Risk Factors for Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide, and each year, approximately 750,000 new cases are diagnosed.[1] Surveillance strategies for patients with cirrhosis, who have an HCC incidence of 1.5% to 6%/year, can lead to a 3 to 9 month increase in mean life expectancy.[2] As the incidence of liver cancer continues to rise, effective surveillance programs are necessary in order to maximize patient outcomes. Symptomatic advanced-stage HCC has dismal outcomes (5-year life expectancy $<$ 10%). In comparison, liver cancer identified before the onset of symptoms is more amenable to treatment, with 5-year survival rates greater than 50% for both resection and liver transplantation.[2] For surveillance programs to be effective in maximizing life expectancy outcomes, identifying risk factors for HCC is essential.

The single largest risk factor in the development of HCC is cirrhosis of any etiology, which is present in 70% to 90% of those who have primary liver cancer[3] (Table 1). Following this, hepatitis B virus (HBV) infection is a significant predisposing factor for the development of HCC and accounts for more than 50% of all cases[4] (Table 1). The relative risk of tumor development is 100-fold for those who are infected with HBV versus those who are not infected. The risk is even higher for those with an HBV infection and cirrhosis.[2] A longer duration of infection and an increased degree of viremia also increase the rate of occurrence.[5] Males are at greater risk than females, and incidence rates peak in males who are older (65-75 years).[6] HCC is more likely to develop in ethnic groups native to regions of East Asia and sub-Saharan Africa.[3] African males commonly contract HBV at a younger age, and this significantly increases their risk for developing liver cancer. HBV genotypes A and D are most prevalent in African populations; reports indicate that infection by the former is associated with an increased rate of HCC.[7] Predominantly infecting Asians, HBV genotype C is associated with a higher risk of liver cancer than genotype B.[2] A family history of liver cancer, particularly among first-degree relatives, in HBV-infected individuals has been shown to increase the incidence of HCC. This finding is most prevalent among siblings.[8]

In Japan, the United States, Latin America, and Europe, hepatitis C virus (HCV)–associated cirrhosis is the major cause of HCC[6] with an estimated annual HCC incidence of 2% to 8%.[2,6] The development of liver cancer is considerably lower in noncirrhotic HCV patients versus patients with HCV and cirrhosis, and current guidelines on surveillance do not recommend surveillance in those without cirrhosis.[2] Coinfection with human immunodeficiency virus (HIV) or HBV increases an individual's likelihood of developing liver cancer.[2,7]

Other notable causes of cirrhosis can increase the risk for the development of HCC (Table 2). Patients with genetic hemochromatosis are susceptible to developing cirrhosis. For those in whom cirrhosis is established, the relative risk for liver cancer is approximately 20-fold higher. The incidence of liver cancer in individuals with stage 4 primary biliary cirrhosis is similar to the incidence in patients with HCV and cirrhosis, and this suggests that primary biliary cirrhosis confers a high risk for HCC.[2] Patients with autoimmune hepatitis and cirrhosis also have an increased incidence of liver cancer.[2,6] Cirrhosis related to nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) has been found to increase an individual's risk for HCC. Liver cancer mortality rates in the United States have been reported to be 5 times as great among men with a very high body mass index (35-40 kg/m^2) versus men with a normal body mass index.[3] Individuals with diabetes mellitus have an approximately 2-fold increased incidence of HCC.[3]

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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TABLE 1: Viral Predisposing Conditions for the Development of HCC

HBV	HCV
Cirrhosis	Cirrhosis
Noncirrhosis	
Longer duration of infection	HIV/HBV coinfection
Increased degree of viremia	
East Asian ethnicities	
Sub-Saharan Africa ethnicities	
African males	
Genotype A (prevalent among Africans)	
Genotype C (prevalent among Asians)	
Family history of HCC	

TABLE 2: Nonviral Cirrhosis-Related Factors and Environmental Factors That Can Lead to the Development of HCC

Cirrhosis-Related Risk Factors	Environmental Risk Factors
Genetic hemochromatosis	Heavy alcohol consumption
Autoimmune liver disease	Cigarette smoking
Primary biliary cirrhosis	Aflatoxin exposure
Autoimmune hepatitis	
Hereditary tyrosinemia	
Alpha-1-antitrypsin deficiency	
NAFLD/NASH	
Obesity	
Diabetes mellitus	

HCC is rare among adolescents and accounts for less than 1% of all malignant neoplasms among children younger than 20 years.[9] Hence, the risk factors are not well studied. Despite this, inherited metabolic disorders---specifically hereditary tyrosinemia, alpha-1-antitrypsin deficiency, and glycogen storage disease type 1---are associated with childhood cirrhosis and HCC.[10] To a lesser degree, primary liver cancer also develops in children with a bile salt export pump deficiency and biliary atresia.[9,11] Because of the infrequency of HCC cases, no guidelines on surveillance in children can be recommended.

Environmental and acquired factors can increase an individual's likelihood of developing liver cancer (Table 2). Heavy alcohol consumption can lead to the development of cirrhosis, which in turn increases the risk for HCC.[2] Cigarette smoking is becoming more recognized as a potential factor in the development of liver cancer. The relative risk for liver cancer is 1.51 for current smokers versus those who have never smoked. A potential link between smoking and HCC is further suggested by the fact that DNA adducts of 4-aminobiphenyl and polycyclic aromatic hydrocarbons are human carcinogens derived from cigarette smoke that cause liver tumors in experimental animals.[12] Exposure to aflatoxin, a group of fungal metabolites produced by *Aspergillus flavus* growing on food stored improperly, is common in sub-Saharan Africa and regions of East and Southeast Asia and has been found to be a predisposing factor for HCC. The high rate of HBV infection in these regions adds to this risk.[13] Proper education and prevention practices potentially will reduce the role of these factors in the development of liver cancer.

TABLE 3: Relative Risk and Incidence of Developing HCC by Group

Population Groups	Incidence of HCC
Cirrhotic HBV carriers	3%-8%/year
HCV cirrhosis	3%-5%/year
Stage 4 primary biliary cirrhosis	3%-5%/year
Genetic hemochromatosis and cirrhosis	Unknown but probably >1.5%/year
Other cirrhosis	Unknown
Male Asian HBV carriers older than 40 years	0.4%-0.6%/year
Female Asian HBV carriers older than 50 years	0.3%-0.6%/year
HBV carriers with a family history of HCC	Higher than incidence without a family history
African/North American blacks with HBV	HCC occurs at a younger age.

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In conclusion, cirrhosis arising from any etiology is a primary risk factor for HCC. Independently of the presence of cirrhosis, HBV infection increases the danger, whereas liver cancer against the background of HCV infection is almost exclusively seen in those with advanced fibrosis and cirrhosis. An emerging risk factor for HCC, at least in the Western world, appears to be cirrhosis secondary to NAFLD. Additionally, there has been a higher rate of cancer in those with diabetes, and it is unclear whether this is mediated via NAFLD-related cirrhosis or is independent of the presence of liver disease. Patients at risk from preventable environmental factors such as alcohol abuse, smoking, and aflatoxin exposure should be educated on relevant risk-reducing practices. An awareness of the factors that potentially can increase the occurrence of liver cancer should help in proper education and in the implementation of cost-effective surveillance strategies for the early detection of HCC, which can lead to interventions with effective treatment strategies and potentially reduce mortality rates (Table 3). ■

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