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HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

NAFLD-Related HCC: How Should the Shift in Epidemiology Change Our Prevention and Surveillance Strategies?

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Abstract
Purpose of Review The purpose of this study is to review the recent literature on the epidemiology of NAFLD-related HCC and discuss published data on primary and secondary prevention of NAFLD-related HCC, including surveillance for HCC.
Recent Findings Hepatocellular cancer (HCC) is the fastest rising cause of cancer-related deaths in the USA. Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the USA, afflicting nearly one in three Americans and is increasingly linked to the development of HCC. NAFLD will likely become the major contributor to the burden of HCC in the USA. While cirrhosis remains the most important risk factor for HCC in NAFLD, mounting evidence indicates that NAFLD patients can rarely develop HCC in the absence of cirrhosis. While effective medical therapies for NAFLD exist, their role as chemopreventive agents against HCC is unclear.
Summary Major knowledge gaps remain in our understanding of the risk of HCC and the interplay between HCC-promoting factors in patients with NAFLD. Currently, efforts should focus on prompt diagnosis of NAFLD and cirrhosis with non-invasive methods, or liver biopsy as needed. This will identify the great majority of NAFLD patients at risk for HCC. Valid and reliable methods for identifying non-cirrhotic NAFLD patients at risk for HCC are lacking, so surveillance cannot be currently recommended in the absence of cirrhosis. Meanwhile, further studies are needed to determine the magnitude of risk and specific risk factors or biomarkers for HCC in patients with NAFLD with or without cirrhosis.

Keywords Hepatoma · Hepatocellular cancer · Burden · Natural history · Fatty liver · Nonalcoholic fatty liver disease · NAFLD · Nonalcoholic steatohepatitis · NASH · Cirrhosis

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is now the leading cause of chronic liver disease in the USA [1]. NAFLD is posited as the hepatic manifestation of the metabolic syndrome and is closely associated with diabetes, hyperlipidemia, obesity, and hypertension. Coinciding with large increases in metabolic syndrome, prevalence of NAFLD has doubled in the past two decades (now ~30%). Although NAFLD is often a non-progressive condition, 20–30% of patients with NAFLD develop progressive liver disease called nonalcoholic steatohepatitis (NASH), characterized by histological evidence of liver cell injury, inflammation, and fibrosis [2] that can result in cirrhosis in 10–20% of cases [3]. NAFLD is the fastest growing cause of cirrhosis in the USA [4, 5]—a concerning trend given the known association between cirrhosis and hepatocellular cancer (HCC). Indeed, NAFLD may be the next major etiological risk factor for HCC. We review the recent literature on the epidemiology of HCC with specific focus on NAFLD-related HCC. We discuss the emergence of NAFLD-related HCC in the absence of cirrhosis. We also discuss the various non-invasive methods to diagnose

NAFLD and cirrhosis, potential chemopreventive agents against NAFLD-related HCC, and finally surveillance for HCC.

Global Epidemiology of HCC

Worldwide, primary liver cancer is the sixth most frequent cancer and the second leading cause of death from cancer. Recent estimates suggest that 782,000 new cases of liver cancer arise worldwide each year, resulting in 746,000 liver cancer-related deaths [6]. However, liver cancer incidence and mortality rates vary greatly around the world and liver cancer is the second most common cancer in developing countries among men [6].

In the USA, liver cancer rates have been rapidly rising since the early 1980s and liver cancer is the fastest growing cause of cancer-related death [7]. In 2016, an estimated 39,230 new cases of primary liver cancer will be diagnosed and about 27,170 people will die from liver cancer in the USA [8]. Of all primary liver and intrahepatic cancer diagnosed in the USA, more than 70% are classified as HCCs [7]. HCC incidence rates among men are twice as high as the incidence rates among women. HCC is rare among persons less than 40 years. HCC incidence rates reach a peak at approximately 70 years of age [9]. Despite improvement in prevention and treatment, 5-year survival rates in HCC remain less than 20% [7].

Epidemiology of NAFLD-Related HCC

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections account for 75% of HCC cases worldwide. In the USA, most of the increase in HCC has been attributed to the burden of chronic HCV in an aging population (persons infected in the 1960s and 1970s). However, recent studies have reported the absence of known major risk factors (HBV, HCV, and heavy alcohol consumption) in a large proportion (20–40%) of patients with HCC, including the absence of cirrhosis in up to 20% [10–13]. Most are speculated to have NAFLD-related HCC. Wong et al. found that although HCV remains the leading etiology of HCC (43.4% of HCC liver transplant recipients in 2002 had HCV vs. 49.9% in 2012), NAFLD was the second leading etiology of HCC-related liver transplantation (8.3% of HCC cases in 2002 vs. 13.5% in 2012) [5]. Similar estimates for the proportion of NAFLD-related HCC have been reported in other recent studies (~13%) [14–16].

There is currently little information regarding the exact magnitude of HCC risk in patients with NAFLD. In a recent systematic review of epidemiology studies characterizing the association between these disorders [17], any given NAFLD patient without cirrhosis has a 0–1% cumulative HCC mortality over 5.6–20 years. However, most studies were small with few (or no) incident HCC cases (range 0–25), resulting in imprecise HCC risk estimates [18–20]. Studies including patients with NAFLD-related cirrhosis reported a cumulative incidence of HCC of 2.4–38% over 3.2–10 years, which was lower than incidence rates in patients with HCV cirrhosis [18, 19, 21, 22]. Nevertheless, because of its very high prevalence in the general population and with the anticipated fall in number of HCV-related HCCs in the era of highly effective direct acting antiviral agents, NAFLD will become the leading contributor to the development of HCC in the USA [23, 24].

The exact risk profile for the NAFLD patient at the highest risk for HCC has not been clearly defined. Relative to patients with HCC from other causes, NAFLD patients with HCC tend to be older, more frequently Caucasian, and have less severe liver dysfunction at diagnosis [14]. In a recent multicenter prospective study, HCC in NAFLD patients was larger, showed more often an infiltrative pattern, and was detected outside surveillance intervals than HCC in HCV patients [25].

Perhaps the most alarming feature of NAFLD-related HCC is that a significantly lower proportion are found in cirrhotics (~50–60%) than alcohol- or HCV-related HCC (~75 and >90%, respectively) [14, 25]. HCC has even been reported in patients with metabolic syndrome and bland steatosis (without inflammation or fibrosis) on liver biopsy [11]. In a review of multiple case series of patients with NAFLD-related HCC, non-cirrhotic HCCs accounted for nearly one-third of all HCCs reported in the literature [26], though the true prevalence of this phenomenon (HCC in the absence of cirrhosis) is unclear as many of these series were limited by reporting bias, selection bias (surgical series selecting for better liver function), and potential sampling errors on liver biopsy [13, 27, 28].

Carcinogenesis in the cirrhotic liver is driven by the production of growth factors from chronically activated stellate cells, leading to the expansion of neoplastic clones of hepatocytes [29]. In contrast, carcinogenesis in non-cirrhotic NAFLD patients is likely related to pro-inflammatory cytokines from adipose tissue expansion, specifically IL-6 and TNF-alpha [30]. In addition, fatty acids may promote carcinogenesis by altering gene transcription [31, 32] and causing direct lipotoxicity via peroxide and free radical production during oxidation [33, 34]. The combination of inflammatory cytokines and direct lipotoxicity promotes insulin resistance systemically and at the level of the hepatocytes [35, 36]. Resultant hyperinsulinemia results in reduced hepatic synthesis of insulin-like growth factor (IGF)-binding protein-1 and increased bioavailability of IGF-1, which further promotes cellular proliferation and inhibits apoptosis [37].

Patients with NAFLD-related HCC have similar or better overall survival rates than persons with HCC from other causes. In a study of 1500 HCC patients diagnosed in the VA between 2005 and 2010, while fewer patients with

NAFLD-related HCC received HCC-specific treatment (61.5 vs. 77.5% for HCV-related HCC; $P < .01$), the 1-year survival rate did not differ by underlying HCC etiology [14]. Because NAFLD patients have been shown to receive lower rates of surveillance and receipt of any treatment in the years prior to HCC diagnosis than other HCC patients, it is plausible that patients with NAFLD-related HCC may indeed have better survival as compared to patients with HCC from other risk factors if barriers in surveillance and treatment can be overcome. Indeed, a recent study among 303 patients undergoing curative treatment for HCC found that patients with NAFLD-related HCC had better overall survival following curative treatment compared to patients with HCV- and alcohol-related HCC [38].

Translating Epidemiology into Action

Accurate Diagnosis of NAFLD and Cirrhosis

One of the most important steps in the prevention of NAFLD-related HCC is establishing the diagnosis of NAFLD and cirrhosis. Most patients in care who may have underlying NAFLD go unrecognized. In a recent study of 251 patients with suspected NAFLD—defined as the presence of persistently elevated liver enzymes and metabolic syndrome in the absence of viral hepatitis or excessive alcohol use—only 21.5% of patients had NAFLD mentioned in clinical progress notes as a possible diagnosis [39]. Liver biopsy remains the gold standard for detecting both NAFLD and cirrhosis. However, it is limited by the risk of complications [40, 41], sampling [42, 43], interobserver variability [44], and the implausibility of performing serial biopsies. Given these limitations, most cases with NAFLD are identified on the basis on abdominal imaging. Ultrasonography (US) and computerized tomography (CT) are both reliable and accurate in detecting moderate to severe fatty liver. US has a sensitivity of 85% and specificity of over 94%, while CT has a sensitivity of 72–82% and specificity over 90% [45, 46]. However, US and CT are not sensitive in detecting mild steatosis. MRI is capable of detecting even minimal histologic steatosis (≥5%) with a sensitivity and specificity of 77–90% and 87–91%, respectively [46, 47]. Given its safety, cost, and accessibility, US is the imaging modality of choice for initial evaluation of fatty liver.

Once the diagnosis of NAFLD is established, determining the presence of cirrhosis remains a key challenge. Several non-invasive scoring systems based on simple blood tests and clinical parameters (age, sex, BMI) have been developed to predict advanced fibrosis and cirrhosis in various chronic liver diseases, including NAFLD. These include the AST-to-platelet ratio index (APRI) [48], AST/ALT ratio [49], FIB-4 score [50], BARD score [51], and NAFLD fibrosis score (NFS) [52]. The BARD score and NFS were specifically designed for NAFLD patients. In a study of 145 patients with biopsy-proven NAFLD, these five non-invasive tests were compared to one another based on their ability to identify NAFLD-related advanced fibrosis [53]. The FIB-4 score had the best diagnostic accuracy for advanced fibrosis. All scores except the APRI had negative predictive values greater than 90% and can reliably exclude advanced fibrosis or cirrhosis and prevent liver biopsy in a large proportion of NAFLD patients. The NAFLD fibrosis score is the most widely investigated noninvasive markers in NAFLD and has been shown to accurately separate NAFLD patients with and without advanced fibrosis or cirrhosis with a pooled AUROC of 0.85, sensitivity of 90% and specificity of 97% [54]. The score is function of age, BMI, aminotransferase levels, hyperglycemia, platelets, and albumin.

The use of transient elastography (Fibroscan) to diagnose cirrhosis has been validated in NAFLD [55–58]. However, Fibroscan M had a substantial failure rate in patients with BMI >30 as the subcutaneous fat increases the distance between the probe and the liver [59, 60]. FibroScan XL probe, which has an increased frequency and amplitude of vibration, produces reliable measurements in approximately 50–80% of patients for whom the M probe previously failed [61–64]. More recently, the presence of NAFLD and the degree of hepatic fibrosis can be accurately diagnosed using liver magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) and magnetic resonance enterography (MRE). MRI-PDFF assessments are highly correlated with histology as assessed by liver biopsy with MRI-PDFF ≥5% as highly diagnostic of NAFLD [65]. Similarly, MRE-based assessments of liver stiffness have a high diagnostic accuracy for differentiating NAFLD with any stage of fibrosis from simple steatosis [66]. These non-invasive tests allow clinicians to stage the severity of fibrosis in NAFLD without the need for a liver biopsy in most cases; the results can then influence counseling, follow-up, and HCC surveillance recommendations in patients with NAFLD [67].

Prevention and Medical Therapy for NAFLD and NAFLD-Related HCC

Weight loss and exercise improve liver enzymes, histology, and insulin resistance in patients with NAFLD [68–74]. Specifically, weight loss over 10% of total body weight was associated with fibrosis regression in the study by Glass et al. [75]. Even physical exercise without weight loss can improve hepatic steatosis [76]. With regard to HCC specifically, a prospective cohort study of 507,897 subjects followed for 10 years found a relative risk of 0.56 for HCC among those who were engaged in vigorous exercise (≥5 days/week) compared to sedentary subjects, independent of BMI [77].

Vitamin E is an antioxidant, which improves liver histology in non-diabetic patients with NAFLD [78]. It is a first-line

therapy at a dose of 800 mg daily for non-diabetics with biopsy-proven NAFLD [79]. An observational study of 132,832 people in China indicates that oral intake of vitamin E was associated with a reduced risk of HCC development, controlling for self-reported liver diseases and family history of liver cancer [80]. While metformin does not improve liver histology in NAFLD [3] and is therefore not recommended as a specific therapy for NAFLD [79], it may reduce the risk of developing HCC among diabetics [81–86]. In a meta-analysis of eight observational studies, metformin use among diabetic patients was associated with a 50% lower risk of HCC [87]. In contrast, thiazolidinediones (PPAR-gamma agonists), which improve NAFLD histology in diabetics and represent the first-line therapy for biopsy-confirmed NAFLD in diabetics [79], were not associated with decreased incidence of HCC [88]. The use of insulin and second-generation sulfonylureas (glipizide) were independently associated with an increased incidence of HCC in HCV patients [88–90]. There was considerable heterogeneity among studies and in particular with regard to the adjusting for concomitant use of other ADMs. The true risk of each ADM on HCC is thus difficult to interpret with studies containing comparator groups taking ADMs with their own inherent cancer-modifying effects.

The use of statins is associated with lower odds of having advanced fibrosis in individuals at risk for NAFLD [91]. With respect to HCC, statin users were 37% less likely to develop HCC than non-users in a meta-analysis [92]. Lastly, obeticholic acid, a bile acid derivative and potent activator of the farnesoid X nuclear receptor, has been shown to reduce steatosis and fibrosis in NAFLD patients in the landmark FLINT trial. A total of 45% of 110 patients in the obeticholic acid group had improved liver histology compared with 21% of 109 patients in the placebo group after 72 weeks [93]. However, its long-term safety and chemopreventive effects on HCC risk in NAFLD patients remain unknown. In general, most of the evidence in support of chemopreventive agents come from observational studies, as a randomized trial to assess the effects of a medication on the incidence of HCC would be quite prohibitive with respect to sample size and duration of follow-up [94].

HCC Surveillance in Patients with NAFLD

The 2010 American Association for the Study of Liver Diseases (AASLD) guidelines recommend screening ultrasound every 6 months for patients with NAFLD cirrhosis [95]. The guidelines do not provide any recommendations for HCC screening in NAFLD/NAFLD patients without cirrhosis.

Despite the accumulating evidence that HCC may occur in the absence of cirrhosis in NAFLD patients, widespread HCC surveillance cannot be recommended for NAFLD patients without cirrhosis because the probability that any given non-cirrhotic NAFLD patient will develop HCC is low. Ultrasound-based surveillance for 10–30% of the American population (with NASH or NAFLD) would be cost-prohibitive. Further, recent data suggest ultrasound quality may be lower in obese patients and those with NAFLD cirrhosis [96, 97]. Similarly, CT and MRI-based surveillance would not be cost-effective. Alpha fetoprotein (AFP) levels were removed from guideline recommendations given suboptimal performance for detecting HCC, although may perform better in non-HCV patients, including those with NAFLD [98].

Determining risk profiles or biomarkers to identify NAFLD patients at risk for HCC (including those that develop HCC in the absence of cirrhosis) should be a focus of further research. Current predictive models for HCC using clinical variables alone have been limited by suboptimal accuracy [99], although there may be hope for increase accuracy with addition of biomarkers or genetic markers [100, 101]. Better understanding of factors that differentially impact risk of HCC in NAFLD—both in the great majority without cirrhosis and among those with cirrhosis—can help identify those who are at the greatest risk for HCC. Targeted use of surveillance, based on individualized clinical risk stratification, may enhance the cost-effectiveness of HCC surveillance efforts by prioritizing “high risk” individuals with NAFLD.

Conclusion

The current epidemiology of HCC suggests a shift towards NAFLD as the primary cause of HCC in the near future. Although some HCC cases may occur in the absence of cirrhosis in NAFLD, there are limited data on the exact risk of HCC in NAFLD patients without cirrhosis. Well-designed longitudinal studies including large numbers of NAFLD cases with both sufficient follow-up time and relevant number of HCC outcomes are needed to quantify this risk. Future studies are also needed to discover non-invasive markers or selective risk profiles that identify NAFLD patients at the highest risk of HCC. Diet and exercise represent the cornerstone of treatment for NAFLD. While several chemotherapeutic agents also hold promise in the treatment of NAFLD, future studies are needed to elucidate the protective effects of these agents, in addition to diet and exercise, on HCC risk in NAFLD. In the interim, HCC surveillance is recommended for patients with NAFLD cirrhosis. For healthcare providers, timely identification of NAFLD and NAFLD cirrhosis remains the essential step towards implementing HCC surveillance in patients with NAFLD.

Compliance with Ethical Standards

Conflict of Interest J. Andy Tau, Aaron P. Thrift, and Fasiha Kanwal each declare no potential conflicts of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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