Hepatocellular carcinoma in non-alcoholic fatty liver disease: An emerging menace

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Summary

Hepatocellular carcinoma (HCC) is a common cancer worldwide that primarily develops in cirrhosis resulting from chronic infection by hepatitis B virus and hepatitis C virus, alcoholic injury, and to a lesser extent from genetically determined disorders such as hemochromatosis. HCC has recently been linked to non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of obesity and related metabolic disorders such as diabetes. This association is alarming due to the globally high prevalence of these conditions and may contribute to the rising incidence of HCC witnessed in many industrialized countries. There is also evidence that NAFLD acts synergistically with other risk factors of HCC such as chronic hepatitis C and alcoholic liver injury. Moreover, HCC may complicate non-cirrhotic NAFLD with mild or absent fibrosis, greatly expanding the population potentially at higher risk. Major systemic and liver-specific molecular mechanisms involved include insulin resistance and hyperinsulinemia, increased TNF signaling pathways, and alterations in cellular lipid metabolism. These provide new targets for prevention, early recognition, and effective treatment of HCC associated with NAFLD. Indeed, both metformin and PPAR gamma agonists have been associated with lower risk and improved prognosis of HCC. This review summarizes current evidence as it pertains to the epidemiology, pathogenesis, and prevention of NAFLD-associated HCC. Published by Elsevier B.V. on behalf of the European Association for the Study of the Liver.

Introduction

Liver cancer is the fifth most frequently diagnosed cancer worldwide and the third leading cause of cancer death. In 2008, an estimated 748,300 new liver cancer cases and 695,900 liver cancer deaths occurred, reflecting the poor prognosis of this disease [1]. HCC represents the major histological subtype of primary liver malignancies, accounting for 70% to 85% of the total liver cancer burden [2]. Most cases of HCC (75% to 90%) develop in cirrhosis resulting from chronic infection by hepatitis B virus and hepatitis C virus, alcoholic injury, and to a lesser extent from genetically determined disorders such as hemochromatosis [3,4].

HCC is increasingly common in the United States, with an age-adjusted incidence rising from 1.5 to 4.9 per 100,000 individuals in the past 30 years [5]. This worrisome trend has been primarily attributed to the high prevalence of chronic hepatitis C in this population and it is predicted to plateau by 2020 [6]. However, epidemiological studies indicate that the etiology of HCC is unclear in up to 50% of all cases, making predictions about nearing the peak of its incidence perhaps too optimistic [3,4].

Epidemiology of HCC associated with NAFLD

HCC in obesity and diabetes

Several large-scale epidemiological studies have associated the increasingly prevalent overweight and obesity with a higher risk of HCC [7,8]. In a cohort of 900,000 American adults, the risk of dying from liver cancer was 4.5 times higher in men with a body mass index of 35 kg/m² or above compared to the reference group with a normal body mass index (18.5 to 24.9 kg/m²) [7]. A recent meta-analysis concluded that the summary relative risk of liver cancer was 117% for overweight subjects and 189% for the obese [9].

Type 2 diabetes is an increasingly common metabolic disorder strongly linked to obesity and characterized by hyperglycemia, insulin resistance, and hyperinsulinemia. It has been associated with increased risk of several cancers [10]. Substantial evidence indicates that diabetes promotes the development and progression of HCC [11]. A population-based study from 14% of the United States population found that diabetes conferred a three-fold risk of HCC [12]. In a large prospective cohort study conducted among US veterans, diabetes was associated with a hazard rate ratio of 2.16 for HCC [13]. The association between diabetes and HCC has been further demonstrated by studies published from different geographical locations [14–20] and ascertained by repeated...
cases of NAFLD-associated HCC have been reported [33–35].

HCC has been linked to NAFLD, the major hepatic manifestation of obesity and associated metabolic conditions [22]. The epidemiology of NAFLD mirrors recent changes in the prevalence of obesity and diabetes. NAFLD has become the most common liver disorder in the United States and other industrialized countries, affecting up to 30% of the general adult population and 90% of those with morbid obesity (body mass index greater than or equal to 40 kg/m²) [23,24]. The overlap between the prevalence of NAFLD and diabetes is equally substantial. The rate of biopsy-proven NAFLD among diabetics may reach 74% [25,26], and NAFLD is commonly associated with insulin resistance and hyperinsulinemia even in the non-obese [27].

HCC in advanced NAFLD

While most individuals with NAFLD have isolated steatosis, approximately 20% of all cases present as steatohepatitis, which is microscopically defined and consists of steatosis and a specific form of hepatocellular injury, parenchymal and portal inflammation, and variable degrees of fibrosis with the potential to progress to cirrhosis [28,29]. The first report on HCC complicating NAFLD with cirrhosis was published in 1990 [30]. Subsequent studies of natural history in NAFLD indicated that while steatosis has an almost negligible effect on liver-related mortality [28,29], steatohepatitis is a risk for the development of cirrhosis and HCC [31]. The exact prevalence of HCC in cirrhotic NAFLD remains unknown. Two groups from Sweden described three and five cases of HCC in cohorts of 129 and 256 subjects with NAFLD followed for 13.7 and 21 years, respectively [29,32]. In the past 10 years, approximately 300 cases of NAFLD-associated HCC have been reported [33–35].

The majority of affected patients have been men of median age over 70 years with diabetes and hypertension as common co-morbidities [33–35]. Reports indicate that the risk of HCC due to NAFLD is less than that of chronic hepatitis C. In a ten-year prospective study, ten out of 149 American patients with NAFLD-associated cirrhosis developed HCC compared to 25 out of 147 patients with hepatitis C virus-associated cirrhosis [36]. Another study from the United States found a 2.6% yearly cumulative incidence of HCC in patients with NAFLD-associated cirrhosis compared with a 4.0% incidence in those with hepatitis C virus-associated cirrhosis over a median follow-up of 3.2 years [37]. A prospective five-year study in Japan for the development of HCC found a rate of 11.3% among 68 patients with NAFLD-associated cirrhosis compared to 30.5% among 69 patients with hepatitis C virus-associated cirrhosis [38].

Nonetheless, based on its prevalence and natural history, NAFLD in the United States and other developed countries may become the primary source of HCC and offset the impact of successful measures on reducing the incidence of hepatitis C virus-related liver cancer [4]. This concern was substantiated by a recent study from Germany analyzing 162 cases of HCC that identified steatohepatitis as the underlying etiology in 24% of patients, surpassing chronic hepatitis C (23.3%), chronic hepatitis B (19.3%), and alcoholic liver disease (12.7%) [34].

HCC in cryptogenic cirrhosis

Current figures probably underestimate the role of NAFLD in HCC development. NAFLD and related metabolic factors may act synergistically with other conditions to promote hepatocarcinogenesis. This has been suggested to occur in cirrhosis associated with both chronic hepatitis C infection and alcoholic liver disease [37,39]. In addition, NAFLD may remain unrecognized as the etiology in cases of HCC arising in cryptogenic cirrhosis, a condition for which no underlying etiology has been clinically identified [40]. It is estimated that 30% to 40% of all HCCs in industrialized countries occur in patients with cryptogenic cirrhosis [4]. Studies suggest that the majority of these cases are associated with either prior NAFLD or other features of the metabolic syndrome [41,42]. Sequential biopsy studies have, in fact, documented that active steatohepatitis may eventually result in bland cirrhosis. Since key elements of steatohepatitis such as hepatocellular lipid accumulation, ballooning injury and necroinflammation are often absent in cirrhosis, the diagnosis of NAFLD may be missed unless detailed medical history reveals its prior existence [43]. Excluding a role of alcohol in these and other forms of chronic liver disease remains challenging.

HCC in non-cirrhotic NAFLD

HCC has been documented to occur in livers without underlying cirrhosis or even liver disease. In fact, up to 54% of all cases of HCC develop in non-cirrhotic livers according to various etiologies and geographic areas [44,45]. An uncertain fraction of these likely arise through transformation of hepatic adenomas. A literature review of over 1600 adenomas has shown that up to 4.2% of hepatocellular adenomas harbor HCC at the time of resection [46]. Most reported cases of non-cirrhotic HCC occur in chronic hepatitis B attributed to the direct oncogenic properties of hepatitis B virus through genomic integration and the transactivation effects of HBx protein. In Sub-Saharan Africa, dietary exposure to aflatoxin may synergize with the carcinogenic effects of chronic hepatitis B infection [47]. HCC may also arise without established cirrhosis in 14% to 19% of patients with chronic hepatitis C infection and alcoholic liver disease, although the mechanisms of carcinogenesis remain unclear [44,48]. A rapidly growing literature indicates that NAFLD contributes to non-cirrhotic HCC. Since 2004, at least 116 cases of HCC have been reported in histologically-confirmed NAFLD without cirrhosis (Table 1). This number represents more than one-third of all NAFLD-associated HCC cases reported, suggesting either that non-cirrhotic HCC may occur more commonly in NAFLD than in liver diseases of other etiologies, or a reporting bias. Indeed, some of these reports include cases with F3 (bridging) fibrosis that may represent sampling error or incomplete cirrhosis. Nonetheless, a retrospective French study showed that the etiology of liver disease in 80 cases of HCC remained unknown in 50 (62%) without portal fibrosis in the background livers as opposed to only 15 out of 250 (6%) in which extensive fibrosis or cirrhosis was present [49]. Since most cases without advanced fibrosis had steatosis (52%) and portal inflammation (79%), the majority of patients with HCC of unknown etiology in this series possibly had NAFLD. More recently, the same group analyzed a subsequent cohort of HCC patients (30 men and one woman) with the metabolic syndrome as the only risk factor for liver disease and found mild or no fibrosis in most cases compared to those harboring HCC...
Table 1. Case reports and case series of HCC diagnosed in non-cirrhotic NAFLD.

<table>
<thead>
<tr>
<th>Study, authors, [Ref.]</th>
<th>Cases (n)</th>
<th>Gender</th>
<th>Tumor</th>
<th>Fibrosis (stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benchegroun et al., (France, 2004) [104]</td>
<td>1</td>
<td>M (1)</td>
<td>Solitary</td>
<td>F2</td>
</tr>
<tr>
<td>Bullock et al., (UK, 2004) [105]</td>
<td>2</td>
<td>M (2)</td>
<td>Solitary</td>
<td>F0</td>
</tr>
<tr>
<td>Gonzalez et al., (France, 2004) [106]</td>
<td>1</td>
<td>M (1)</td>
<td>n.r.</td>
<td>F1</td>
</tr>
<tr>
<td>Regimbeau et al., (France, 2004) [42]</td>
<td>10</td>
<td>M (10)</td>
<td>n.r.</td>
<td>F2-F3</td>
</tr>
<tr>
<td>Cuadrado et al., (Spain, 2005) [107]</td>
<td>1</td>
<td>M (1)</td>
<td>Solitary</td>
<td>F2</td>
</tr>
<tr>
<td>Hai et al., (Japan, 2006) [108]</td>
<td>1</td>
<td>M (1)</td>
<td>Solitary</td>
<td>F2</td>
</tr>
<tr>
<td>Ichikawa et al., (Japan, 2006) [109]</td>
<td>2*</td>
<td>M (1), F (1)</td>
<td>Solitary</td>
<td>F2-F3</td>
</tr>
<tr>
<td>Hashizume et al., (Japan, 2007) [110]</td>
<td>3</td>
<td>M (3)</td>
<td>Solitary (2), multifocal (1)</td>
<td>F1-F3</td>
</tr>
<tr>
<td>Guzman et al., (USA, 2008) [51]</td>
<td>3</td>
<td>M (1), F (2)</td>
<td>Multifocal</td>
<td>F0</td>
</tr>
<tr>
<td>Paradis et al., (France, 2009) [50]</td>
<td>16**</td>
<td>M (16)**</td>
<td>n.r.</td>
<td>F0-F2</td>
</tr>
<tr>
<td>Kawada et al., (Japan, 2009) [90]</td>
<td>6</td>
<td>M (3), F (3)</td>
<td>Solitary</td>
<td>F2-F3</td>
</tr>
<tr>
<td>Hashimoto et al., (Japan, 2009) [102]</td>
<td>4</td>
<td>n.r.</td>
<td>Solitary (70%)</td>
<td>F1-F2</td>
</tr>
<tr>
<td>Chagas et al., (Brazil, 2009) [111]</td>
<td>1</td>
<td>M (1)</td>
<td>Multifocal</td>
<td>F1</td>
</tr>
<tr>
<td>Takuma et al., (Japan, 2010) [33]</td>
<td>7</td>
<td>M (3), F (4)</td>
<td>Solitary (5), multifocal (2)</td>
<td>F1-F3</td>
</tr>
<tr>
<td>Ikura et al., (Japan, 2011) [112]</td>
<td>1</td>
<td>M (1)</td>
<td>Solitary</td>
<td>F0</td>
</tr>
<tr>
<td>Ertle et al., (Germany, 2011) [34]</td>
<td>10</td>
<td>M (83.3%)</td>
<td>n.r.</td>
<td>F0-F3</td>
</tr>
<tr>
<td>Yasui et al., (Japan, 2011) [35]</td>
<td>43</td>
<td>M (76.7%)</td>
<td>Solitary (72%)</td>
<td>F1-F3</td>
</tr>
</tbody>
</table>

M: male; F: female; S: solitary; M: multifocal; n.r.: not reported. (See above-mentioned references for further information.)

**Distribution of four cases with steatosis <5% among non-cirrhotic and cirrhotic HCC could not be determined from the published data and only 16 out of 20 reported cases with F0–F2 fibrosis are included here.

***One out of 30 patients in the entire cohort was a female, but gender-specific data for the stage of fibrosis were not reported.

Pathogenesis of HCC associated with NAFLD

General molecular mechanisms

Similar to other cancers, development of HCC in cirrhosis is a stepwise process following a dysplasia–carcinoma sequence that may take several decades to evolve in chronic liver disease [53,54]. In this setting, sustained cycles of hepatocellular destruction and compensatory proliferation in response to metabolic and oxidative toxicity, inflammation, innate and adaptive immunity, and fibrosis create an environment conducive to carcinogenesis. Genomic aberrations accumulate as chronic hepatitis evolves through cirrhosis into HCC. Initially, epigenetic mechanisms may lead to aberrant hypo- or hypermethylation of DNA on CpG groups in the promotor regions and other chromosomal segments in addition to inducing cis- and transactivation and chromatin acetylation [55,56]. Subsequently, these epigenetic changes lead to structural genomic lesions such as point mutations, multiple allelic deletions, chromosomal gains, telomere erosion, and telomerase reactivation [53]. A critical step in these processes is the selection of monoclonal populations of pre-malignant hepatocytes or progenitor cells from which HCC will emerge [57].

The extraordinary heterogeneity of genomic aberrations in HCC suggests that multiple regulatory pathways may be compromised [58]. Indeed, hepatocarcinogenesis has been associated with reactivation of the developmental pathways (e.g., Wnt/β-catenin, hedgehog, and c-Met/hepatocyte growth factor), upregulation of multiple growth factors (e.g., platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor, and transforming growth factor), and stimulation of

associated with an overt cause of liver disease (65% vs. 26%, p <0.0001) [50]. Of note, five of the hepatocellular carcinomas in this series definitely arose from pre-existing inflammatory (telangiectatic) adenoma [50].

The largest group of NAFLD-associated non-cirrhotic HCC to date was recently described in a cross-sectional study from Japan. The authors analyzed 87 cases of HCC occurring in patients with histologically confirmed steatohepatitis and found no established relationship of cirrhosis in 43 cases [35]. Men developed HCC at a less advanced stage of fibrosis than women, and the prevalence of cirrhosis was significantly lower in men than in women (39% vs. 70%, p = 0.008) [35].

HCC has also been reported to develop in patients who have features of the metabolic syndrome and histological evidence of NAFLD, but have neither steatohepatitis nor fibrosis [51]. This observation is particularly alarming as it indicates that hepatic steatosis alone may be complicated by the development of HCC. Relationships between steatosis, steatohepatitis, cirrhosis, and HCC are not necessarily linear and this pattern possibly applies to HCC arising in non-alcoholic, non-cirrhotic fatty liver disease (Fig. 1). Recent analysis of a US health care claim database covering 18 million lives yearly from 2002 to 2008 found that NAFLD was the leading condition with no other risk factor claimed for 38.2% of patients with HCC and cirrhosis was reported in only 46% of these cases [52]. Accordingly, the number of individuals with NAFLD potentially at risk for developing HCC may be much larger than previously thought. This presents a compelling need to understand the pathogenesis and natural history of malignant transformation in NAFLD and review potential strategies for HCC prevention and surveillance in the affected population.
proliferative cell signaling cascades (e.g., mitogen-activated protein kinases, the Janus kinase/signal transducers and activators of transcription [STAT] kinase system, and the phosphoinositide-3-kinase/Akt pathway) [53,54]. The process may be augmented through inhibition of cell cycle regulators (e.g., the retinoblastoma-1 protein) and disruption of pivotal tumor suppressors (e.g., the phosphatase and tensin homolog and the p53) that would normally antagonize uncontrolled and erroneous cell proliferation [53,54].

Complexity of hepatocarcinogenesis results in functional redundancy and robustness that may account for the poor overall prognosis [59]. Moreover, heterogeneous phenotypes of malignant hepatocytes may reflect disease mechanisms that correspond to different etiologies and exhibit different growth characteristics and clinical course [54]. Specific patterns of molecular alterations defined by genomic, microRNA, and protein-based analyses may be linked to the emergence of HCC in liver diseases of various origins [53,60]. Accordingly, the molecular signature of HCC developing in NAFLD may allow identification of specific targets for the prevention, recognition, and treatment of HCC associated with obesity and diabetes.

Mechanisms of hepatocarcinogenesis in NAFLD

Several mechanisms may account for a tumor-promoting environment in obesity and diabetes, distinguishing the pathogenesis of HCC linked to NAFLD from that of viral and other etiologies [61,62]. Obesity is characterized by a low-grade, chronic inflammatory response implicated in increased cancer risk in general [63,64]. Adipose tissue expansion promotes the release of pro-inflammatory cytokines providing a key element to this process [64,65]. Tumor necrosis factor (TNF) is a major adipose-derived cytokine and a potent activator of pro-oncogenic pathways involving NF-κB, JNK, the mammalian target of rapamycin (mTOR), and extracellular signal-regulated kinases [61,66]. In addition, interleukin-6 (IL-6) has a key role in the obesity-associated inflammatory response and exerts cell proliferative and anti-apoptotic effects through activation of its major transcriptional target, STAT3 [61,66]. The role of adipose-derived TNF and IL-6 in the development of HCC has recently been demonstrated in an experimental model where either dietary or genetic obesity strongly promoted malignant liver tumor growth induced by diethyl nitrosamine in mice if production of these cytokines and their key oncogenic signaling pathways were intact [67].

Adipose tissue expansion promotes an adverse secretory profile of adipose-derived hormones or adipokines. Adiponectin, an abundant adipokine with potent anti-inflammatory effects, is expressed at reduced levels in obesity, diabetes, and NAFLD [68,69]. Low adiponectin levels may be insufficient to suppress endotoxin-mediated inflammatory signaling in Kupffer cells and other macrophages [70], to activate adenosine monophosphate kinase, an inhibitor of the mTOR oncogenic pathway [71], and to control angiogenesis, a pivotal mechanism of tumor growth [72]. In contrast, circulating levels of leptin, another major
adipokine, are high in NAFLD [73]. Since leptin exerts pro-inflammatory and pro-fibrogenic effects by activating Kupffer cells and stellate cells, it has been connected to disease progression in fibrotic NAFLD [74–76].

Cancer cells often exhibit increased rates of fatty acid synthesis and accumulation of lipid droplets [77,78], suggesting that increased availability of lipids in hepatocytes may provide bioenergetic and structural support to the rapidly proliferating cells of HCC. Increased expression of key genes regulating lipogenesis correlates with cell proliferation rates and poor prognosis in HCC [79], and lipid accumulation in hepatocytes is accompanied by distinct patterns of expression and distribution of perilipins, a family of lipid droplet-associated proteins [78,80]. The precise mechanisms of altered formation and utilization of lipid droplets in the development of HCC in NAFLD remain to be elucidated.

Lipotoxicity is defined as the cellular dysfunction caused by ectopic deposition of fat in non-adipose tissues such as the liver [65] and may contribute to the development of HCC in NAFLD. Accumulation of fatty acids may interfere with cellular signaling pathways and promote oncogenic mechanisms through altered regulation of gene transcription [81,82]. Enhanced rates of fatty acid oxidation yield lipid peroxides and free radicals that may cause macromolecular oxidative injury, mitochondrial dysfunction, endoplasmic reticulum stress, and apoptosis [83,84]. These molecular events may promote the liver inflammatory response and thus increase the risk for hepatocarcinogenesis.

Adipose tissue expansion, release of pro-inflammatory cytokines, and lipotoxicity collectively promote systemic and hepatic insulin resistance, which result in hyperinsulinemia. Both are common features of NAFLD and have been linked to tumor development [85,86]. Deregulated metabolic effects of insulin result in excessive activation of proliferative cell signaling cascades that remain responsive to insulin action and have been implicated in the development of HCC [87]. Moreover, 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 [88]. The relative contribution of systemic insulin resistance and liver tissue-specific molecular events to the development of HCC in NAFLD remains incompletely understood.

**HCC growth in non-cirrhotic livers**

When discussing the emergence of HCC in the absence of cirrhosis, it is important to acknowledge that in the literature the term ‘non-cirrhotic’ pertains to a variety of histopathologic features in the background livers ranging from the normal to the diseased liver but with no detectable fibrosis, to stages of non-cirrhotic fibrosis to incomplete cirrhosis [42]. The distinctions are likely significant, since the pathogenesis may differ according to the presence or absence of underlying liver disease, and the extent thereof. A few groups have investigated biomarkers that may distinguish the molecular pathogenesis of HCC in cirrhotic vs. non-cirrhotic livers. For example, Paradis and colleagues found that deregulation of the Wnt/β-catenin pathway had little role in the development of HCC associated with the metabolic syndrome in the absence of significant liver fibrosis [50].

HCC diagnosed in cirrhotic and non-cirrhotic livers may display different imaging and pathologic attributes such as size, differentiation, and encapsulation [45,50]. When associated with NAFLD, HCC is often moderately or well differentiated and occurs as solitary large mass [42,89]. HCCs that develop in livers with mild or no fibrosis may share these characteristics [35,90,91]. Similarly, HCC complicating the metabolic syndrome and arising in non-cirrhotic livers often remains well differentiated despite a larger size [50]. These imaging attributes are not necessarily specific to NAFLD and may rather reflect the development of HCC in the absence of cirrhosis, for which NAFLD seems to have preponderance [91].

A major step in the development of cirrhotic HCC is activation of hepatic stellate cells. Stimulated by various forms of chronic liver injury, these cells are primarily responsible for secreting collagen that results in liver fibrosis [92]. In addition, activated stellate cells produce various growth factors and may stimulate oncogenic pathways that contribute to the expansion and selection of neoplastic clones of liver cells [93]. The pathogenic role of stellate cells may be limited in non-cirrhotic HCC characterized by different growth pattern and appearance on imaging studies such as lack of encapsulation. Accordingly, diminished activation of stellate cells with delayed formation of fibrotic septa may result in larger liver nodules that are not obscured by extensive scarring [94].

**Prevention of HCC associated with NAFLD**

**Role of diabetes control by insulin-sensitizing therapy**

Based on the overwhelming epidemiologic evidence that diabetes overlapping with NAFLD is an independent risk factor of HCC [11–16,19,21], effective treatment of insulin resistance and hyperinsulinemia may be critical to prevent hepatocarcinogenesis in the affected population. Several reports indicate that the use of insulin-sensitizing agents in diabetes may reduce the risk of HCC [20,95–97]. Metformin improves insulin resistance through the activation of AMPK, which blocks glucose output from the liver and boosts glucose uptake in the skeletal muscle. In addition, metformin has direct antiproliferative effects primarily by inhibiting the mTOR oncogenic pathway [98]. A case control study from Italy involving 610 patients with HCC of mixed etiology found an odds ratio of 0.15 for HCC in metformin-treated diabetic patients with cirrhosis when compared to those treated with sulphonylureas or insulin [95]. In a French observational cohort of 100 consecutive diabetic patients with ongoing HCV cirrhosis, the hazard ratio for developing HCC was found to be 0.19 during a median follow-up of 5.7 years among those treated with metformin [96]. Moreover, a case control study from a large US cancer center reported that treatment with metformin or the insulin-sensitizing peroxisome proliferators activated receptor-γ (PPARγ) agonist thiazolidinediones resulted in an adjusted risk ratio of 0.3 for HCC among diabetics while the use of insulin secretagogue sulphonylurea drugs was associated with a 7.1-fold increase in HCC risk compared to non-users [97].

Insulin-sensitizing therapy may also improve the prognosis of HCC. A recent study showed that metformin therapy is associated with lower mortality in diabetic patients with early stage HCC after radiofrequency ablation [99]. While current guidelines for the management of HCC have no specific recommendations for cases associated with NAFLD, obesity, and diabetes [100], the use of insulin-sensitizing drugs and avoidance of treatments contributing to hyperinsulinemia is likely to enhance prevention and improve disease outcomes of HCC.

**Surveillance of HCC in NAFLD**

The prognosis of HCC is generally poor with dismal overall survival rates for all stages combined [2,100]. However, it is
Conclusion

NAFLD, by itself and in synergy with other risk factors, is becoming the most common cause of HCC in developed countries. As the global prevalence of obesity and diabetes is increasing, other parts of the world are likely to follow suit. To make things more difficult, a considerable number of NAFLD-associated HCC cases develop in non-cirrhotic livers. Thus, we may need to contemplate a paradigm shift in liver cancer surveillance. Fortunately, there is still some good news. For now at least, HCC appears to be a rare complication of NAFLD in the complete absence of fibrosis. In addition, the prognosis of HCC is significantly better without cirrhosis [100]. Since fibrosis in NAFLD is linked to steatohepatitis, reliable distinction from steatosis alone by liver biopsy or, preferably, emerging non-invasive biomarkers will identify those at risk of disease progression and in need of cancer surveillance. Better understanding of molecular pathways that accelerate hepatocarcinogenesis in obesity and diabetes as well as mapping of the molecular carcinoma sequence in a non-cirrhotic background will facilitate these efforts and provide new diagnostic and therapeutic targets. Nonetheless, prevention of obesity, diabetes, and NAFLD remain the best long-term strategy.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


