Nonalcoholic Fatty Liver Disease, Diabetes, Obesity, and Hepatocellular Carcinoma

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SUMMARY

HCC and NAFLD are growing epidemics that seem to be interrelated and pose an important burden to public health. Obesity, T2DM, and NAFLD clearly augment the risk of HCC via multiple pathways, many of which are common to all 3 conditions. Resultant dysregulation of adipocytokines, oxidative stress, and insulin resistance contribute to a proinflammatory milieu that fosters the development of HCC via many oncogenic pathways. Mounting evidence that cirrhosis is not a requisite for tumor development in NASH should make us take pause and urge for strategies to identify such patients at an early stage. Furthermore, effective chemopreventive strategies are urgently needed to temper the increase of HCC in patients with obesity, T2DM, and NAFLD.

Keywords

Nonalcoholic steatohepatitis; Cirrhosis; Noncirrhotic; Insulin resistance; Hepatocellular carcinoma; Obesity; Diabetes; Chemoprevention

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is now the most common liver disease in the United States, with more than 80 million Americans affected. It represents a spectrum of diseases ranging from isolated hepatic steatosis (IHS) to steatosis in association with inflammation and cellular injury—the progressive subtype of NAFLD referred to as nonalcoholic steatohepatitis (NASH). NASH is often but not always associated with varying degrees of fibrosis that can develop into cirrhosis and all of its associated complications.[1,2] The prevalence of the disease parallels the epidemic of the meta-bolic syndrome, namely obesity, type 2 diabetes mellitus (T2DM) and its other manifestations worldwide. It is no surprise that the mechanisms underlying the meta-bolic syndrome, insulin resistance, and obesity are also important in the development of both IHS and NASH.[3]

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Hepatocellular carcinoma (HCC), known to occur most commonly in the setting of cirrhosis, is also increasing in incidence, and is now the second leading cause of cancer deaths worldwide.[4] Historically, the risk factors for HCC in the United States have primarily included alcoholic cirrhosis, hepatitis B virus (HBV) infection, hemo-chromatosis, and hepatitis C virus (HCV) infection. Because of its link to the HCV epidemic, HCC is considered the fastest growing cause of cancer mortality overall in the United States as well.[5] However, the clinical landscape of HCV is changing rapidly into a future where cure is not only probable, but will be nearly universal for those who have access to therapy. No doubt, this will reduce the development of HCV-related HCC in the future. Results of recent studies demonstrate that HCC is more prevalent in the setting of obesity and insulin resistance, and may occur in NAFLD patients without cirrhosis.[4] Therefore, if the incidence of obesity, diabetes, and NASH continues to increase, and the HCV-related association decreases with effective treatment strategies, NAFLD could become the most common cause of HCC in the United States and other developed countries. Indeed, in a recent retro-spective cohort study that evaluated trends in HCC etiology among adult liver transplant recipients from 2002 to 2012, the number of patients undergoing liver trans-plant for HCC secondary to NASH increased by nearly 4-fold, whereas the number of patients with HCC secondary to HCV increased by only 2-fold.[6] During that same 10-year period, the prevalence of NASH-related HCC increased steadily, becoming the second leading etiology of HCC-related liver transplant in the United States (increasing from 8.3% in 2002 to 10.3% in 2007 and to 13.5% in 2012).

To clarify these relationships, this review discusses the pathophysiologic mecha-nisms that underpin the close relationship between obesity, insulin resistance, NAFLD, and the progression to HCC, both in the presence and absence of cirrhosis.

OBESITY, DIABETES, NONALCOHOLIC FATTY LIVER DISEASE, AND NONALCOHOLIC STEATOHEPATITIS AS RISK FACTORS FOR HEPATOCELLULAR CARCINOMA

The results of several studies have elucidated the relative risk of several disease pro-cesses that are implicated in the pathogenesis of HCC. In a population-based study, authors analyzed 6991 cases from the Surveillance, Epidemiology, and End Results– Medicare databases that link cancer registry data and Medicare enrollment during the period from1994 to 2007.[7] The authors estimated the population-attributable fractions (PAFs), that is, the proportions of cases that can be attributed to specific risk factors. They found that T2DM and/or obesity had the greatest PAF (36.6%), followed by alcohol-related disorders (23.5%), HCV (22.4%), HBV (6.3%), and rare genetic disorders (3.2%; Fig. 1). Although the relative risk of HCV for HCC incidence (39.9) was higher than the relative risk of T2DM and/or obesity (2.47), the high prevalence of T2DM and obesity in the United States accounted for more cases of HCC than HCV. However, the exact PAF of NAFLD remains to be determined, because NAFLD cases per se were not identified in the Surveillance, Epidemiology, and End Results database. Although the study was limited to age groups 68 years or older, it repre-sented about 25% of the general population of the United States.[7]

In other studies, a direct relationship between obesity and HCC has been demonstrated. Available data suggest that obesity increases the risk of HCC 1.5- to 4-fold (Table 1).[8–10] In Danish and Korean studies, an association between obesity and an increased relative risk of HCC (1.9 and 1.56, respectively) was seen.[9,11] Data from the United States also suggest that with obesity there is a significantly elevated relative risk of death from many cancers including HCC (4.52 for men; see Table 1).[8] One large meta-analysis included 7 cohort studies in 5037 overweight subjects (body mass index of 25–30 kg/m^2) and 10 studies in 6042 obese subjects (body mass index of 30 kg/m^2). The authors found that, compared with normal weight people, HCC risk increased 17% in those who were overweight and 89% in those who were obese.[12] Furthermore, in a study from Japan that looked at the recurrence of HCC after ablation therapy in NASH patients, the authors found that increased visceral fat was an indepen-dent risk factor for recurrence of HCC at 3 years (75.1% vs 43.1% with low visceral fat).[13] The mechanism through which obesity leads to increased HCC is thought to be related both to a direct effect of obesity on insulin resistance and the perpetuation of a proinflam-matory milieu, as well as via its role in the development and progression of liver disease in patients with NAFLD. In a 2008 review of studies of the epidemiology of NAFLD, Lazo and Clark[14] found that, on average, 76% (range, 33%–99%) of obese patients undergoing bariatric surgery are reported to have steatosis and 37% (range, 9.8%–72.5%) NASH.

In a similar trend seen in many studies, T2DM was associated with a substantially increased risk of HCC (see Table 1). In a large cohort from Sweden consisting of 153,852 diabetics, the risk of HCC was increased 4-fold. Even after exclusion of other risk factors for HCC, such as cirrhosis and viral hepatitis, T2DM was associated with a 3-fold increased risk of HCC.[15] In a large study from the Veterans Administration (VA) hospitals in the United States similar conclusions were drawn. Of 173,643 diabetic patients and 650,620 nondiabetic controls followed over 10 to 15 years, the incidence of HCC was increased more than 2-fold in diabetic patients, with the risk remaining significant even after the exclusion of patients with other causes of liver disease, including NAFLD.[16] One limitation of these studies is that other causes of liver disease, such as alcohol and viral hepatitis, could have been underestimated because diag-nosis identification codes were used to identify patients. In a large Danish study of 109,581 patients hospitalized for T2DM, the standardized incidence ratio for HCC was 4 in men and 2.1 in women.[17] Two large meta-analyses in 2011 confirmed that the relative risks of T2DM for the development of HCC were 1.87 and 2.31, respec-tively.[18,19] Most recently, a 2014 meta-analysis of 21 studies that included a total of 9767 HCC patients evaluated the association of T2DM with overall and disease-free survival in HCC.[20] In this study the pooled hazard ratios were 1.46 for overall survival and 1.57 for disease-free survival for patients with DM. Although it is possible that the increased HCC risk associated with diabetes seen in these studies may be mediated through the development of NAFLD, the presence of multiple pathogenic mechanisms common to obesity, insulin resistance and NAFLD[21] suggests that this link may not be mediated through NAFLD per se.[12]

Data from several retrospective and prospective studies demonstrate a direct rela-tionship between NASH and HCC. Retrospective results suggest that between 4% and 27% of NASH patients develop HCC at one point [22,23]; however, the true prevalence of HCC across the

whole spectrum of NAFLD remains unknown. In prospective studies, the reported prevalence of HCC was 0% to 0.5% in patients with IHS, and as high as 12.8% in those with NASH.[24–26] In a cross-sectional study of 4406 HCC patients, 59% had NAFLD/NASH, 36% T2DM, and 22% HCV infection.[27] In this context, it is noteworthy that patients with HCV cirrhosis develop HCC at a higher rate than those with NAFLD/NASH. Ascha and colleagues[28] followed 195 patients with NASH cirrhosis and 315 patients with HCV cirrhosis for 3.2 years and identified HCC in 12.8% and 20.3% of patients in the NASH and HCV groups, respectively. Here, the yearly cumula-tive incidence of HCC was 2.6% in patients with NASH-associated cirrhosis, whereas it was 4.0% in those with HCV-associated cirrhosis. Bhala and colleagues[29] studied patients with advanced fibrosis and cirrhosis, including 247 owing to NASH and 264 owing to HCV, who were followed for a mean of 85.6 months. They found that NAFLD patients had a lower incidence of HCC compared with those with HCV (2.4% vs 6.8%; $P<.03$). In comparison to Ascha and associates' study, [28] Bhala and colleagues attributed the lower incidence of HCC in both their NASH and HCV populations to potential differences in population risk factors and the fact that only those with biopsy-proven NASH were included in the Ascha and colleagues study.

NASH is increasing in importance as an indication for liver transplantation (LT) and may exceed HCV as an indication numerically over the next decade. Interestingly, although HCC may occur more commonly in patients with HCV cirrhosis, the rate at which patients are transplanted for HCC in the setting of NASH is increasing rapidly. Indeed, in a recent retrospective cohort study that evaluated trends in HCC as an etiology among adult LT recipients from 2002 to 2012, the authors found that the num-ber of patients undergoing LT for HCC secondary to NASH increased by nearly 4-fold, whereas the number of LT patients with HCC secondary to HCV increased by only 2.5- fold in the Model of End-stage Liver Disease era of LT listing.[6] As noted, during that 10-year period, NASH-related HCC increased steadily, becoming the second leading etiology of HCC-related LT in the United States.

HEPATOCELLULAR CARCINOMA IN NONALCOHOLIC FATTY LIVER DISEASE WITHOUT CIRRHOSIS

The fact that fibrosis and cirrhosis are not necessary for the development of HCC in NASH patients indicates that obesity, insulin resistance, and the proinflammatory milieu of NASH may mediate carcinogenesis directly. Evidence of the development of HCC in noncirrhotic patients continues to accumulate in case reports or case series (Table 2).[29–52] In a recent study analyzing 1419 HCC cases that were related to NASH (120 cases), HCV (1013), and alcohol (286) in the VA system, cirrhosis was present in only 58.3% of NASH-related HCC cases.[51] The researchers also found less robust adherence to HCC surveillance in NASH patients than in patients with HCV or alco-holic liver disease, and attributed the high rate of incidence of HCC in NASH without cirrhosis (41.7%) to the lower rate of surveillance, because there is currently no recom-mendation for surveillance in this population. There is also the incorrect perception that NASH patients without cirrhosis are unlikely to develop HCC. Interestingly, despite the lack of surveillance and resulting early detection, the 1-year survival rate did not differ among the different etiologies of HCC.[53]

Interesting insights into possible areas of further research can be derived from NASH–HCC studies in which potential differences between NASH- and HCV- associated HCC are suggested. In the Mittal and colleagues'[51] analysis of the VA population previously discussed, the authors noted that patients with NASH more often had fewer alpha-fetoprotein–secreting tumors. The authors speculated that less aggressive tumor biology in NASH-related HCC could be partially explained by this finding, but it could also be related to the short period of survival rate estimation of only 1 year. A Japanese group also reported lower alpha-fetoprotein synthesis in NASH-associated HCC (35.3%) compared with 69.6% of tumors in patients with HCV.[48] Furthermore, they found that 52.9% of patients with NASH-related HCC had elevated des-gamma-carboxy prothrombin, a biomarker of HCC, compared with 41.3% of patients with HCV-related HCC.[46] This result suggests that the tumor markers and cancer biology in NASH-related HCC may differ from HCV-related HCC, and should be investigated further.

Results of several studies support the possibility that NASH-related HCC may behave differently in certain subpopulations. Limited available data suggest that risk factors for the development of NASH without cirrhosis include older age, male gender, and the metabolic syndrome (see Table 2). Indeed, HCC was even reported to develop in patients with the metabolic syndrome and features of IHS without steatohepatitis or fibrosis.[40] In a study of 87 Japanese NASH patients with HCC, Yasui and colleagues[47] found that 56% of patients were noncirrhotic. The authors stratified the data by gender and noted that men developed HCC at a less advanced stage of liver fibrosis than women. Hashimoto and colleagues[44] examined 34 cases of NASH-related HCC and found that there was a prevalence of advanced age, male gender, obesity, and T2DM; 12% of the patients had stage 1 or 2 fibrosis and 88% had advanced fibrosis (stage 3–4). These HCC patients tended to be older, male, and to have the metabolic syndrome. Although there are currently no recommendations to initiate HCC screening in noncirrhotic NASH, mounting data suggest that it should be a concern, particularly for older men with the metabolic syndrome. Inexpensive and reliable methods of HCC detection are needed to capture reliably patients at risk for HCC before the develop-ment of cirrhosis. Revisiting the surveillance guidelines may be warranted.

PATHOGENESIS OF HEPATOCELLULAR CARCINOMA IN OBESITY, DIABETES, AND NONALCOHOLIC FATTY LIVER DISEASE

Although the precise pathogenesis by which obesity and insulin resistance foster the development of HCC is not defined clearly, several mechanisms could operate in the setting of NAFLD. The inflammatory milieu associated with obesity and insulin resis-tance is characterized by abundant oxidative stress, activation of the unfolded protein response (UPR), and other inflammatory processes, including activation of the innate immune system. Many of these pathways could play a major role in the tumorigenicity and development of DNA damage, which provide a favorable setting for the develop-ment of HCC.[53] Insulin resistance and obesity promote an aberrant adipocytokine pro-file, including increased interleukin-6, leptin, and tumor necrosis factor (TNF)-a and decreased adiponectin, which seems to contribute to increased cellular proliferation, angiogenesis, inhibition of apoptosis, and worsening insulin resistance.[54,55]

Insulin Resistance

In a prospective study of 6237 French men, hyperinsulinemia was associated with an approximately 3-fold increased risk for HCC.[56] In addition to its role in glucose and lipid metabolism, insulin has pleotropic effects that regulate inflammatory and other pathways. Insulin-like growth factor-1 (IGF-1) and insulin receptor substrate-1 (IRS-1), an important substrate of IGF-1, are downstream targets of insulin that are crucial to cellular proliferation (Fig. 2).[57,58] Human HCC cells overexpress both IGF-1[59] and IRS-1.[60] IRS-1–mediated signals may act as survival factors and protect against transforming growth factor b1–induced apoptosis in HCC, which may contribute to hepatic oncogenesis.[61] In addition, IRS-1 can promote hepatocyte proliferation via mitogen-activated protein kinase and phosphatidylinositol–3 kinase (PI3K), important pathways in HCC development.[61] Interestingly, cirrhotic patients with HCC and impaired glucose metabolism that causes postprandial hyperin-sulinemia have accelerated HCC growth.[62] The PI3K/phosphatase and tensin homo-log (PTEN)/Akt axis is a key regulator of critical cellular functions such as insulin and other growth factor signaling, glucose and lipid homeostasis, and apoptosis.[63]

PTEN acts as a phosphoinositide phosphatase which terminates PI3K-propagated signaling.[63] Thus, PTEN is a tumor suppressor that is dysregulated in obesity, insulin resistance, and T2DM, thus offering another mechanism through which NAFLD, T2DM, and insulin resistance could promote tumor growth in the setting of HCC.[63]

c-Jun amino-terminal kinases

The c-Jun amino-terminal kinases (JNKs) are associated with development of NASH and hepatic carcinogenesis.[64–67] Free fatty acids, reactive oxygen species and TNF-a are increased in the setting of hyperinsulinemia and are activators of JNK1, which in turn phosphorylates IRS-1 (see Fig. 1). JNK1 activation and the subsequent phosphorylation of IRS-1 are very important factors in obesity-induced insulin resis-tance and increased hepatic inflammation and apoptosis; JNK2 has been shown not to play a role.[64,65,68] Puri and colleagues[64] have shown that the extent of JNK activation is associated with the level of histologic activity in NASH patients. Several studies have described an important role of JNK1 in the development of HCC.[66,67,69] Chang and col-leagues[66] demonstrated enhanced JNK1 activation in 55% of human HCC samples compared with non-HCC liver tissue. JNK1 plays an important role in the development of HCC, partially through activation of the mammalian target of rapamycin mTOR com-plex 1, which is involved in several human cancers.[70,71]

Endoplasmic Reticulum Stress

Emerging data suggest that endoplasmic reticulum (ER) stress plays an important role in NASH and HCC.[72–74] The ER regulates protein synthesis and folding for a variety of cellular processes. Various stressors, such as nutrient or glucose deprivation, viral infections, disrupted calcium homeostasis, protein glycosylation, and excess fatty acids, can promote the accumulation of unfolded or misfolded proteins in the ER lumen and activation of an adaptive response called the UPR, which can result in salvage or further injury and apoptosis, depending on the trigger and milieu.[75–77] JNK is a downstream target of the inositol-requiring enzyme-1, a branch of the UPR that has been shown to perpetuate

inflammatory processes and insulin resistance.[76] Both ER stress and the subsequent activation of the UPR have been found to play a role in HCC.[78] Although the exact mechanism is not understood completely, it is thought to be owing to the effect of the activation of extracellular signal-regulated pro-tein kinase (ERK) which is highly expressed in HCC via PIK13 activation. ER stress also activates the nuclear factor erythroid 2-related factor 2 and transcription factor-6, both of which regulate the small heterodimer partner nuclear receptor, leading to its sup-pression. This in turn activates cyclin D1 and hence increases tumorigenicity and he-patocyte proliferation.[79,80]

Insulin resistance is also associated with increased oxidative stress. The generation of reactive oxygen species leads to upregulation of proinflammatory cytokines such as TNF-a. This upregulation then can promote tumor growth via both anti-apoptotic action and further upregulation of proinflammatory cytokines through activation of nu-clear factor-kappa B (NF-kB).[81] Oxidative stress may favor tumorigenesis via inflam-mation and dysregulated cell proliferation; however, it may also directly induce cancer-promoting gene mutations. Trans-4-hydroxy-2-nonenal (4HNE), a product of lipid peroxidation, is important in cancers that are caused by mutations of the p53 gene (see Fig. 2).[82] The p53 pathway targets include wild-type p53 activated fragment (p21WAF), a cyclin-dependent kinase inhibitor and the growth arrest DNA damage gene, GADD45, a p53-regulated and DNA damage-inducible protein, and the 14–3-3 protein, which plays a role in G2/M arrest.[83] Nuclear respiratory factor-1 (Nrf-1) is an essential transcription factor in the prevention of oxidative injury. Nrf-1 knockout mice develop NASH and progress to HCC owing to increased oxidative stress.[84] In a human study, Maki and colleagues[85] showed a higher incidence and recurrence of HCC in patients with high levels of 8-Oxo-2'-deoxyguanosine (8-OHdG) and 4HNE in liver tissue, suggesting that oxidative stress may influence HCC carcinogenesis or tumor biological behavior.

Leptin

Leptin, a product of the obese (*ob*) gene, is a regulator of food intake and energy expenditure via hypothalamic-mediated mechanisms.[86] The importance of leptin in angiogenesis, hematopoiesis, and lipid and carbohydrate metabolism as well as in immune systems, has been demonstrated recently.[86,87] Furthermore, leptin has a direct effect on hepatic stellate cells and is likely to play an important role in the pro-gression of liver fibrosis in NASH.[87] The leptin receptor has 6 isoforms, of which obRB is the most important. Leptin levels are increased in obese individuals, suggesting a state of leptin resistance.[86] Suppressors of cytokine signaling and insulin resistance are associated with leptin resistance, with higher levels of leptin found in NASH patients and in patients with HCC.[88,89] In a human study, the expression of leptin and its receptor in both adjacent nontumor liver tissue and HCC tissue was explored using immunohistochemical staining. It was found that adjacent nontumorous liver tissue expressed higher levels of leptin and its receptor than the HCC tissue.[89] The authors suggested that leptin might act as an endocrine growth factor that stimulates hepatocytes toward the initiation and progression of HCC.

Available evidence suggests that leptin mediates its effect through the Jak2/Stat 3 pathway, which in turn augments cyclin D1 protein expression, leading to cellular pro-liferation and

thereby the development of HCC.[90] In addition, leptin inhibits apoptosis by inhibiting transforming growth factor-b1. Therefore, leptin may mediate HCC onco-genesis via stimulation of proliferation and inhibition of proapoptotic pathways. Inter-estingly, these pathways also lead to increased methionine adenosyl transferase (MAT) 2A and MAT2b gene expression, which are known to play a role in hepatocyte proliferation.[91] Finally, leptin promotes fibrogenesis by stimulating hepatic stellate cells. Stellate cells are critical mediators of fibrogenesis and angiogenesis via multiple pathways including ERK/Akt, nuclear factor kappa D (NF-kD), and hypoxia-inducible factor 1, each of which has been associated with the development of HCC.[87,92]

S-Adenosylmethionine

Recently, a role for abnormal levels of *S*-adenosylmethionine (SAMe) in the develop-ment of NASH and HCC has been proposed.[93] SAMe is the principal biological methyl donor made in all mammalian cells. The liver plays a central role in the homeostasis of SAMe.[93,94] SAMe is endogenously produced from methionine and adenosine triphos-phate by MAT.[93] MAT has 2 subunits, a1 and a2, encoded by MAT1A and MAT2A. MAT1A is expressed mostly in differentiated liver and encodes the a1 subunit, whereas MAT2A encodes for the catalytic subunit a2, which is distributed widely. Mice deficient in MAT1A develop NASH and HCC. Deletion of MAT1A may impair very-low-density lipoprotein (VLDL) assembly, leading to the synthesis of small, lipid-poor VLDL particles and decreased secretion of triglycerides. Additionally, low SAMe levels promote proinflammatory cytokine release and development of NASH.[93] Several abnormal pathways have also been identified in MAT1A-knockout mice that can contribute to HCC formation, including (1) a decrease in apurinic/apyr-imidinic endonuclease activity, which leads to DNA instability and malignant transfor-mation, (2) increased liver kinase B1 activity, which induces the activation of 50 adenosine monophosphate-activated protein kinase (AMPK) and enhanced hepatocyte proliferation, (3) leptin signaling, which induces MAT2A and MAT2b genes via activation of these survival pathways and promotes enhanced cell proliferation (the MAT2A-encoded protein induces leptin's mitogenic response by raising intracellular SAMe levels, leading to polyamine biosynthesis and growth), and (4) activation of the ERK pathway, which is highly expressed in HCC.[93]

These pathways suggest that the tumorigenic process is closely related to insulin resistance, oxidative stress and changes in adiponectin and leptin levels which pre-cede the development of fibrosis. Thus, it is plausible that HCC development in NASH patients without cirrhosis is the result of the activation of these pathways.

Toll-Like Receptors

TLRs are a family of pattern-recognition receptors that recognize pathogen-associated molecular patterns and endogenous components that result from cell death, known as damage-associated molecular patterns, and activate the innate immune system.[95–97] Ten members of the TLR family have been identified. They play a role in ligand recog-nition after which a signal via myeloid differentiation factor (MyD)88 leads to activation of NF-kB and production of proinflammatory cytokines, including TNF-a and IL-6.[96,98] The MyD88-dependent pathways activate JNK signaling as well. TLR4 may play a specific role in HCC

progression by increasing proliferation, preventing apoptosis, and increasing production of cytokines (TNF-a and interleukin-6).[99,100]

Potential Chemoprevention of Hepatocellular Carcinoma in Obesity and Nonalcoholic Fatty Liver Disease

There is currently no effective chemoprevention to decrease the incidence of HCC, irrespective of disease etiology, with the possible exceptions of the treatment of HBV and HCV infection.[101] With soaring numbers of NAFLD/NASH patients and the incremental increase in HCC, chemopreventive agents are crucially needed. Indeed, with increasing evidence that HCC can develop in NASH without cirrhosis, the lack of clear recommendations for surveillance in this population and the absence of effec-tive treatments for NASH is concerning. Preliminary data point to statins, metformin, and SAMe as potentially effective chemopreventive compounds. Clinical trials are urgently needed to evaluate methods to prevent or hinder the development of HCC in patients with NASH.

Statins

In previous studies, a beneficial effect of statins in reducing the risk of HCC has been shown.[102–104] Multiple mechanisms have been proposed from animal studies, including (1) statin inhibition of cell proliferation via inhibition of v-myc avian myelocy-tomatosis viral oncogene homolog (MYC) protein phosphorylation which seems to play a role in liver tumorigenicity (atorvastatin blocked MYC and suppressed tumor initiation in an animal model of MYC-induced HCC and in human cell lines of HCC[105]), (2) induction of apoptosis (simvastatin was found to induce apoptosis selectively in living cancer cells but not in normal cells[106,107]), and (3) inhibition of angiogenesis.[107]

In a randomized trial of 91 patients with HCC who were treated with local therapy followed by randomization to either 40 mg of atorvastatin or placebo, survival was increased in the atorvastatin group (18 vs 9 months; P 5 .006).[104] In a matched case-control study conducted within a VA cohort of patients with T2DM, the incidence of HCC was reported at least 6 months after entry in the cohort.[103] Statin use was recorded by searching filled prescriptions. The study identified 1303 HCC cases and 5212 controls and found a significant reduction in the incidence of HCC (range, 25%–40%) in statin-treated diabetic patients. This beneficial effect was evident in pa-tients with and without cirrhosis. This study was limited by many confounding vari-ables, including in particular that patients with T2D have lipid abnormalities and that NAFLD was not identified per se given the lack of a diagnostic code for NAFLD in the VA system. In a recent nationwide case-control study from Sweden, 3994 HCC patients treated with statins (determined from the national drug registry) were compared with 19,970 controls matched by age and sex.[102] In this study, the odds ratio for HCC among statin users was 0.88, suggesting a modest effect of statins on decreasing the risk of HCC.[102] Although these data are intriguing, they have important limitations and the true effect of statins on chemoprevention in HCC will need to be ascertained through carefully conducted, randomized, controlled trials.

Metformin

Although metformin may not have significant efficacy in the treatment of NASH itself, it may have a role in decreasing the risk of HCC. In several studies, insulin sensitizers in patients with T2DM may have reduced the risk of HCC.[108–114] Metformin has an anti-tumor effect in HCC through the suppression of the mTOR pathway which occurs via 2 mechanisms. The first mechanism involves inhibition of mitochondrial oxidative phosphorylation leading to AMPK activation and subsequent mTOR pathway suppression; the second mechanism works via glycemic control leading to inhibition of IGF-R and thus inactivation of the mTOR pathway in insulin-responsive cancers.[115] A large Italian case control study compared 610 HCC patients treated with metformin with 618 un-treated cirrhotic patients and 1696 controls.[109] Metformin use was associated with a decreased incidence of HCC in diabetic patients (odds ratio, 0.15). Given the complex relationship between T2DM, HCC, and cirrhosis and the fact that this was a retrospec-tive case control study, a definitive conclusion cannot be drawn from this research. Two recent meta-analyses included 10 studies with 22,650 cases of HCC in 334,307 patients with T2DM. Metformin use was associated with a 50% reduction in the incidence of HCC, whereas sulfonylurea and insulin use increased HCC inci-dence by 62% and 161%, respectively.[111] Similarly, another metaanalysis of 17 case-controlled studies and 32 cohort studies of HCC reported a combined relative risk estimate of 2.31 for HCC among diabetic patients. In these studies, sulphonylur-eas and treatment with insulin increased the risk of HCC. The authors attributed this increased risk to the effects of hyperinsulinemia on stimulating oncogenesis. In another study, survival in 135 patients with early stage HCC who underwent radiofrequency ablation was assessed; of the 53 diabetic patients, 21 were treated with metformin and 32 were not. The authors found that the survival rate after ablation was less in diabetic patients compared with nondiabetic patients (1 year, 82.8% vs 93.9%; 3 years, 55.1% vs 80.2%; 5 years, 41.3% vs 64.7%; $P5$ .004) and that survival was further decreased in diabetics who were not on metformin (hazard ratio, 0.24; $P5$ .02) compared with those who were.[112] Large, randomized trials are needed to better understand the role of metformin or other antidiabetic drugs in HCC chemoprevention.

S-Adenosylmethionine

Lu and colleagues[116] examined the effect of SAMe for chemoprevention of HCC in animal models. Here, SAMe led to inhibition of HCC progression and showed proap-optotic and antiangiogenic properties. Because of the potential direct effect of SAMe on HCC pathogenesis and its proapoptotic and antiangiogenic properties,[93,117] there is an ongoing phase II clinical trial using SAMe as a chemopreventive agent in HCC patients with hepatitis C in the setting of NAFLD.

Acknowledgments

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KEY POINTS

- Obesity, type 2 diabetes mellitus (T2DM), and insulin resistance are strongly associated with nonalcoholic fatty liver disease (NAFLD) and increased incidence of hepatocellular carcinoma (HCC).

- HCC incidence is increasing as NAFLD becomes the most common cause of liver disease.

- HCC can develop in NAFLD patients without cirrhosis so cancers may be missed given the high prevalence of NAFLD and the limitations of current screening strategies.

- Activation of pathways that promote inflammation, insulin resistance, angiogenesis, and cellular proliferation seen in these diseases promote the development of HCC.

- Clinical studies to prevent the development of HCC in patients with obesity, T2DM or NAFLD are critically needed.
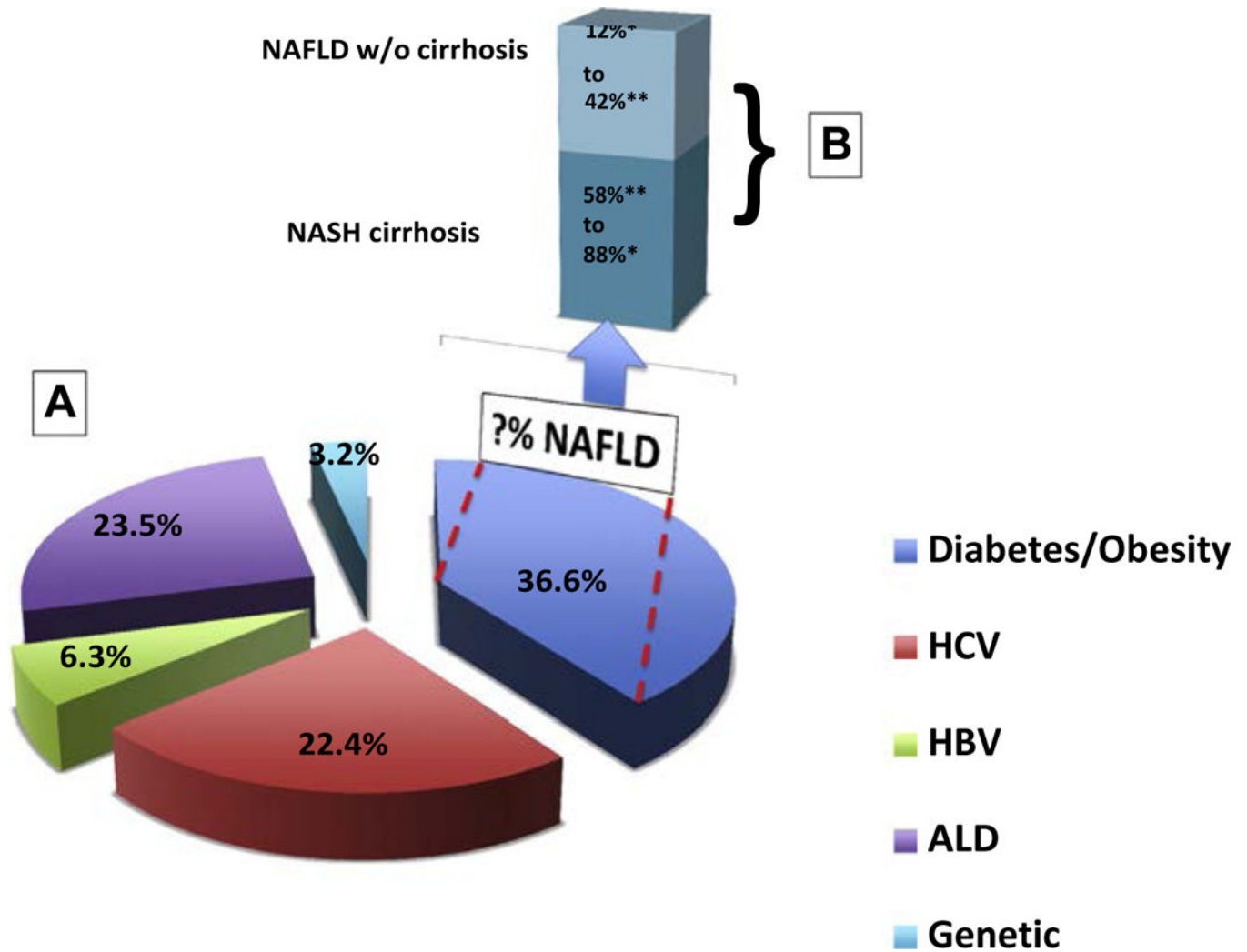
Fig. 1.

Risk factors for hepatocellular carcinoma (HCC) incidence in the United States. (*A*) Risk factors of HCC in the United States (presented as percentage). In a study by Welzel and colleagues of 6991 cases from the Surveillance, Epidemiology, and End Results (SEER)–Medicare databases from 1994 to 2007 the authors estimated the PAFs, that is, the proportions of cases that can be attributed to specific risk factors. The PAF owing to type 2 diabetes mellitus (T2DM) and/or obesity was the highest (36.6%), followed by alcohol-related disorders (23.5%), HCV (22.4%), HBV (6.3%), and rare genetic disorders (3.2%). Although the contribution of NAFLD is not exactly known, it is thought to contribute to the majority of the obesity and diabetes cases. (*B*) A breakdown of cases of HCC occurring in the setting of NAFLD in the presence or absence of cirrhosis to HCC. ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. (*Data from* [*A*] Welzel TM, Graubard BI, Quraishi S, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol 2013;108(8):1314–21; [*B*] *Hashimoto E, Yatsuji S, Tobari M, et al. Hepatocellular carcinoma in patients with nonalcoholic

steatohepatitis. J Gastroen-terol 2009;44 Suppl 19:89–95; and **Mittal S, Sada YH, El-Serag HB, et al. Temporal trends of non-alcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs pop-ulation. Clin Gastroenterol Hepatol 2014;146(5):S–917.)
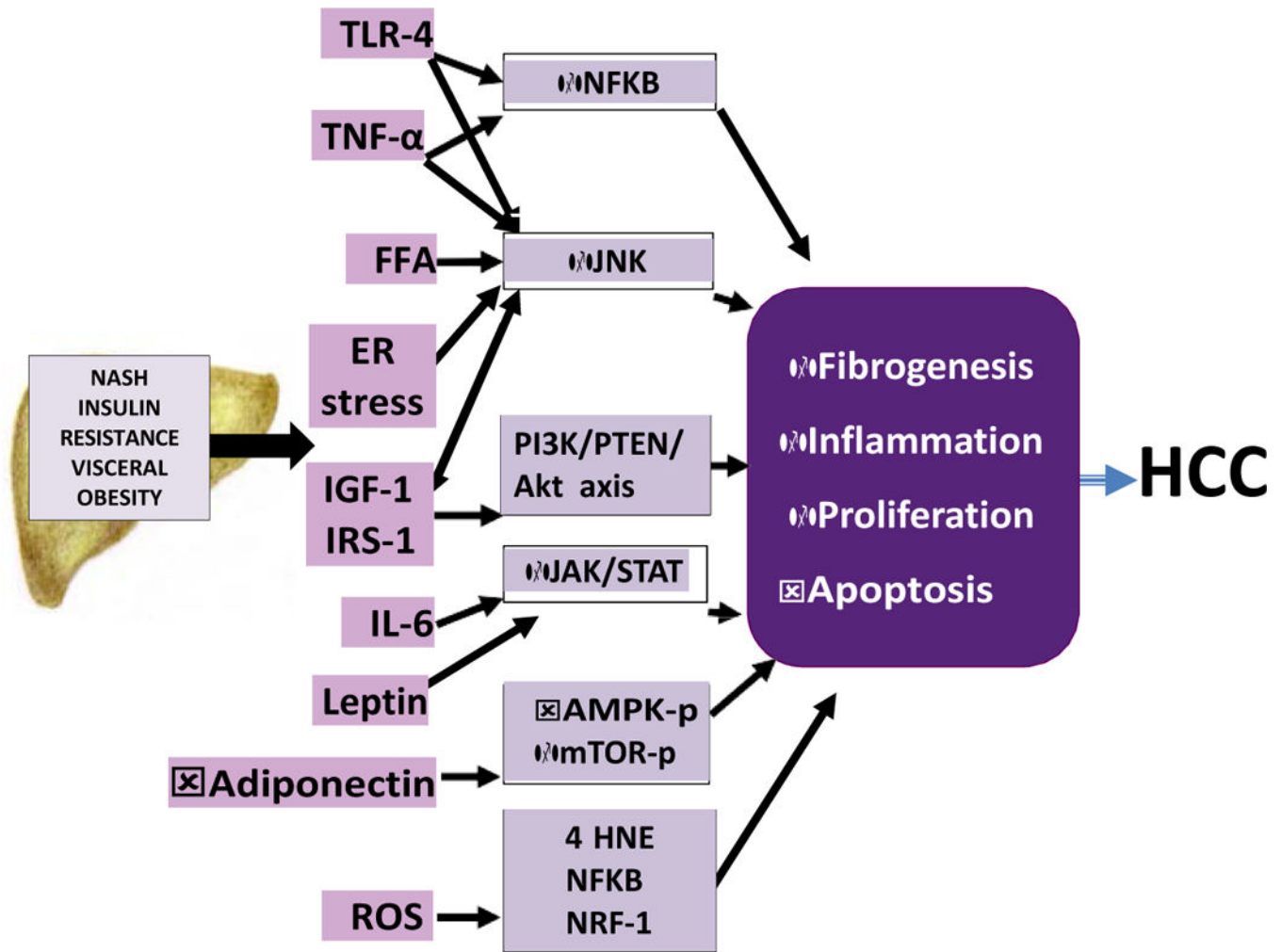
Fig. 2.
Potential pathways linking NASH to HCC. The inflammatory milieu associated with obesity, insulin resistance and NASH leads to the activation of multiple pathways that impair insulin signaling, induce oxidative stress, ER stress and other inflammatory processes. These in turn lead to the activation of oncogenic signaling pathways such as PI3K/PTEN/Akt, JAK/STAT, NF-kB, mTOR, 4HNE and NRF-1. In concert, these pathways promote cellular proliferation, increased angiogenesis, decreased apoptosis that can then foster the development of HCC. 4 HNE, trans-4-hydroxy-2-nonenal; AMPK-p, activated protein kinase; ER, endoplasmic reticu-lum; FFA, free fatty acids; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; IRS-1, insulin receptor substrate-1; mTOR-p, mammalian target of rapamycin complex 1; NF-kB, nuclear factor kappa B; NRF-1, nuclear factor erythroid 2-related factor; PI3k, phosphatidylinositol-3 kinase; PTEN, PI3K/phosphatase and tensin homolog; TLR, Toll-like receptors; TNF-a, tumor necrosis factor-a.

Table 1

Risk of obesity, diabetes, and NAFLD on incidence of HCC

Author, Year	Location	Cases	Study Type	Risk Measurement	Reported Risk
Obesity					
Moller et al,[9] 1994	Denmark	43,965	Case control	RR	1.9
Wolk et al,[10] 2001	Sweden	28,129	Case control	SIR	2.4
Calle et al,[8] 2003	USA	90,000	Prospective	RR	1.68 (F), 4.52 (M)
Oh et al,[11] 2005	Korea	781,283	Prospective	RR	1.56
Larsson et al,[12] 2007	NA	11,079	Meta-analysis	RR	1.89
Diabetes					
Adami et al,[15] 1996	Sweden	153,852	Case control	SIR	4.1
Wideroff et al,[17] 1997	Denmark	109,581	Case control	SIR	4 (M), 2.1 (F)
El-Serag et al,[16] 2004	USA	824,263	Case control	HRR	2.16
Yang et al,[18] 2011	NA	NR	Meta-analysis	RR	1.87
Wang et al,[111] 2012	NA	NR	Meta-analysis	RR	2.31
NAFLD/NASH					
Adams et al,[26] 2005	USA	420	Prospective	Prevalence	0.5%
Ekstedt et al,[24] 2006	Sweden	129	Prospective	Prevalence	2.3%
Rafiq et al,[25] 2009	USA	173	Retrospective	Prevalence	0% NAFLD and 2.8% NASH
Ascha et al,[28] 2010	USA	195	Retrospective	Prevalence	12.8% in NASH cirrhosis

Abbreviations: CC, cryptogenic cirrhosis; F, female; HCC, hepatocellular carcinoma; HRR, hazard rate ratios; M, male; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio.

Data from Refs.[8–12,15–19,24–26,28]

Table 2

Reports of HCC incidence in NAFLD/NASH without cirrhosis

Study, Year	No. of Cases	Average Age (y)	Gender	Fibrosis	Comorbidities	Tumor
Zen et al,[30] 2001	1	62	F	Pericellular	DM	Multifocal
Orikasa et al,[31] 2001	1	67	F	Bridging	DM	Solitary
Bencheqroun et al,[32] 2004	1	68	M	F2	DM	Solitary
Bullock et al,[33] 2004	2	64/74	M	None (F0)	DM, HTN, obesity	Solitary
Gonzalez et al,[34] 2004	1	73	M	F1	DM, HTN, obesity	Solitary
Cuadrado et al,[35] 2005	1	71	M	Portal	DM, obesity	Solitary
Sato et al,[36] 2005	1	64	M	Bridging	Obesity, dyslipidemia	Solitary
Hai et al,[37] 2006	1	72	M	F2	DM	Solitary
Ichikawa et al,[38] 2006	2	60/66	M/F	F2–F3	DM, obesity	Solitary
Hashizume et al,[39] 2007	3	54/72/82	M	F1–F3	DM, HTN, obesity	Solitary (2), Multifocal (1)
Guzman et al,[40] 2008	3	45/57/70	M (1), F (2)	F0	DM, HTN, obesity, dyslipidemia	Multifocal
Chagas et al,[41] 2009	1	65	M	F1	Obesity, dyslipidemia	Multifocal
Paradis et al,[42] 2009	16	NR	M (16)	F0–F3	DM, HTN, obesity, dyslipidemia	NR
Kawada et al,[43] 2009	6	59–81	M (3), F (3)	F2–F3	DM, HTN, obesity, dyslipidemia	Solitary
Hashimoto et al,[44] 2009	4/34 (12%)	NR	M, F	F1–F2	NR	NR
Takuma et al,[45] 2010	7	67–75	M (3), F (3)	F1–F3	DM, HTN, obesity, dyslipidemia	Solitary (5), multifocal (2)
Tokushige et al,[46] 2010	10	NR	NR	F1 (1), F2 (3), F3 (10)	NR	NR
Yasui et al,[47] 2011	43	NR	M (77%)	F1 (10), F2 (15), F3 (18)	DM, HTN, obesity, dyslipidemia	Solitary (72%)
Ikura et al,[49] 2011	1	72	M	F1	HTN	Solitary
Ertle et al,[52] 2011	10	69	M (89%)	F0–F3	DM, HTN, obesity, dyslipidemia	NR
Mittal et al,[51] 2014	Z50	NR	NR	NR	DM, HTN, obesity, dyslipidemia	NR

Abbreviations: DM, diabetes; F, female; HTN, hypertension; M, male; NR, not reported.

Data from Refs.[30–47,49,51,52]