Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis and Hepatocellular Carcinoma

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KEYWORDS

• Nonalcoholic steatohepatitis • Obesity • Hepatocellular carcinoma
• Metabolic syndrome

KEY POINTS

- The progressive increase in the prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis are likely to make nonalcoholic fatty liver disease/nonalcoholic steatohepatitis the most common predisposing factor of hepatocellular carcinoma in the upcoming decades.
- The frequency of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis –related hepatocellular carcinoma in the absence of cirrhosis is unclear.
- Screening and surveillance for hepatocellular carcinoma should, for now, be limited to patients thought to have cirrhosis.
- Obesity can make screening for hepatocellular carcinoma in patients with nonalcoholic steatohepatitis cirrhosis challenging, increasing the technical failure rate of ultrasound scan as a screening method.
- The delay in the diagnosis of hepatocellular carcinoma in the setting of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis and the presence of multiple comorbidities in this population negatively impacts prognosis.

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) in the United States has tripled over the last 3 decades. A recent study using the Surveillance, Epidemiology and End Result (SEER) database found an increase in the incidence rate of HCC from 1.6 per 100000 in 1975 to 4.9 per 100000 in 2000.[1] HCC is the fastest growing cause of

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cancer death in the United States male population.[2] The primary risk factor for HCC is cirrhosis, which is present in 70% to 90% of cases.[2] The most common causes of cirrhosis are viral hepatitis (hepatitis B and hepatitis C), alcoholic hepatitis, and nonalcoholic steatohepatitis (NASH), the most common cause of liver disease in the West and globally.[3–10] However, 15% to 50% of HCC cases occur in patients with cryptogenic cirrhosis without other known chronic liver disease.[2] Further, there is a growing body of literature showing that HCC can develop from noncirrhotic NASH or even simple hepatic steatosis.[11] In addition, obesity has been established as a risk factor for the development of a variety of malignancies, including liver cancer.[12–14] This review discusses the association between HCC and NASH cirrhosis, noncirrhotic NASH/nonalcoholic fatty liver disease (NAFLD), diabetes, obesity, and metabolic syndrome. This review also discusses the pathogenesis of HCC in cirrhosis and noncirrhosis and reviews the challenges of surveillance for HCC in NASH/NAFLD population.

HEPATOCELLULAR CARCINOMA AND NONALCOHOLIC FATTY LIVER DISEASE/ NONALCOHOLIC STEATOHEPATITIS–RELATED CIRRHOSIS

The first report on HCC complicating NASH with cirrhosis was published in the 1990s. Further studies indicated that NASH is a risk factor for the development of cirrhosis and HCC.[15] Although most cases of HCC occur in the setting of hepatitis C virus (HCV) or alcoholic cirrhosis, in 15% to 50% of cases, HCC occurs in the setting of cryptogenic cirrhosis.[2,10] It is widely believed that cryptogenic cirrhosis represents "burnt out" NASH, bearing metabolic features of metabolic syndrome but no longer having the classic biopsy features of NASH, such as steatosis, which dissipates with more advanced liver disease.[14,16] The risk of HCC in NASH-related cirrhosis seems to be lower than in viral or alcohol-related cirrhosis.[17] In a large cohort study, HCC was significantly more common in HCV than in NAFLD (6.8% vs 2.4% overall, respectively).[18] The perception that HCC is less common in NASH-related cirrhosis has, however, recently been challenged. In a report from England, the overall incidence of HCC increased 1.8-fold from 2000 to 2010 with more than 10-fold increase in HCC associated with NAFLD, accounting for 34.8% of all the cases in 2010 and making it the single most common underlying etiology.[19] The lower incidence of HCC with NASH cirrhosis may be outweighed by the progressive increase in NASH-related cirrhosis.[17]

Ascha and colleagues[20] compared the incidence of HCV- and NASH-related cirrhosis. Among 510 patients with cirrhosis, 196 had underlying NASH, whereas 315 had cirrhosis secondary to HCV. Median follow-up of 3.2 years found an annual cumulative HCC incidence of 2.6% for NASH-related cirrhosis compared with 4% for HCV-related cirrhosis cases. Despite the estimated low HCC incidence rate of 2.6% in patients with NASH-related cirrhosis, the surge in the number of cases with NAFLD is projected to lead to an increase in the number of patients with NASH-related HCC.[10] A recent study found a 4-fold increase in the prevalence of NASH-related HCC among liver transplant recipients since the implementation of the model for end-stage liver disease in 2002. In this large US population-based study, which used the United Network for Organ Sharing database from 2002 to 2012, Wong and colleagues[21,22] reported 10,061 patients with HCC among 61,868 liver transplant recipients. To achieve a more accurate assessment of the true prevalence of NASH, the investigators created a modified NASH category, which included patients with a formal diagnosis of NASH and obese patients (body mass index [BMI] more than 30 kg/m^2) with cryptogenic cirrhosis and obese patients with unknown etiology of HCC. The proportion of HCC patients undergoing liver transplantation increased from 3.3% in 2000 to 13.5% in 2012 (**Table 1**). Although HCV remained the leading