NAFLD, Hepatocellular Carcinoma, and Extrahepatic Cancers

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10.1 Introduction

Hepatocellular carcinoma (HCC) stands as the most overlooked complication of NAFLD and probably the most challenging in clinical practice. The large burden of the underlying liver disease, the chance of HCC arising in the absence of cirrhosis, and the incomplete knowledge of the mechanisms leading to carcinogenesis in NAFLD hampers the development of markers for targeting subjects at high risk and contributes to impede an effective care of patients with HCC.

10.2 Risk Factors for the Development of HCC in NAFLD

Beyond the well-known risk factors of underlying cirrhosis and male gender, several specific factors concur to increase the risk of HCC in NAFLD and translate into the unpredictable onset of cancer even in a non-cirrhotic liver.

10.2.1 Obesity and Type 2 Diabetes

Obesity and type 2 diabetes (T2DM) have a well-established, independent, and cumulative impact in the development of HCC, also in cirrhosis of viral and alcohol-related

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etiology [1, 2]. The likelihood of dying from liver cancer in men with a body mass index (BMI) of 35 kg/m^2 or above over 16 years of follow-up is increased by 4.5-fold compared to men with a normal BMI (18.5–24.9 kg/m^2) [1]. The association between BMI and liver cancer is more marked in men than women and the risk linearly increases starting from BMI above 22 kg/m^2 [3]. A meta-analysis of 11 cohort studies estimated that the risk of HCC is increased by 17% in overweight and by 89% in obese subjects, with an average 24% increase in risk for each 5 kg/m^2 increase in BMI [4].

The association of obesity and incident HCC has an ethnic specificity as it is observed in white Caucasian, Latino, and Asian men, but not in Afro-Americans [5]. Visceral fat accumulation is likely to play an important role, particularly in the non-obese population. The waist-to-hip ratio, a rough estimate of abdominal fat, can predict better than BMI the incidence of HCC [6].

Similarly to obesity, in diabetes the risk of HCC is on average increased by 20%, with a hazard ratio (HR) of 2.24 in males and 1.94 in females compared with non-diabetic subjects [7].

Among the single features of MetS, T2DM is associated with the highest risk for HCC (up to fourfold compared with nondiabetics), followed by obesity (up to twofold compared with non-obese). Combining multiple hallmarks of MetS, the risk of HCC increases in parallel with the number of features considered, reaching the highest risk (+475%) in patients who are overweight and diabetics [8]. Both obesity and T2DM per se exert a carcinogenic potential, but the underlying presence of NAFLD and NASH is usually underestimated, and HCC may be the presenting feature of a clinically insidious and asymptomatic liver disease.

10.2.2 Genetic Background

Multiple risk factors related to host phenotype significantly interact with the genetic background to increase the risk of malignancy (see also Chap. 8). The PNPLA3 rs738409 [G] risk allele, found in 40% of the European population, is repeatedly reported to increase about 12-fold the risk of developing HCC [9]; further, among HCC patients, GG homozygosity is also associated with younger age, shorter history of cirrhosis or less advanced liver disease, and more diffuse HCC at diagnosis, hence reduced survival. Other uncommon genetic variants seem to influence HCC development in a fatty liver. The most important is the human telomerase reverse transcriptase (TERT) gene, which is upregulated in human cancer and is a hallmark of HCC in patients carrying loss-of-function TERT mutations [10].

10.2.3 Other Risk Factors

The combination of metabolic and genetic risk factors above described could be a fertile soil for the malignant degeneration of benign liver lesions, such as hepatocellular adenomas (HCA), also in the absence of cirrhosis. There is an association

between the rising prevalence of obesity and MetS and the recent increase in the HCA prevalence, more likely inflammatory (I-HCA) [11, 12]. Obesity and MetS has been often associated with multiple and bilobar adenomas, leading to a higher rate of incomplete resection, and with progression of HCA; conversely, stability or regression of tumor burden is described in up to one-third of patients complying with lifestyle changes (weight loss >5%) [11]. In a French study which analyzed 31 HCC patients who had MetS as the only risk factor, one-third of these cases developed in a preexisting hepatocellular adenoma [13], while a literature review of 1600 adenomas showed that nearly 4% of them presented HCC features at the time of resection [14].

10.3 Epidemiology of HCC in NAFLD

NAFLD is the source of HCC most rapidly increasing, in parallel with the spread of obesity and diabetes across the general population [15, 16]. It is necessary to recall that NAFLD may remain unrecognized in cases of HCC arising in cryptogenic cirrhosis, a condition for which no underlying etiology has been clinically identified. It is estimated that 20–40% of all HCC cases in industrialized countries occur in patients with cryptogenic cirrhosis. Most of the cases have been identified as "burnout NASH," bearing historical or metabolic vestiges of MetS but no longer having classic biopsy features (31, 32 di ARM), which often disappear in cirrhosis.

In the United States, NAFLD represented the third most common cause of HCC, after hepatitis C and alcohol-related disease, being diagnosed in 14.1% of patients with HCC [17]. In North-East England, HCC associated with NAFLD had a more-than-tenfold increase in between 2000 and 2010, accounting for 35% of all the cases of HCC [18]. Hence, it is not surprising that NAFLD is the most rapidly increasing indication for liver transplantation (LT) due to HCC in USA, where from 2002 to 2012 the number of NAFLD-related HCC increased by 365% and become the second leading cause of LT after HCV-related cases [19]. The growing importance of HCC arising in NAFLD will become obvious after the decline of HCV infection thanks to direct-acting antivirals therapy although it will take decades to occur.

The risk of HCC occurrence in NAFLD is lower than in chronic hepatitis C. Overall, the 1-year cumulative incidence of HCC in patients with NAFLD has been estimated at around 2.5% compared with 4% in patients with hepatitis C, while the 5-year incidence rises to 11% and 30%, respectively [20]. However, the lower prevalence and incidence of HCC in NAFLD must be outweighed by the much larger spread in industrialized countries and the steady rise of its risk factors also in developing countries. Importantly, the alarming growth of NAFLD in the pediatric population can bear an increased risk of liver-related complications in adulthood. A longitudinal study [21] including Danish schoolchildren aged 7–13 years showed that each unit increase in BMI *z*-score will rise by 20–30% the risk of liver cancer 30 years later. Similarly, a study in the USA [22] reported that each unit increase in BMI in the mid-twenties can hasten by 4 years the occurrence of liver cancer,

confirming that obesity in early adulthood is associated with increased risk of developing HCC at a younger age in the absence of other relevant risk factors. These data highlight once again the importance of a global policy for the prevention of obesity and its related complication since childhood.

10.4 HCC in Non-cirrhotic NAFLD

HCC can also develop in non-cirrhotic NASH, with at least 116 such cases reported so far since 2004. The initial observation had been made in a single-center pathological study on 128 patients undergoing liver resection for HCC between 1995 and 2007 [23]; HCC arising in livers without significant fibrosis occurred more frequently in patients with metabolic syndrome (MetS) and NAFLD (65.5%) than in patients with known liver disease of other origin (25%). This peculiar feature has been afterwards confirmed by epidemiological studies. In a U.S. Veterans Administration cohort [24], the risk of HCC in the absence of cirrhosis was fivefold higher in patients with NAFLD, compared to those with chronic hepatitis C. In a tertiary center for HCC referral in Northern England [18], those with NAFLD as underlying liver disease had a lower prevalence of cirrhosis (77.2%) compared with other etiologies. As these patients were not in surveillance programs, the majority (62.3%) presented symptomatically, with larger tumors, and their median survival was just 7.2 months.

10.5 Molecular Mechanisms of Carcinogenesis

Some HCC developing in NAFLD patients could belong to a particular subtype of hepatic tumors with distinct histological features, called "steatohepatitic hepatocellular carcinoma," characterized by histological hallmarks resembling steatohepatitis, such as steatosis, hepatocyte ballooning, Mallory bodies, and peri-hepatocellular fibrosis [25]. Mechanisms linking the progression of steatosis to HCC, with or without cirrhosis, are probably more related to the pathogenesis of the underlying disease rather than to fibrosis, with an important role attributed to environmental factors leading to obesity and diabetes (Fig. 10.1). The common soil of insulin resistance (IR) and hepatic steatosis favors liver carcinogenesis by promoting adipose tissue-derived inflammation, hormonal changes, oxidative stress and lipotoxicity, and stimulation of the IGF-1 axis by hyperinsulinemia. Other mechanisms involving diet, gut microbiome, and genetic factors are increasingly important. Western high-fat diet can induce the expression of cytokines like IL-6 and TNFα and increase NF-κB activation [26]. Fructose may play an important role by increasing lipoperoxidation [27], downregulating the expression of sirtuin-1, involved in the regulation of cellular survival, or altering the intestinal microbioma composition [28]. Gut microbioma contributes to hepatic inflammation by increasing intestinal permeability, promoting translocation of bacterial components such as lipopolysaccharides and favoring the activation of the toll-like receptors.

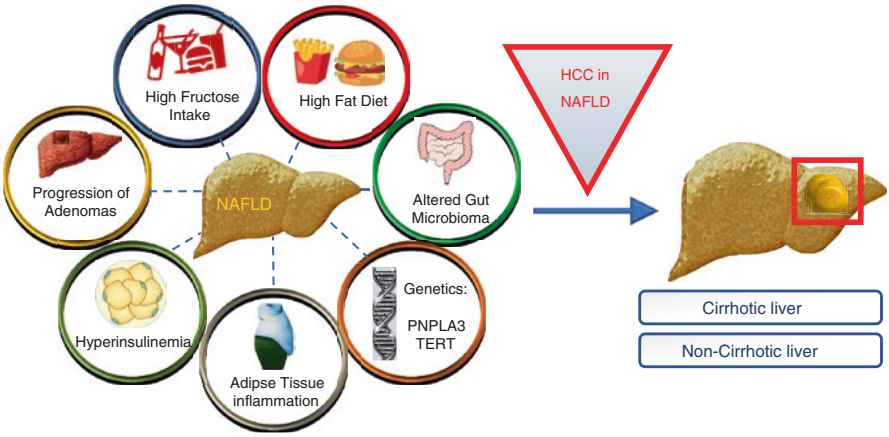

Fig. 10.1 Mechanisms promoting the onset of HCC in NAFLD

10.6 Surveillance of HCC

Poor surveillance is a constant problem for NAFLD patients, and liver-related complications can be the presenting features. Approximately 60% of patients with HCC related to NAFLD missed regular surveillance resulting in more advanced HCC burden at diagnosis compared to patients with hepatitis C [29, 30]. Systemic surveillance for HCC is currently impracticable in patients without cirrhosis. In a retrospective analysis, 86% of patients with HCC in non-cirrhotic liver had a larger nodule size and/or a greater rate of recurrence compared with 14% of patients with HCC in cirrhosis [13], leading to a reduced chance of curative treatment [31].

Programming an optimal screening strategy for the early detection of HCC in NAFLD is not trivial because of the burden of potential candidates for systemic surveillance (including non-cirrhotic patients) and the absence of reliable non-invasive tools and molecular signatures able to stratify the risk in the NAFLD population. In consequence, specific recommendations are lacking in current guidelines. The practice of oncologic follow-up on an individual basis is supported by three out of five guidelines on the management of NAFLD [32–34]. The guidelines of the Asia-Pacific region suggest the extension of screening to those "cancers whose incidence is increased by MetS," but without a generalized and standardized program. The most recent EASL-EASD-EASO clinical practice guidelines still indicate that the large number of NAFLD cases at risk of HCC makes systematic surveillance largely impracticable [32]. In the current guidelines for management of HCC, surveillance is recommended in NAFLD patients with cirrhosis only, according to standard practice (twice-yearly ultrasound examination of the liver) [33]. Surveillance is deemed as cost-effective if the expected risk for incident HCC exceeds a threshold of 1.5% per year, but epidemiological studies in non-cirrhotic NASH are still inadequate to answer this question [33, 35]. Of note, surveillance by abdominal ultrasound has a suboptimal performance in NAFLD patients, with a high rate of under-recognition

of small nodules [36, 37]. Recently a scoring system based on age, sex, medical history of diabetes and viral hepatitis, aminotransferases, and α-fetoprotein was able to identify almost all HCC cases detected by ultrasound in Taiwan high-risk patients [38].

10.7 Prevention of HCC

Despite many uncertainties, available knowledge suggests that HCC in NAFLD develops slowly during a lifetime; however, the earlier the exposure to risk factors, the earlier the onset of malignancy, particularly on a genetically predisposed background. Hence, prevention of obesity starting from childhood should be a priority in the agenda of educational programs and of health-care providers. Lifestyle modification can be able itself to change the natural history of the disease. In a prospective cohort study in Taiwan analyzing risk prediction models for HCC (n = 428,584, HCC = 1668) during an average follow-up of 8.5 years, physical activity reduced the risk of developing HCC proportionally to the intensity of exercise and regardless to the etiology of liver disease [38]. Secondly, effective therapies to cure NASH can reduce the burden of patients at high risk for developing HCC. In the last years, the landscape of potentially curative treatments is rapidly growing, as reviewed in Chapter 17.

Among old drugs often prescribed in NAFLD patients, metformin seems to enhance antitumor mechanisms by mTOR inhibition [39]. In a meta-analysis, the use of metformin in 105,495 patients with T2DM was associated with a reduction of 50% in HCC risk, while the risk was increased when sulfonylurea or insulin was used [40]. Further, metformin seems to improve the outcome of HCC treatment: in a prospective Taiwanese study in diabetic patients with early stage HCC undergoing radiofrequency ablation, a lower mortality rate was observed in patients under metformin [41]. Statins may also decrease the risk of cancers through antiproliferative, proapoptotic, antiangiogenic, and immunomodulatory effects. A systematic meta-analysis from 26 randomized, controlled trials, including almost 1.5 million patients and 4298 cases of HCC, showed that the use of statins was associated with a 37% reduction in HCC incidence after adjusting for potential confounders [42]. All these data suggest that the use of these medications should be encouraged in patients with NAFLD beyond their metabolic and cardiovascular benefits.

10.8 Treatment of HCC

The therapeutic options for NAFLD-related HCC are the same as those for any patient with liver disease (LT, resection, radiofrequency ablation, chemoembolization, sorafenib) [35], but late diagnosis, older age, and concurrent metabolic or vascular disease restrict the options for potentially curative treatments. Furthermore, loco-regional treatments can be limited by technical difficulties in ultrasound detection or by peripheral atherosclerosis, while increased risks for infection, metabolic

decompensation, and cardiovascular complications can hamper surgical options [43]. The drawbacks of older age, higher rate of cardiovascular and metabolic comorbidities, and higher rate of unresectable HCC can be partially outweighed by a better preserved liver function or a lower prevalence of cirrhosis in these patients. In a retrospective cohort in USA assessing the outcome of curative treatments for HCC [10], NAFLD patients had a better hepatic synthetic function than patients with hepatitis C or alcohol-related liver disease, and were more likely to undergo liver resection (41% in the NAFLD group compared with 13% in the hepatitis C and alcohol-related liver disease group, $p = 0.002$).

In accordance with these data, recent findings suggest that NAFLD patients do not have a different morbidity and mortality compared to other etiologies after surgical treatment for HCC. In a study which evaluated the outcome of HCC treatment in 303 patients from 2000 to 2010, after a median follow-up of 50 months, no difference was found in recurrence-free survival and overall survival between NAFLD and HCV or alcohol-related HCC, independent of other pathologic factors and type of curative treatment [10]. Regarding liver transplantation, from 2002 to 2012, the indication for LT in patients with HCC and NAFLD has increased by nearly fourfold compared to a twofold increase in those with HCV-related HCC [19]. However, patients with NAFLD are less likely to receive a liver graft than patients with HCV or alcoholic liver disease [44]. Very high BMI, especially morbid obesity, represents a contraindication to LT, and some centers begin to consider obesity treatment like bariatric surgery as preparation for LT. Even though it might be difficult or impossible in patients with end-stage liver disease, preliminary results suggest that combined LT along with sleeve gastrectomy might be considered in selected cases [45]. After LT, the 5-year survival in NAFLD does not differ from non-NAFLD because the greater risk of death from cardiovascular complications and sepsis is outweighed by a lower risk of graft failure [46].

10.9 NAFLD and Extrahepatic Cancers

The second most common cause of death among NAFLD patients is attributed to malignancies at either gastrointestinal (liver, colon, esophagus, stomach, and pancreas) or extraintestinal sites (kidney in men and breast in women) [47–50]. Although the evidence is still preliminary, the colon is the main extrahepatic site where a link between NAFLD and cancer seems to be consistent. Most studies, both community-based and hospital-based, have been conducted in East Asia. Almost all of these studies showed a higher prevalence of colorectal lesions in patients with NAFLD compared to patients without NAFLD. In a large retrospective cohort study of 5517 Korean women, Lee et al. observed a twofold increase in the occurrence of adenomatous polyps and a threefold increase in the risk of colorectal cancer (CRC) in patients with US-diagnosed NAFLD compared to controls [51]. The risk of CRC is further increased in NASH. In a Chinese study, NASH patients harbored a fivefold increased risk of both adenomas (OR 4.89) and advanced neoplasms (OR 5.34) even after adjusting for demographic and metabolic factors [52]. Importantly,

a significant proportion of lesions developed in the proximal colon and at a much younger age. In Caucasians, much less data are available. In a large European study ($n = 1382$), Stadlmayr et al. observed that male patients with US-diagnosed NAFLD had a higher prevalence of colorectal adenomas and early CRC compared to those without NAFLD, and the increased risk (OR 1.47) was independent of other known factors [53].

The role of fatty liver in the increased risk of CRC is purely speculative. A generic increased risk of cancer in NAFLD is common to all the components of MetS and is due to increased insulin and insulin growth factor (IGF) levels [54], which exert their normal activity as growth factors and stimulate cell proliferation, apoptosis, and production of vascular endothelial growth factor [55]. Conversely, decreased adiponectin levels restrain its proapoptotic activity and anticarcinogenic action [56, 57]. The increased pro-inflammatory state characteristic of NASH may further influence apoptosis and tumor cell proliferation [58, 59]. However, the increased risk of cancers in the bowel rather than in other sites does not appear casual in NAFLD as the liver stays at the cross-road of the complex interaction between IR and gut microbiota. A dysbiotic microbiota can promote tumorigenesis through chronic inflammation, increased interleukin-6 (IL-6) signaling, and decreased inflammasome-derived interleukin-18 (IL-18), which confers protection against tumors. Several bacterial metabolites, including hydrogen sulfide, secondary bile acids, polyamines, and reactive oxygen species (ROS), have the potential to cause deoxyribonucleic acid (DNA) damage or local inflammation via IL-6 and TNFα production, promoting carcinogenesis. Although it is still early to provide evidence-based recommendations, NAFLD patients should be a target group for CRC screening to reduce its incidence and mortality [52].

10.10 Future Directions

In consideration of the spread of obesity and NAFLD in the general population, the growing incidence of HCC can become a serious challenge for public health, with high costs for surveillance and treatment, including LT. Importantly, a considerable number of NAFLD-associated HCC cases develop in non-cirrhotic livers, particularly in patients with multiple metabolic risk factors. Delay in diagnosis and the presence of relevant comorbidities often limit the possibility of therapeutic intervention. Although weight loss can generally ameliorate obesity-induced complications, the capability to prevent the development of HCC or halt its progression is unknown. Many other questions remain to be answered, including the best strategy for targeting high-risk subjects in the general population. A better understanding of the molecular events leading from obesity to NASH and HCC will allow the discovery of new targets for therapeutic and preventive intervention. In the meanwhile, the best and probably sole effective intervention to address this growing problem is to hinder the spread of obesity and NAFLD through public awareness and education programs.

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