocarcinogenesis is the dynamic course of chronic hepatitis B. It is characterized by periodic down-regulations of viral titers accompanied by immune-mediated liver injuries known as flares. Such periodic injuries result in repeating cycles of death and proliferation of hepatocytes (21). Liver injuries caused by chronic hepatitis B are considered to be immuno-mediated and are mainly due to the activity of HBV-specific T cells. However, some data suggests important roles of non-specific chemokine-mediated infiltration of neutrophils, natural killer cells and activated bystander lymphocytes in causing HBV-related liver damage. These inflammatory cells release cytokines and chemokines which may favor cancer growth. High hepatocyte proliferation rate is a major risk factor for hepatocellular carcinoma development in the cirrhotic liver (22).

Chronic inflammation also results in increased production of reactive oxygen species (ROS) which can cause DNA damage and lead to gene mutations (23). Increased intracellular ROS levels can also activate several signal transduction pathways that regulate proliferation, differentiation and apoptosis, including the mitogen-activated protein kinase/activated protein-1 and nuclear factor kappa-light-chain-enhancer of activated B cells (MAP-kinase/AP-1 and NF-kappaB) pathways (23). Inflammation-induced oxidative stress and influx of Kuppfer cells can promote the activation of stellate cells. The latter are the main producers of extracellular matrix

in the liver (24). Their persistent activation can finally lead to cirrhosis, which is characterized by the co-existence of regenerative nodules, irreversible fibrosis and severe liver injury (21).

Cirrhosis is an important predisposing state for HCC development. About 80–90% of HCCs of all etiological backgrounds arise in cirrhotic livers. In HBV endemic areas, infected patients with cirrhosis have an approximately 3-fold higher risk for HCC than those with only chronic hepatitis B, and a 16-fold higher risk than asymptomatic carriers (25). The incidence of HCC development is approximately 3–5% per year in HBV associated cirrhosis. The long-term persistence of occult might also exert an indirect oncogenic role by chronically sustaining a mild necroinflammation contributing to cirrhosis and HCC development (26).

A higher rate of cirrhosis has been reported in HBeAg-negative as compared to HBeAg-positive patients. Also, older age and persistent viral replication are predictors for development of cirrhosis as well as mortality. Genotype C is associated with a higher risk of cirrhosis than genotype B based on studies in Asian patients (27). The presence of any other independent hepatotoxic factors such as alcohol ingestion and HCV co-infection can contribute to progression to cirrhosis. Once cirrhosis is established, individuals can decompensate over time. In a EUROHEP cohort study, a 5-year cumulative incidence of hepatic decompensation was 16%, the incidence per 100 person years was 3.3 and the mean interval between the time of diagnosis of cirrhosis and the onset of first episode of decompensation was 31 months (range 6-109) (28). After decompensation, the survival may drop to 55% from 70% at 1 year and to 14% from 28% at 5 years. Interestingly, an improvement in liver function activity has been observed in those individuals who subsequently lose their HBsAg positivity (25).

Almost all cases of HCC take place after many years of chronic immune-mediated hepatitis (29) characterized by continuous cycles of low-level liver cell destruction and regeneration that (over long periods of time) lead to fibrosis, cirrhosis, steatosis, and probably HCC (30). Indeed, transgenic mice that produce hepatotoxic quantities of L-HBs (29) display hepatocellular injury, regenerative hyperplasia, chronic inflammation, Kupffer cell hyperplasia, oxygen radical production, glutathione depletion, oxidative DNA damage, transcriptional deregulation and aneuploidy that inexorably progresses to HCC (31). More importantly, transgenic mice that express nontoxic concentrations of the HBV envelope proteins in the hepatocyte and don't develop evidence of liver disease develop HCC after many months of chronic hepatitis mediated by HBV-specific CTLs (32).

Importantly, the appearance of HCC in these settings occurs despite the absence of cofactors such as viral integration and X gene expression. Since the immunological, virological and histological features of this chronic immune-mediated HCC model closely resemble the features of human chronic hepatitis, the results suggest that an ineffective immune response is a critical oncogenic factor during chronic HBV infection in man. The pathogenetic importance of immune-mediated hepatocellular injury in hepatocarcinogenesis in HBV is strengthened by the fact that hepatocellular carcinoma occurs in the context of necrosis, inflammation and regeneration (cirrhosis) in several human liver diseases other than hepatitis B, including chronic hepatitis C (33), alcoholism (34), hemochromatosis (35), glycogen storage disease (36), α -1-antitrypsin deficiency (37), and primary biliary cirrhosis (38).

Irrespective of etiology or pathogenesis, therefore, it would appear that chronic liver cell injury is a premalignant condition that initiates a cascade of events characterized by increased rates of cellular DNA synthesis and production of endogenous mutagens coupled with compromised cellular detoxification and repair functions. If these processes are sustained for a sufficiently long period of time, they would be expected to cause the multiple genetic and chromosomal changes necessary to trigger the development of hepatocellular carcinoma (30).

Integration of viral DNA into the host genome

The extent by which HBV genome insertions contribute to hepatocarcinogenesis is still controversial (12). Integration events are thought to precede the development of the tumor, since they are also found in individuals with chronic hepatitis B and are even observed during the acute stage of infection (20). The integrations of HBV DNA into the genome of host hepatocytes are found in 85–90% of HBV-related HCCs (39).

Viral genome insertions have been shown to be facilitated by cellular conditions that disrupt host genomic stability or increase cellular DNA replication, such as exposure to oxidative stress or DNA-damaging agents, deficiency of the DNA repair machinery, co-infection with other viruses and chronic liver injuries that increase hepatocyte turnover (39). Unlike the woodchuck hepatitis B virus (WHV), which preferentially inserts its DNA genome into c-Myc or N-Myc genes in the woodchuck genome, no specific genes in humans have been identified so far to be the preferential target for HBV insertion (39). However, the insertion itself can induce general genomic instability in host cells, leading to chromosome deletions, duplications, amplifications,

translocations and transpositions of viral and flanking host sequence between chromosomes (20). In addition, the regulatory proteins HBx and the PreS2 activators can exert a tumor promoter-like function, resulting in positive selection of cells producing a functional regulatory protein (40).

Indeed, in HCC cells and liver tissues from HCC patients, cancer-relevant cellular genes have been shown to be altered by HBV DNA insertion, in particular those regulating cellular immortalization (hTERT), proliferation (MAPK1, cyclin A), and viability (TNF receptor-associated protein 1), suggesting that hepatocytes harboring these insertions are preferentially selected during hepatocarcinogenesis (39). The rearrangement of viral and host DNA sequences during integration can lead to the production of altered protein products whose functions may render hepatocytes prone to transformation. For example, a C-terminal truncated form of the X protein resulting from a deletion of inserted viral DNA has been reported to enhance oncogene-induced transformation, whereas the wild-type full-length protein suppresses such transformation (40). HBx mutations have been frequently described among occult HBV infections (15).

Taken together, though the insertion of HBV DNA into the host genome might be a random event that contributes to the formation of an unstable environment, and occasionally induces genomic alterations that facilitate hepatocyte transformation even in the case of occult HBV infections. Therefore, HBV integration may contribute, at least in part, to the development of most of HBV induced HCCs (12).

Studies of HBV insertions in HBV-related HCCs have shown that also HBV integration can occur in genes that target telomerase and mixed lineage leukemia encoding genes suggesting potentially common pathways in HBV-related carcinogenesis (41). HBV DNA integration has also been observed in patients with chronic hepatitis suggesting that integration is likely an early step in the process of hepatocarcinogenesis (42). However, HBV integration is not likely to occur in resting hepatocytes. Thus if integration of HBV genome contributes to hepatocarcinogenesis, it is likely to be secondary to procarcinogenic events that trigger hepatocyte turnover (30).

Recently, it was reported that HBV is more often integrated in liver tumor cells than normal liver tissue cells, and that multiple integrations may be linked to more aggressive disease progression and poorer survival. In a study Sung *et al.*, (43) performed parallel sequencing of 81 HBV-positive and 7 HBV-negative HCC tumors and adjacent normal tissues. Their analyses revealed that the incidences of HBV integrations were high since 76 of the 88 patients had HBV

integration. Specifically, they discovered that HBV will integrate into genes CCNE1, SENP5, and ROCK1, causing an increase in the expression levels of these genes, and subsequently enhancing the tumor growth. This discovery is in addition to the previously reported integration into the TERT and MLL4 genes. The scientists also observed that HBV integration induced chromosome instability, resulting in the scrambling of the genome.

Role of HBV proteins

In addition to the integration of viral genome into host DNA, another direct role of HBV in hepatocarcinogenesis involves the long-term expression of viral proteins such as surface proteins and the X protein (HBx). This is supported by the observation that in a large portion of HCCs, viral DNA sequences encoding these proteins are found to be integrated in the host genome (20).

HBV surface protein

the oncogenic potential of HBV surface proteins have been suggested by experiments showing that a truncated form of the large surface protein can increase hepatocyte proliferation by upregulating cyclin A expression, and that a truncated M surface protein can specifically activate c-Raf-1/Erk2 signaling an increased hepatocyte proliferation (44).

In addition, HBV surface proteins may contribute to HCC development by accumulating in the endoplasmic reticulum (ER) and inducing ER stress. ER stress is defined by the imbalance between the quantity of unfolded or misfolded proteins that enters the ER, and the capacity of the ER machineries to handle the folding of these proteins. Such imbalance activates intracellular signaling pathways that are often referred to as unfolded protein response (UPR) (45). Activation of UPR can lead to various biological outcomes depending on the intensity and duration of ER stress. Under mild and temporary ER stress, UPR lowers the ER burden by attenuating protein synthesis and increasing protein degradation, as well as by increasing the expression of chaperones that refold misfolded proteins (46; 45). In the case of severe or prolonged ER stress, UPR triggers apoptosis through yet poorly understood mechanisms (45).

An important side effect of UPR relevant to carcinogenesis is the induction of oxidative stress. UPR has been shown to increase the production of intracellular ROS through upregulating the oxidative folding machinery (47). The latter is responsible for oxidizing thiol groups to form disulfide bonds, and has been shown to be an important source of intracellular ROS (48). UPR-mediated upregulation of ROS has been reported to contribute to ER stress induced apoptosis (47). Similarly, the oxidative stress caused by increased ROS can lead to various oncogenic

consequences, such as DNA damage, activation of mitogenic response and the deregulation of signaling pathways that control proliferation, cell survival and cell death (22).

During viral infection, the ER serves as an essential organelle for viral replication and maturation. Recent evidence suggests that infection by many types of virus, including HBV and HCV, can induce ER stress due to the large amount of unfolded and misfolded viral proteins synthesized in infected cells (46). In human liver tissues with chronic HBV infection, cytoplasmic accumulation of HBsAg is often observed and has long been associated with the formation of “ground-glass” hepatocytes (49). These hepatocytes often demonstrate ER proliferation and distortion (50). Several studies have shown that ground-glass hepatocytes contain mutations in the pre-S region of the HBV genome, which may lead to the overproduction of the large surface protein that blocks the secretion of all forms of surface proteins from the ER (40). Accumulation of these viral proteins in the ER triggers ER stress, leading to the induction of oxidative stress and DNA damage, and to the predisposition of hepatocytes to transformation (51).

The above scenario has been reproduced in transgenic mice containing the entire HBV envelope coding region. Four transgenic mice lineages presenting progressively higher intrahepatic concentration of HBsAg were studied. Similar to human chronic HBV infection, these mice also demonstrated ground-glass alteration in their hepatocytes due to the ER accumulation of the large surface protein. Such accumulation results in a series of oncogenic events, including liver dysplasia. Severe prolonged liver damage, regenerative hyperplasia nodule formation and incidence of HCC was directly related to the amount of HBsAg accumulated in the hepatocytes (52). Similarly, increased levels of oxidative DNA damage has been observed in the liver of these mice (53). These observations, together with data obtained using human HCC cells described above, support the notion that HBV surface proteins harbor oncogenic effects, and that such effects are mainly mediated by the induction of ER stress and the consequent elevation of intracellular ROS levels (50).

HBV X protein

HBV X protein has been shown to interfere with numerous cellular activities, in particular, proliferation, apoptosis, senescence and DNA repair. However, controversial or even opposite effects of HBx on the same cellular function are often reported, depending on the experimental models used (54).

HBV X protein (HBx) is a small protein of 154 amino acids, and is encoded by the X ORF which is highly conserved among mammalian Hepadnaviruses. HBx has been shown to be required for infectivity in vivo in the woodchuck model, and in some experimental conditions it may enhance viral DNA replication in tissue culture. Contradictory observations have been reported concerning the intrinsic tumorigenic effect of HBx in vivo, with HCC developing in some, but not all of transgenic mice carrying the X gene. However, in these mice, HBx was shown to increase HCC development in the presence of c-Myc expression or upon exposure to low levels of carcinogens, suggesting that the viral protein may assist hepatocarcinogenesis in the context of a cancer-prone environment as it has been shown to activate moderately in trans, a variety of cellular gene expression (54).

Furthermore, HBx was reported to inhibit apoptosis induced by p53, TNF, Fas, or TGF-beta, while it was shown to promote cell death by inducing mitochondrial aggregation and cytochrome C release, or by sensitizing cells to TNF-mediated killing. Several groups also reported its interaction with DNA repair proteins (UVDDDB1). HBx was observed to increase proliferation by inducing G₀–G₁ transition, and stimulating cell cycle progression in differentiated hepatocytes, whereas it causes S phase arrests in dedifferentiated cells. HBx may also play a major role in the epigenetic control of viral and host gene expression (55). The G₀ phase (referred to the G zero phase) or resting phase is a period in the cell cycle in which cells exist in a quiescent state, the G₁ phase, or Gap 1 phase, is the first of four phases of the cell cycle that takes place in eukaryotic cell division, while the S-phase (synthesis phase) is the part of the cell cycle in which DNA is replicated, occurring between G phase and G₂ (56).

Combined hepatitis B and hepatitis C

Follow up studies have shown that patients with combined HCV and HBV infection have a higher risk of developing HCC than those with HCV or HBV alone (57; 58). The cumulative risk of developing HCC was 10%, 21%, and 23%, respectively, after 5 years and 16%, 28% and 45%, respectively, after 10 years (58). The HCC risk in subjects with both infections was investigated in a meta-analysis of 32 epidemiological studies between 1993 and 1997 (59). The OR for development of HCC in HBsAg positive, anti-HCV/HCV RNA negative subjects was 20.4; in HBsAg negative, anti-HCV/HCV RNA positive subjects, 23.6; and subjects positive for both markers, the OR was 135. These data suggest a more than additive effect of HBV and HCV coinfection on HCC risk. The two viruses may possibly act through common, as well as

different, pathways in the carcinogenic process. Given that HBV acts as a cofactor in the development of HCV related cirrhosis and HCC, vaccination of patients with chronic hepatitis C against HBV has been recommended aiming to avoid further liver injury (60).

Coinfection with hepatitis D virus (HDV)

HDV coinfection with HBV is associated with increased liver damage. Kao *et al.*, (61) showed that HBsAg positive patients with HDV superinfection develop cirrhosis and HCC at an earlier stage (mean age 48 years) compared to HBsAg carriers without HDV infection (mean age 62 years).

RISK FACTORS IN HBV-INDUCED HCC

Chronic hepatitis B is the most frequent etiology of HCC in countries with scarce medical resources (62). In fact, more than half of all HCCs in the world are attributed to chronic hepatitis B (10). In a population-based cohort study from the 1980s, which involved 22,708 Taiwanese men who were followed up for 8.9 years, the incidence of HCC was 98.4 times higher in HBV carriers than non-carriers (63). A subsequent study conducted in Taiwan and published in 2010 showed that even inactive HBV carriers (asymptomatic individuals who have normal liver tests, minimal replication of HBV and undetectable or minimal levels of virus in their blood) have a fourfold increased risk of HCC compared with healthy controls (64).

Similarly in a 5-year retrospective study in Ado-Ekiti, Nigeria, it was discovered that in addition to positive HBsAg and HCV-Ab positive, other risk factors for HCC in the country included heavy alcohol ingestion, multiple scarification marks, multiple sexual partners, history of blood transfusion, and ingestion of foods stored in humid conditions (a likely suspected source of aflatoxin exposure) (65)

The risk and presentation of HCC in hepatitis B carriers may depend on ethnicity. Western HBV carriers tend to develop HCC at an advanced age after a period of progressive liver cirrhosis, whereas Asian and African individuals tend to develop HCC in young adulthood and middle age and might exhibit fewer signs of cirrhotic liver disease than western hepatitis B carriers. Genetic variation might underlie the differences between these ethnic groups. Alternatively, this disparity might be explained by differences in the age at which HBV infection is acquired in different populations: vertical transmission is the major route of HBV acquisition in Asia, whereas horizontal transmission in early life is the predominant route of transmission in Africa. By

contrast, in western countries HBV is mostly transmitted in adolescence and adulthood through high-risk behaviors, such as intravenous drug use, sexual exposure or iatrogenic causes including blood transfusion, unsafe needle practices, invasive procedures, hemodialysis or organ transplantation (66).

In the past few years, a calculator to predict HCC risk in patients with HBV has been developed (67; 68). Infection with specific HBV genotypes or HBV strains that carry common mutations (including the basal core promoter mutation and pre-s deletion mutation) increase the risk of HCC, as do a high HBV load, advanced age, male sex, persistent HBV replication and a long duration of infection (69).

The class II cytokine receptor gene cluster on chromosome 21 includes *IFNAR2* (which encodes the type I interferon receptor) and *IL10RB* (which encodes the receptor for Il-10-related cytokines, including the interferon λ family) (70). This cluster is strongly implicated in hepatitis B persistence. Protective alleles at this locus occur more frequently in white European individuals than in West African people. Variations in the HBV genotype might also partly explain differences in the risk and presentation of HCC between different populations. HBV genotype C is most commonly found in Asian individuals and is associated with the persistent presence in serum of hepatitis B e antigen (HBeAg), a decreased rate of spontaneous HBeAg clearance, increased rates of reversion to HBeAg seropositivity after HBeAg clearance, and a raised risk of HCC, independent of HBV DNA viral load levels (71).

CONCLUSION

HBV is the single most common cause of HCC worldwide. HBV-related HCC is most common in developing countries, particularly Eastern Asia and sub-Saharan Africa. Although the pathogenesis of HBV-related HCC remains uncertain, there is strong evidence of a direct effect of HBV itself in causing HCC. Population-based vaccination programs against HBV have been associated with reductions in incidence of HCC and it is expected that widespread programs of universal infant vaccination will have the potential to dramatically reduce the incidence of HCC in the future. Although the impact of antiviral therapy is also uncertain, there is good evidence that prolonged suppression of HBV replication with nucleoside or nucleotide analogues may reduce the risk of HBV in patients with chronic hepatitis B.

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