# REVIEWS

# Hepatocellular Carcinoma: Overcoming Challenges in Disease Management

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**Hepatocellular carcinoma is the third most frequent cause of death from cancer and the eighth most commonly occurring cancer in the world. In the United States, hepatocellular carcinoma appears to be increasing along with evolution of chronic hepatitis infection, especially in the immigrant population, a major risk group. A disease of multifactorial etiology, hepatocellular carcinoma confers many management challenges. Hepatocarcinogenesis is a multistep process involving different genetic alterations that ultimately lead to malignant transformation of the hepatocyte. Early hepatocellular carcinoma is characteristically silent and slow growing with few symptoms until late in disease. Early and accurate diagnosis of hepatic tumors relies on clinical suspicion, screening protocols, serologic testing, radiologic imaging, and tissue confirmation. Lack of clinically validated biomarkers and clinical identification of hepatocellular carcinoma at advanced disease make diagnosis and treatment difficult. Advances in computed tomography and magnetic resonance imaging have markedly increased the sensitivity and specificity of testing, yet they are still flawed with a relatively high false-positive rate. Several surgical and nonsurgical therapies have been developed and used with varying degrees of success. Options include surgical resection, liver transplantation, local ablation therapies, and pharmaceutical interventions. At 5 years after resection, in those patients who are surgical candidates, the recurrence rate ranges between 30% and 60%. In patients with nonresectable disease, the prognosis is dismal, with a median survival of less than 12 months even with chemotherapy. The medical community faces numerous challenges in hepatocellular carcinoma and must work toward better management and multidisciplinary care of this complex disease.**

Hepatocellular carcinoma (HCC) is a leading solid organ malignancy in the world as a result of the high prevalence of chronic liver damage caused by hepatitis or cirrhosis. A malignancy of worldwide significance, HCC has become increasingly important in the United States likely because of complex factors involving a growing awareness of hepatitis C virus (HCV) and the evolution of this disease to cirrhosis as well as an increase in prevalence of hepatitis B virus (HBV) as a result of immigration patterns. A disease of multifactorial etiology, HCC confers many management challenges including variable morphology, poor prognosis, lack of validated serologic markers and imaging techniques, and a need for coordinated medical care and better overall screening strategies. Multiple specialties are required for optimal early detection, diagnosis, and treatment, demanding a multidisciplinary and multimodality approach. A thorough exploration of the ever-changing status of HCC is warranted. This article offers a comprehensive overview of the epidemiology, characteristics, diagnosis, and treatment of HCC with a discussion of particular challenges and the role of the hepatologist in the management of the disease.

## Epidemiology

With an incidence of half a million to a million cases per year in the world, nearly equal to its mortality rate, HCC is the world's fifth most common solid tumor[1] and third most frequent cause of cancer death.[2] As summarized in Table 1, disease prevalence varies widely. HCC cases are heavily concentrated in Asia and sub-Saharan Africa, where more than 30 new cases per 100,000 persons are diagnosed each year.[3] Generally speaking, older age and male gender carry a much greater risk for development of HCC.[4] Men develop HCC more

*Abbreviations used in this paper:* AFP, α-fetoprotein; AFP-L3%, lectin-reactive α-fetoprotein percent; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; PEI, percutaneous ethanol injection; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; US, ultrasonography.



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**Table 1.** Epidemiology of Hepatocellular Carcinoma

| Region | HCC incidence (occurrences/100,000 population), male | HCC incidence (occurrences/100,000 population), female | No. of HCC cases | Principal associations |
|---|---|---|---|---|
| Asia, sub-Saharan Africa | 30–120 | 9–30 | >500,000 cases per year | HBV, aflatoxin exposure |
| Japan | 10–30 | 3–9 | | HCV |
| Southern Europe, Argentina, Switzerland | 5–10 | 2–5 | | HCV |
| Western Europe | <5 | <3 | | HCV |
| United States | <5 | <3 | 18,000 predicted for 2005 | HCV, alcohol, HBV |

Adapted with permission from Thomas and Zhu.[1]

often than women in all populations, with male-to-female ratios reported from 2:1–8:1.[5] This might be due to androgen receptors on HCC[6] or an increased prevalence of viral hepatitis, iron loading, and/or alcoholic cirrhosis in men.[7]

Much attention has been given to a recent increased incidence of HCC in Western regions. During the past 2 decades, the United States has documented a startling increase in HCC cases.[8] Although HCC represents <2% of all tumors in the United States, its incidence of 1–4 cases per 100,000 population continues to increase at an alarming rate.[9] The cause for this increase is not entirely understood, although it is clearly linked to a historical rise in the incidence of chronic hepatitis C and recent high rate of the development of cirrhosis.[10]

Cirrhosis is the tenth most common cause of death in the United States. Because of the fact that cirrhosis is present in up to 80% of patients diagnosed with HCC,[1] its presence greatly affects patient prognosis and tolerance of treatment. Patients might die of end-stage liver disease and its complications or as a result of progressive HCC or both. In addition, complications of HCC such as portal vein invasion can result in the acceleration to decompensated liver disease. Therapeutic options such as chemotherapy, surgical resection, and ablative therapies are all potentially limited by the presence of cirrhosis and its complications. In the United States, HCV infection, alcohol use, and nonalcoholic fatty liver disease (NAFLD) are the most common causes of cirrhosis, whereas worldwide, HBV and HCV infections are the leading causes of HCC.[1]

## Risk Factors

Several theories have been proposed to explain the fact that 18,000 new cases of HCC are projected to occur in the United States in 2005 (Table 1).[1] One such theory attributes the recent rise in HCC risk to the complex epidemics of increased risk in HCV patients as the disease evolves to cirrhosis and HBV in immigrant populations.[11] A recent population-based study found that the risk for HCV- and HBV-related HCC has increased by 226% and 67%, respectively, whereas idiopathic HCC has decreased from 43%–39%.[9] A second theory implicates alcohol abuse, which afflicts more than 18 million American adults, comprising a prevalence that is 5 times higher than that of hepatitis C.[12] The concomitant occurrence of alcohol use and chronic hepatitis C doubles the risk of HCC compared with that of hepatitis C alone. Moreover, a synergistic effect has been proposed for concomitant alcohol intake and hepatitis C infection in the development of HCC.[12] Other studies have attempted to link HCC to NAFLD-associated cirrhosis and to diabetes, which are increasing in the United States.[1,13,14]

In summary, HCC is multifactorial in etiology and varies by region. Nonetheless, several major and minor causal associations with the tumor have been identified (Table 2). In the United States, cirrhosis is considered to be the most predominant risk factor for HCC and greatly affects patient prognosis and tolerance of treatment, whereas HCV infection, alcohol use, and NAFLD are the most common causes of cirrhosis.[1] Chronic HCV infection with cirrhosis confers at least a 100-fold increased risk of HCC.[9]

**Table 2.** Hepatocellular Carcinoma Risk Factors

| Major risk factors | Minor risk factors |
|---|---|
| Cirrhosis | Oral contraceptive steroids |
| Chronic hepatitis C virus infection | Cigarette smoking |
| Alpha-1 antitrypsin deficiency | Dietary iron overload in Africans |
| Iron overload | Hereditary hemochromatosis |
| Fatty liver | Alcohol |
| Metabolic liver disease, ie, glycogen storage disease | |
| Alcohol-induced cirrhosis | |
| Chronic hepatitis B virus infection | |
| Repeated dietary exposure to aflatoxin $B_1$ food contamination | |
| Family history | |
| Elevated AFP | |