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HBV: A HEPATOCELLULAR CARCINOMA (LIVER CANCER) CAUSING VIRUS ITS MECHANISM AND PREVENTION

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ABSTRACT

Hepatocellular Carcinoma (HCC), commonly referred to as liver cancer, stands as a global health concern. According to recent statistics by the World Health Organization (WHO), HCC ranks as the sixth most frequently diagnosed cancer and the fourth leading cause of cancer-related fatalities. Predominantly prevalent in Asia and Africa, HCC is intimately associated with chronic Hepatitis B Virus (HBV) infection, high alcohol consumption, and type 2 diabetes. A staggering 50 to 80% of HCC cases are attributed to HBV infection, underscoring the urgency of addressing this viral threat. HBV, a double-stranded DNA virus, presents ten distinct genotypes and encodes five essential proteins, including the pivotal HBx protein. Understanding the HBV life cycle, from attachment to hepatocytes to the release of mature virions, is crucial in developing effective prevention and treatment strategies. Primary prevention strategies primarily revolve around vaccination, with the hepatitis B vaccine demonstrating remarkable efficacy in reducing HBV-related HCC risk. Safe sex practices, needle exchange programs, and antiviral treatments form the pillars of secondary prevention, offering further hope in curbing HCC incidence. Additionally, lifestyle

modifications, such as weight management, a balanced diet, and abstaining from alcohol and tobacco, prove pivotal in reducing HCC risk. tertiary prevention strategies are vital due to high recurrence rates post-treatment. Adjuvant interferon therapy remains a subject of debate, with mixed evidence on its effectiveness in preventing recurrence.

KEYWORDS: A staggering 50 to 80% of HCC cases are attributed to HBV infection, underscoring the urgency of addressing this viral threat.

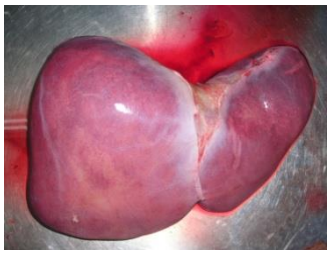
INTRODUCTION

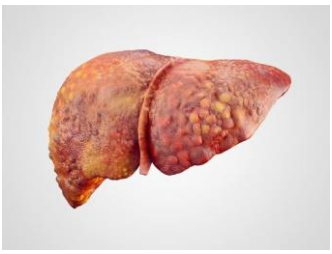
Liver cancer, also known as Hepatocellular Carcinoma (HCC), is a common malignant tumor worldwide. According to a report by the International Agency for Research on Cancer of the World Health Organization (WHO) in 2020, liver cancer is predicted to be the sixth most commonly diagnosed cancer. It is also the fourth leading cause of cancer-related deaths globally in 2018. HCC is a common type of liver cancer, with the highest number of cases occurring in Asia and Africa in 2017, accounting for 10.1% of cases per 100,000 people.[1]

The main risk factors for Hepatocellular carcinoma include chronic Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection, high alcohol consumption, and type 2 diabetes. Recent research suggests that 50 to 80% of HCC cases are caused by HBV infection. Hepatitis refers to an infection that causes inflammation and damage to the liver. It is a viral infection that can lead to liver cancer by replacing healthy liver cells with infected hepatocytes.[2]

For the being of time, hepatitis B virus (HBV) has becomes a significant global morbidity and mortality. Despite preventive vaccination which are effective and well-tolerated in viral suppression. Since 1998 roughly 250 million people have remained with the virus that causes hepatitis disease over the world.[1] Nearly 1 million cases of mortality per year are observed. HBV has become a major threat that causes liver cancer and surpasses malaria and mycobacterium tuberculosis. Correlation to care to be deficient in various countries. Inin developed countries like the United states of America, Japan, Europe, etc. in united states, by CDC estimated that only one-third of HBV infected persons or patients are ignorant of their infection. Some reasons for these low rates due to lack of surveillance, diagnosis, prevention, and treatment include the asymptomatic nature of chronic until the final stage, absence of therapy with accurate treatment, lack of knowledge, and complex natural history about the disease by both the clinical pharmacist and patient. In the last 5 years, more cases observed in HBV thus worldwide are more focused on screening for HBV, diagnosis of HBV infection,

and carrier for cure. Major world health organizations are estimated to get rid of HBV within the year 2030.[2]

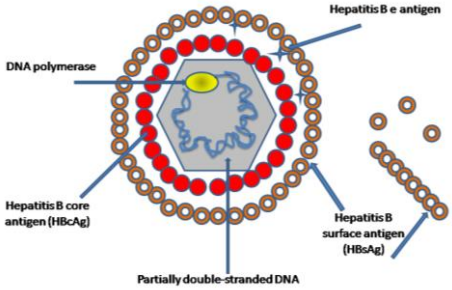




HEALTHY LIVER **CIRRHOSIS LIVER**

TYPES OF VIRAL HEPATITIS CAUSING HCC

Hepatitis B.



(Fig. 1)Hepatitis B Virus.

Hepatitis B virus (HBV) infection is a primary purpose of chronic liver sickness. HBV is a small and enveloped, partially double-stranded DNA virus. Hepatitis B Virus is a *Hepadnaviridae* family. The HBV virion is structurally like a lipid-based spherical structure, that consists of three viral envelop proteins (small, middle, and large) (Fig. 1).[3]

HBV is a double-stranded DNA virus with 4 open reading frames, (S,C,X,P).[4]

S - (surface or envelope, hepatitis B surface antigen [HBsAg]) gene.

C – (core, hepatitis B core antigen [HBcAg]) gene.

X - X gene.

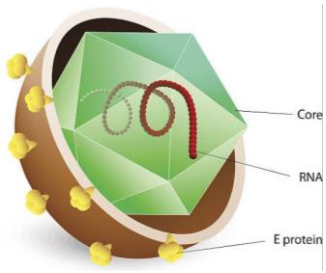
P – (polymerase) gene.

Chronic hepatitis B virus (HBV) infection is a major health problem globally. HBV can cause progressive liver fibrosis which leads to cirrhosis with the end of liver disease, Which increases the risk of hepatocellular carcinoma. Antiviral agents, like interferon and nucleotide analogues (NAs), have been used to treat chronic hepatitis B (CHB) affected patients. Antiviral treatment effectively suppresses HBV replication and slows down the progression

to cirrhosis and hepatocellular carcinoma (HCC). However, The current Antiviral drugs do not cure HBV, because covalently closed circular DNA (cccDNA) forms in the hepatocyte nucleus.[3]

Hepatitis B vaccination is strongly recommended for the control and prevention the HBV. This vaccine was preferred only for medically suitable infants weighing about 2,000 g or more, And that vaccine is injected within 24 hours of birth. The unvaccinated infants, children, and adults requesting protection from hepatitis B. Currently, available antiviral therapy, that directly suppression of HBV replication in the majority of patients, hepatitis B surface antigen (HBsAg) loss or seroconversion the lower range of HBsAg detection of 0.05 IU/mL, is rare in the history of Chronic Hepatitis B, Which is combined with and reduced the risk of HCC.[3]

Hepatitis C.



(Fig. 2)Hepatitis C Virus.

Hepatitis C Virus (HCV) is the most commonly spread chronic stage disease, It is a small and enveloped virus. HCV is a positive single-stranded RNA virus that was discovered in 1989 (Fig.2). The Hepatitis C Virus (HCV) is a member of the *Flaviridae* family and genus of *Hepacivirus*, HCV was transmitted into the body via bloodstream inoculation containing contaminated blood needles injected percutaneously.[5] It is also entered non-percutaneously via sexual intercourse, piercings, tattoos, organ transplantation, hemodialysis, blood transfusions, immunoglobulin injection, and religious scarification.

HCV efficaciously evades the immune system to motivate chronic hepatitis in the general public of instances, which frequently leads to superior fibrosis and cirrhosis if untreated. Even as there are not any effective vaccines for HCV prevention. The Scavenger receptor class B type I, Occludin, Claudin-I, and CD81, they are 4 host-derived elements that facilitate the access of HCV into the bloodstream. Even though it is taken into consideration a non-cytopathic virus, as soon as HCV enters the hepatocyte, it replicates and causes cell necrosis

through immune-mediated cytolysis (adaptive immunity and innate immunity) and metabolism-mediated inflammation (oxidative stress, insulin resistance, and hepatic steatosis).[5]

Hepatitis C Virus (HCV) infection is present in acute or chronic hepatitis, The acute hepatitis usually is asymtamatic and seldom leads to hepatic failure, The symtamatic acute HCV has a moderate clinical route with <25% of patients suffering from jaundice. About 60-80% of human beings with acute infection expand chronic infection. They are six primary genotypes (1-6) of HCV have been diagnosed, and they have various geographical distributions. Genotypes 1, 2, and 3 are disbursed globally with genotype 1 accounting for 40-80% of all instances. Genotype 4 was discovered in the Middle East and Egypt. Genotype 5 in South Africa, and Genotype 6 in South East Asia.[6]

EPIDEMIOLOGY

Hepatocellular carcinoma (HCC) is a prevalent form of cancer, accounting for over 5% of all cases. It is estimated that there are more than 500,000 new cases each year, with an average annual occurrence of approximately 3-4%.[7] In terms of worldwide prevalence, HCC is the fifth most common cancer overall, ranking fifth in men and eighth in women. Among digestive tract cancers, it is the second most common, following stomach cancer.

The presence of liver cirrhosis is the main risk factor for the development of HCC, regardless of its cause. Among individuals with cirrhosis, the highest risk of developing HCC is associated with viral infections and heavy alcohol consumption. Among the primary hepatitis viruses, only hepatitis B viruses are known to cause HCC. Most cases of HCC, which make up 80% of all cases, are found in sub-Saharan Africa and Eastern Asia. In these regions, the typical incidence rate is more than 20 cases per 100,000 individuals. Southern European countries like Spain, Italy, and Greece tend to have medium incidence levels, ranging from 10.0 to 20.0 cases per 100,000 individuals. On the other hand, North America, South America, Northern Europe, and Oceania have a low incidence of HCC, with 5.0 cases per 100,000 individuals.[8]

The regions in Eastern Asia have the highest risk, with rates of 27.6 to 36.6 cases per 100,000 men. Middle Africa has a risk of 20.8 to 31.1 cases per 100,000, and some Western African countries have a risk of 30 to 48 cases per 100,000. On the other hand, the regions at the lowest risk include Northern Europe, Australia, New Zealand, and the Caucasian populations

of North and Latin America, with rates of 1.5 to 3.0 cases per 100,000. In Southern Europe, the risk is around 10 cases per 100,000 men.[9]

The Role of Hepatitis B in HCC

HBV and HCV contribute to the development of cirrhosis, which is present in 80%–90% of patients with HCC. The risk of developing HCC within 5 years for individuals with cirrhosis varies between 5% and 30%, depending on the cause (highest in those with HCV infection), geographical location or ethnicity (highest in Asians), and the stage of cirrhosis (highest in those with decompensated disease).[10]

Around 5% of the global population (350–400 million individuals) has chronic HBV infection. Among the infected, 75% are of Asian descent, while the prevalence is lower (0.3%–1.5%) in Western nations.[11] There is a strong correlation between areas with high HBV prevalence and the incidence and mortality rates of HCC worldwide. Chronic HBV infection accounts for roughly 50% of all cases of HCC and almost all cases in children. It is the primary risk factor in most areas of Asia and sub-Saharan Africa with a high occurrence of HCC, except for Japan.[11]

In Asian regions with a high occurrence of HCC, the transmission of HBV infection is mostly through mother-to-child contact. The differing prevalence of HCC based on age may impact the effectiveness and outcomes of treatments such as liver transplantation. The high ratio of male to female HCC cases can be attributed, at least in part, to the higher prevalence of HBV and HCV infection among men compared to women. It is estimated that more than 90% of countries include HBV vaccination as part of routine immunization for newborns, with about 70% now administering three doses of the vaccine. Taiwan was the first country to start vaccinating newborns against HBV in 1984.[11]

Screening Test

Screening tests for hepatocellular carcinoma (HCC) in patients with chronic viral hepatitis are important, despite the known risk factors. HCC is most commonly found in patients with cirrhosis or advanced fibrosis, so studies have primarily focused on these at-risk individuals. The most frequently used tests for screening are serum alfa-fetoprotein (AFP) and hepatic ultrasound (US). A recent study conducted without randomization and with a prospective cohort design indicates that early detection of hepatocellular carcinoma (HCC) is more feasible and the probability of successful surgical removal is higher in patients who undergo

biannual screening using serum alpha-fetoprotein (AFP) and hepatic ultrasound (US). These results were compared to those who received standard care.[8]

A surveillance study of 1,125 patients with HCV, HBV, or both, combined US and AFP testing. The research found that combining a serum AFP level greater than 10 ng/mL with the US resulted in a sensitivity of 100%. In comparison, using only AFP greater than 10 ng/mL had a sensitivity of 75%, while using US alone had a sensitivity of 87%.[20] Although computed tomography and magnetic resonance imaging have high sensitivity and specificity in detecting HCC, they are too expensive for routine surveillance.[7]

MECHANISM OF HBV: Viral characteristics of HBV

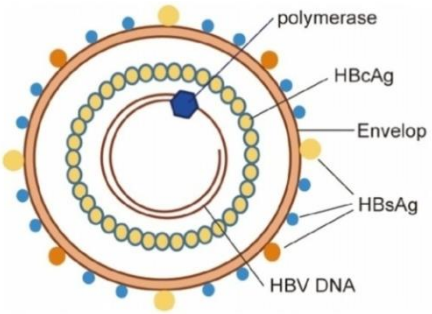


Fig. 3 Hepatitis B Virus.

HBV is a type of virus grouped as an enveloped virus in the *Hepadnaviridae* family. It possesses a genome made up of DNA that is partially double-stranded and arranged in a circular shape. It's specific to certain species and tissues. Genotypes A to J infect humans and belong to the Orthohepadnavirus genus, which includes viruses affecting other mammals such as bats, ground squirrels, or shrews.[12]

All Orthohepadnavirus members have a ~3.2 kb genome with four overlapping open reading frames (ORFs). After entering liver cells, the viral DNA is transformed from relaxed circular DNA (rcDNA) to covalently closed circular DNA (cccDNA) in the nucleus. This acts as a template for transcription into various RNAs. The cccDNA levels can rise through newly synthesized genomes, increasing the integration of viral DNA into the host genome.[13] Seven viral proteins are produced from five viral mRNAs, (Fig. 3) including core (HBcAg), polymerase (P), surface antigens (S-HBsAg), and regulatory protein (HBxAg).

General factors correlated with disease

Numerous risk factors that contribute to the progression of pathogenesis have been identified. These factors can either lead to a generalized heightened risk of cancer development or an increased susceptibility to contracting HBV. Among transmission routes, vertical transmission results in the highest rate of patients developing chronic HBV infection compared to horizontal transmission. Notably, males display a considerable bias in the risk of HCC development upon chronic infection and liver cirrhosis, possibly due to the presence of sex hormone receptors that promote HBV replication.[14]

The integration of HBV into the genome significantly contributes to genomic instability, thereby promoting the progression towards HCC. These integrated elements primarily yield HBsAg and HBx, but they are unable to generate complete viral genomes due to the absence of a circulation pathway.[15]

HBx and its viral replication

HBV is a double-stranded DNA virus in the Orthohepadnavirus genus, Hepadnaviridae family. It's classified into 10 genotypes (A-J). The HBV virion carries 3020 to 3320 nucleotides, forming relaxed circular DNA (rcDNA) within a nucleocapsid composed of hepatitis B core antigen (HBcAg). This is enveloped by a host-derived lipid bilayer with hepatitis B surface antigens (HBsAg). The genome encodes 4 genes (P, preC/C, S, X), producing 5 proteins: polymerase (P), HBcAg (C), HBeAg (preC), HBsAg (S), and X protein (X).[16]

HBx from gene X plays key roles in HBV pathogenesis, transcription, and HCC development. Infection begins as virions attach to the entry receptor NTCP on hepatocytes. Host DNA repair enzymes convert rcDNA to covalently closed circular DNA (cccDNA), which acts as a template for viral mRNAs. Synthesis of rcDNA or linear DNA occurs via reverse transcription in the nucleocapsid, maturing with HBsAg enveloping and secretion into the blood.[17] Nuclear dslDNA genomes can form replication-defective cccDNA or integrate into the host genome.[18]

The virus interacts with cell-surface receptors.

↓

The core nucleocapsid is released into the cytoplasm and then transported to the nuclear membrane.

↓

Discharge of HBV genome into the nucleus and its conversion in cccDNA.

↓

Transcription of cccDNA by the host RNA polymerase II into all viral mRNA, including pgRNA.

↓

HBV transcripts are moved into the cytoplasm, where they are translated to produce viral envelope, core, "e", polymerase, and X proteins.

↓

Assembly of nucleocapsids and synthesis of new viral DNA from pgRNA by viral reverse transcriptase.

↓

Recycling of a small portion of nucleocapsids into the nucleus to maintain a stablereservoir of cccDNA.

↓

Most nucleocapsids are coated with viral surface proteins in the endoplasmic reticulum, and then mature virions are released.

Schematic representation of the HBV life cycle main steps[19]

HBx protein and its aspect

The HBx protein, weighing 17 kDa, lacks direct genome interaction. Still, it plays a role in the HV lifecycle and HCC development.[20] It localizes in cytoplasm, nucleus, and mitochondria, affecting signal transduction, transcription, and mitochondrial function. This leads to gene transactivation and four HCC mechanisms: (1) HBx gene integration promoting genetic instability; (2) induction of oxidative stress via mitochondrial protein interactions; (3) activation of survival pathways and tumor-suppressor inactivation; (4) induction of epigenetic changes (histoneacetylation, DNA methylation, microRNA).[21] HBx modulates oncogenic pathways (MAPK/Ras/Raf/c-Jun, NF-κβ, etc.), MMPs, and catalase DNMT1. It promotes histoneacetylation/deacetylation, altering cancer gene/RNA expression. Notably, it downregulates miR-122, a liver-specific anti-tumormiRNA.[22]

HBx as a target protein for functional cure

HBx serves a key role in supporting virus gene expression and replication. The HBx protein was detected in the serum of patients with replicating HBV. Longitudinal studies indicated that HBx disappeared from the blood upon virus clearance, coinciding with the appearance of anti-HBx antibodies, following the transition from HBeAg to anti-HBe.[23] Research showed elevated levels of HBx in the liver and anti-HBx in serum among patients with liver cirrhosis and HCC compared to hepatitis patients.[22] HBx was found to trans-activate both the X (HBx) and C (core) gene promoters in vivo and in vitro, supporting HBV replication.[24] Experimental infection with a mutant lacking Woodchuck Hepatitis x antigen (WHx) failed to establish carrier states and CLD, demonstrating WHx's essential role in supporting WHV replication.[24,25] In human serum samples, naturally occurring HBx-deletion variants were discovered in HBsAg-negative patients with mild hepatitis, suggesting HBx's role in HBV replication. HBx-specific siRNAs inhibited virus replication in vitro and in vivo.[26]HBx-specific T-cell epitopes were identified, although their exact function in virus replication and CLD pathogenesis remains uncertain.[27] Recently, HBx's role in virus replication was clarified. ccc HBV DNA forms aminichromosome in cell nuclei. During virus replication, HBx is in the nucleus, associated with transcriptional complexes that support ccc HBV DNA and host gene expression related to cancer hallmarks.[28] HBx contributes to replication by increasing Ca2+ levels and activating Pyk2/Src and FAK pathways. HBx-mediated Ca2+ signaling aids viral core assembly and pregenomic RNA (pgRNA) production, essential for virus replication.[29] High HBx expression stimulates cell growth, potentially leading to G1 arrest or apoptosis among differentiated hepatocytes. Quiescent hepatocytes optimally support virus replication, balancing HBx levels and localization for effective replication. In cell nuclei, HBx interacts with the HBV minichromosome, epigenetically modifying ccc HBV DNA transcription by inhibiting histonedeacetylases.[30] HBx inactivates PRMT1, degrades WDR77, and facilitates SMC5/6 proteasomal degradation, influencing ccc HBV DNA transcription.[31,32]

SIGNS AND SYMPTOMS

- **Jaundice**

Jaundice is a condition where the skin, eyes, or mucus membranes turn yellow. It occurs when there is an excess of bilirubin, a substance produced when red blood cells break down in the liver. Jaundice is a common sign of HCC. Studies have shown that it is present in 28% of African patients at the time of HCC diagnosis, but it is less frequent in Chinese, Japanese,

or European countries. Various pathological conditions associated with HCC can explain the onset of jaundice. Jaundice can be a result of hepatic failure due to extensive tumor infiltration of a cirrhotic liver or worsening of underlying hepatitis in the presence of HCC.[33]

- **Abdominal pain, portal vein thrombosis**

Abdominal pain is a common symptom that occurs at the onset of hepatocellular carcinoma (HCC). Typically, the pain is mild and located in the right upper abdomen, and it may radiate to the right shoulder. Non-cirrhotic patients and those with portal vein thrombosis are more likely to experience abdominal pain. Portal vein thrombosis is found in 14-44% of autopsies of HCC patients. The risk of developing portal vein thrombosis is highest in patients with both cirrhosis and hepatic carcinoma. In cirrhotic patients, 18% of cases of acute abdominal pain are diagnosed as portal vein thrombosis.[34]

- **Gastrointestinal Bleeding**

Gastrointestinal bleeding can also be a manifestation of HCC, particularly bleeding from esophagealvarices. However, this presentation is not common and only occurs as the first clinical sign in 1%-8% of HCC cases. Variceal bleeding is caused by increased pressure in the portal system, which can be a result of tumor invasion or portal hypertension. The size of the tumor does not appear to be related to this type of clinical presentation. Bleeding from esophagealvarices is more frequent in HCC patients with advanced liver cirrhosis and high levels of portal hypertension.[35]

- **Hypoglycemia**

Hypoglycemia is a relatively common paraneoplastic syndrome in patients with advanced HCC, occurring in approximately 4,6-27% of cases. It is caused by the tumor's increased demand for glucose, coupled with reduced gluconeogenesis and glycogenolysis due to the decreased liver tissue, cachexia, and malnutrition often seen in these patients.[35] Hypoglycemic episodes typically occur in the weeks leading up to the patient's death.[36]

- **Hypercalcemia**

Hypercalcemia occurs in about 7-12% of patients with HCC.[37] This paraneoplastic syndrome is likely due to a PTH-like humoral factor produced by the tumor. It can also be caused by the presence ofosteolytic bone metastases. In some cases, hypercalcemia can lead to a coma that may be mistaken for hepatic encephalopathy.[38]

- **Hypercholesterolemia**

Paraneoplastic hypercholesterolemia is present in 11-20% of patients with HCC.[37] This condition is associated with a reduced expression of LDL receptors, similar to familial hypercholesterolemia.

- **Erythrocytosis**

Erythrocytosis occurs in 2-16% of patients with HCC.[37] It is characterized by higher levels of erythropoietin, which is produced by the tumor. Erythrocytosis accompanied by high levels of erythropoietin can be a rare primary presentation of HCC.[39]

- **Thrombocytosis**

Thrombocytosis is reported in 3% of HCC cases. This paraneoplastic syndrome tends to occur in younger patients (<60 years old) and is associated with larger tumors and main portal vein tumor thrombosis, which is a negative prognostic factor. Thrombocytosis in HCC is believed to be related to the production of thrombopoietin by the tumor. There have been reports of HCC cases with both thrombocytosis and acquired Von Willebrand disease.[40]

- **Diarrhea**

Another symptom that can occur in patients with HCC is watery diarrhea. The overproduction of intestinal peptides such as gastrin and vasoactive intestinal peptide (VIP) may be one possible explanation for the onset ofdiarrhea in these patients.[41]

- **Caval invasion**

If HCC spreads to the inferior vena cava, it can cause signs and symptoms of venous insufficiency. This can lead to the development of pitting edema, usually in both lower limbs from the inguinal region. The invasion of the venous system can also worsen ascites and hepatomegaly.[42]

In some cases, the tumor thrombus can extend to the right atrium, resulting in dyspnea and heart failure. When a patient shows signs and symptoms of right heart failure, such as jugular turgor, dyspnea, new onset of lower limb edema, and worsening of hepatic insufficiency, the presence of heart tumor invasion should always be suspected. However, atrial invasion can also be asymptomatic. Although rare, pulmonary embolization due to venous invasion has been reported as a primary manifestation of HCC.[41]

➢ **Feminization**

Feminization can be observed in patients with HCC, even in those without liver cirrhosis. This can be seen through clinical signs and symptoms such as gynecomastia, loss of body hair, and loss of libido. The presence of spider naevi may indicate an underlying HCC, and this finding is more commonly reported in men than in women.[43]

Nonspecific signs and symptoms

If patients at risk for this tumor present with these clinical features, it is important to suspect HCC.[41,42]

- Nausea.
- Weight loss.
- Anorexia.
- Asthenia.
- Peripheral oedemas.
- Palmer erythema.
- Spider angiomas.
- Chest hair loss.
- Hypogonadism (Testicular atrophy, Loss of libido).

PREVENTION

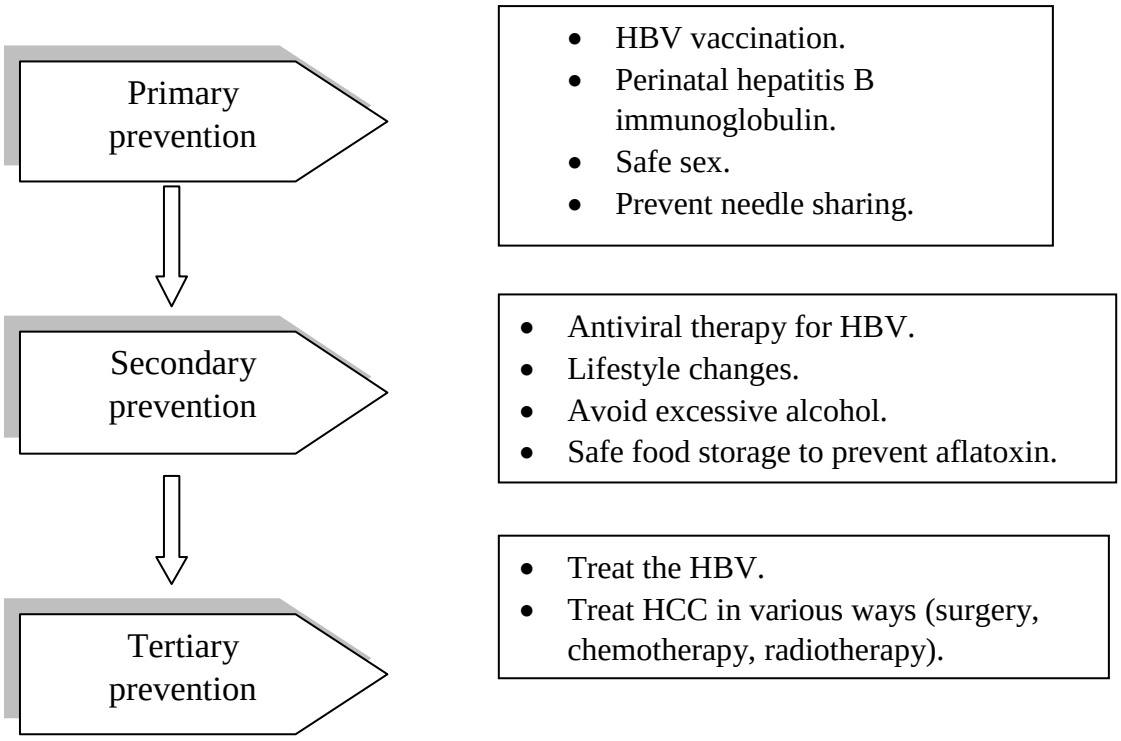


Fig. 4: Preventive strategies of hepatitis B-related HCC.[47]

The diagnosis of HCC is often made at an advanced stage, limiting treatment options and resulting in a poor prognosis. Therefore, it is urgent to develop effective preventive measures to improve patient prognosis by preventing the occurrence of HCC.[44] Preventive strategies for HBV-related HCC can be categorized into primary, secondary, and tertiary prevention (Fig. 4). The primary prevention goal is to prevent susceptible individuals from acquiring acute HBV infection. Secondary prevention focuses on providing effective treatment to control precancerous or cancerous processes in patients with chronic HBV infection. Tertiary prevention aims to provide effective treatment to reduce HCC recurrence in HBV patients who have undergone curative HCC therapy.[47]

Primary prevention

- **Vaccination**

The first HBV vaccine was created using human serum and approved by the United States Food and Drug Administration in 1981.[49] It was later replaced by a vaccine made from recombinant yeast in 1984. The vaccination is given in three doses through intramuscular injections. The first and second doses are administered 1 to 2 months apart, while the third booster dose is given 6 to 12 months later. One way to prevent viral infections is by blocking the transmission route and getting vaccinated. The hepatitis B vaccine, which is a purified hepatitis B surface antigen, is the most important method for preventing HBV infection. After receiving the vaccine, the immune system is stimulated to produce protective antibodies. By vaccinating against chronic HBV infection, the risk of HCC can be reduced by 85%.[44] However, many adults do not realize the importance of getting vaccinated for hepatitis B.

The effectiveness of the vaccine decreases with age. Since the prevalence of HBV infection is high in most middle and low-income countries, it is recommended to immunize children starting from birth. After completing all three doses of the vaccine, about 90% of healthy adults and over 95% of children will develop protective antibodies. Infants born to mothers with chronic hepatitis B receive additional protection when given hepatitis B immune globulin. Only 6% of infants who receive both the immune globulin and vaccine test positive for HBsAg, compared to 29% who only receive immune globulin, 25% who only receive the vaccine, and 88% who received no prophylaxis.[50]

The positive data from Taiwan and other countries show that universal HBV vaccination has a significant impact on reducing the prevalence of HBsAg and the incidence of HCC in

vaccinated individuals. This proves that HBV vaccination is an effective way to prevent HBV-related HCC, making it the first cancer preventive vaccine in history.[47]

- **Safe sex**

In addition to preventing transmission from mother to child, it is crucial to also prevent horizontal transmission in individuals at risk of acquiring HBV infection. Providing accurate information about safe sex, offering preventive measures, and promoting HBV vaccination are effective strategies to reduce the risk of HBV infection in groups such as people who inject drugs (PWID), homosexual men, HIV carriers, and sex workers.[47]

- **Prevent needle sharing**

Sharing needles for intravenous injection is the main risk factor for serious HBV infections. When injection equipment is not sterilized, it can lead to the spread of HBV among drug users. However, this can be prevented to a large extent through the Needle Exchange Program (NEP). The NEP is a project aimed at preventing blood-borne diseases, with a main focus on intravenous drug users who share syringes.[44] It was first implemented in the Netherlands in 1984 and has been adopted by many countries to prevent hepatitis B epidemics among drug users. A 4-year study was conducted on a population of 2,860 intravenous drug users, which found that the needle exchange program significantly reduced the risk of participating in injections. Additionally, the NEP provides services such as HBV vaccination.[44]

Secondary prevention

- **Antiviral treatment**

Antiviral treatment not only decreases the occurrence of HCC but also prevents its recurrence. The basic approach to treating HBV infection is through anti-hepatitis drug therapy, which also plays a crucial role in preventing HCC. Common anti-HBV drugs include entecavir, adefovir, tenofovir, lamivudine, telbivudine, and other nucleotide analogs (NAs). According to the 2013 Asia-Pacific Association for the Study of Liver Diseases (APASL), nucleotide drug therapy can significantly lower HBV DNA levels and decrease the risk of HCC. Administering anti-hepatitis drugs to HCC patients can also greatly enhance their chances of survival.[44]

The most recent AASLD meeting in 2019 presented four studies that examined the effectiveness of entecavir and tenofovir in reducing the risk of HCC. These studies came

from Taiwan, the United States, and Canada, and included a meta-analysis. All of the studies showed that tenofovir treatment was more successful than entecavir. If a patient with HBV infection develops liver cirrhosis or does not respond to NA treatment, there is a higher probability of HCC progression during NA treatment.[45]

During pregnancy, the main way hepatitis B is transmitted from mother to child is through mother-to-child transmission. In different countries, the preferred treatment for hepatitis B during pregnancy is tenofovir, which is an antiviral medication. The European Association for Liver Research recommends tenofovir for pregnant women who have previously received nucleoside analogue (NA) treatment. Alongside traditional antiviral medications, there are currently several drugs that can help prevent the occurrence of hepatocellularcarcinoma (HCC). Among these, aspirin, silybin, and metformin are the most extensively studied. Aspirin, which is a commonly used antiplatelet drug, can decrease the risk of HCC in individuals with hepatitis B virus (HBV). The exact mechanism by which aspirin prevents HCC is not fully understood, but it is believed to involve the inhibition of the proinflammatory enzyme cyclooxygenase 2 (COX-2). COX-2 plays a role in the development of liver cancer by promoting the production of inflammatory factors, stimulating cell growth and angiogenesis, inhibiting tumor apoptosis, and enhancing the invasion of tumor cells.[44]

- **Lifestyle Changes**

Lifestyle is an important factor in preventing HCC, with weight management and a nutritious diet being crucial. Consuming plenty of fruits and vegetables can help decrease the chances of developing HCC. It is essential to refrain from drinking alcohol and smoking, as well as to manage hypertension and diabetes with medication. Additionally, maintaining healthy levels of blood sugar and cholesterol is necessary.[46]

Tertiary Prevention

High recurrence is a major reason why the prognosis for patients with HBV-related HCC is unfavorable. After receiving curative treatment through surgical resection or local ablation therapy, the cumulative recurrence rates for early-stage HCC can reach up to 75% within 5 years. As a result, there is a clear clinical need for tertiary prevention in HBV-related HCC patients after curative treatment.[47]

Initial studies conducted on HBV-related HCC patients after curative treatment showed that those who received adjuvant IFN therapy had lower recurrence rates and improved overall

survival compared to those who did not receive it. However, a randomized controlled trial carried out in Taiwan contradicted these findings, as it showed that adjuvant IFN did not reduce post-operative recurrence for HBV-related HCC. Additionally, a meta-analysis also found that adjuvant IFN therapy following curative treatment of HCC did not reduce early or late HCC recurrence.[48] Therefore, the effectiveness of interferon-based therapies in preventing HBV-related HCC remains controversial and requires further research.[47]

CONCLUSION

Hepatitis B virus (HBV) plays a role in the progression of hepatocellular carcinoma (HCC) via both direct and indirect mechanisms. largely due to the complex actions of the HBx antigen. HBx disrupts cellular processes, triggers inflammation, and impairs DNA repair, creating a favorable environment for cancer. The integration of HBV DNA into the host genome takes place during the initial stages of clonaltumor expansion, resulting in genomic instability and direct insertional mutagenesis of various genes associated with cancer. While current treatments for HBV can reduce the risk of HCC, they do not entirely eliminate it.

Preventing hepatitis B virus (HBV) infection involves two main strategies: vaccination and adopting protective practices. The hepatitis B vaccine is highly effective and recommended for various age groups. The vaccination programs that have been expanded to the general population are proving to be highly effective in reducing the occurrence of HCC. This clearly shows that preventing HBV infection through vaccination is the most effective way to combat this dangerous threat to human health. Alongside vaccination, measures such as safe sexual practices, avoiding needle sharing, using sterile equipment, and healthcare precautions play a vital role in reducing HBV transmission. Pregnant women and high-risk individuals should seek specialized guidance. By combining vaccination and cautious habits, the spread of HBV can be significantly minimized, promoting better public health outcomes.

REFERENCES

1. Caines A, Selim R, Salgia R. The Changing Global Epidemiology ofHepatocellular Carcinoma. *Clin Liver Dis*, 2020; 24(4): 535-47. doi:10.1016/j.cld.2020.06.001.
2. Venook AP, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regionalperspective. *Oncologist*, 2010; doi:10.1634/theoncologist.2010-S4-05.

3. Hye Won Lee, Jae Seung Lee, and Sang HoonAhn. Hepatitis B Virus Cure: Targets and Future Therapies. *International Journal Of Molecular Sciences*, 2021; 22: 213 doi:https://doi.org/10.3390/ijms22010213.
4. PonsianoOcama, MD, Christopher K. Opio, MD, William M. Lee, MD. Hepatitis B Virus Infection: Current Status. *The American Journal of Medicine*, 2005; 118: 1413.e15-1413.e22 doi: 10.1016/j.amjmed.2005.06.021.
5. Matthew August Odenwald, Sonali Paul. Viral hepatitis: Past, present, and future. *World Journal of Gastroenterology*, 2022 April 14; 28(14): 1405-1429 doi: 10.3748/ wjg.v28.i14.1405.
6. Modi AA, TJ Liang. Hepatitis C: a clinical review. *Oral Disease*, 2008; 14: 10-14. doi:10.1111/j.1601-0825.2007.01419.x.
7. Llovet JM, Beaugrand M. Hepatocellular carcinoma: present status and future prospects. *J Hepatol*, 2003; 38(Suppl 1): 136-149.
8. Peter P Michielsen, Sven M Francque and Jurgen L van Dongen. Viral hepatitis and hepatocellular carcinoma. *World Journal of Surgical Oncology*, 2005; 3: 27. doi: 10.1186/1477-7819-3-27.
9. Bosch FX, Ribes J, Borras J. Epidemiology of primary livercancer. *Semin Liver Dis*, 1999; 19: 271-285.
10. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis. incidence and risk factors. *Gastroenterology*, 2004; 127(Suppl 1): S35-S50.
11. McMahon BJ, Alberts SR, Wainwright RB, et al. Hepatitis B-relatedsequelae. Prospective study in 1400 hepatitis B surface antigenpositive Alaska native carriers. *Arch Intern Med*, 1990; 150: 1051–1054.
12. Sunbul, M. Hepatitis B virus genotypes. Global distribution and clinical importance. *World J. Gastroenterol*, 2014; 20: 5427-5434.
13. Tu, T.; Budzinska, M.A.; Vondran, F.W.R.; Shackel, N.A.; Urban, S.Hepatitis B Virus DNA Integration Occur Early in the Viral Life Cycle in an In Vitro Infection Model via Sodium Taurocholate Cotransporting Polypeptide-Dependent Uptake of Enveloped Virus Particle. *J. Virol*, 2018; 92: e02007-17.
14. Wang, S.-H.; Chen, P.-J.; Yeh, S.-H. Gender disparity in chronic hepatitis B: Mechanisms of sex hormones. *J. Gastroenterol. Hepatol*, 2015; 30: 1237-1245.
15. Wooddell, C.I.; Yuen, M.-F.; Chan, H.L.-Y.; Gish, R.G.; Locarnini, S.A.; Chavez, D.; Ferrari, C.; Given, B.D.; Hamilton, J.; Kanner, S.B.; et al. RNAi-based treatment of

chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HBsAg. *Sci. Transl. Med*, 2017; 9: eaan0241.

16. Nguyen, D.H.; Ludgate, L.; Hu, J. Hepatitis B virus-cell interactions and pathogenesis. *J.Cell. Physiol*, 2008; 216: 289-294.
17. Blondot, M.L.; Bruss, V.; Kann, M. Intracellular transport and egress of hepatitis B virus. *J.Hepatol*, 2016; 64(Suppl. S1): S49-S59.
18. Yang, W.; Summers, J.Integration of hepadnavirus DNA in infected liver: Evidence for a linear precursor. *J. Virol*, 1999; 73: 9710-9717.
19. Teresa Pollicino, Carlo Saitta and Giovanni Raimondo. Hepatocellular Carcinoma: the point of view of the hepatitis B virus. *Advance Access publication.* June 10, 2011. doi: 10.1093/carcin/bgr108.
20. Ma, J.; Sun, T.; Park, S.; Shen, G.; Liu, J. The role of hepatitis B virus X protein related to its differential intracellular localization. *ActaBiochim. Biophys. Sin*, 2011; 43: 583-588.
21. Shlomai, A.; de Jong, Y.P.; Rice, C.M. Virus associated malignancies: The role of viral hepatitis in hepatocellular carcinoma. *Semin. Cancer Biol*, 2014; 26: 78-88.
22. Liang, H.W.; Wang, N.; Wang, Y.; Wang, F.; Fu, Z.; Yan, X.; Zhu, H.; Diao, W.; Chen, X.; et al. Hepatitis B virus-human chimeric transcript HBx-LINE1 promotes hepatic injury via sequestering cellular microRNA-122. *J. Hepatol*, 2016; 64: 278-291.
23. Shang, B.; Liu, Y.; Jiang, S.J.; Liu, Y. Prognostic value of tumor-infiltrating FoxP3+ regulatory T cells in cancers: A systematicreview and meta-analysis. *Sci. Rep*, 2015; 5: 15179.
24. Jung, S.Y.; Kim, Y.J. C-terminal region of HBx is crucial for mitochondrial DNA damage. *Cancer Lett*, 2013; 331: 76–83.
25. Wang, H.C.; Huang, W.; Lai, M.D.; Su, I.J. Hepatitis B virus pre-S mutants, endoplasmic reticulum stress and hepatocarcinogenesis. *Cancer Sci*, 2006; 97: 683-688.
26. Alfaiate, D.; Clement, S.; Gomes, D.; Goossens, N.; Negro, F. Chronic hepatitis D and hepatocellular carcinoma: A systematicreview and meta-analysis of observational studies. *J. Hepatol*, 2020; 73: 533–539.
27. Farci, P.; Niro, G.A.; Zamboni, F.; Diaz, G. Hepatitis D Virus and Hepatocellular Carcinoma. *Viruses*, 2021; 13: 830.
28. Omata, M.; Cheng, A.L.; Kokudo, N.; Kudo, M.; Lee, J.M.; Jia, J.; Tateishi, R.; Han, K.H.; Chawla, Y.K.; Shiina, S.; et al. Asia-Pacificclinical practice guidelines on the management of hepatocellular carcinoma: A 2017 update. *Hepatol. Int*, 2017; 11: 317–370.

29. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J. Hepatol*, 2018; 69: 182–236.
30. Heimbach, J.K.; Kulik, L.M.; Finn, R.S.; Sirlin, C.B.; Abecassis, M.M.; Roberts, L.R.; Zhu, A.X.; Murad, M.H.; Marrero, J.A. AASLDguidelines for the treatment of hepatocellular carcinoma. *Hepatology*, 2018; 67: 358–380.
31. Guo, J.; Gao, X.S. Prediction models for development of hepatocellular carcinoma in chronic hepatitis B patients. *World J. Clin. Cases*, 2021; 9: 3238–3251.
32. Wong, V.W.; Chan, S.L.; Mo, F.; Chan, T.C.; Loong, H.H.; Wong, G.L.; Lui, Y.Y.; Chan, A.T.; Sung, J.J.; Yeo, W.; et al. Clinical scoringsystem to predict hepatocellular carcinoma in chronic hepatitis B carriers. *J. Clin. Oncol*, 2010; 28: 1660–1665.
33. Lau, W, Leung, K, Leung, T. W, Liew, C. T, Chan, M. S, Yu, S. C, et al. A logical approach to hepatocellular carcinoma presenting with jaundice. *Annals of surgery*, 1997 Mar; 225(3): 281-5
34. Ogren, M, Bergqvist, D, Björck, M, Acosta, S, Eriksson, H, &Sternby, N. H. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. *World journal of gastroenterology*, 2006; Apr 7; 12(13): 2115-9.
35. Lang, B. H, Poon, R. T, Fan, S. T, & Wong, J. Outcomes of patients with hepatocellular carcinoma presenting with variceal bleeding. *The American journal of gastroenterology*, 2004 Nov; 99(11): 2158-65.
36. Sorlini, M, Benini, F, Cravarezza, P, & Romanelli, G. Hypoglycemia, an atypical early sign of hepatocellular carcinoma. *Journal of gastrointestinal cancer*, 2010; Sep; 41(3): 209-11.
37. Teniola, S. O, & Ogunleye, I. O. Paraneoplastic syndromes in primary liver cell carcinoma in Nigeria. *Tropical and geographical medicine*, 1994 Jan; 46(1): 20-2.
38. Clines, G. A. Mechanisms and treatment of hypercalcemia of malignancy. *Current opinion in endocrinology, diabetes, and obesity*, 2011 Dec; 18(6): 339-46.
39. Matsuyama, M, & Yamazaki, O. Erythrocytosis caused by an erythropoietin producing hepatocellular carcinoma. *Journal of Surgical Oncology*, 2000; May: 197-202.
40. Hwang, S-J, Luo, J-C, Li, C-P, Chu, C-W, Wu, J-C, Lai, C-R, et al. Thrombocytosis: a paraneoplastic syndrome in patients with hepatocellular carcinoma. *World journal of gastroenterology*, 2004; Sep 1; 10(17): 2472-7.
41. ValerioBarghini, Debora Donnini, Alessandro Uzzau and Giorgio Soardo. Signs and Symptoms. doi: https://dx.doi.org/10.5772/56162.

42. Ribero, D, & Morris-stiff, G V. J. Presentation and Diagnosis. Hepatocellular Carcinoma-*Lau W. Y*, 2007; 143-158.
43. Lai, C, Gregory, P, Wu, P, &Lok, A. Hepatocellular carcinoma in Chinese males andfemales. Possible causes for the male predominance. Cancer, 1987; 60(5): 1107-10.
44. Xinhe Zhang, Lin Guan, HaoyuTian, ZiluZeng, Jiayu Chen, Die Huang, Ji Sun, JiaqiGuo, Huipeng Cui and Yiling Li. Risk Factors and Prevention of Viral Hepatitis-Related Hepatocellular Carcinoma. *Frontiers in Oncology*, 2021; 11: 686962. doi: 10.3389/fonc.2021.686962.
45. Orito E, Hasebe C, Kurosaki M, Osaki Y, Joko K, Watanabe H, et al. Risk of Hepatocellular Carcinoma in Cirrhotic Hepatitis B Virus Patients DuringNucleoside/Nucleotide Analog Therapy. *Hepatol Res*, 2015; 45(8): 872–9. doi: 10.1111/hepr.12427.
46. Simon TG, Chan AT. Lifestyle and Environmental Approaches for thePrimary Prevention of Hepatocellular Carcinoma. *Clin Liver Dis*, 2020; 24(4): 549–76. doi: 10.1016/j.cld.2020.06.002.
47. C.L. Lin, J.-H. Kao. Review article: the prevention of hepatitis B-related hepatocellular carcinoma. *Aliment PharmacolTher*, 2018; 1-10. doi: 10.1111/apt.14683.
48. Zhang W, Song TQ, Zhang T, et al. Adjuvant interferon for early orlate recurrence of hepatocellular carcinoma and mortality from hepatocellular carcinoma following curative treatment: a meta-analysis with comparison of different types of hepatitis. *Mol ClinOncol*, 2014; 2: 1125-1134.
49. Vincent Wai-Sun Wong, Henry Lik-Yuen Chen. Prevention of hepatocellular carcinoma: a concise review of contemporary issues. *Annals of Hepatology*, 2012; 11(3): 284-293.
50. Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, HuangFY, Chen CL. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet*, 1983; 2: 1099-102.