

Mini-Review

Nutrition and Hepatocellular Cancer

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Key Words

Diet · Hepatocellular carcinoma · Malnutrition · Nutrition · Prognosis · Risk

Abstract

Background: Hepatocellular carcinoma (HCC) significantly contributes to the global burden of cancer. Liver cancer is the third most frequent cause of cancer-related death with HCC representing more than 90% of primary liver cancers. The majority of patients are not only affected by the malignant disease but do also suffer from chronic liver disease. Therefore, several factors impact on the prognosis of patients with HCC, including tumor-related factors, liver function and patient-related factors such as performance status and other comorbidities. The nutritional status is of high significance for the patients' performance status, the tolerance of tumor-targeting therapy and the prognosis of cancer of any type and is specially referenced in HCC. This overview is on current concepts on the role of nutritional factors in hepatocarcinogenesis and the role of nutrition in patients affected by HCC. **Summary:** Nutritional status and composition of diet are relevant factors related to the risk of HCC. They also have an important role concerning the prognosis of patients with HCC. Besides risk factors, several macro- and micronutrient components have been found to be inversely correlated with the risk of HCC. To prevent disease progression to liver cirrhosis or HCC in patients with nonalcoholic steatohepatitis, it is crucial to optimize the metabolic state. **Key Message and Practical Implication:** Evidence from well-designed prospective interventional trials with the aim to reduce the HCC incidence or to prolong survival in patients with HCC based on nutritional modification is still to be generated.

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Introduction

Hepatocellular carcinoma (HCC) significantly adds to the global burden of cancer. The most significant risk factor for HCC is liver cirrhosis, which is present in 70–90% of patients [1]. However, all risk factors that can lead to HCC in the presence of liver cirrhosis are also

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risk factors for the development of HCC in the absence of cirrhosis [2]. Worldwide, chronic viral hepatitis B (HBV) and C (HCV) are the most relevant factors associated with hepatocarcinogenesis. In industrialized countries, fatty liver disease, apart from viral hepatitis, is closely related to nutritional factors, and the prevalence of fatty liver disease is on the rise. High consumption of alcohol is one of the most significant risk factors for development of liver cirrhosis and HCC. However, in recent years, nonalcoholic fatty liver disease (NAFLD) has become more and more prevalent and nowadays has become the leading cause of HCC in some regions of Europe [3]. In patients with NAFLD the progression to HCC is frequent in the absence of cirrhosis. Metabolic risk factors such as obesity and diabetes mellitus have been identified as independent risk factors for HCC development [4–7].

The knowledge on the role of dietary habits which are protective or contribute to hepatocarcinogenesis, either associated with metabolic risk factors or independent of these, is limited.

In patients diagnosed with HCC, the nutritional status is of critical importance concerning the tolerability of tumor-directed therapy and survival.

Nutritional Factors in Hepatocarcinogenesis

Alcohol

Alcohol is a well-established cardinal risk factor for HCC development. There is little evidence of a direct carcinogenic effect of alcohol. The effect of alcohol on HCC development is driven by the alcohol-induced hepatic inflammation with progression to liver fibrosis or cirrhosis. However, alcohol is metabolized to acetaldehyde, which is capable of damaging DNA. A dose-effect relationship has been demonstrated for alcohol-related HCC [8]. Alcohol has a synergistic effect with other risk factors for HCC, in conjunction with HBV and HCV infections and, to a lesser extent, with diabetes [9].

Aflatoxin B1

Aflatoxin B1, a product of fungi of the *Aspergillus* species, is a common contaminant of grains, nuts and vegetables in regions in which climate and storage favor its development such as Asia and Africa, and is a direct carcinogen inducing specific point mutations in TP53 [10]. A simultaneous infection with the HBV potentiates the carcinogenic effect of aflatoxin B1 significantly [11]. It has been estimated that by reducing aflatoxin exposure in high-risk regions the number of HCC cases can be reduced by more than 20% [12].

Iron

Iron overload of the liver is a factor contributing to carcinogenesis. It can occur in hereditary hemochromatosis or as secondary iron overload because of chronic inflammation, especially in patients with alcohol abuse. Treatment with chelating agents and repeated phlebotomy in patients with hemochromatosis reduces the HCC risk [13]. In some regions of the world, e.g. Sub-Saharan Africa, high levels of ingested iron lead to hepatic iron overload [14] with levels comparable to those in hereditary hemochromatosis. The high amount of ingested iron results from large volumes of beer consumed which is home-brewed in cast iron drums or pots. It is estimated that this dietary iron overload, formerly referred to as Bantu siderosis, affects about 15% of black rural Africans [15, 16].

Obesity and the Metabolic Syndrome

Obesity is one of the driving factors of NAFLD. Additionally, several studies have identified obesity as independent risk factor for HCC with a reported OR of 1.39–4.52 [4–6].

Weight loss is the cornerstone in the treatment of NAFLD. Changes in life style, pharmacological interventions and/or bariatric surgery can contribute to weight normalization. Whether persistent weight loss in obese patients also has the potential to positively influence the risk for HCC has not been adequately addressed in prospective clinical studies.

The options to positively influence NAFLD by pharmacotherapy are limited. Insulin resistance is an important factor in promoting NAFLD and may also be a causative factor in hepatocarcinogenesis. Drugs decreasing insulin resistance and lowering insulin levels, like the insulin sensitizer metformin, glitazones or GLP1 analogues like liraglutide, potentially have a positive impact on the risk for HCC in patients with NAFLD [14, 17]. The same holds true for other interventions correcting aspects of the metabolic syndrome such as statins [18, 19]. Obeticholic acid might expand the therapeutic options in nonalcoholic steatohepatitis, but its long-term beneficial effects in the prevention of HCC are not clear yet [20].

Composition of the Diet

There is sufficient evidence that NAFLD is associated with certain dietary patterns [21–23]. Several large cohort studies and few prospective randomized controlled trials have been conducted to analyze the role of diet and nutrition in liver cancer prevention, but the evidence for potential associations between nutrition and HCC is much weaker. While some of these studies evaluate the role of dietary patterns, others focus on distinct nutrients.

A prospective study from China analyzed food patterns in two large and prospectively followed cohorts. Using food frequency questionnaires at baseline, it was shown that a vegetable-based dietary pattern is associated with reduced liver cancer risk, while fruit- and meat-based diets did not show any association [24]. This observation was confirmed by a meta-analysis on published studies on the association between vegetable and fruit consumption and the risk of HCC: the risk of HCC decreases by 8% for every 100 g/day increase in vegetable intake [25]. In a large prospective evaluation in a large US cohort addressing the association of two dietary indices, the Healthy Eating Index-2010 (HEI-2010) and the alternate Mediterranean Diet Score (aMED), with HCC incidence and chronic liver disease mortality, it was shown that adherence to dietary recommendations has the potential to reduce the risk of both diseases. Higher HEI-2010 scores were significantly associated with a lower risk of HCC (HR 0.72; 95% CI 0.53–0.97), and the same holds true for high aMED scores (HR 0.62; 95% CI 0.47–0.84) [26]. In a European study on two cohorts from Greece and Italy, it was also demonstrated that the adherence to a Mediterranean diet pattern is associated with a lower risk for HCC [27]. In both cohorts, a high glycemic load of diet had a negative impact on the HCC risk [28, 29].

EPIC is an ongoing multicenter prospective cohort study on the role of diet, lifestyle and environmental factors in the etiology of cancer and other diseases and has recruited more than 500,000 participants from all over Europe. From these studies several important data have been collected. An inverse association between total fat intake and risk of HCC (per 10 g/day HR 0.80; 95% CI 0.65–0.99) has been observed and appears to be mainly driven by monounsaturated fats [30]. Total fish intake was also inversely associated with HCC risk (per 20 g/day HR 0.83; 95% CI 0.74–0.95) while there was no association with meat consumption [31]. Higher consumption of dietary fiber (per 10 g/day HR 0.70; 95% CI 0.52–0.93), but not the intake of total carbohydrate, or the glycemic load or the glycemic index of diet, influenced the risk for HCC significantly [32]. A protective potential of fruits and vegetables high in flavonoids and antioxidants did not reach statistical significance [33]. These data obtained from populations from the European EPIC study are different from the results obtained from US cohorts. The NIH-AARP study that has prospectively enrolled almost 500,000 men and women

reports an increased risk for HCC associated with the intake of red meat and saturated fat, and a stronger effect with the intake of saturated fat as compared to monounsaturated fat.

A recent meta-analysis on the risk of HCC and meat consumption identified seven cohort studies and ten case-control studies. It did not show an association of the intake of red meat, processed meat or total meat with HCC risk. High levels of white meat or fish consumption on the other hand can reduce the risk of HCC significantly [34].

Data from randomized controlled trials on nutrition and cancer prevention are scarce. A prospective randomized controlled trial in postmenopausal women could not show a beneficial effect of a low-fat diet on the incidence of liver cancer [35].

The nutritional status is a significant prognostic factor in patients with liver cirrhosis [36]. International guidelines recommend nutritional therapy for these patients whenever necessary. Optimal nutritional support prolongs survival, improves liver function and the nutritional status in patients with liver cirrhosis [37, 38]. However, when focusing on the prevention of HCC, evidence-driven recommendations are lacking.

Coffee

Numerous studies have given evidence for an inverse association of coffee consumption and the risk for HCC [39–43]. An updated meta-analysis resulted in a risk reduction of 40% for any coffee consumption. The summary RR was 0.80 (95% CI 0.77–0.84) for an increment of 1 cup of coffee per day [44].

Branched-Chain Amino Acids

Oral branched-chain amino acid supplementation in patients with decompensated liver cirrhosis improves the nutritional status and prevents liver-related complications. In prospective clinical trials, this therapy was also shown to significantly lower HCC occurrence rates in patients with liver cirrhosis [45, 46].

Vitamin D

Epidemiological studies show the inverse association between vitamin D status and the incidence of cancer, and biochemical studies suggest that vitamin D deficiency may play a role in the cause and progression of cancer [47]. Results of the EPIC trial revealed that higher baseline levels of 25(OH)D are associated with a lower risk of HCC (per 10 nmol/l increase IRR 0.80; 95% CI 0.68–0.94) [48]. In contrast, dietary calcium, vitamin D, fat and protein from dairy sources are associated with increased HCC risk while the same nutrients from nondairy sources show inverse or null associations [49].

Nutrition and Prognosis of HCC

Malnutrition is a frequent but underdiagnosed problem in cancer patients and is defined as ‘decline in lean body mass with the potential for functional impairment’ at multiple levels [50]. There is no commonly accepted gold standard for the diagnosis of malnutrition, but about one third of cancer patients are malnourished [51]. Patients with HCC are at a special increased risk for malnutrition. In patients with liver cirrhosis, malnutrition is a common finding and associated with mortality and reduced quality of life [52, 53]. In HCC, the majority of cases are associated with liver function impairment because of liver cirrhosis [1], and tumor progression and tumor-directed therapies may further deteriorate liver function [54].

Prospective clinical studies have identified malnutrition as an independent negative prognostic factor in HCC, but interventional studies addressing the effect of nutritional therapy in HCC patients are few [55].

In patients undergoing resection of HCC in curative intent, perioperative nutritional management has been identified as key determinant of treatment success [56]. Modifications of the macronutrient and micronutrient composition of the diet as well as pharmacological interventions targeting nutritional and metabolic pathways are suggested to positively influence the patients' prognosis [14]. In patients on therapy for HCC, the supplementation of branched-chain amino acid improves liver function [57, 58] and has the potential to prolong recurrence-free survival and overall survival [59]. These observations made from individual studies were only partially confirmed by a recent meta-analysis [60].

A prospective study of 200 patients with HCC revealed that 25(OH)D₃ deficiency is associated with advanced stages of HCC and is a further prognostic indicator for poor outcome [61]. However, large prospective randomized controlled trials are still to be performed on the effect of nutritional interventions on prognosis of patients with HCC.

Conclusion

Nutritional status and composition of diet are relevant factors related to the risk of HCC. They also have an important role concerning the prognosis of patients with HCC. Several macro- and micronutrient components have been found to be inversely correlated with the risk for HCC. To prevent disease progression to liver cirrhosis or HCC in patients with nonalcoholic steatohepatitis, it is crucial to optimize the metabolic state. However, evidence from well-designed prospective interventional trials with the aim to reduce HCC incidence or to prolong survival in patients with HCC based on nutritional modification is still to be generated.

Disclosure Statement

The authors declare no conflicts of interest related to this paper.

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