

## **Chronic Viral Hepatitis and Liver Cancer**

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Most cases of liver cancer (hepatocellular carcinoma, HCC) are now known to be the result of chronic infection with the hepatitis B virus, the hepatitis C virus or a combination of these agents. In China, Southeast Asia, sub-Saharan Africa and southern Europe, the infection with the hepatitis B virus is the primary underlying cause whereas in Japan, the United States, most of Europe and the rest of the world, the hepatitis C virus is the predominant infectious agent able to induce this kind of cancer. The progression from infection to cancer generally goes through a silent acute phase, followed by chronic inflammation, progressive fibrosis and cirrhosis. Neither of the two viruses appear to be directly oncogenic, but the inflammatory microenvironment and the high level of genetic mutation that accompanies the evolution of cirrhosis are thought to facilitate the development of cancer. Alcoholism and other diseases that affect the liver, like hemochromatosis and non-alcoholic steatohepatitis, also can induce cirrhosis and HCC and may accelerate progression when they coexist with chronic hepatitis virus infection.

The longer the duration of infection, the more likely is the development of HCC. The majority of hepatocellular carcinoma related to infection with the hepatitis B virus occurs in adults who were infected at birth from a carrier mother. In contrast, infection with the hepatitis C virus is more frequent in young adulthood, through drug-related shared-needle usage and rarely, sexual transmission. Infection through contaminated blood transfusions, once responsible for about 30% of cases, is now reduced to almost zero, due to the development of effective donor screening procedures. Both viral infections smolder usually for three or more decades before evolving into cancer. This is well demonstrated by the contrasting incidence of this kind of cancer in the US and Japan. Although both countries have a similar prevalence of infection with the hepatitis C virus, Japan has an 8-10 fold higher rate of hepatocellular carcinoma. Molecular clock studies now show that the predominant hepatitis C virus strain in Japan emerged and spread approximately 30 years before the most common strain in the US started to spread. These time differences suggest that the Japanese have been infected with the hepatitis C virus, on average, 30 years longer than Americans, and predicts that the rate of hepatocellular carcinoma in the US, and probably Europe as well, will increase dramatically over the next 2-3 decades (this concept is already being substantiated as the rate of hepatocellular carcinoma related to the hepatitis C virus has already increased 3 fold in the US since 1980).

Once hepatocellular carcinoma develops, small tumors (<3cm) can be treated by injection of alcohol or other toxins or with radiofrequency ablation. Larger masses that have not metastasized can be treated by surgical resection of the involved segment or lobe with or without chemotherapy. Unresectable lesions require liver transplantation. While treatments for this kind of cancer have improved, the primary intervention is prevention. For hepatitis B virus, prevention is achieved by administering hepatitis B vaccine at birth, particularly in endemic regions. In non-endemic areas that do not have universal infant administration, vaccine should be given before early adolescence to prevent acquisition through sexual exposure. There is no vaccine for hepatitis C virus currently available, but treatment for chronic hepatitis C is increasingly effective, with "cure" rates ranging from 45-50% to near 80% depending on viral genotype, and novel therapies are projected to increase cure rates significantly. It is thus essential to identify as soon as possible asymptomatic, infected persons with hepatitis C virus, so that they can be treated before cirrhosis and cancer ensue.