

The Story of HCC in NAFLD

From Epidemiology, Across Pathogenesis, to Prevention and Treatment

Cristina Margini; Jean F. Dufour |
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Abstract

Background & Aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide. An increasing number of reports describe HCC in the setting of obesity and diabetes, two major risk factors for non-alcoholic fatty liver disease (NAFLD). The increasing incidence of these conditions and the emerging evidence of HCC in non-cirrhotic NAFLD prioritize a better understanding of NAFLD-related HCC epidemiology and pathogenesis in order to target screening policies and develop preventive-therapeutic strategies. In this review, we focus on the epidemiological impact of this condition, suggesting a possible link between HCC in cryptogenic cirrhosis and NAFLD. Furthermore, we analyse the suggested pathogenic mechanisms and the possible preventive-therapeutic strategies.

The Magnitude of the Problem

In 2008, primary liver cancer was estimated to be the fourth most often diagnosed cancer in males and the seventh in females;^[1] moreover, it represented the second and fifth causes of cancer deaths, in males and females respectively. The estimate in 2012 was even more alarming, as liver cancer represented the overall second cause of cancer death in the world.^[2] These statistics reflect the poor prognosis of liver cancer worldwide.

The prevalent histological subtype of primary liver malignancies is hepatocellular carcinoma (HCC) that accounts for 70–85% of cases.^[3] The major risk factor for HCC is cirrhosis and the underlying aetiologies are viral infections,^[4,5] alcohol and metabolic factors.

While the epidemiological data concerning HCC in viral hepatitis and alcoholic hepatitis are consistent, there is a lack of strong epidemiological data concerning the incidence and prevalence of HCC in non-alcoholic fatty liver disease (NAFLD). A few longitudinal outcome studies, reviewed by White *et al.*, explored the prevalence of HCC in NAFL/non-alcoholic steatohepatitis (NASH), reporting a prevalence varying from 0% to 3% on a follow-up period between 5.6 and 21 years.^[6] The percentage was increased if the incidence of HCC in NAFLD-cirrhosis was considered, with a cumulative HCC incidence ranging between 2.4% with a median follow-up of 7.2 years and 12.8% with a 3.2-year median follow-up.^[6]

HCC and Obesity

Obesity is associated with an increased relative risk (RR) of dying of cancer. It has been associated with colorectal, breast, endometrial and kidney cancer and oesophageal adenocarcinoma.^[7] This association has also been established for HCC in a population perspective study in the US. More than 900,000 people were enrolled and stratified according to their body mass index (BMI). Interestingly, if matched with normal weight individuals, the RR of dying of HCC was 4.52 and 1.90 in patients with obesity grade II and I respectively.^[8]

A study from Korea confirmed the same connection between HCC and obesity.^[9] The authors selected more than 700,000 men and followed them up for 10 years. They found an increased risk (RR 1.56) of developing HCC in patients with a BMI >30 kg/m². A higher RR for HCC in obese patients has also been described in a Swedish population study of 362,552 subjects (3.1).^[10] An article collecting data from Norway, Austria and Sweden found a RR for HCC in obese subjects of 1.52. Interestingly, in this analysis the RR was adjusted to the alcohol consumption in order to avoid confounding factors.^[11] In a European prospective cohort study, general (RR 2.19) and abdominal obesity (RR 2.03)

correlated with the risk of HCC and this was confirmed in a subanalysis that excluded hepatitis C virus (HCV)/hepatitis B virus (HBV)-positive subjects.^[12] Also, in a study cohort in Italy the correlation of obesity and HCC was confirmed; remarkably, the OR progressively increased if the patients had concomitant metabolic syndrome factors^[13] ().

Table 1. Risk of developing HCC in obese and diabetic patients

Article	
BMI >30	
Oh <i>et al.</i> (9)	RR 1.56
Samantic <i>et al.</i> (10)	RR 3.1
Borena <i>et al.</i> (11)	RR 1.52
Schlesinger <i>et al.</i> (12)	RR 2.19
Turati <i>et al.</i> (13)	OR 1.97
Diabetes	
Adami <i>et al.</i> (14)	SIR 4.1
El-Sarag <i>et al.</i> (15)	HR 2.16
Turati <i>et al.</i> (13)	OR 4.33

HR, hazard ratio; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio.

HCC and Diabetes

A population-based study published in 1996 followed up 153,852 subjects and found a standardized incidence ratio (SIR) for HCC in diabetic patients of 4.1.^[14] A retrospective analysis on the US Veteran Registry found that diabetes increased the risk of primary liver cancer only in the presence of other risk factors such as hepatitis C or B or alcoholic cirrhosis.^[15] These results were not supported by further analysis that found an increased HCC risk in diabetic patients^[13] independently from alcoholic liver disease and viral hepatitis^[16] ().

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HCC in Cryptogenic Cirrhosis

In a varying percentage (6.9–50%) of HCC, the underlying etiology of liver disease cannot be determined.^[17–19] In 2002, Bugianesi *et al.* retrospectively studied 641 cases of HCC and identified 44 patients (6.9%) with cryptogenic cirrhosis (CC). The prevalence of diabetes and obesity was significantly higher in these subjects if compared to patients with viral and alcohol cirrhosis. Obesity and diabetes are also two recognized risk factors of NASH and the authors suggest that NASH might represent the missing link between CC and HCC.^[20] This hypothesis might generate particular interest, especially if we consider that the pathological features typical of NASH, which are necessary for its diagnosis, may not be present in late stages of liver disease^[21–23] and that in decompensated cirrhosis, the typical clinical characteristics of NAFLD, like obesity, may be missing. Another prospective study from the US analysed liver disease aetiology in HCC and CC accounted for up to 29% of the cases. Half of these patients expressed histological or clinical features of NAFLD and at least 13% had histologically confirmed NAFLD.^[19] These data suggest that the role of NAFLD in HCC might be underestimated by the current epidemiological data and that NAFLD could account for part of the CC-related HCC.

We are therefore facing a disease, HCC in NAFLD, whose epidemiology is not well defined and whose impact is expected to grow, together with the increasing incidence of obesity and diabetes.^[7] It is in fact estimated that up to 70% of patients with type 2 diabetes and up to 90% of obese patients might have some degree of fatty liver disease.^[24,25]

Pathogenesis: Proposed Mechanisms

The emergence of HCC in chronic liver disease requires time – decades of gradual transition through a dysplasia-carcinoma sequence.^[26] There are multiple oncogenic mechanisms involved that contribute to genomic instability, including telomere erosion, chromosome segregation defects and alterations in the DNA-damage-response pathways.^[27]

The mechanisms involved in the development of HCC in NAFLD, are also related to obesity and diabetes^[28] (Fig. 1).

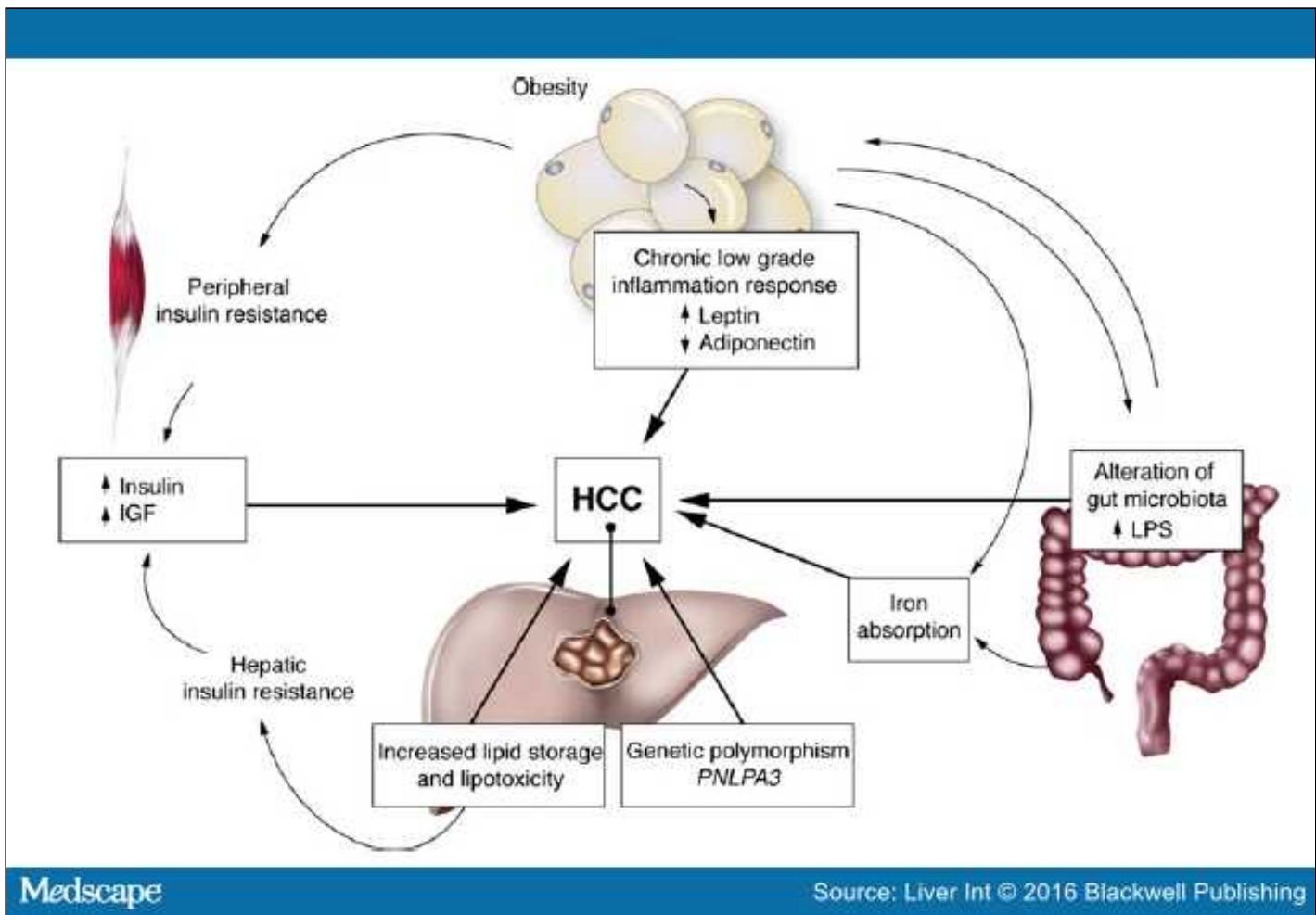


Figure 1.

Pathogenesis of HCC in NAFLD. The development of HCC in NAFLD is most likely multifactorial and involves obesity-mediated mechanisms including low-grade chronic inflammatory response, increased lipid storage and lipotoxicity, alteration of gut microbiota with increased levels of LPS (lipopolysaccharide) and insulin resistance with hyperinsulinaemia and increased IGF levels. Genetic polymorphisms might also contribute to the development of HCC in NASH. Increased iron absorption in NASH has also been reported recently; although the mechanisms are at present still being investigated, a contribution of iron in the development of HCC has been suggested. All these mechanisms are, at least partially, independent from fibrosis and this might explain the epidemiology of HCC in NASH where non-cirrhotic HCC is more than a sporadic event.

Obesity and excessive adipose tissue contribute to a chronic general low-grade inflammatory response that is believed to play an important role in HCC development.^[29] Particularly, obesity is linked to increased levels of leptin, a proinflammatory, proangiogenic and profibrogenic cytokine with a growth-promoting effect through the activation of the Janus kinase (JAK) pathway.^[30,31] In contrast, levels of adiponectin, an anti-inflammatory cytokine, are diminished in obesity.^[32]

Increased lipid storage in the liver is also present through the following mechanisms: overspill from peripheral adipose depots, increased supply via the portal vein, impaired export of very low density lipoprotein (VLDL), impaired elimination by fatty acid oxidation and increased *de novo* hepatic lipogenesis.^[33] The consequence of lipid accumulation in the liver is lipotoxicity that leads to the generation of reactive oxygen species (ROS), endothelial reticulum stress and production of saturated free fatty acids (FFAs) and monounsaturated FFAs. FFAs have the ability to interfere with cellular signalling mechanisms and regulation of gene transcription promoting gene transcriptions

alterations.^[34]

Obesity and increased lipid storage in the liver are also implied in the development of liver specific and systemic insulin resistance and compensatory hyperinsulinaemia. There is supporting evidence that insulin and insulin-like growth factor (IGF) may promote the development of primary liver cancer by activating various oncogenic pathways.^[35]

Obesity may also affect the progression of NAFLD and the development of HCC through the alteration of gut microbiota. Lipopolysaccharide (LPS) is the major component of the outer membrane of Gram-negative bacteria and is an endotoxin that causes inflammation after entering the circulation. Increased levels of LPS in obesity were first described in mice. It is not possible yet to determine if obesity might be the *primum movens* for LPS accumulation or if it might be the alteration of the gut microbiota contributing to obesity. Probably both these interactions are relevant.^[36,37] Interestingly, the role of LPS in the development of HCC is further supported by the observation that gut sterilization and LPS removal result in diminished tumour growth in the chronically injured liver.^[38,39]

An increased iron absorption in NASH patients has been demonstrated in a recent study conducted by Hoki *et al.* through the administration of an oral iron absorption test in patients with NASH and NAFL.^[40] Iron deposition has also been related to HCC development in NAFLD- cirrhosis in a retrospective study published by Sorrentino *et al.*^[41] The underlying mechanisms might be related to oxidative DNA damage^[42] but further studies are needed to better understand the role of iron accumulation in NAFLD and HCC.

Genetic polymorphism might also play a role in the development of HCC in NAFLD. Carriage of the PNPLA3 rs738409 c444C >G minor allele (encoding the I148M variant) has been associated with advanced NAFLD.^[43,44] Burza *et al.* explored whether this polymorphism might also be associated with HCC development^[45] and Liu *et al.* confirmed these results on a larger group of patients^[46] They compared 100 HCC-NAFLD patients with 275 non-HCC NAFLD subjects and found that PNPLA3 rs738409 C>G polymorphism was strongly associated with an increased risk (×2) of HCC. Interestingly, this polymorphism conferred an increased risk independently of potentially confounding factors including age, gender, co-existent diabetes, obesity and the presence of cirrhosis.^[46] Both these studies found a higher risk to develop HCC in patients homozygotes for this polymorphism.^[45,46] The mechanisms by which this PNPLA3 polymorphism may be involved in HCC development could be related to the role of PNPLA 3 in retinol metabolism in hepatic stellate cells, but further studies are needed in order to prove this correlation.^[47]

In contrast, carriage of the FNDC-5 rs3480 minor G allele has been associated with less severe steatosis and milder fibrosis in a population of European Caucasian patients. Although the protective underlying mechanisms are still debated, the authors suggest that FNDC5, released by muscles during exercise, could have a favourable metabolic action.^[48]

HCC in Non-cirrhotic NAFLD

The mechanisms of hepatocarcinogenesis in steatosis might be different from the classic mechanisms involved in cirrhosis and this could explain the high number of reported HCC in non-cirrhotic NAFLD.^[49] It has, in fact, been reported that a significant number of patients with NAFLD-related HCC (more than one-third) have no extensive fibrosis at presentation [reviewed in Baffy *et al.* (.^[50])]. HCC in NAFLD has usually large dimensions, is moderately or well differentiated and generally lacks encapsulation,^[51] and these same characteristics are typical of the non-cirrhotic HCC independently of the aetiology.^[52] A retrospective study of an Australian population compared HCC in cirrhotic and non-cirrhotic NAFLD and found that HCC dimensions were larger in non-cirrhotic livers.^[53]

A recent multicenter study described a large cohort of 157 patients with morphologically characterized HCC and cholangiocellular carcinoma in the background of histologically proven non-cirrhotic hepatic steatosis who underwent liver resection.^[54] Steatohepatitis was more prevalent in the HCC cohort in comparison to the cholangiocellular cohort that showed an incidence similar to the general population, suggesting that steatohepatitis could play an important role in the development of non-cirrhotic HCC. These results showed that 80% of the specimens had a fibrosis F0, and

indeed just 15% had steatohepatitis. Although it is not possible to exclude that at some point in their natural history these patients had steatohepatitis, these results raise the hypothesis that HCC in NAFLD may arise in the absence of histologically evident inflammation.^[54]

An interesting conceptual possibility is the malignant transformation of hepatocellular adenoma (HCA) in non-cirrhotic patients with NAFLD. A correlation between HCA's malignant transformation and metabolic syndrome has been described in a series of American patients.^[55] These data suggest that NAFLD, as the hepatic manifestation of metabolic syndrome, may lead to the development of HCC in the setting of HCA without cirrhosis. Moreover, the Inflammatory-HCA, a subtype related with an increased risk of malignant transformation, has been associated with obesity, further supporting this connection.^[56] Additional epidemiological and pathophysiological data are although needed in order to prove this correlation.

Screening?

As pointed out by the ITALICA study group, HCC was significantly less likely to be diagnosed during surveillance in CC patients if compared with HCV patients and this translated into a greater prevalence of advanced HCC stage and poor survival.^[57] These data are further supported by a study on 1500 HCC patients where NASH-related HCC received less HCC surveillance and treatment compared with HCV and alcohol-related HCC.^[58]

The AASLD and EASL-EORTC guidelines recommend that all patients with cirrhosis should be screened for HCC every 6 months.^[59] In general, surveillance should be performed by ultrasound, but the limits of these methods in obese patients are well known.^[60]

Although some data suggest that HCC may arise from non-cirrhotic and non-steatohepatitis liver, caution is needed in the planning of screening. The lack of robust data on the cirrhotic, and even more in the non-cirrhotic population makes it hard to develop evidence-based, cost-effective screening policies. It could also be suggested that NAFLD might increase the risk of HCC in other liver diseases as it is for aflatoxin in hepatitis B and that screening policies should be implemented earlier in patients with multiple risk factors for HCC, but the available epidemiological data are at present limited. There is a need for trials addressing the problem of screening in NAFLD, and particularly in non-cirrhotic individuals.

Prevention and Treatment

Considering the pathogenesis of HCC in NAFLD, one has to face the burden of obesity and diabetes and implement preventive strategies based on lifestyle changes. Physical activity has been reported to have a preventive effect on the development of HCC.^[61,62] We recently explored the impact of physical activity in a mouse model of NASH and found a protective effect on the development of HCC.^[63] The impact of physical exercise on HCC was evaluated in a prospective cohort study on 507,897 subjects followed up for 10 years: a RR of 0.56 for HCC was found in vigorously active (≥ 5 days/week) compared to sedentary subjects. This result was independent of BMI, suggesting that physical activity might have a role in HCC prevention independently from weight reduction. The hypothesized mechanisms involve the activation of AMPK and the inhibition of mTORC1 activity which are two key growth regulator promoters.^[64]

It has also been suggested that dietary antioxidants (coenzyme Q(12), vitamin C and E, selenium) and certain phytochemicals present in fruit, vegetables, herbs and medicinal plants can prevent hepatocarcinogenesis.^[65] This might be of special interest if we consider that patients with NASH have been reported to have vitamin E and D deficiency^[66] and that vitamin D deficiency might also play a role in hepatocarcinogenesis.^[67] A protective effect in the development of HCC has also been attributed in general to the Mediterranean diet.^[68]

A recent cross-sectional study showed a protective effect of statin in at risk individuals regarding the development of steatohepatitis and fibrosis F2-F4.^[69] More specifically an interesting study showed a decreased incidence of HCC in diabetics treated with statins; this protective effect is probably related to the anti-inflammatory properties of statins

mediated through the inhibition of JAK.^[70]

The use of metformin has been associated with a reduced incidence of HCC in diabetic subjects.^[71–75] The mechanisms involved are related to the activation of AMPK, the same mechanisms supposed to mediate the preventive effects of physical exercise in HCC.^[76] A decreased expression of several lipogenic enzymes has also been suggested as a potential mechanism.^[77] The use of metformin in cirrhotic patients has been reported to be safe in a retrospective analysis on 250 subjects with compensated and decompensated cirrhosis, and conferred an increase in survival in this population.^[78] In contrast, insulin therapy has been suggested to increase the incidence of HCC in diabetics,^[79,80] but these data are still debated.

The therapeutic algorithm used in HCC patients should be applied to patients with HCC due to NAFLD,^[81] and treatment allocation should be based on the BCLC allocation system. One of the limits of this allocation system is the exclusion of the non-cirrhotic population. This might represent an obstacle to the application of the BCLC system in NASH-related HCC if we consider that non-cirrhotic HCC in NAFLD is more than a sporadic event.

Non-alcoholic steatohepatitis-related HCC curatively treated with liver resection has been reported to have a better outcome compared with HCV and alcohol-associated HCC^[82] but problems associated with reduced liver regeneration and tolerance to ischaemia in steatosis might worsen the outcome.^[83] On the other hand, a retrospective study from Germany showed a generally worse outcome for NASH-related HCC in comparison to other liver aetiologies^[84] because of a lower percentage of cases treated curatively. In this context, implementing screening strategies in order to detect HCC in early stages appears to be central.

Conclusion

The present data do not give us the perfect epidemiological image of HCC's burden in NAFLD, but they do let us glimpse the future impact of this condition. Prospective trials addressing the problem are needed in order to identify risk factors for HCC development and to implement screening strategies, particularly in the non-cirrhotic population. Furthermore, new insights in the pathogenesis of HCC in NAFLD might allow therapeutic and preventive strategies to be developed.

Sidebar

Key Points

- HCC risk is increased in obesity and diabetes which are two major risk factors for NAFLD.
- NAFLD might represent the missing link between cryptogenic cirrhosis and HCC.
- The pathogenesis of HCC in NAFLD is also independent of cirrhosis and HCC in the setting of NAFLD might arise in the absence of fibrosis and of histologically detectable inflammation.
- Lifestyle changes and control of metabolic risk factors might prevent the development of HCC; better epidemiological data are needed in order to target screening policies, especially in the non-cirrhotic population.

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Abbreviations

BMI, body mass index; CC, cryptogenic cirrhosis; FFAs, free fatty acids; HBV, hepatitis B virus; HCA, Hepatocellular adenoma; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IGF, insulin-like growth factor; JAK, janus kinase; LPS, lipopolysaccharide; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; ROS, reactive oxygen species; RR, relative risk; SIR, standardized incidence ratio; VLDL, very low density lipoprotein.

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Conflict of interest

The author do not have any disclosures to report.

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