Editorial

Nonalcoholic fatty liver disease and hepatocellular carcinoma: new insights on presentation and natural history

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Hepatocellular carcinoma (HCC) is the most rapidly increasing cause of cancer-related mortality in many countries including the United States (1). In 2012, primary liver cancer was estimated to be the overall second cause of cancer related death in the world (2). These alarming reports stress the desperate need for better understanding of the risk and prognostic factors as well as the screening and treatment methods of HCC.

Over the last decades nonalcoholic fatty liver disease (NAFLD) has emerged as rapidly growing cause of end-stage liver disease and HCC, in addition to chronic hepatitis C, hepatitis B and alcohol use. While sufficient and consistent epidemiological studies are available concerning HCC in viral hepatitis and alcoholic hepatitis, there is a clear lack of data addressing the incidence and prevalence of HCC in patients with nonalcoholic steatohepatitis (NASH). According to the available literature, the incidence of HCC developing in NASH cirrhosis ranges from 2.4% over 7 years to 12.8% over 3 years (3). Interestingly, a prospective study in 2002 showed that cryptogenic cirrhosis was the etiology for approximately 29% of HCC cases. When further investigated, half of these patients expressed histological or clinical features of NAFLD suggesting that NAFLD could have accounted for a good part of cryptogenic cirrhosis related HCC (4). Additionally, strong evidence now exists showing that a proportion of NASH can progress to HCC with the absence of cirrhosis (5). In a recent meta-analyses, Younossi *et al.* reported that in NAFLD patients, the annual incidence of HCC was 0.44 per 1,000 person-years, whereas for those with NASH, the annual HCC incident rate was 5.29 per 1,000 person-years (6).

Whether patients with NAFLD-HCC have a survival comparable to that of patients with HCC related to other etiologies remains unknown. In a recent issue of *Hepatology*, Piscaglia *et al.* presented important data to tackle this critical and yet unresolved question. The group conducted a prospective observational multicenter study between 2010 and 2012 that included 145 patients with NAFLD-related HCC and 611 patients with HCV-related HCC (7). Patients with NAFLD-HCC were significantly younger (67.8 *vs.* 71.1 years, P<0.0001), were more often male, had less severe liver disease and, as expected, more metabolic risk factors than patients with HCV-related HCC. Crude mean survival was statistically shorter in NAFLD patients compared with HCV patients (27.2 *vs.* 34.4 months, respectively; P=0.015). Tumor burden significantly differed between the two groups, as NAFLD patients had larger tumor size on the time of diagnosis. To clarify the intrinsic tumor aggressiveness despite the difference in tumor size, a propensity analysis was carried out trying to eliminate possible confounding factors which could have an impact on survival. According to the analysis and after matching for confounding factors of differences in age, liver function, and tumor burden survival rates were fully comparable between NAFLD and HCV-HCC patients;

being 30.2 months (95% CI, 25.3–35.2) in NAFLD-HCC patients and 36.9 months (95% CI, 32.6–41.1) in HCV-HCC patients (P=0.330). After adjusting for lead time, the difference in survival between the two groups remained non-significant; 28.5 months in the NAFLD-HCC patients and 35 months in the HCV-HCC patients (P=0.344).

NAFLD-HCC patients usually present with less aggressive tumors and are not typically diagnosed by surveillance, compared to patients with HCV-HCC (6,7). HCC in NAFLD patients is usually moderately or well differentiated and lacks encapsulation. A retrospective study of Australian population compared HCC in cirrhotic and non-cirrhotic NAFLD and found that HCC dimensions were larger in non-cirrhotic livers (8). The relative late diagnosis of HCC in NAFLD patients could be due to the absence of recognizable indicators of cirrhosis which result in the lack of any surveillance program. This highlights another important finding of this study; only 47.7% of NAFLD-HCC were diagnosed during specific surveillance or periodic ultrasound compared to 63.3% of HCV-HCC (P<0.0001). These alarming findings were also observed in other studies. Even among patients with established cirrhosis, NASH patients received sub-optimal HCC surveillance that is significantly lower than that of patients with HCV cirrhosis (HR =0.44; P<0.05) (9).

All patients with cirrhosis should be screened for HCC every 6 months, as stated by the AASLD and EASL guidelines. Surveillance is generally performed by ultrasound. It is evident; however, that ultrasound as a screening method for HCC is far from perfect. Recent data have shown that surveillance ultrasounds are inadequate for the exclusion of HCC in 20% of cirrhotic patients regardless of the etiology of cirrhosis, emphasizing the concerns over the effectiveness of ultrasounds in achieving survival benefit in clinical practice (10). For patients with NASH, who tend to be overweight or obese, there lies an additional limitation to the effectiveness of surveillance ultrasounds.

The other important question, apart from the impact of this condition, concerns the pathogenic mechanism that links NAFLD to increased risk of HCC. Two major risk factors for NAFLD are obesity and insulin resistance. In fact, NAFLD may be present in up to 90% of patients undergoing obesity surgery and in 70% of patients with diabetes (11,12). Diabetes was independently linked to the development of HCC on various reports. Hyperinsulinemia and insulin-like growth factor may promote the development of primary liver cancer by activating various oncogenic pathways (13,14). Obesity by itself, on the other hand, is associated with an increase in death rates of all cancers combined. In a large population-based study of 900,000 people in the United States, the relative risk of death from HCC ranged from 1.90 to 4.52 for obese patients when matched with normal weight individuals (15). A Korean study of more than 700,000 patients found similar association between having body mass index >30 kg/m^2 and developing HCC (relative risk 1.56) (16). Different European studies of considerable sample size reached similar conclusions for both general and abdominal obesity as well (17,18).

The underlying mechanism of this development is not fully understood. Nevertheless, the chronic low-grade inflammatory state accompanying obesity, the increased levels of leptin (a proinflammatory and proangiogenic cytokine), the generation of reactive oxygen species and saturated free fatty acids as a result of lipid accumulation and lipotoxicity in the liver, leading to potential interference with cellular signaling and gene transcription are all theoretically attractive hypotheses for the development of HCC in NASH (19,20).

It is expected to see an increase in the incidence of NAFLD related HCC in the near future. The study by Piscaglia *et al*. demonstrates that the shorter survival of NAFLD-HCC, compared to HCV-HCC patients, is mainly due to the late diagnosis and greater tumor burden and not because HCC in NAFLD is more aggressive. However, liver cancer continues to carry poor prognosis worldwide. It is of extreme importance to perform further research to better elucidate the pathogenesis of this condition and to establish excellent methods of screening NAFLD patients for HCC, both cirrhotics and non-cirrhotics.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-27.
2. GLOBOCAN. Estimated cancer incidence: mortality and

prevalence worldwide in 2012. Available online: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
3. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol 2012;10:1342-59.e2.
4. Marrero JA, Fontana RJ, Su GL, et al. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology 2002;36:1349-54.
5. Kawada N, Imanaka K, Kawaguchi T, et al. Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. J Gastroenterol 2009;44:1190-4.
6. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
7. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. Hepatology 2016;63:827-38.
8. Leung C, Yeoh SW, Patrick D, et al. Characteristics of hepatocellular carcinoma in cirrhotic and non-cirrhotic non-alcoholic fatty liver disease. World J Gastroenterol 2015;21:1189-96.
9. Tavakoli H, Robinson A, Liu B, et al. Cirrhosis Patients with Nonalcoholic Steatohepatitis Are Significantly Less Likely to Receive Surveillance for Hepatocellular Carcinoma. Dig Dis Sci 2017;62:2174-81.
10. Simmons O, Fetzer DT, Yokoo T, et al. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. Aliment Pharmacol Ther 2017;45:169-77.
11. Williamson RM, Price JF, Glancy S, et al. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care 2011;34:1139-44.
12. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology 2012;142:711-25.e6.
13. Chettouh H, Lequoy M, Fartoux L, et al. Hyperinsulinaemia and insulin signalling in the pathogenesis and the clinical course of hepatocellular carcinoma. Liver Int 2015;35:2203-17.
14. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126:460-8.
15. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.
16. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol 2005;23:4742-54.
17. Schlesinger S, Aleksandrova K, Pischon T, et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. Int J Cancer 2013;132:645-57.
18. Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control 2006;17:901-9.
19. Stickel F, Hellerbrand C. Non-alcoholic fatty liver disease as a risk factor for hepatocellular carcinoma: mechanisms and implications. Gut 2010;59:1303-7.
20. Vinciguerra M, Carrozzino F, Peyrou M, et al. Unsaturated fatty acids promote hepatoma proliferation and progression through downregulation of the tumor suppressor PTEN. J Hepatol 2009;50:1132-41.

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