Hepatocellular carcinoma (HCC) is now the seventh most common cancer in men and the ninth in women, with an estimated worldwide incidence of 0.25-1.2 million new cases per year. The coastal areas of Mainland China including Hong Kong, are high-risk areas with more than 25 cases per 100,000 population per year.

Association Between Hepatitis B Virus and HCC

Epidemiological observations clearly indicated that age, male sex, alcohol abuse, hepatitis B virus (HBV), and hepatitis C virus (HCV) and liver cirrhosis are the most important risk factors for developing HCC. Among all the related etiologic agents, HBV infection has the strongest association with HCC. It has been observed that there is close correlation between the geographic distribution of HBsAg carriers and occurrence of HCC. In endemic areas such as China where the HBsAg carrier rate is more than 10%, HCC presents an incidence of up to 150 cases per 100,000 per year. On the contrary, in nonendemic areas like the United States where the HBsAg carrier rate is less than 1%, HCC presents an incidence of less than 4 cases per 100,000 per year. A prospective study from Taiwan showed that the relative risk of HCC among HBsAg-positive men was 98 as compared with HBsAg-negative men. A recent study in Taiwanese children showed a significant decrease in the incidence of childhood HCC accompanying a decline in the prevalence of chronic HBV infection after implementation of universal vaccination of newborns.

The clinical manifestations and outcome of HBV infection depend on the level of HBV replication, the age at infection, and the immune status of the host. Chronic hepatitis B progresses across a spectrum that includes asymptomatic carriers, chronic active hepatitis, liver cirrhosis and, finally, HCC. With longer infection or more advanced liver disease, the likelihood of infected hepatocytes undergoing malignant transformation becomes progressively higher. The annual incidence of HCC is only 0.1% in asymptomatic HBsAg individuals, 1% in patients with chronic hepatitis B and 3-10% in patients with cirrhosis. This progressive risk may reflect an accumulation of multistage genetic mutations in the chromosomes of infected hepatocytes. Furthermore, persistent viral infection and the host immune response work together and contribute to the development of HCC.

Mechanisms of Hepatocarcinogenesis

Although most HCCs arise in a cirrhotic liver, in HBV-related HCC tumor can frequently develop on top of chronic active hepatitis. Hepatocyte necrosis secondary to chronic HBV infection triggers an inflammatory response with the synthesis of various cytokines. Some of them, such as tumor necrosis factor, may stimulate liver-cell proliferation during which DNA mutations and chromosomal rearrangements may be produced. Furthermore, extensive fibrosis disrupts the normal lobular structure and potentially leads to a further loss of control over cell growth.

HBV has been implicated as an oncogenic virus based on the frequent integration of HBV into HCC chromosomes. HBV-DNA integration into the host genome causes chromosomal DNA instability and rearrangement, and activation of oncogenes or tumor suppressor genes, which are critical events in carcinogenesis. One of the most important tumor
suppressor genes is p53, located on the short arm of chromosome 17. In its wild-type form p53 regulates the entry of the cell into S-phase of the cell cycle by inhibiting replicative DNA synthesis following DNA damage. Mutant p53 proteins modify growth regulatory properties and lose their ability to suppress cell transformation. Furthermore, in the animal model, the HBV X protein (HBx) has been shown to modulate both hepatocyte proliferation and viability by activating various proto-oncogenes and stimulates the transcription of vascular endothelial growth factor, which is important in angiogenesis during hepatocarcinogenesis.

**The Role of HBV in HBsAg-negative HCC**

It is generally accepted that diagnosis of HBV infection is based on serum HBsAg detection, and that disappearance of this antigen indicates HBV clearance. However recent studies have shown that HBV-DNA is frequently detected in healthy individuals with antibodies to hepatitis B core antigen (anti-HBc) and in patients with chronic liver disease who are negative for HBsAg, but positive for anti-HBc. A study from Japan showed that HBV genomes were frequently found in HCCs and adjacent liver tissue in a high proportion of HBsAg-negative patients, suggesting that the persistence of HBV genomes may play an important role in the development of HCC in HBsAg-negative patients. However, the real prevalence and clinical implication of this situation have not been defined.

**Coinfection with HBV and Other Hepatic Viruses in HCC**

Liver disease is usually more severe in patients with dual HBV and HCV infections than in patients infected with HBV alone. The coinfected patients also have a higher rate of development of HCC than patients infected by either virus alone. In a prospective study, Tsai et al. showed that the annual incidence of HCC was 2% in cirrhotic patients negative for HBsAg and HCV antibodies, 6.6% in patients with HBsAg alone, and 13.3% in HBV and HCV coinfected patients. In contrast, hepatitis D virus or hepatitis G virus superinfection does not appear to accelerate the development of HCC.

**Screening for HCC**

The rationale for screening for HCC is based on the assumptions that tumors usually begin as a single lesion, often have a long doubling time, are often encapsulated, and typically have a long asymptomatic stage and the concept that groups at high risk for developing HCC can be identified. The most commonly used screening tests are serum α-fetoprotein (AFP) and ultrasonography. Serum AFP values are greater than 20 ng/ml in up to 90% of cases of HCC. However, AFP has a low specificity, and levels may be elevated in pregnancy and germ cell tumors. In individuals with viral hepatitis who do not have HCC, AFP levels may be transiently or intermittently elevated which are parallel with elevation in transaminases. Hepatic ultrasound has a greater sensitivity and specificity than AFP when used for HCC screening. In healthy HBsAg carriers and in patients with cirrhosis, the sensitivity was 71% and 78%, respectively, and the specificity was 93%. The positive predictive value was 14% and 73%, respectively. A 6-month surveillance interval has been recommended, as it is a reasonable interval to detect tumors growing from undetectable to detectable size. A recent study from Queen Mary Hospital showed that HCC diagnosed by screening with AFP and/or ultrasound was significantly smaller and had fewer bilobar involvement, portal vein infiltration and distant metastasis when compared with symptomatic HCC. Furthermore, a prospective 16-year population-based cohort study among Alaska natives with chronic hepatitis B showed that semiannual AFP was effective in detecting most HCC tumors at a resectable stage and significantly prolonged 5- and 10-year survival rates.

**Treatment**
Surgical resection and liver transplantation are considered major modalities for treatment of HCC. Patients with hepatitis B- or C-related HCC did not present differences regarding survival or recurrences rate. The early results of liver transplantation for both hepatitis B and HCC were discouraging. It is mainly because of the rapid progressive disease of hepatitis B that resulted in death or graft loss, and the lack of selective criteria for patients with HCC. Experience has now shown that restriction of liver transplantation to patients with a single tumor less than 5cm in diameter or no more than 3 nodules (none of which is greater than 3 cm in diameter) provides excellent long-term results with the 5-year survival rate of 75%. Together with the use of continuous hepatitis B immune globulin (HBIG) alone or in combination with lamivudine, short and long-term survival of patients who undergo liver transplantation for chronic HBV infection with HCC is now similar to that of patients who undergo liver transplantation for other conditions.

**Summary**

HBV is the most important etiological factor for HCC in humans. It can induce HCC directly by activating cellular oncogenes or indirectly through chronic liver injury, which facilitates mutation. HCC screening among patients with chronic hepatitis B has proved to be useful in improving the resectability of HCC and prolonging survival. In the era of lamivudine, liver transplantation for chronic HBV infection with HCC can provide excellent long-term survival.