TABLE 111-2 FACTORS ASSOCIATED WITH AN INCREASED RISK OF DEVELOPING HEPATOCELLULAR CARCINOMA

Common	Unusual
Cirrhosis from any cause	Primary biliary cirrhosis
Hepatitis B or C chronic infection	Hemochromatosis
Ethanol chronic consumption	α_1 Antitrypsin deficiency
NASH/NAFL	Glycogen storage diseases
Aflatoxin B_1 or other mycotoxins	Citrullinemia
	Porphyria cutanea tarda
	Hereditary tyrosinemia
	Wilson's disease

Abbreviations: NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis.

HCC incidence rates in the last three decades is thought to be from hepatitis C. A large-scale World Health Organization (WHO)-sponsored intervention study is currently under way in Asia involving HBV vaccination of the newborn. HCC in African blacks is not associated with severe cirrhosis but is poorly differentiated and very aggressive. Despite uniform HBV carrier rates among the South African Bantu, there is a ninefold difference in HCC incidence between Mozambicans living along the coast and inland. These differences are attributed to the additional exposure to dietary aflatoxin B_1 and other carcinogenic mycotoxins. A typical interval between HCV-associated transfusion and subsequent HCC is approximately 30 years. HCV-associated HCC patients tend to have more frequent and advanced cirrhosis, but in HBV-associated HCC, only half the patients have cirrhosis, with the remainder having chronic active hepatitis (Chap. 362).

Other Etiologic Conditions The 75–85% association of HCC with underlying cirrhosis has long been recognized, more typically with macronodular cirrhosis in Southeast Asia, but also with micronodular cirrhosis (alcohol) in Europe and the United States (Chap. 365). It is still not clear whether cirrhosis itself is a predisposing factor to the development of HCC or whether the underlying causes of the cirrhosis are actually the carcinogenic factors. However, ~20% of U.S. patients with HCC do not have underlying cirrhosis. Several underlying conditions are associated with an increased risk for cirrhosis-associated HCC (Table 111-2), including hepatitis, alcohol, autoimmune chronic active hepatitis, cryptogenic cirrhosis, and NASH. A less common association is with primary biliary cirrhosis and several metabolic diseases including hemochromatosis, Wilson's disease, α_1 antitrypsin deficiency, tyrosinemia, porphyria cutanea tarda, glycogenesis types 1 and 3, citrullinemia, and orotic aciduria. The etiology of HCC in those 20% of patients who have no cirrhosis is currently unclear, and their HCC natural history is not well-defined.

Current Directions Many patients have multiple etiologies, and the interactions of HBV, HCV, alcohol, smoking, and aflatoxins are just beginning to be explored.

CLINICAL FEATURES

Symptoms These include abdominal pain, weight loss, weakness, abdominal fullness and swelling, jaundice, and nausea (Table 111-3). Presenting signs and symptoms differ somewhat between high- and low-incidence areas. In high-risk areas, especially in South African blacks, the most common symptom is abdominal pain; by contrast, only 40–50% of Chinese and Japanese patients present with abdominal pain. Abdominal swelling may occur as a consequence of ascites due to the underlying chronic liver disease or may be due to a rapidly expanding tumor. Occasionally, central necrosis or acute hemorrhage into the peritoneal cavity leads to death. In countries with an active surveillance program, HCC tends to be identified at an earlier stage, when symptoms may be due only to the underlying disease. Jaundice is usually due to obstruction of the intrahepatic ducts from underlying liver disease. Hematemesis may occur due to esophageal varices from the underlying portal hypertension. Bone pain is seen in 3–12% of patients, but necropsies show pathologic bone metastases in ~20% of patients. However, 25% of patients may be asymptomatic.

TABLE 111-3 HEPATOCELLULAR CARCINOMA CLINICAL PRESENTATION (N = 547)

Symptom	No. of Patients (%)
No symptom	129 (24)
Abdominal pain	219 (40)
Other (workup of anemia and various diseases)	64 (12)
Routine physical exam finding, elevated LFTs	129 (24)
Weight loss	112 (20)
Appetite loss	59 (11)
Weakness/malaise	83 (15)
Jaundice	30 (5)
Routine CT scan screening of known cirrhosis	92 (17)
Cirrhosis symptoms (ankle swelling, abdominal bloating, increased girth, pruritus, GI bleed)	98 (18)
Diarrhea	7 (1)
Tumor rupture	1
Patient Characteristics	
Mean age (yr)	56 ± 13
Male:Female	3:1
Ethnicity	
White	72%
Middle Eastern	10%
Asian	13%
African American	5%
Cirrhosis	81%
No cirrhosis	19%
Tumor Characteristics	
Hepatic tumor numbers	
1	20%
2	25%
3 or more	65%
Portal vein invasion	75%
Unilobar	25%
Bilobar	75%

Abbreviations: CT, computed tomography; GI, gastrointestinal; LFT, liver function test.

Physical Signs Hepatomegaly is the most common physical sign, occurring in 50–90% of the patients. Abdominal bruits are noted in 6–25%, and ascites occurs in 30–60% of patients. Ascites should be examined by cytology. Splenomegaly is mainly due to portal hypertension. Weight loss and muscle wasting are common, particularly with rapidly growing or large tumors. Fever is found in 10–50% of patients, from unclear cause. The signs of chronic liver disease may often be present, including jaundice, dilated abdominal veins, palmar erythema, gynecomastia, testicular atrophy, and peripheral edema. Budd-Chiari syndrome can occur due to HCC invasion of the hepatic veins, with tense ascites and a large tender liver (Chap. 365).

Paraneoplastic Syndromes Most paraneoplastic syndromes in HCC are biochemical abnormalities without associated clinical consequences. They include hypoglycemia (also caused by end-stage liver failure), erythrocytosis, hypercalcemia, hypercholesterolemia, dysfibrinogenemia, carcinoid syndrome, increased thyroxin-binding globulin, changes in secondary sex characteristics (gynecomastia, testicular atrophy, and precocious puberty), and porphyria cutanea tarda. Mild hypoglycemia occurs in rapidly growing HCC as part of