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Nonalcoholic fatty liver disease and hepatocellular carcinoma

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ABSTRACT

The fastest growing cause of cancer-related death is hepatocellular carcinoma (HCC), which is at least partly attributable to the rising prevalence of non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of conditions, ranging from non-progressive bland steatosis to malignant transformation into hepatocellular cancer. The estimated annual HCC incidence in the progressive form of NAFLD – non-alcoholic steatohepatitis (NASH) – is about 0.3%. The risk of HCC development is higher in men and increases with age, more advanced fibrosis, progressive obesity, insulin resistance and diabetes mellitus. Studies on the molecular mechanism of HCC development in NAFLD have shown that hepatocarcinogenesis is associated with complex changes at the immunometabolic interface. In line with these clinical risk factors, administration of a choline-deficient high-fat diet to mice over a prolonged period results in spontaneous HCC development in a high percentage of animals. The role of altered insulin signaling in tumorigenesis is further supported by the observation that components of the insulin-signaling cascade are frequently mutated in hepatocellular cancer cells. These changes further enhance insulin-mediated growth and cell division of hepatocytes. Furthermore, studies investigating nuclear factor kappa B (NF-κB) signaling and HCC development allowed dissection of the complex links between inflammation and carcinogenesis. To conclude, NAFLD reflects an important risk factor for HCC, develops also in non-cirrhotic livers and is a prototypic cancer involving inflammatory and metabolic pathways.

Strengths/weaknesses and summary of the translational potential of the messages in the paper. The systematic review summarizes findings from unbiased clinical and translational studies on hepatocellular cancer in non-alcoholic fatty liver disease. This provides a concise overview on the epidemiology, risk factors and molecular pathogenesis of the NAFL-NASH-HCC sequence. One limitation in the field is that few HCC studies stratify patients by underlying etiology, although the etiology of the underlying liver disease is an important co-determinant of clinical disease course and molecular pathogenesis. Molecular profiling of NAFL and associated HCC holds great translational potential for individualized surveillance, prevention and therapy.

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1. Background and Introduction

Fatty liver is histologically characterized by increased hepatocellular storage of triglycerides, where – according to a recent consensus paper – the histo-pathological diagnosis "steatosis" is defined by the finding of lipid deposition in >5% of hepatocytes whereas the involvement of more than 50% of hepatocytes is referred to as "fatty liver" [1]. Hepatic steatosis

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and fatty liver are typically associated with high alcohol intake, but can also occur in patients without significant alcohol consumption. Based on this observation, the term "non-alcoholic steatohepatitis" NASH had been coined by Jürgen Ludwig in 1980 [2]. Follow up studies with serial liver biopsies have shown that the association of hepatic steatosis with inflammation ("steatohepatitis"), apoptosis, fibrosis, Mallory–Denk bodies and hepatocellular ballooning was not universally associated with progressive liver disease [3,4]. Further long-term follow up studies led to the recognition that in the absence of significant inflammation "non-alcoholic fatty liver" indicates no increased risk of liver-related complications [5].

The implications from these observations for clinical practice are that non-alcoholic fatty liver encompasses a broad spectrum of disorders ranging from a benign and reversible condition with increased triglyceride storage to a progressive and potentially lethal liver disease. To appropriately reflect the variable course of the disease, non-alcoholic fatty liver disease (NAFLD) is categorized into the non progressive form non-alcoholic fatty liver (NAFL) and a potentially progressive form termed non-alcoholic steatohepatitis (NASH) [6]. This classification follows the concept that inflammation in patients with NASH can progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC).

The concept of linear progression of NAFLD where fibrosis and cirrhosis result from repair mechanisms induced by inflammation (NASH) and hepatocellular carcinoma is a complication of cirrhosis has been recently challenged mainly for two reasons. First, more recent studies have shown that even NAFL can progress to NASH in 44% even in patients without histological inflammation at baseline [7]. Second, HCC has been increasingly recognized in patients without cirrhosis [8,9]. Although fibrosis, cirrhosis and hepatocellular carcinoma appear to be the generic responses to any kind of liver injury, the time-course and sequence of events appear to be even less predictable in NAFLD than in chronic hepatitis C or alcoholic liver disease.

The aim of this article is to review the distinct pathogenesis of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease for research and patient care.

2. Epidemiology of Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver and Risk Factors for Hepato-Carcinogenesis

2.1. *Prevalence and Incidence*

The incidence and prevalence of HCC in NAFLD depend on the stage of underlying fatty liver disease, patient characteristics and comorbidities (Table 1 and Table 2). According to a recent meta-analysis in cohorts of patients with non-cirrhotic stages of NAFLD, the cumulative HCC mortality was 0%–3% for study periods up to 20 years. In cohorts with NASH cirrhosis the cumulative incidence ranges from 2.4% over 7 years to 12.8% over 3 years [10]. Hence, disease stage is the most important risk factor and the HCC risk is highest in patients with NASH-cirrhosis. However, studies comparing NASH cohorts with HCV-cirrhosis have shown that the relative risk for the development of HCC is actually lower in NASH cirrhosis than in HCV cirrhosis [11–14].

2.2. *Obesity*

Observational studies have further shown that obesity [15], diabetes [16], high iron [17] and alcohol consumption [18] are further risk factors for HCC development in NAFLD [19,20].

Obesity is generally associated with an increased risk of developing malignancies. In particular the risk for the development of gastrointestinal tumors, urinary tract malignancies, non-Hodgkin's lymphoma and myeloma increases with body mass index. For liver cancer, a clear relationship between the degree of obesity and cancer risk has been shown. The relative risk for HCC development increases from 1.13 in patients with BMI 25–29.9 kg/m^2 to 4.52 in individuals with BMI 35–39.9 kg/m^2 [21]. A more recent and detailed study shows, that especially childhood obesity predisposes to the development of hepatocellular cancer [22]. Epidemiological evidence also supports the positive correlation between obesity and HCC. A potential limitation of such studies is that controlling for confounders associated with obesity such as diabetes is notoriously difficult [23]. For a comprehensive and recent review on the molecular

Table 1 – HCC incidence in NAFLD.

Author	Year	n	Population	Diagnostic tool	Median follow up (*mean follow up)	Cumulative incidence	Estimated annual incidence
Ascha et al. [18]	2010	195	NASH cirrhosis	Abdominal CT and AFP every 6 months	3.2 years	12.8%	4.0%
Adams et al. [72]	2005	420	NAFLD	Review of medical records	7.6 years	0.5%	0.1%
Hui et al. [12]	2003	23	NASH cirrhosis	Clinical monitoring every 6 months	5 years	0%	0.0%
Teli et al. [5]	1995	40	NAFL	Review of medical records	11 years	0%	0.0%
Powell et al. [4]	1990	42	NASH	Review of medical records	4.5 years	2.4%	0.5%
Ratziu et al. [13]	2002	27	Cryptogenic cirrhosis	Review of medical records	0.78 years	8.0%	10%
Sanyal et al. [73]	2006	152	NASH cirrhosis	Ultrasound and AFP yearly to 6 monthly	10 years	2.0%	0.2%
Yatsuji et al. [14]	2009	69	NASH cirrhosis	Not reported	5 years	11.3%	2.3%
Bhala et al. [11]	2011	257	NASH cirrhosis and advanced fibrosis	Not reported	7.1 years*	2.4%	0.3%

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