Published in final edited form as:
*Hepatology*. 2009 May ; 49(5 Suppl): S56–S60. doi:10.1002/hep.22962.

# Hepatitis B And Hepatocellular Carcinoma

**Adrian M. Di Bisceglie, M.D.**
Saint Louis University Liver Center, Saint Louis University, St. Louis, MO

## Abstract

Chronic infection with the hepatitis B virus has been linked epidemiologically to the development of hepatocellular carcinoma for more than 30 years. Although the mechanisms by which chronic hepatitis B viral infection results in hepatocellular carcinoma is unclear, there is good evidence that the virus itself exerts a direct hepatocarcinogenic effect thus having implications for prevention. Firstly, programs of universal infant vaccination have been shown to be effective in reducing the rate of hepatocellular carcinoma among children. This benefit should be translated into adulthood among vaccine recipients. Secondly, it has been suggested that antiviral therapy against hepatitis B may reduce the risk of hepatocellular carcinoma. Antiviral therapy against hepatitis B is effective in causing prolonged lowering of serum levels of HBV DNA. There are emerging data that prolonged antiviral therapy may reduce the risk of hepatocellular carcinoma among certain patients with chronic hepatitis B.

### Keywords

hepatitis B virus; cirrhosis; antiviral therapy; risk factors; hepatitis B virus levels

## Introduction and Historical Perspective

As early as 1970, chronic infection with the hepatitis B virus (HBV) was noted to be associated with the development of hepatocellular carcinoma (HCC) (1). Subsequent studies during the 1970's and 1980's found that more than 80% of patients with HCC in high incidence areas, such as east Asia and sub-Saharan Africa, were seropositive for hepatitis B surface antigen (HBsAg), whereas population controls typically had rates of HBsAg of between 10% and 15%. Furthermore, more than 90% of HCC cases had antibody to hepatitis B core antigen (anti-HBc) detected in serum, serological evidence of active or prior HBV infection, also present substantially more frequently than in controls. A powerful substantiation of the association between HBV infection and HCC was the results of a prospective cohort study reported by Beasley and colleagues in 1981 (2). These investigators followed more than 22,000 male municipal workers in Taiwan and found that those who were seropositive for HBsAg had rates of HCC that were highly significantly greater than were the rates in uninfected controls. They calculated the relative risk for HCC among those who were HBV-infected to be 63 compared to uninfected controls.

Address: Adrian M. Di Bisceglie M.D., FACP, Professor of Internal Medicine, Department of Internal Medicine, 3635 Vista Avenue, St. Louis, MO 63110, Telephone: (314) 577-8760, Fax: (314) 268-5108, dibiscam@slu.edu.

***Potential conflicts of interest:*** Dr Di Bisceglie has served as a consultant for Roche, Schering Plough, Gilead Sciences, Idenix, Novartis, Bristol-Myers-Squibb, Abbott and Pharmasset and has received research support from Roche, Gilead Sciences, Idenix and Pharmasset.

## Epidemiology

HCC is one of the most frequent solid tumors occurring worldwide. In 2002, the most recent year in which comprehensive data are available, the estimated number of cases of HCC that developed worldwide that year was 625,000 (3), Because of the exceedingly high mortality rate of HCC, the occurrence rate of this cancer is almost equivalent to the mortality rate. More than 80% of these cases occurred among individuals in developing countries, and the male to female ratio was approximately 2.4 to 1. In the United States, the American Cancer Society has estimated that about 18,000 deaths occurred due to cancer of the liver and intra-hepatic bile ducts (mostly HCC) in the United States in 2008, again with a strong male preponderance (4). Of some concern is that the rate of HCC deaths appears to have increased by about 40% over the period 1990 to 2004, whereas the overall rate of cancer deaths has declined by about 18% during this same period. Although much of this increase in the United States has been attributed to hepatitis C, there is speculation that it may be due in part to an increase in HBV-related HCC, particularly among immigrants to the country from endemic countries.

More recent cohort studies have confirmed the high risk of HCC in HBsAg-positive individuals as originally identified in the Beasley study. An example is the Haimen City cohort that included about 11,000 HBsAg-positive subjects followed over a mean period of 8 years (5). The relative risk of HCC in HBsAg-positive persons compared to HBsAg-negative controls was 18.8 for men and 33.2 for women. Interestingly, a long-term follow up study of apparently healthy blood donors in Italy found that only 0.6% developed HCC over an average period of follow up of 29 years (6). This rate was no different than the 0.6% rate of HCC in group of HBsAg-negative blood donor controls followed for a similar period of time. The reason for this apparently lower risk of HCC is not known, but may be due to the western cohort having milder, inactive hepatitis B than the typical Asian cohorts. Furthermore, in western populations hepatitis B is usually acquired during adolescence or adulthood commonly through sexual contact rather than in infancy from maternal-infant spread. These differences in epidemiology may modulate the risk of HCC.

## Risk factors for HCC

Known risk factors for HCC include chronic viral hepatitis, cirrhosis, heavy alcoholism, non-alcoholic fatty liver disease and certain inherited metabolic conditions such as hemochromatosis and alpha-1-antitrypsin deficiency. The proportion of cases of HCC associated with these risk factors has been estimated. In Africa and East Asia, the largest attributable fraction is due to hepatitis B (60%), whereas in the developed western world, approximately 20% of cases can be attributed to HBV infection (7).

In a retrospective survey of cases of HCC referred to 13 liver disease centers in the United States, 700 cases were identified, 20.1% of which were seropositive for HBsAg (including 4.7% who were also seropositive for antibody to hepatitis C virus) (8). Interestingly, among Asians, 55.1% had HBsAg, compared to only 9.2% among whites, while African Americans had intermediate rates of HBsAg-positivity. Many of the Asians with HBV-related HCC were foreign born. These findings highlight the heterogeneity of patients with HCC in the United States.

## Pathogenesis

The mechanism by which HBV infection causes HCC is not completely known (reviewed in (9), Table 1). Evolution to HCC may be the direct effect of the virus itself, or it may be an indirect effect, through the process of the inflammation, regeneration and fibrosis associated with cirrhosis due to the HBV infection. HBV DNA has been shown to become integrated

within the chromosomes of infected hepatocytes, the integration of viral genetic material occuring in a critical location within the cellular genome. For example, integration of HBV DNA has been observed within the retinoic acid receptor alpha gene and within the human cyclin A gene, both playing crucial roles in cellular growth. However, in many if not most cases, the HBV DNA integration site does not appear to be in a critical location and the process appears to be random. Furthermore, the length and the components in the HBV DNA integrant varies considerably and the viral DNA may be rearranged, deleted or present in repeats (10). These findings suggest that it is not the process of integration itself that leads to HCC.

The hepatitis B x gene (HBx) product has been implicated in causing HCC because it is a transcriptional activator of various cellular genes associated with growth control (11). The HBx gene expression is also associated with activation of the Ras-Raf-MAP kinase pathway, an important cellular pathway that has been implicated in hepatocarcinogenesis. In addition, HBx has been found to interact with p53, interfering with its function as a tumor suppressor. Another viral gene product that has been implicated in causing HCC is the truncated HBsAg gene product, although the mechanism by which this might result in HCC is not clear.

In keeping with the suggestion that HCC may be directly related to HBV infection, is the observation from several studies that elevated serum levels of HBV DNA (a marker of higher levels of HBV replication) are associated with a higher risk of HCC (12-15). A recent longitudinal study of 3,653 HBsAg-positive subjects in Taiwan found that an elevated serum level of HBV DNA (>10,000 copies/mL; ~ 2000 IU/mL) at baseline was a strong predictor of subsequent development of HCC, independent of serum hepatitis B e antigen (HBeAg) status, serum aminotransferases levels or the presence of cirrhosis (15). Although these data were compelling, serial measurements of serum HBV DNA levels were not available from the cohort. Thus, data are lacking on the impact of persistently high versus changing or fluctuating serum HBV DNA levels.

Another line of evidence suggesting a direct hepatocarcinogenic role of HBV is the association of certain genotypes with higher rates of HCC (16). Thus, in Asian cohorts, HBV genotype C is generally thought to increase the risk of HCC above that of genotype B. It has been speculated that this may be because patients infected with genotype C are likely to remain seropositive for HBeAg for longer periods and thus have higher serum levels of HBV DNA for a greater period of time. However, studies in other populations have found genotype B or even F to be more strongly associated with HCC (17). Thus the exact role of HBV genotype in hepatocarcinogenesis remains to be clarified.

Consistent with the hypothesis that HBV-related HCC may occur indirectly, via cirrhosis, is the observation that approximately 70% of cases of HBV-related HCC occur in association with cirrhosis, although the rate of cirrhosis appears to be lower in younger patients with HCC (18). Cirrhosis independent of its cause (alcohol, hepatitis C, metabolic errors) is associated with a high rate of HCC. Thus, the high rate of HCC in persons with chronic HBV infection may merely reflect the fact that hepatitis C is a common cause of cirrhosis.

## Animal models

HBV is a member of the hepadnavirus family, that includes several rodent and avian viruses such as the woodchuck hepatitis virus (WHV), the ground squirrel hepatitis virus and the duck hepatitis virus (DHBV) (19) Each of these agents may result in chronic infection, but only WHV is consistently associated with the development of HCC. Thus, data derived from woodchucks experimentally infected with WHV indicates that almost all animals with chronic infection will develop HCC after approximately 3 to 4 years of life whereas the the cancer is not found in animals that have never been infected (20). Interestingly, ducks

chronically infected with DHBV do not appear to be at high risk of HCC. The difference in HCC risk between woodchucks and ducks with chronic hepadnavirus infection may be due to the fact that the DHBV lacks the HBx gene or similar analogue, providing further supporting evidence for a role of the HBx gene product in hepatocarcinogenesis.

## Screening and Surveillance for HCC

Because individuals with chronic HBV infection can be readily identified, and because they are known to be at risk for HCC, surveillance programs have become instituted as a means to identify HCC at an early stage, when more treatment options are available. An example is a surveillance program for HBsAg-positive persons in Alaska that has now been in existence for several decades (21). Experience with this program has shown that HCC can be routinely detected at an early stage which has led to a improved patient survival compared to the era before surveillance (22).

The American Association for the Study of Liver Disease (AASLD) has promulgated recommendations for screening of HBsAg-positive individuals in a practice guideline published in 2005 (23). Essentially, HBsAg-positive patients with active liver disease, or who are older or have a family history of HCC, are recommended for regular surveillance with ultrasound examination every 6 to 12 months (Table 2).

## Prevention

Considerable progress has been made in the prevention of HBV-related HCC, specifically through the implementation of large-scale programs of vaccination against hepatitis B. Thus, many countries have introduced universal infant vaccination, particularly in regions where there is a high incidence of HCC. One of the best examples is in Taiwan, where universal infant vaccination was introduced in the mid-1980s. This national program has been shown to be associated with a decrease in the rate of HBsAg-positivity among children and infants, from nearly 10% in 1984 to only 1.3% in 1994 (24,25). In conjunction with this decrease in hepatitis B, there has been a significant reduction in the incidence of childhood HCC, much of which was HBV-related. Thus, the rate of childhood HCC (between the ages of 6 and 14 years) was 0.7 per 100,000 population in the early 1980s, prior to the introduction of the vaccine, whereas between 1996 and 1999, it had fallen to 0.19 per 100,000 population (24,25). It is reasonable to expect that as these vaccinated children grow into adulthood, they will remain protected against hepatitis B and the risk of HCC. Similar success is also likely in the other countries that have introduced universal infant vaccination. Some barriers to full implementation of a policy of universal infant vaccination against hepatitis B in under-developed countries include the cost of the vaccine, the availability of health programs to deliver the vaccine and technical issues such as the lack of a reliable refrigeration in areas where the vaccine is administered.

The other main approach to preventing HBV-related HCC is antiviral therapy of hepatitis B. The risk of developing HCC appears to be greatest among individuals with the highest serum levels of HBV DNA. From these findings it follows that the risk of HCC might be reduced by therapy which successfully lowers HBV DNA levels. The introduction of the nucleoside analogues as therapy of chronic hepatitis B has provided a safe and effective means of accomplishing this outcome. The largest and most compelling study suggesting that antiviral treatment might decrease the risk of HCC was a randomized, controlled trial of lamivudine versus placebo in patients with advanced chronic hepatitis B and high serum levels of HBV DNA (26). The primary outcome of the study was progression of liver disease, including an increase in Child-Pugh score, bleeding from esophageal varices and the development of HCC. The study was halted early because of an excess of serious outcomes among the placebo recipients. Indeed, the rate of HCC by that time was 3.9%

among lamivudine recipients versus 7.4% among placebo recipients, a difference that approaced statistical significance (p=0.047).

## Summary and Needs for Future Research

HBV is the single most common cause of HCC worldwide. HBV-related HCC is most common in developing countries, particularly in the Far East 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.

The most important challenges remaining in the area of hepatitis B and HCC are development of improved means of early detection and treatment. Currently, HBV-related HCC is often detected late, at a time that surgical interventions and liver transplantation is no longer feasible. Inexpensive, easily applied and non-invasive biomarkers for HCC in high risk patients would be helpful in identifying patients at a stage that the tumor can be resected or more successfully treated. Better imaging methods that reliably separated small HCCs from regenerative nodules (that are common in patients with cirrhosis) would complement screening using biomarkers. Therapies for HCC are also critically needed. Standard cancer chemotherapy is largely ineffective against HCC and newer, non-cytolytic approaches are now becoming practical and are of great promise. Finally, better approaches of 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 this important form of cancer.

## Acknowledgments

***Financial Support:*** Dr Di Bisceglie is supported by grants and contracts from NIAID (1R21AI076834-01) and NIDDK (1U01 DK082871-01 and NO1-DK-9-2324).

## References

1. Sherlock S, Fox R, Niazi S, Scheuer P. Chronic liver disease and primary liver-cell cancer with hepatitis-associated (Australia) antigen in serum. Lancet. 1970; i:1243–1247. [PubMed: 4192492]
2. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus: A prospective study of 22,707 men in Taiwan. Lancet. 1981; ii:1129–1133. [PubMed: 6118576]
3. Parkin D, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. International Journal of Cancer. 2001; 94:153–156.
4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun M. Cancer Statistics, 2008. CA. A cancer journal for clinicians. 2008; 58:71–96. [PubMed: 18287387]
5. Evans A, Chen GH, Ross E, Shen FM, Lin WY, London W. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality. risk factors, and gender differences. Cancer Epidemiology, Biomarkers & Prevention. 2002; 11:369–376.
6. Manno M, Camma C, Schepis F, Bassi F, Gelmini R, Giannini F, Miselli F, et al. Natural history of chronic HBV carriers in Northern Italy: Morbidity and mortality after 30 years. Gastroenterology. 2004; 127:756–763. [PubMed: 15362032]
7. Parkin DM. The global health burden of infection-associated cancers in the year 2002. International Journal of Cancer. 2006; 118:3030–44.

8. Di Bisceglie A, Lyra A, Schwartz M, Reddy R, Martin P, Gores G, Lok A, et al. Hepatitis C-related hepatocellular carcinoma in the United States: influence of ethnic status. American Journal of Gastroenterology. 2003; 98:2060–2063. [PubMed: 14499788]
9. Blum HE, Moradpour D, Blum HE, Moradpour D. Viral pathogenesis of hepatocellular carcinoma. Journal of Gastroenterology & Hepatology. 2002; 17 3:S413–420. [PubMed: 12472973]
10. Kew MC, Miller RH, Chen HS, Tennant BC, Purcell RH. Mutant woodchuck hepatitis virus genomes from virions resemble rearranged hepadnaviral integrants in hepatocellular carcinoma. Proceedings of the National Academy of Sciences of the United States of America. 1993; 90:10211–5. [PubMed: 8234278]
11. Muroyama R, Kato N, Yoshida H, Otsuka M, Moriyama M, Wang Y, Shao RX, Dharel N, Tanaka Y, Ohta M, Tateishi R, Shiina S, Tatsukawa M, Fukai K, Imazeki F, Yokosuka O, Shiratori Y, Omata M. Nucleotide change of codon 38 in the X gene of hepatitis B virus genotype C is associated with an increased risk of hepatocellular carcinoma. Journal of Hepatology. 2006; 45:805–12. [PubMed: 17050029]
12. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao C, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med. 2002; 347:168–174. [PubMed: 12124405]
13. Tang B, Kruger W, Chen GH, Shen FM, Lin W, Mboup S, London W, et al. Hepatitis B viremia is associated with increased risk of hepatocellular carcinoma in chronic carriers. Journal of Medical Virology. 2004; 72:35–40. [PubMed: 14635008]
14. Ohkubo K, Kato Y, Ichikawa T, Kajiya Y, Takeda Y, Higashi S, Hamasaki K, et al. Viral load is a significant prognostic factor for hepatitis B virus-associated hepatocellular carcinoma. Cancer. 2002; 94:2663–2668. [PubMed: 12173334]
15. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006; 295:65–73. [PubMed: 16391218]
16. Ding X, Mizokami M, Yao G, Xu B, Orito E, Ueda R, et al. Hepatitis B virus genotype distribution among chronic hepatitis B virus carriers in Shanghai, China. Intervirology. 2001; 44:43–47. [PubMed: 11223719]
17. Livingston S, Simonetti J, McMahon B, Bulkow L, Hurlburt K, Homan C, Snowball M, et al. Hepatitis B virus genotypes in Alaska native people with hepatocellular carcinoma: Preponderance of genotype F. Journal of Infectious Diseases. 2007; 195
18. Kew MC, Hodkinson J, Paterson AC, Song E. Hepatitis-B virus infection in black children with hepatocellular carcinoma. Journal of Medical Virology. 1982; 9:201–7. [PubMed: 6284871]
19. Robinson WS. Molecular events in the pathogenesis of hepadnavirus-associated hepatocellular carcinoma. Annual Review of Medicine. 1994; 45:297–323.
20. Tennant BC, Toshkov IA, Peek SF, Jacob JR, Menne S, Hornbuckle WE, Schinazi RD, Korba BE, Cote PJ, Gerin JL. Hepatocellular carcinoma in the woodchuck model of hepatitis B virus infection. Gastroenterology. 2004; 127(5 Suppl 1):S283–93. [PubMed: 15508096]
21. Heyward W, Lanier A, McMahon B, Fitzgerlad M, Kilkenny S, Paprocki T. Early detection of primary hepatocellular carcinoma. Screening for primary hepatocellular carcinoma among persons infected with hepatitis B virus. JAMA. 1985; 254:613–616.
22. McMahon BJ, Bulkow L, Harpster A, Snowball M, Lanier A, Sacco F, Dunaway E, Williams J. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology. 2000; 32:842–6. [PubMed: 11003632]
23. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005; 42:1208–1236. [PubMed: 16250051]
24. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. New England Journal of Medicine. 1997; 336:1855–1859. [PubMed: 9197213]
25. Chang MH, Chen TH, Hsu HM, Wu TC, Kong MS, Liang DC, Ni YH, et al. Prevention of hepatocellular carcinoma by universal vaccination against hepatitis B virus: the effect and problems. Clinical Cancer Research. 2005; 11:7953–7957. [PubMed: 16278421]

26. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. New England Journal of Medicine. 2004; 351:1521–1531. [PubMed: 15470215]

## Abbreviations

| | |
|---|---|
| **HBV** | hepatitis B virus |
| **HCC** | hepatocellular carcinoma |
| **HBsAg** | hepatitis B surface antigen |
| **anti-HBc** | antibody to hepatitis B core antigen |
| **HBx** | hepatitis B x protein |
| **(HBeAg)** | hepatitis B e antigen |
| **WHV** | woodchuck hepatitis virus |
| **DHBV** | duck hepatitis B virus |
| **AASLD** | American Association for the Study of Liver Disease |

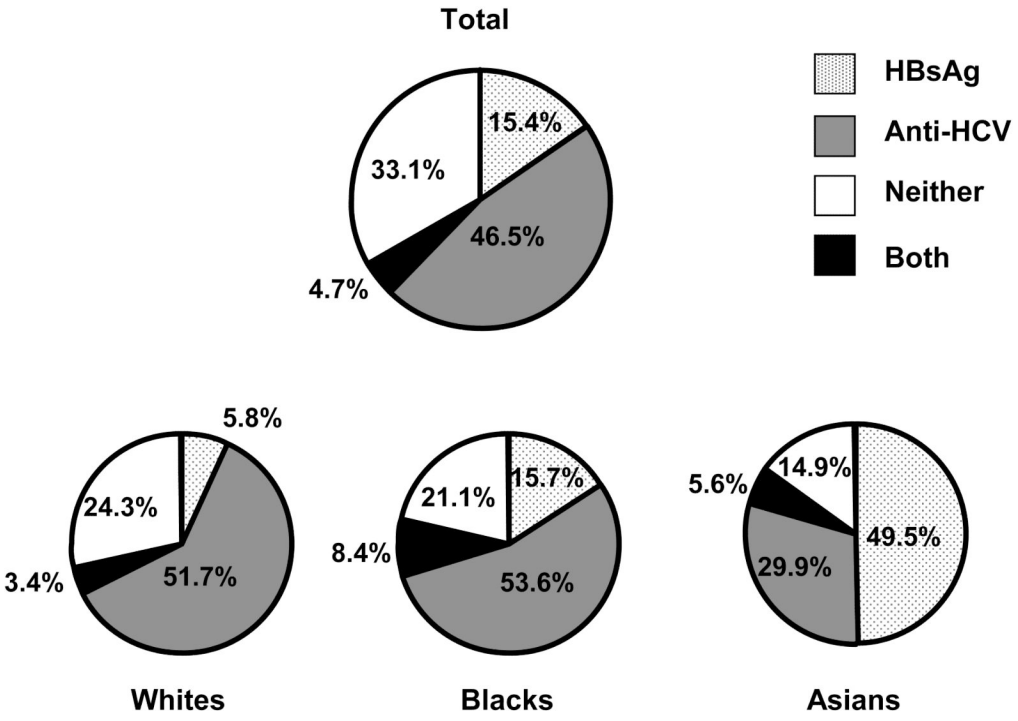


**Figure 1. Etiology of HCC in the United States. Survey of 691 patients with HCC from 13 referral centers (8)**

**Table 1**
**Possible mechanisms of HBV-Induced HCC (9)**

| |
|---|
| Direct |
| Integration of HBV DNA into chromosomes of hepatocytes |
| • Integration within or near functional cellular genes |
| HBx protein |
| • HBx is a transcriptional activator |
| • Activates the Ras-Raf-MAPK pathway |
| • Interacts with p53, a tumor suppressor |
| Truncated HBsAg gene product is a transactivator |
| Indirect |
| Inflammation and regeneration associated with chronic HBV infection |
| Via cirrhosis associated with chronic HBV infection |

**Table 2**
**AASLD Recommendations for HCC surveillance among HBsAg carriers (23)**

| |
|---|
| Asian males over the age of 40 years |
| Asian females over the age of 50 years |
| All cirrhotics who are seropositive for HBsAg |
| Those with a family history of HCC |
| Those born in Africa and who are over the age of 20 years |
| Patients with high serum levels of HBV DNA and ongoing hepatic injury |