

Chronic Viral Hepatitis and Liver Cancer

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Most cases of hepatocellular carcinoma (HCC) are now known to be the result of chronic infection with the hepatitis B virus (HBV), the hepatitis C virus (HCV) or a combination of these agents. In China, Southeast Asia, sub-Saharan Africa and southern Europe, HBV infection is the primary underlying etiology whereas in Japan, the United States, most of Europe and the rest of the world, HCV-induced HCC predominates. Progression from a generally silent acute infection to HCC transitions through chronic inflammation, progressive fibrosis and cirrhosis. Although HCC can occur in the absence of cirrhosis, the high mutation rate that accompanies compensatory liver regeneration during the evolution of cirrhosis is felt to facilitate random induction of oncogenes. HBV and HCV do not appear to be directly oncogenic. Alcoholism, hemochromatosis and non-alcoholic steatohepatitis (NASH) can induce cirrhosis on their own, but also confound virus-induced cirrhosis and HCC.

One of the main determinants of HCC development is duration of infection. Hence, the majority of HBV-related HCC occurs in adults who were infected at birth from a HBV carrier mother. In contrast, HCV is rarely transmitted perinatally, but rather comes from percutaneous exposures in young adulthood. These infections then smolder for three or more decades before evolving to HCC. This is well demonstrated by contrasting HCC incidence in the US and Japan. Although both countries have a similar prevalence of HCV infection, Japan has an 8-10 fold higher rate of HCC. Molecular clock studies now show that HCV genotype 1B infection, the predominant genotype in Japan, entered that population approximately 30 years before HCV genotype 1A emerged in the US. Further, HCV type 1B began to spread rapidly in Japan from 1930-1950 whereas HCV 1A spread rapidly in the US from 1960-1980. These intervals suggest that the Japanese have been infected with HCV, on average, 30 years longer than Americans and predicts that the rate of HCC 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 HCV-related HCC has already increased 3 fold in the US since 1980. .

Once HCC 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 resection of the involved segment or lobe with or without systemic chemotherapy or hepatic perfusion chemotherapy. Unresectable lesions require liver transplantation. While treatments for HCC have improved, the primary intervention is prevention. For HBV, 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 cure for HCV currently available, but treatment for chronic hepatitis C is increasingly effective, with "cure" rates now at 45-50% for the least sensitive genotypes and near 80% for genotypes 2 and 3. New therapies with HCV-specific protease and/or helicase inhibitors are projected to increase cure rates to 70% for patients with genotype 1 infection. It is thus essential to now identify asymptomatic, HCV-infected persons with hepatic fibrosis so that they can be treated before cirrhosis and HCC ensue.