

Nutrition and metabolism in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma is the fifth most common human cancer worldwide, with an overall 5-year survival in the range of 10%. In addition to the very substantial role of chronic viral hepatitis in causing hepatocellular carcinoma, nutritional status and specific nutritional factors appear to influence disease risk. This is apparent in the increased risk associated with non-alcoholic hepatic cirrhosis occurring in the context of obesity, the metabolic syndrome, and type 2 diabetes. Specific nutrients and ingested toxins, including ethanol, aflatoxin, microcystins, iron, and possibly components of red meat, also are associated with increased hepatocellular carcinoma risk. Other dietary components, including omega-3 fatty acids and branched chain amino acids, may have protective effects. Recent data further suggest that several metabolic regulatory drugs, including metformin, pioglitazone, and statins, may have the potential to decrease the risk of hepatocellular carcinoma. The available data on these nutritional and metabolic factors in causing hepatocellular carcinoma are reviewed with the goal of identifying the strength of current knowledge and directions for future investigation.

Key Words: Hepatocellular carcinoma; obesity; type 2 diabetes; branched-chain amino acids; metformin; statins



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Hepatocellular carcinoma (HCC) is a globally important disease by any measure. As the most frequently occurring primary hepatic malignancy, it represents the fifth most common human cancer and the second most common cause of cancer death worldwide (1), accounting for an estimated 500,000 fatal outcomes per year. These prevalence figures highlight a need for improved preventive strategies for HCC, especially in individuals known to be at increased risk. The medical challenges presented by HCC lie not just in the high incidence of the disorder, but also in its generally unfavorable clinical course, which includes a current overall mean 5-year survival from the time of diagnosis in the range of 10% (2). These unfavorable survival statistics clearly define a need for improved medical treatments and improved medical adjuncts to surgical treatment in patients diagnosed with HCC.

There is substantial clinical knowledge about factors predisposing to the development of HCC and potentially

influencing the response to treatment. Multiple epidemiological studies have established a particularly strong association between chronic hepatitis B (HBV) and hepatitis C (HCV) infection and the development of HCC. It is estimated that approximately 80% of HCC worldwide occurs in the context of infection by these viruses (3). The risk of developing HCC in chronically virus-infected individuals correlates not just with viral infection, but with the presence of chronic hepatic cirrhosis. This association may be a mechanistic consequence of inflammatory processes typically present in hepatic cirrhosis, as well as associated changes in hepatocyte turnover and differentiation following liver cell injury.

Beyond HBV and HCV infection, there is compelling evidence for the increased incidence of HCC in association with hepatic cirrhosis resulting from other causes. These non-viral causes include the genetic disorder hereditary hemochromatosis, in which hepatic inflammation and cirrhosis develop secondary to iron overload. While relatively

uncommon, hemochromatosis provides valuable insight into the potential for a metabolite or nutrient, in this instance the micronutrient iron, to induce an injury response in the liver leading to inflammation, cirrhosis, and increased risk of HCC. More common non-viral causes of HCC may similarly result from toxic effects of nutrients or metabolites in the liver, although the mechanisms are less well defined. Such disorders include chronic alcoholism, obesity, the metabolic syndrome, and type 2 diabetes.

A role for nutrients or metabolites in causing primary liver cancer may ultimately have its basis in the central role of the liver in the processing of ingested nutrients, the synthesis, degradation and storage of body fuels, and the clearance of ingested toxins. In addition to the effects of nutrition and metabolic factors in predisposing to the development of HCC, it is of interest to consider the role of nutrition and metabolic processes in influencing responses to treatment of established HCC. This includes the potential for nutritional status to influence responses to surgical or medical treatments, and the possibility of purposefully utilizing nutritional or metabolic factors as adjuncts to treatment.

Nutritional and metabolic factors in the genesis of HCC

HCC develops most commonly in the setting of chronic hepatic cirrhosis. In hepatitis virus-associated HCC, 70-90 percent of HCC patients with chronic HBV and an even higher percentage of HCC patients with chronic HCV infection are reported to have hepatic cirrhosis (4,5). There is evidence that the specific mechanisms of progression to HCC may differ in these two types of viral infections, with a stronger role for elevated oncogene levels in HBV and more prominent inflammation-driven cell turnover responses in HCV (6,7). Irrespective of these initiating mechanisms, it is thought that the association of HCC and hepatic cirrhosis ultimately reflects their shared development as consequences of accelerated hepatocyte proliferation and turnover, with progressive emergence of sclerotic, dysplastic nodules in the liver parenchyma containing poorly differentiated hepatocytes that can transition to cancerous cells.

Hepatic cirrhosis and an associated increased risk of developing HCC independent of viral hepatitis frequently occurs consequent to fatty liver disease, which often has a nutritional basis. A well recognized example of this is the increased risk of HCC in alcohol-induced liver cirrhosis. Ethanol represents a specific macronutrient with metabolic

properties overlapping those of dietary fat. While its metabolism in the liver generates caloric energy, ethanol also exerts toxic effects that can cause cellular injury and a reactive response culminating in hepatic cirrhosis. The extent of hepatic injury and the resulting proliferative and fibrotic response appears to be influenced by genetic factors and also by the not infrequent co-occurrence of HCV infection in individuals with chronic alcoholism. Epidemiologic data have raised the possibility that chronic alcohol exposure and HCV infection may not only have individual effects, but that these two factors may act synergistically to further augment risk of developing HCC (8).

Nonalcoholic fatty liver disease (NAFLD) has more recently been recognized as another important nutrition-related disorder associated with increased risk for hepatic cirrhosis and HCC. NAFLD is defined as the accumulation of hepatic intracellular triglycerides in individuals consuming less than 20 gm of alcohol per day (9). NAFLD often develops in the context of obesity, and it is particularly associated with central (visceral) obesity and with other features of the metabolic syndrome, including hypertension, dyslipidemia, and type 2 diabetes mellitus (1,10). As the prevalence and severity of obesity have increased worldwide in association with population level increases in daily calorie intake and decreases in exercise, the prevalence of NAFLD has become progressively more common, such that it now is the most frequently reported liver disorder in industrialized countries (11). Although the pathogenesis of NAFLD has not been fully elucidated, insulin resistance is thought to have an important mechanistic role in driving the accumulation of lipid stores in the liver (12). The frequent occurrence of insulin resistance in individuals with obesity and the metabolic syndrome thus may explain the epidemiological association of NAFLD with these disorders. While NAFLD may be a relatively benign abnormality in many individuals, a substantial subset of patients with NAFLD develop an associated inflammatory response. This disorder, which is designated nonalcoholic steatohepatitis (NASH), appears quite similar to alcoholic hepatitis on liver biopsy. As with alcohol-induced steatohepatitis, NASH progresses to cirrhosis and liver failure in a substantial percentage of patients, and it represents an important risk factor for the development of HCC (13). The mechanistic processes driving hepatocyte proliferation, dedifferentiation, and evolution to HCC in NASH are not well understood, but may involve the combined effects of insulin resistance (with altered insulin and insulin-like growth factor pathway signaling), inflammation, and oxidative injury. The exact

prevalence of NASH in individuals with NAFLD is difficult to establish, because the diagnosis of NASH requires liver biopsy, and this is not routinely done in NAFLD. It is likely, however, that the subset of individuals with NASH largely accounts for the increased incidence of HCC in obesity-associated NAFLD. Both NAFLD and NASH occur in association with type 2 diabetes, and it is thought that the development of NASH and its progression to hepatic cirrhosis is a major factor accounting for the approximately 2-fold increased risk of HCC in type 2 diabetes documented in several meta-analyses (14-16).

There is a need for better understanding of the metabolic events that lead to liver fat deposition and the transition from steatosis to steatohepatitis in the context obesity and the metabolic syndrome. In this regard, studies in mice genetically engineered for deficiency in the rate-limiting enzyme for hepatic triglyceride and glycerophospholipid synthesis, glycerol-3-phosphate acyltransferase 1 (GPAT1), have demonstrated protection of these animals against hepatic fat accumulation during high-fat diet feeding (17). The *Gpat1*^{-/-} mice have not only decreased liver fat accumulation on a high-fat diet, but also decreased formation of hepatic foci, adenomas, and HCC (18). This mouse model offers the potential to further examine whether the decrease in GPAT1 enzyme activity is protective against the development of HCC through the lowering of levels of specific toxic lipid metabolites or a more general effect on hepatocyte turnover (19). Perhaps more importantly, the recognition that the activity of a specific enzyme can profoundly influence the amount of hepatic fat accumulation on a lipogenic diet could prove to have practical relevance to human hepatic steatosis and the progression to steatohepatitis. A better understanding of human genetic variability in the *GPAT1* gene and genetic factors controlling expression of the *GPAT1* gene and related pathways might lead to strategies for identifying individuals particularly at risk for developing hepatic steatosis or progressing from steatosis to steatohepatitis and HCC. It can be further hypothesized that the GPAT1 protein, plus related endogenous factors influencing hepatic lipid synthesis, such as the bile acid-activated farnesoid X receptor (20), may prove useful as targets for the development of new drugs that can decrease the development of fatty liver or the transition to steatohepatitis and HCC in susceptible individuals.

In considering the mechanisms leading from hepatic steatosis to steatohepatitis and HCC, it has been hypothesized that specific toxic lipid metabolites may drive both the inflammatory response, and the altered

hepatocyte proliferation and differentiation characteristic of steatohepatitis. In a sense, such toxic lipid metabolites might be seen as endogenously generated equivalents of ingested micronutrients and toxins with known links to the development of HCC. The role of ingested toxins in causing HCC has been well established though the examples of the fungal toxin, aflatoxin, and the blue-green algae toxin, microcystin (21,22). While exposures to these toxins are common only in specific geographic locations and uncommon worldwide as causes of HCC, their powerful effects illustrate the potential for specific toxins to induce HCC. In contrast to these toxic substances, which are not normally part of the human diet, iron represents an ingested micronutrient in the normal diet with the potential to cause HCC when absorbed in excess. High levels of ingested iron in certain populations, for example among Sub-Saharan Africans, has been associated with a substantially increased risk of HCC (23). The impact of iron overload as a cause of HCC has been most extensively investigated in the context of hereditary hemochromatosis, which results from a genetic defect causing increased absorption of dietary iron. Hepatocellular oxidative injury resulting from elevated iron levels is thought to mediate hepatic cirrhosis and inflammation in hereditary hemochromatosis, leading to a 20-fold or greater increased risk of HCC (24). Studies on hemochromatosis have further shown that the prevention or remediation of iron overload with chelating agents can decrease the risk of developing HCC (25). One can speculate that additional yet unidentified macronutrients or micronutrients may explain the reported increases in HCC risk associated with the consumption of red meat or saturated fats (Freedman *et al.*, Cross *et al.*) (26,27).

Role of nutritional and metabolic interventions in reducing HCC risk

It is of interest to consider potential protective effects of nutritional factors in decreasing risk for developing HCC. Multiple epidemiological studies have demonstrated increased risk of HCC in association with obesity, but it is important to appreciate that weight loss in obese individuals has not yet been convincingly shown to decrease HCC risk. While this appears logical given the positive association between obesity and HCC, adequately powered studies comparing HCC incidence in individuals who have achieved and maintained weight loss in comparison with persistently obese subjects are needed. The widespread use of bariatric surgical procedures and the marked degree of

weight loss achieved in most of these patients may provide an opportunity to test the effects on HCC risk, as would more effective weight loss drugs.

In contrast with obesity treatment, which involves decreasing overall nutrient intake, there are intriguing data suggesting that increased intake of branched chain amino acids (BCAA), as specific nutrients, may protect against the development of HCC. This concept has its basis in the long-standing observation that the BCAA/aromatic amino acid ratio is typically decreased in hepatic cirrhosis. There may thus be a relative deficiency of BCAA in cirrhotic patients, which is hypothesized to result from the combined effects of changes in nutritional intake, catabolic processes, and ammonia detoxification in association with compromised liver function (28). The administration of BCAA-enriched nutrition in the context of hepatic cirrhosis has been shown to decrease insulin resistance (29) and also has the potential to alter hepatic redox state and augment immune system function (30). These consequences of BCAA supplementation in a state of relative BCAA deficiency might be predicted to lower the risk of HCC.

In a study published several years ago, the oral administration of 12 gm BCAA/day, in comparison with a diet matched in energy and protein intake, to patients with cirrhosis and liver dysfunction appeared to decrease incident HCC in a subgroup of the BCAA-treated subjects with a relatively high BMI and elevated alpha-fetoprotein levels (31). Further evidence for this effect of BCAA feeding is provided in a more recent controlled, prospective study on patients with both compensated and decompensated cirrhosis and no prior history of HCC (32). In 56 BCAA-treated subjects, oral administration of 12 gm BCAA per day as a dietary supplement for at least 6 months resulted in a decrease in HCC incidence in the BCAA-treatment group in comparison with 155 controls (hazard ratio 0.46, CI, 0.216-0.800, $P=0.0085$). While the magnitude of the effect is substantial, it will be important to confirm this finding in a larger number of subjects and investigate different population groups. In addition, longer term studies are needed to better distinguish between the potential alternative actions of BCAA supplementation in affecting the emergence of new foci of HCC *vs.* delaying the presentation of pre-existing HCC.

As additional specific dietary factors that should be further investigated, the ingestion of fish and omega-3 fatty acids have been associated with decreased risk of HCC through mechanisms that are not yet understood (33). Similarly, coffee ingestion has been associated with decreased risk of HCC in

two meta-analyses (34,35). This could hypothetically result from either antioxidant effects or a decrease in hepatic cirrhosis and hepatocyte turnover mediated by components of coffee. Understanding the potential role of such dietary interventions in modifying HCC risk in vulnerable individuals is limited in general by a lack of prospective, controlled studies. The challenge is to design studies of adequate power and duration in the context of slow and variably progressive cirrhosis and development of HCC.

As an alternative approach to modifying the metabolic milieu in individuals at increased risk for HCC, there is substantial current interest in the potential for metabolic regulatory drugs to decrease the risk of HCC as well as several other cancer types. As noted above, type 2 diabetes is associated with an approximately 2-fold increased incidence of HCC (14-16). It is hypothesized that insulin resistance, which is commonly present in type 2 diabetes and obesity, may be a causal factor in the development of HCC through mechanisms that could include direct trophic actions on hepatocytes (36) and indirect effects in promoting hepatic lipid deposition, NAFLD, and NASH (37). Metabolic regulatory drugs that decrease insulin resistance and lower insulin levels may therefore have the potential to decrease the risk of HCC in insulin resistant states. This concept is supported by recent observational and retrospective case-control studies that have shown a very strong inverse correlation between use of the insulin-sensitizing drug metformin and the development of HCC in patients with type 2 diabetes, with a relative risk on the order of 0.15 (38,39). The magnitude of the metformin effect is compelling even in the absence of prospective, controlled trials on metformin and HCC, which have not yet been reported. Metformin might lower HCC risk by decreasing insulin resistance and ameliorating hyperinsulinemia, and there also are multiple other molecular mechanisms that could contribute to anti-tumor effects of the drug. These include potential direct anti-tumor actions from metformin activation of AMPK, leading to increased levels of the LKB1 tumor suppressor, or modified signaling via cell growth regulatory pathways, such as mTOR (40,41). Additionally, metformin has the potential to decrease the development of HCC indirectly by suppressing hepatic fat deposition, or through anti-oxidant, anti-inflammatory, growth inhibitory, or anti-angiogenic actions (42-44).

More limited data on a second insulin-sensitizing drug, the thiazolidinedione, pioglitazone, further support the potential role of insulin resistance and insulin sensitizing drugs in modifying HCC risk. In a recently published large

population-based study in Taiwan, the incidence of HCC was confirmed to be increased in type 2 diabetes, with an adjusted hazard ratio of 1.7, and this risk was decreased in individuals on pioglitazone (hazard ratio 0.56) (45). The same study also showed decreased risk of HCC with metformin (hazard ratio 0.49). Further investigation will be required to confirm the metformin and pioglitazone effects and to examine the multiple possible causal mechanisms.

As another class of metabolic regulatory drugs, there has been recent interest in a role for statins in decreasing the risk of developing HCC. Observational studies initially suggested that statins may decrease risk for multiple cancer types (46-49), although these anti-tumor effects of statins have not been confirmed in meta-analyses of randomized trials (50-54). Data specifically on HCC risk with statin treatment are more limited, but also have been conflicting. A population based study in Taiwan showed decreased HCC risk in association with statins (55), whereas no association was observed in a Danish study (47). A nested case-control study reported that statin use in diabetes patients was associated with decreased risk of HCC (56). Most recently, a very large population-based study in HBV patients in Taiwan showed a significant decrease in HCC incidence with statins, which appeared to be dose-related (hazard ratio of 0.34 with statin use for more than 365 days) (57). Potential mechanisms proposed for decreased HCC risk with statins include disruption of the generation of geranylgeranyl pyrophosphate and farnesyl pyrophosphate (thus interfering with the growth of malignant cells), inhibition of the proteasome pathway (and consequent interference with mitosis), and inhibition of cholesterol synthesis (resulting in slower HBV replication) (57).

Nutritional and metabolic factors in HCC treatment

In patients with established HCC undergoing treatment, optimal nutritional management has potential benefits on morbidity and mortality. The treatment of choice for HCC, when feasible, is complete tumor resection. This often requires removal of a significant portion of cirrhotic, functionally compromised liver. Postoperative nutrition support appears to be an important factor in the success of such surgical procedures (58,59), possibly serving to both improve hepatocyte survival and promote a regenerative response in remaining liver segments. Preoperative nutritional status, as well as postoperative management, may also be a key determinant of success in liver resection,

although this has been less extensively investigated (60). Since preoperative nutritional status might simply serve as a surrogate index for the state of advancement of liver disease in association with HCC and the extent of remaining viable liver function, more data are needed to clarify the potential benefits of preoperative nutritional interventions in promoting survival and recovery from HCC resection surgery.

For patients with advanced HCC who are not candidates for resection, further study is needed to evaluate several nutritional or metabolic interventions with theoretical potential for clinical benefit. These include modifications in macronutrient composition of the diet, such as the use of BCAA supplementation (32), and consideration of micronutrient modifications, such as iron chelation even in the absence of hemochromatosis (61). There also is a need to further investigate opportunities for pharmacologically targeting nutritional and metabolic pathways as adjuncts to the treatment of non-resectable HCC. In this regard, an inhibitor of the nutrient-regulated mTOR pathway in currently is in phase III trials for the treatment of HCC (62). Agents that modify the GPAT-1 linked pathways or the bile acid-activated farnesoid receptor are of theoretical interest as adjuncts to HCC (see discussion of these pathways above), although clinically practical examples of such compounds have not yet been developed.

Summary and conclusions

There are compelling clinical data implicating nutritional status (exemplified by obesity) and metabolic state (e.g., type 2 diabetes) as risk factors for HCC. The impact of these nutritional and metabolic disorders as causal factors in HCC can be expected to increase substantially, if the prevalence of obesity and type 2 diabetes continue to rise as predicted over the next several decades. It is likely that these and other nutritional factors operate through multiple mechanisms influencing the development of HCC, both in the presence and absence of chronic hepatitis virus infection.

Although nutritional and metabolic mechanisms may have causal roles in the development of HCC, it has not yet been possible to translate current knowledge into mechanistic- or evidence-driven guidelines for nutritional management of individuals at risk for HCC or being treated for HCC (63). It is possible, however, to define specific questions and areas of investigation with considerable promise for informing nutritional and metabolic approaches

to reducing risk of HCC and managing existing HCC. One important goal is determining whether there are strategies for weight reduction in obese individuals that can decrease the risk for HCC. Using NAFLD and NASH as surrogates for HCC risk, and ultimately directly assessing incident HCC, it will be important to link effects on HCC risk to specific patient groups (e.g., obese subjects with or without the metabolic syndrome), as well as the magnitude of weight loss. It also will be important to assess the impact of different strategies for achieving weight loss, including specific diet protocols, bariatric surgery, and a now increasing spectrum of pharmacological agents for weight loss in obesity. Studies currently in progress should help to resolve the question of whether metformin has clinically useful benefit in ameliorating the increased risk of HCC in type 2 diabetes, and whether there may be role for metformin in prediabetes. There is need for a better understanding of the mechanisms of anti-neoplastic effects of metformin, as well as the potential effects on HCC risk of other existing pharmacological agents, such as the thiazolidinedione, pioglitazone. Similarly, more clinical and mechanistic data are needed on the potential effects of statins on HCC risk. This might be helpful not only in determining whether the use of statins to reduce HCC risk is indicated in some groups of patients, but also whether there may be other useful strategies for modifying HCC risk linked to the ingestion or metabolism of complex lipids.

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