Mini-review

NAFLD leads to liver cancer: Do we have sufficient evidence?

Xiao-Yan Duan1,2, Lei Zhang1, Jian-Gao Fan2,*, Liang Qiao2,3,*

1Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Children’s Digestion and Nutrition, Shanghai 200092, China
2Department of General Surgery, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu, China
3Storr Liver Unit, University of Sydney at the Westmead Millennium Institute, Westmead, NSW 2145, Australia

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A B S T R A C T

Primary liver cancer has several well-recognized risk factors, such as HBV and HCV infection, alcohol abuse and aflatoxin. Recent studies show that nonalcoholic fatty liver disease (NAFLD), especially its aggressive form nonalcoholic steatohepatitis (NASH), is associated with an increased risk of liver cancer, mainly hepatocellular carcinoma (HCC). On the other hand, clinical and epidemiological data have showed that HCC has rarely been found in a “pure” fatty liver in human. Thus, the question we need to ask is do we have sufficient evidence to support a causative role of NAFLD in liver cancer? Furthermore, if NAFLD is indeed a causative factor for liver cancer, what is the mechanism? Perhaps at this stage, fatty liver and NASH can be regarded as a definite risk factor for liver cancer, but to conclude that NAFLD induces HCC requires more robust in vitro and in vivo data.

1. Introduction

Since the first case of nonalcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma (HCC) was reported in 1990 [1], mounting evidence, as reported in several excellent review articles [2–8], shows a significant association between NAFLD and liver cancer, both of which are considered parts of the metabolic syndrome. HCC is a common and deadly malignancy worldwide. Although some risk factors (such as HBV, HCV, or alcohol abuse) are well recognized in most cases of HCC, between 15% and 50% of HCC cases develop in the absence of these known etiologic factors. In developed countries, these “cryptogenic” HCC is mostly attributed to NAFLD [2,4], which encompasses a clinicopathologic spectrum ranging from simple fatty liver through nonalcoholic steatohepatitis (NASH) to cirrhosis.

Supporting evidence linking NAFLD and liver cancer stems from a variety of sources. (1) Numerous case reports and series studies have showed that patients with simple hepatic steatosis, NASH and cirrhosis can all progress to HCC [9–30]; (2) retrospective studies showed that NAFLD is a risk factor for HCC [1,31–34]; (3) prospective studies have showed that liver cancer is one of the long term complications of NAFLD [35–38]; and (4) experimental studies have showed that liver cancer may derive from fatty liver and NASH [39–46]. Below, we will briefly discuss the currently available evidence supporting a causative role of NAFLD in the development of liver cancer.

2. NAFLD: a generally benign but a progressive disease

Clinically, NAFLD should not be regarded as a single disease entity. It consists of a constellation of nonalcoholic fatty liver disorders ranging from simple hepatic steatosis to its more aggressive form NASH. These liver disorders are generally chronic but progressive. Simple hepatic steatosis is the very mild form of NAFLD and most of them follow a relatively benign clinical course. However, if left untreated, it may progress to NASH, liver fibrosis, cirrhosis and HCC [47]. Several prospective studies in NAFLD patients have revealed that over a period of 5.6 years, 26–37% of patients with NASH progressed to liver fibrosis, 9% progressed to cirrhosis, and 34–50% remain stable [48–51]. In patients with simple hepatic steatosis, spontaneous histological improvement was observed in 18–29% of patients [48–51]. In another follow-up study, one third to one half of NASH patients exhibited progressive liver fibrosis over 3.5–5 years, and 20% progressed to advanced fibrosis [37].

3. Different stages of NAFLD can progress to HCC

Although simple hepatic steatosis generally follows a benign clinical course, if no intervention is taken, it may progress to NASH and end-stage liver diseases. Simple hepatic steatosis, the most...
mild form of NAFLD, has been reported to progress into HCC, although the malignant transformation usually occurs over a number of decades [47]. Most NAFLD-related HCC cases were derived from patients with more severe form of the spectrum, i.e., NASH and cirrhosis. Several good review articles have described the relevant clinical characteristics of NAFLD-associated HCC [3,52,53]. More than half of the NAFLD-associated HCC occurred in males. The age of the patients in whom the diagnosis of NAFLD was made ranged from 20 to 82 years, and the age at which HCC was diagnosed ranged from 35 to 89 years [3,53]. Compared to HBV- and HCV-derived HCC, NAFLD-associated HCC usually occurs at a more advanced age (4–6 years older) than the patients with cirrhosis of other etiology. It was reported that the longest interval from NAFLD to HCC was 26 years [22], and the average length of NASH-related cirrhosis before the diagnosis of HCC was shortened to 10–16 years [2], suggesting a more oncogenic nature of NASH. Indeed, many studies have showed that NASH is the more aggressive form of NAFLD. A 7-year follow-up study showed that 40–62% of patients with NASH developed end-stage liver disease, such as cirrhosis and HCC [37]. Retrospective data suggested that 4–27% of patients with NASH-related cirrhosis transform to HCC after the development of cirrhosis [54].

Although cirrhosis has long been regarded as an important risk factor for HCC, it is not an indispensable stage for the development of HCC in patients with NAFLD. In a recent US study, only 46% of NAFLD- and NASH-related HCC patients have underlying cirrhosis [33]. High grade steatosis in the non-cirrhotic liver was also found to be significantly associated with HCC development [55]. Furthermore, compared to NAFLD with cirrhosis, NAFLD without cirrhosis was reported to be a more related to HCC development [56]. Based on long term follow-up studies of up to 19.5 years, the prevalence of HCC in patients with NAFLD was 0–0.5%, and when the disease has progressed to NASH, the prevalence of HCC mounted to 0–2.8% [38,57] (Fig. 1). Clearly, patients with NASH are at an increased risk of developing HCC. However, more caution needs to be exercised in confirming the causal link between NAFLD and HCC, as in 72% of NAFLD patients the diagnosis of NAFLD was confirmed only after HCC was found in these patients [53], thus, whether NAFLD is a cause of HCC, or it is just a co-existing condition for HCC still requires validation in appropriate disease models.

4. Risk factors for HCC in patients with NAFLD

Most of the NAFLD-associated HCC patients have two or more types of metabolic disease, and nearly all patients had insulin resistance [53]. Obesity and diabetes mellitus (DM) are the most common metabolic disorders associated with NAFLD-associated HCC. Cirrhosis, the most important precancerous condition for HCC was detected in 46–60% of the NAFLD-associated HCC patients [31,33,53]. Numerous studies have showed that NASH with or without cirrhosis, T2DM, obesity particularly abdominal obesity, metabolic syndrome and insulin resistance are all risk factors for the development of HCC [58].

4.1. Cirrhosis

Liver cirrhosis is the main risk factor for the development of HCC regardless of the causes of liver disease. About 80% of HCC patients have cirrhosis which is commonly derived from chronic viral hepatitis (HBV and HCV infection) and alcohol abuse. In 7–30% of HCC patients, cirrhosis of unknown origin (the so-called cryptogenic cirrhosis) was present [59]. The increasing prevalence of obesity and the metabolic syndrome, especially in developed countries, has resulted in increasing incidence of cirrhosis secondary to NAFLD [60]. Similar to HCV infected individuals, patients with NAFLD associated cirrhosis are also at increased risk for developing HCC. In a recently published study involving 68 cirrhotic patients complicated with NASH and 69 patients with cirrhosis caused by chronic HCV infection [61], approximately 11.3% of patients with NAFLD-associated cirrhosis and 30.5% of patients with HCV-related cirrhosis develop HCC over a period of 5 years. In another study, 195 patients with NASH-associated cirrhosis and 315 patients with HCV-related cirrhosis were followed up for a period of 3.2 years, during which period 12.8% of patients with NASH-associated cirrhosis and 20.3% of patients with HCV-related cirrhosis developed HCC, with an estimated yearly cumulative incidence of HCC being 2.6% and 4.0%, respectively [62]. Recently, a systematic review showed that NAFLD or NASH patients without cirrhosis had a cumulative HCC mortality of 0–3% up to 20 years, and cohorts with NASH and cirrhosis had a consistently higher risk (cumulative incidence ranging from 2.4% over 7 years to 12.8% over 3 years) [7]. Clearly, patients with NASH associated-cirrhosis are at an increased risk of liver cancer.

4.2. Diabetes mellitus

Patients with NASH are frequently complicated with DM, and DM causes more severe NASH and cirrhosis. In a recent systematic review of 13 case-control studies, diabetic subjects were found to have a twofold increase in the risk of HCC [63]. Together with obesity, DM may be responsible for a proportion of HCC cases in whom HBV and HCV infection were not identified [64]. In addition, DM has been shown to synergistically increase the risk for HCC with other risk factors such as alcoholic liver disease (ALD), chronic HBV and HCV infection [65]. The correlation between DM and HCC is also reflected by the fact that DM increases the risk for HCC recurrence after curative therapy [66,67]. Overall, it is estimated that DM increases the risk of HCC by 2–3 folds [63,65,68], and DM by itself is believed to be an important risk factor for HCC [65,69]. The development of HCC is the most worrisome liver-related complication in diabetic patients [63,65,68,69].

However, other studies have showed that DM increases the risk of HCC only when other well-recognized risk factors are present, such as alcoholism, cirrhosis, and viral hepatitis [70]. Therefore, DM may be just a compounding factor on top of other risk factors for HCC. The discrepancy between different studies regarding the role of DM in HCC may be caused by differences of the underlying studies such as the types of DM, clinical course and treatment of DM, the type of liver cancer (primary or secondary), the sample size and study populations. Thus, a generalized causal link between DM and HCC requires further validation in large multinational studies.

4.3. Obesity

Nowadays, around 25–30% of world’s population is classified as overweight and obese [71–73]. Overweight and obesity have been well-recognized as independent risk factors for the development of several types of malignancies including liver cancer [74–76]. The relative risk (RR) of obesity-related liver cancer ranged from 1.5 to 4.0 [2]. In a meta-analysis, it was revealed that the RR for overweight (Body Mass Index (BMI), 25–30 kg/m²) and obese (BMI ≥ 30 kg/m²) patients to develop liver cancer was 1.17 (95% confidence interval, 1.02–1.34) and 1.89 (95% confidence interval 1.51–2.36), respectively [77]. These data were further supported by another recently published meta-analysis involving 11 cohort studies, in which overweight and obese patients were found to increase their risk of developing HCC by 17% and 89%, respectively [63]. In overweight and obese patients, increased visceral fat accumulation is not only responsible for the increased risk of HCC development [78], but is also an independent risk factor of HCC.
NAFLD and HCC are summarized in Fig. 1. The presence of metabolic syndrome, alterations in adipokines, toxin exposure, key genetic mutations have roles in the progression of steatosis to HCC in the presence or absence of inflammation, fibrosis and cirrhosis. However, HCC never has been diagnosed in a simple fatty liver in human (the arrow with dotted line represents questionable evidence). The prevalence of HCC in NAFLD and NASH are respectively 0–0.5% and 0–2.8% within 19.5 years. About 4–27% of NASH-related cirrhosis patients progress to HCC over time. (Solid lines: with clear experimental or epidemiological evidence; dotted line: possible mechanisms).

5. Potential mechanisms of liver cancer in the setting of NAFLD

Detailed mechanisms for NAFLD-related HCC remain to be resolved. Some of the hypothetical mechanisms have been summarized in several review articles [2,4,79]. In addition to the most reported mechanisms such as oxidative stress, insulin resistance, adipocytokine functional disorder, and cell hyperplasia, hepatic iron overload has been closely linked with the development of HCC in the setting of NAFLD. To date, HCC has rarely been found in a “pure” fatty liver in human. However, the OB/Ob mice with insulin resistance develop fatty liver and HCC without overt hepatic inflammation or cirrhosis. HCC have also been described in animal models of hepatic steatosis unrelated to insulin resistance but characterized by increased oxidative stress [80].

The liver is the main storage site for iron in the body because of its rich reticuloendothelial system. Abnormal iron deposition in the liver is more frequent in NASH, in which necroinflammation may be the driving factor. Iron and the coexistence of hyperinsulinemia are risk factors for the development of NASH and together they may contribute to the development of insulin resistance [81], disease progression and HCC [82]. The role of iron in the development of NASH-related HCC is illustrated by a recent study which revealed that iron deposition in the liver was more frequent in patients with NASH-related cirrhosis who later developed HCC than in those without HCC [83]. Raised hepatic level of iron is associated with increased liver fibrosis, and iron excess in the liver can act as a co-morbid factor (along with fat, hepatitis viruses and alcohol) and fuel oxidative stress-driven cell toxicity. Iron has been shown to activate the signaling pathways involved in liver fibrogenesis and carcinogenesis [84]. Free iron also induces immunologic abnormalities that may decrease immune surveillance for malignant transformation. The ionic iron may directly cause hepatocarcinogenesis [85]. Iron deprivation can suppress HCC growth in vivo and in vitro experiments and animal models, as well as the studies concerning the long term impact of effective intervention of NAFLD on the development of HCC should be carried out in order to reach a generalized conclusion.

6. Conflict of Interest Statement

None.

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