

The impact of diet and nutrition in the prevention and progression of hepatocellular carcinoma

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**Dalvinder S Mandair^{1,2},
Roberta E Rossi^{1,3},
Marinos Pericleous¹,
Tara Whyand⁴ and
Martyn Caplin^{*1}**

¹Centre for Gastroenterology, Royal Free Hospital, Pond Street, London, UK

²Cancer Institute, University College London, Huntley Street, London, UK

³Department of Pathophysiology and Transplant, Università degli Studi di Milano, and Gastroenterology Unit II, Fondazione IRCCS Ca' Granda, Ospedale Maggiore, Milan, Italy

⁴Department of Nutrition and Dietetics, Royal Free Hospital, London, UK

*Author for correspondence:
m.caplin@ucl.ac.uk

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide. There is growing evidence for a chemopreventive role of nutrition in the development of HCC in at risk populations. Bibliographical searches were performed in PubMed for the terms 'nutrition and hepatocellular carcinoma', 'nutrition and liver cancer', 'nutrition and hepatic cancer', 'diet and hepatocellular carcinoma', 'diet and liver cancer'. High dietary sugar intake should be discouraged in at risk populations. Coffee, polyphenols, vanadium, dietary fibre, fruits and vegetables show encouraging results in terms of chemoprevention. Red meat intake may be associated with increased risk of HCC. The evidence for fatty acids is inconclusive, but they might exert anti-cancer effects. Inconclusive results are available on vitamins, selenium probiotics and prebiotics. There is increasing evidence that diet may play an important role in the development of HCC, and may also have a chemopreventive role in at risk populations.

KEYWORDS: carcinogenesis • chemoprevention • diet • hepatocellular carcinoma • nutrition

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is the third leading cause of cancer mortality worldwide, resulting in approximately 600,000 deaths annually [1]. The majority of cases present after the development of chronic liver disease (CLD) in patients with hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic steatohepatitis (NASH), heavy alcohol intake and exposure to aflatoxins.

HBV is the leading risk factor for HCC globally and accounts for at least 50% of the cases of HCC [2]. In the USA, chronic HCV is the leading risk factor for HCC. A meta-analysis of case-control studies showed that individuals positive for anti-HCV had 17-times the risk of HCC compared with anti-HCV-negative cohort [3].

NASH is now the leading cause of CLD in the Western world, and some epidemiological evidence exists for an increased risk of HCC development in cirrhotics although much less than with HBV and HCV [4].

Heavy alcohol intake increases the risk of HCC through the development of cirrhosis,

and although there is no direct evidence of its carcinogenic potential, it has been estimated that approximately a third of HCC cases in the USA are linked to excessive alcohol consumption [5]. There is also strong evidence to suggest synergy between alcohol consumption and HBV, HCV, and also NASH, which can accelerate the development of cirrhosis leading to the development of HCC.

Several studies have suggested that tobacco smoking is another modifiable significant risk factor for the development of HCC. Indeed, the International Agency for Research on Cancer classified liver cancer as a tobacco-related malignancy [6].

Better education and preventative strategies to control excessive alcohol consumption, decrease smoking and to reduce the prevalence of obesity and weight gain in adulthood are necessary to help control these epidemics, but other preventative measures are vital. The treatment of patients with HCC is associated with high costs with limited resources available and often high rates of recurrence. In many HCC patients, liver transplantation is the

recommended treatment, but this places further burden on already long waiting lists due to organ donor shortage.

There is growing evidence for the role in nutrition in delaying the development of HCC in at-risk populations. A multicenter case cohort study by Talamini *et al.* in 2006 concluded that there was a key role of diet in HCC etiology and suggested that dietary modifications may be indicated in high-risk populations [7]. More recently, the combination of two large case-control studies in Italy and Greece found that strong adherence to a 'Mediterranean diet' appeared to be protective against HCC, with benefit also seen in patients with chronic viral hepatitis [8]. Further associations with diet and HCC have been investigated in the European Prospective Investigation into Cancer and Nutrition (EPIC) study – a multicenter prospective cohort study designed to investigate the association between diet, lifestyle and environmental factors and the incidence of various types of cancer [9].

Here, we review the impact of different dietary components on the prevention and progression of HCC both in these populations and the wider demographic.

Methods

A PubMed search was performed for publications from 1985 through 2013, using the following key words, including both medical subject heading terms and free language words/phrases: 'nutrition and hepatocellular carcinoma', 'nutrition and liver cancer', 'diet and hepatocellular carcinoma', 'hepatocellular carcinoma epidemiology', 'hepatocellular carcinoma and prevention', 'hepatocellular carcinoma and progression' and 'diet and liver cancer'.

Articles that described and compared the impact of diet and nutrition on the prevention and progression of hepatocellular cancer were first screened according to abstract and titles, and the selected papers were assessed for eligibility as full-text articles. Only articles related to primary liver cancer were considered. No language restriction was applied. Reference lists from studies selected by the electronic search were manually searched to identify further relevant reports. Reference lists from all available review articles, primary studies and proceedings of major meetings were also considered. The quality and strength level of the results were considered, with randomized control trials included where possible. Animal or cell line work was only included if it aided the understanding of a potential chemopreventive role of the nutrient.

Results

There were a very large number of results returned for each of our search parameters. Nutrition and HCC led to 2034 hits, nutrition and liver cancer had 524, diet and HCC had 1014, HCC epidemiology had 9850 HCC and prevention had 3521 and HCC and progression had 6112. After filtering for year range, human studies and article type, the numbers fell to 1058, 355, 309, 8598, 2645 and 4764, respectively.

After we manually screened for full-text articles and for documents, which were specific for the scope of this systematic review,

we identified the nutrients and dietary factors with the strongest level of evidence. In more detail, we considered 38 articles for 'meat', 23 articles for 'fish', 59 articles for 'fatty acids', 11 articles for 'sugar intake', 7 articles for 'rice', 57 articles for 'coffee', 83 articles for 'polyphenols', 112 articles for 'vitamins and minerals', 102 articles for 'fiber, fruit and vegetables' and 11 articles for 'probiotics and gut microbiota'. Branched chain amino acids (BCAAs) were also included due to a wealth of literature and strong findings from translational studies.

Protein-rich food

Red versus white meat

Red meat is an important dietary source of saturated and monounsaturated fatty acids and iron. A number of studies have demonstrated a positive association with HCC and intake of red meat. The mechanisms are thought to involve the generation of reactive oxygen species when dietary iron undergoes reduction and through the generation of heterocyclic amines when meat is cooked at high temperatures. The higher fat content in red meat could also explain the effect. An Italian case-control study found a positive association between iron intake and HCC development with odds ratio (OR): 3.00; 95% CI: 1.25–7.23 and also an inverse relationship between white meat and HCC (OR: 5 0.44; 95% CI: 0.20–0.95) [10].

An even larger study examined the relationship between meat and associated exposures with CLD mortality and HCC incidence in 495,006 men and women in the National Institutes of Health AARP Diet and Health Study. In this large prospective cohort study, red meat intake was associated with a higher risk of CLD mortality and HCC incidence (HR: 1.74; 95% CI: 1.16–2.61, 14.9 vs 5.7 cases/100,000 person-years), whereas white meat was inversely associated with both endpoints [11].

Other studies have previously suggested an association between red meat intake and the development of HCC. One study of daily beef, pork and poultry intake observed a statistically significant positive association in an age- and sex-adjusted model (relative risk [RR]: 1.22; 95% CI: 1.04–1.43) [12].

The EPIC study has been designed to investigate the association between diet, lifestyle and environmental factors and the incidence of various types of cancer and other chronic disease. A total of 5,415,385 person-years of follow-up were recruited between 1992 and 2010 during which 191 HCC were diagnosed [10]. Total meat intake was not independently associated with an increased HCC risk, and there was no association between different kinds of meats (red/processed meats or poultry) and increased HCC risk. Meat intake was not associated with HCC risk independently on HBV/HCV status and/or liver function score. A 16% decrease in HCC risk was observed for a 20 g/day substitution of fish for meats.

Conclusion: Red meat intake, particularly processed meat, appears to be associated with increased risk of HCC.

Fish

Fish is a rich source of omega-3 fatty acids, which might protect against HCC due to possible anticarcinogenic and anti-

inflammatory effects [13]. High amounts of vitamin D and selenium, which may be protective against the development of several cancers, are also contained in fish [14]. In the EPIC study, total fish intake (per 20 g/day) was inversely associated with HCC risk (RR: 0.87; 95% CI: 0.70–1.10). In the subgroup analyses, lean fish (per 10 g/day, HR: 0.91; 95% CI: 0.81–1.02), fatty fish (per 10 g/day, HR: 0.92; 95% CI: 0.82–1.03) and crustaceans and molluscs (per 10 g/day, HR: 0.86; 95% CI: 0.70–1.06) were independently associated with lower HCC risk. The inverse association was maintained after adjusting for HBV/HCV status and liver function score (per 20 g/day increase, RR: 0.86; 95% CI: 0.66–1.11 and RR: 0.74; 95% CI: 0.50–1.09, respectively) [10].

Further large prospective randomized trials focusing on the relationship between fish intake and risk of HCC are lacking. The only other prospective evidence is limited to the NIH-AARP Diet and Health Study [15] and four Japanese cohorts [16–19]. The NIH-AARP suggested an inverse liver cancer risk association, but the study had some limitations, including a lower fish intake compared with the EPIC study, older study participants and the lack of the information on HBV/HCV status and the inclusion of other primary liver cancers.

Conclusion: Consumption of fish might reduce the risk of HCC.

Branched chain amino acids – in granules

BCAAs – in granules have been found to have a potential chemopreventive effect. This was demonstrated in a study of 211 patients with cirrhosis, including 152 patients with Child-Pugh A cirrhosis, but no history of HCC. Of these, 56 received oral administration of 12 g/day BCAA for 6 months (BCAA group), and 155 were followed up without BCAA treatment (control group). The incidence of HCC was significantly lower in the BCAA group than in the control group (HR: 0.416; 95% CI: 0.216–0.800; $p = 0.0085$). Their use in posthepatic resection has also been investigated with evidence suggesting a beneficial role in improving liver function [20]. A further study investigated 60 patients with HCV-related cirrhosis, where 30 patients received BCAA supplements (12 g/day) for 3 months or more and the remaining 30 patients were observed without BCAA supplementation. The HCC incidence of patients in the BCAA group was significantly lower than that of patients in the control group ($p = 0.032$), with a 3- and 5-year HCC incidence 13.7 and 13.7%, respectively, compared with 35.1 and 44.5% in the control group. Multivariate analysis for factors that were associated with hepatocarcinogenesis indicated that BCAA supplementation was independently associated with a reduced incidence of HCC (hazard ratio [HR]: 0.131; 95% CI: 0.032–0.530; $p = 0.004$) along with sex and serum α -fetoprotein. Decrease of oxidative stress, antiangiogenesis and improvement of immune system are possible mechanisms responsible for the anticancer effect of BCAA [21].

Conclusion: Supplementation with BCAAs appears to reduce the risk of HCC.

Fatty acids

The potential anticancer effects of fatty acids are drawing increasing attention. A large population-based prospective cohort study of 90,296 Japanese subjects found that consumption of n-3 polyunsaturated fatty acids (PUFAs)-rich fish or n-3 PUFAs supplementation appears to protect against the development of HCC, even among subjects with HBV and/or HCV infection [22].

Fatty acids might exert anticancer effects via their ability to induce apoptosis of cells, to regulate cell cycle and to manipulate eicosanoid production [23]. In solid tumors, hypoxia due to the lack of adequate blood vessels enhances hypoxia-inducible factor (HIF) 1 α levels. HIF 1 α regulates the expression of several genes, which are responsible for tumor development [24]. Increased HIF 1 α levels have been reported to be expressed in HCC [25]. Yamasaki *et al.* analyzed the effects of different fatty acids on the stabilization of HIF 1 α protein in human HCC cell lines under hypoxic conditions [26]. Of the fatty acids examined, 9cis, 11trans (c9, t11)-conjugated linoleic acid (CLA) and 10trans, 12cis (t10, c12)-CLA inhibited hypoxia-induced HIF-1 α stabilization and induced apoptotic cell death under hypoxia. However, some fatty acids themselves can also have harmful effects, particularly the saturated fats and trans fatty acids where increased consumption is strongly linked with the development of NASH and its progression to fibrosis and cirrhosis [27–29].

Conclusion: Polyunsaturated fatty acids, particularly n-3 PUFA's, might exert an anticancer effect, but there is significant risk with saturated fat and trans fatty acids, which needs to be emphasized to at-risk populations. There is much heterogeneity in fat subtypes within most foods, so increasing fatty acid consumption is not currently recommended although more studies are needed on the potential benefits of specific PUFA supplement.

Dietary sugar & glycemic load

Dietary Glycemic load (GL) is the extent to which carbohydrate-rich foods increase the concentration of glucose in the blood to represent the total glycemic effect of diet and is calculated by adding the products of the carbohydrate content per serving for each food, multiplied by the average number of servings of that food per day, multiplied by the food's glycemic index. GL has been consistently linked to diabetes mellitus and has been shown to be positively associated with several types of cancer [30]. The proposed mechanism for a role of high GL in carcinogenesis is through increased insulin concentrations, glucose intolerance and insulin resistance, even in the absence of diabetes mellitus [31]. Foods such as added sugars, syrups, sweets, white bread and soft drinks are the main culprits. A case-control study in Italy in 1999–2002 looked at 185 HCC patients and 412 controls and showed a positive association between GL and HCC overall, with an OR of 3.02 (95% CI: 1.49–6.12). A stronger association was found in patients with HBV and HCV [32].

In the recent EPIC study [33], however, glycemic index, GL and total carbohydrate were not associated with HCC risk.

When analyzing specific carbohydrates, a positive association was observed for total sugar (for high vs low quartile, HR: 1.88; 95% CI: 1.16–3.03; $P_{\text{trend}} = 0.008$). The increased fructose consumption, which may underlie the development of nonalcoholic fatty liver disease, could be a possible explanation for the positive association observed for HCC [34]. Although EPIC was a large prospective study, it did have limitations such as the fact that diet was assessed only at baseline without evaluating potential dietary changes during follow-up, that a period of exposure relevant to cancer initiation may not have been considered, that dietary measurement errors may have occurred which might underestimate the true associations and that dietary practices of different European countries may not have been fully accounted for.

Other studies have examined the association between high insulin levels and HCC, particularly in the viral hepatitis populations [34].

Conclusion: Although a recommended figure for GL has not been determined, and available studies have shown conflicting results, it can be inferred that dietary sugar intake should be monitored and controlled in at-risk populations to attempt to slow down the development of cirrhosis and HCC.

Dietary fiber, fruit & vegetables

Dietary fiber

In a recent study, Fedirko *et al.* [33] suggested a possible inverse association between total dietary fiber consumption and HCC risk, confirmed also in patients negative for HBV and/or HCV. Fiber from cereals and cereal products was statistically significantly inversely associated with HCC risk (HR: 0.78; 95% CI: 0.64–0.96/5 g/day; $P_{\text{trend}} = 0.012$). Fiber from vegetable (HR: 0.79; 95% CI: 0.55–1.15/5 g/day; $P_{\text{trend}} = 0.424$) or other sources (HR: 0.90; 95% CI: 0.75–1.08/5 g/day; $P_{\text{trend}} = 0.221$), but not from fruits (HR: 1.06; 95% CI: 0.83–1.35 per 5 g/day; $P_{\text{trend}} = 0.854$), were also inversely associated with HCC risk, though statistical significance was not reached.

These results support the possible beneficial role of cereals in liver carcinogenesis [14], likely due to their high-fiber content. Diets with a high percentage of fiber could lower the risk of HCC occurrence by decreasing subjective appetite and energy intake, contributing to the maintenance of normal body weight [36] as well as exerting beneficial effects on postprandial glucose level and blood lipid profile [37].

Conclusion: Dietary fiber (i.e., cereals) appears to decrease the risk of HCC occurrence.

Raspberries

Raspberries made some headlines as potential chemopreventive agents. Cell line work found that raspberry extract inhibited the growth of mammary, oral, colon, prostate and liver cancer cells in a dose-dependent manner. An interesting study by Liu *et al.* looked at the protective effects of raspberry extract in a rat hepatic lesions model. They found that raspberries suppressed the induced hepatic lesions in rats, as well as reducing the definite diagnostic features of a neoplasm [38].

Conclusion: *In vitro* studies showed a potential chemopreventive role for raspberries, but further studies are warranted.

Tomatoes & tomato-based products

Tomatoes and tomato-based products are a rich source of lycopene, which is one of the major antioxidant carotenoids. Epidemiological studies have found that higher lycopene intakes are associated with a lower risk of several types of cancer, including prostate and pancreas [39]. A number of *in vivo* and *in vitro* studies have taken place to examine the role of lycopene in preventing hepatocarcinogenesis, with the majority demonstrating a chemopreventive role with inhibitory effects on adhesion and migration of hepatoma cells. A study looking at the effect of lycopene in lung metastasis development in athymic mice injected with human hepatoma cells found significant inhibition in the lycopene-supplemented mice [40]. An additional study looking at high-risk groups randomized 24 patients to receive a mixture of phytochemicals, of which lycopene was the main component, and compared this to 46 controls. The patients were followed for 2.5 years, and they found the cumulative incidence of HCC in the treated group to be 4.2 compared with 22.2 in the control group [41]. Moreover, no harmful effects of lycopene have been reported.

Conclusion: Increased lycopene intake (i.e., tomatoes) can be recommended to reduce the risk of HCC. Furthermore, lycopene intake might prevent metastases in patients with HCC.

Cruciferous vegetables

Cruciferous vegetables such as Chinese cabbage, turnips, rutabagas, watercress and radishes are a rich source of phenethyl isothiocyanate. Phenethyl isothiocyanate has been shown to inhibit the tumorigenic effects of various carcinogens both *in vivo* and *in vitro* [42]. The association between green–yellow vegetables and fruit consumption and the risk of cancer death was investigated in a prospective study of 38,540 men and women who were atomic bomb survivors in Hiroshima and Nagasaki, Japan. Their findings that a high intake of green–yellow vegetables significantly decreased the risk of primary liver cancer mortality are consistent with other studies [43]. Few other larger epidemiological studies have specifically looked at HCC, but animal studies have suggested a protective effect against the effect of heterocyclic amines and aflatoxins. There are certainly no suggestions of any risk associated with high intake of cruciferous vegetables and as part of a well-balanced diet, they are likely to have a beneficial role against hepatocellular carcinogenesis.

Conclusion: Cruciferous vegetables may exert chemopreventive effects against HCC occurrence, but further studies, focused on HCC, are needed.

Peanuts, grapes & red wine

Peanuts, grapes and red wine are a good source of resveratrol, which inhibits the activation of the carcinogen-activating enzyme, cytochrome P450 1A1, suggesting a potential chemopreventive

role [44]. Both *in vitro* and *in vivo* studies with resveratrol have produced encouraging results.

A study by Miura *et al.* showed that 20 days oral administration of resveratrol to hepatoma-bearing rats suppressed tumor growth and the number of metastasis, with growth remaining static after 12 days administration [45]. In a transplanted murine model, Yu *et al.* demonstrated that intraperitoneal administration of resveratrol for 10 days significantly inhibited tumor growth [46]. Resveratrol has also been shown to enhance the cytotoxicity of conventional chemotherapeutics.

A recent review reported that evidence from numerous studies using various liver cancer cell lines and chemically induced tumors as well as animal models, showed that resveratrol may play an important role not only in the prevention but also in the therapy of metastatic disease of the liver, although some aspects need to be further evaluated, particularly the issue of low bioavailability of resveratrol [47]. A Phase I study focused on this issue. As micronization increased the availability of the drug by increasing its absorption, micronized resveratrol (SRT501) was administered, as 5 g daily for 14 days, to patients with colorectal cancer and hepatic metastases scheduled to undergo hepatectomy. This study showed that SRT501 was well tolerated. Moreover, markers of apoptosis were significantly increased in malignant hepatic tissue, following SRT501 treatment compared with tissue from the placebo-treated patients [48].

Conclusion: Available results suggest a promising role for resveratrol as a chemotherapeutic agent but the appropriateness of advocating an increase in consumption of red wine as a measure to prevent CLD and HCC need to be further assessed.

Fermented brown rice & rice bran

Rice germ or fermented brown rice has been reported to exert a preventive effect on colorectal carcinogenesis [49]. The same Japanese group reported that brown rice fermented by *Aspergillus Oryzae* (FBRA) might have an inhibitory effect on the hepatocarcinogenesis in rats. In their animal model, they analyzed the potential anticancer role of FBRA in male F344 rats using inhibition of diethylnitrosoamine (DEN) and phenobarbital-induced hepatocarcinogenesis as the measure of preventive efficacy when this agent was administered at 5 and 10% levels in diet. The incidence of HCC was significantly reduced after the administration of 10% FBRA during the initiation phase (43 vs 8%) compared with the control group. Furthermore, the incidence of HCC decreased significantly as a result of the administration of 5 and 10% of FBRA in the diet during postinitiation phase (43 vs 15% and 9%, respectively) [50].

Conclusion: Fermented brown rice might be protective against the development of HCC according to animal studies, but further evidence from human studies is warranted.

Polyphenols

Polyphenols are secondary metabolites largely present in plant foods, and they are divided into four main classes: flavonoids

(anthocyanins, flavonols, flavanones, flavones, flavanols and iso-flavones), phenolic acids, stilbenes and lignans. They have been reported to have antioxidant, anti-inflammatory and anticarcinogenic properties [51,52]. Coffee and green tea are the major dietary sources of polyphenols.

Flavonoids

Several *in vitro* studies have suggested an antitumor effect of flavonoids in some hepatocarcinoma cell lines [53,54] and in animal models, flavonoids seem to modulate mechanisms related to proliferation, invasion, angiogenesis, survival and metastasis of tumor cells [55].

In a Greek case-control study, flavone intake and its main food sources (spinach and peppers) were inversely associated with HCC risk in both chronic hepatitis virus positive (OR: 0.50; 95% CI: 0.27–0.94) and negative cases (OR: 0.41; 95% CI: 0.16–1.06) [56]. The association of dietary intakes of flavonoids and lignans on the risk of HCC has been assessed within the EPIC study. According to the study data, the main food sources of flavonoids were fruits (39.5%), tea (19.1%), wine (11.9%), fruit juices (5.7%) and vegetables (3.3%). During a mean follow-up of 11 years, 191 incident HCC cases were diagnosed. A nonsignificant association of HCC with total flavonoid intake was observed (highest vs lowest tertile, HR: 0.65; 95% CI: 0.40–1.04; $P_{\text{trend}} = 0.065$), but not with lignans. Among flavonoid subclasses, flavanols were inversely associated with HCC risk (HR: 0.62; 95% CI: 0.39–0.99; $P_{\text{trend}} = 0.06$) [57,58]. According to this large prospective epidemiological study, dietary flavanols might have a favorable role in reducing the risk of HCC occurrence.

The antioxidant effect of polyphenols is still a matter of much debate. Hollman *et al.* recently questioned the antioxidant properties of polyphenols *in vivo*, particularly against cardiovascular diseases [59]. Furthermore, the concentrations of flavonoids and lignans in the body are quite limited due to the low-to-moderate intake [54] and low bioavailability [60]. Pharmacological doses of flavonoids may be required before modulation of carcinogen metabolism and inflammatory pathways is seen [61].

Conclusion: Flavonoids appear to reduce the risk of HCC, but pharmacological doses might be required in order to effectively modulate carcinogenesis.

Green tea

Green tea contains polyphenols, the most abundant of which is epigallocatechin gallate. Evidence from both *in vivo* studies and animal models suggests that green tea catechins are likely to prevent steatosis by decreasing intestinal lipid and carbohydrate absorption, by decreasing adipose lipolysis and by stimulating hepatic β -oxidation and thermogenesis by improving insulin sensitivity. Furthermore, catechins are likely to prevent the progression from liver steatosis to NASH and then cirrhosis through their antioxidant and anti-inflammatory properties [62].

Many *in vivo* and *in vitro* studies have also reported antitumor effects of green tea. The antioxidant and anti-

inflammatory effects of phenols, especially epigallocatechin gallate, are thought to prevent development of many cancers including HCC. However, few translational studies have, to date, taken place. One epidemiological study looked at 215 HCC patients compared with 415 controls in Taipei, China. Individuals who drank green tea for longer than 30 years were at the lowest risk (adjusted OR: 0.44; 95% CI: 0.19–0.96) of developing HCC. Other favorable effects reported were possible delayed entry of HCV and HBV into cells and potential effects on polymorphism of targets for antiviral therapy [63]. Other epidemiological studies have found an inverse relationship between mortality from HCC and drinking green tea, but as yet, no RCTs have taken place to confirm this. Some *in vivo* studies have reported potentiation of action of chemotherapy agents by green tea on HCC cell lines.

Some studies focused on overall tea consumption, and a recent meta-analysis including 13 epidemiological (6 case–control and 7 prospective cohort) studies showed evidence for a protective effect of overall tea consumption against the development of primary liver cancer [64].

Furthermore, in animal models, administration of black tea showed promising chemopreventive effects against HCC [65].

Previous findings have been confirmed in a recent review, which highlighted that tea polyphenols (i.e., green and black tea) remain promising chemopreventive and therapeutic agents in the treatment of HCC [66].

Conclusion: Green and black tea may be preventive against HCC, but further randomized control trials would be useful to determine optimum dosing.

Coffee

Coffee has long been purported to have a chemopreventive role in HCC. Coffee is a complex blend of different chemicals including antioxidants, mutagenic and antimutagenic compounds. The mechanisms of action are unclear, but may involve the modification of cysteine residues in proteins that play important roles in liver carcinogenesis [67]. Coffee is likely to have both anti-inflammatory and antioxidant properties that can prevent fibrosis and cirrhosis, which has been demonstrated in animal studies [68]. A meta-analysis by Bravi *et al.* looked at 10 epidemiological studies including 6 case–control studies from southern Europe and Japan. The summary RR for coffee drinkers versus nondrinkers was 0.54 (95% CI: 0.38–0.76) for the case–control studies and 0.64 (95% CI: 0.56–0.74) for the cohort studies [69].

A similar meta-analysis by Larsson *et al.* found the summary RR of HCC for an increase in consumption of two cups of coffee per day was 0.69 (95% CI: 0.55–0.87) for people without a history of liver disease and 0.56 (95% CI: 0.35–0.91) for those with a history of liver disease. The study demonstrated a clear inverse relation between coffee drinking and HCC across study design and geographical areas [70]. More recently, the Singapore Chinese Health Study looked at a prospective cohort of 63,257 middle-aged and older Chinese men and women and found that individuals who consumed three or more cups of

coffee per day experienced a statistically significant 44% reduction in risk of HCC (HR: 0.56; 95% CI: 0.31–1.00; $p = 0.049$) [71].

Conclusion: Although there have been no randomized control trials to look at coffee exclusion or coffee supplementation in high-risk groups, there is strong epidemiological evidence that increasing coffee consumption may have a chemopreventive role in the development of HCC and indeed against progression of liver disease.

Curcumin

Curcumin is a polyphenol derived from turmeric, a commonly used spice in Indian cooking and has received much media interest after the commencement of a national trial combining curcumin supplementation and chemotherapy in bowel cancer. Curcumin has been shown to induce apoptosis in several tumor cell lines *in vitro*, and animal models have shown that it inhibits hepatocarcinogenesis in rat model and murine models [72].

Interestingly, combination therapy with curcumin and either cisplatin or doxorubicin resulted in synergistic reduction in tumor cell proliferation and an increase in apoptosis of tumor cells *in vitro* compared with either traditional chemotherapeutic agent alone [73]. This suggests that curcumin has considerable potential as both a chemopreventive and chemotherapeutic agent in HCC. As yet, no RCTs have taken place, but with a wealth of *in vitro* and *in vivo* studies behind it, these may follow depending on the results of the bowel cancer study.

A recent review confirmed curcumin to be a potential chemopreventive and chemotherapeutic agent in the treatment of HCC, but also raised some concerns in terms of safety (i.e., long-term effects and optimum dose) [74].

Conclusion: Curcumin might have a considerable potential as both a chemopreventive and chemotherapeutic agent in HCC, but randomized trials are required.

Soybeans & soy products

Soybeans and soy products are enriched in isoflavones, which are structurally similar to 17 β -oestradiol and have the ability to bind to estrogen receptors [75]. Epidemiological studies have demonstrated consistently that HCC is commoner in men than women, even after adjusting for alcohol and cigarette smoking. Animal studies have demonstrated a protective benefit of soy, and a potential mechanism is thought to be the activation of these estrogen receptors [76]. However, one of the larger epidemiological studies by a Japanese group found that among 20,000 patients with HCC, there was a positive association between isoflavone consumption and HCC in women, but no association in men [77]. When you also consider that tamoxifen (an antiestrogen agent) has been used in the past to treat HCC, it is apparent that there remains far too much uncertainty in the role of estrogens and HCC development to advocate isoflavone supplementation.

Conclusion: Isoflavone supplementation cannot be advocated to prevent HCC occurrence as the results are still inconclusive.

Vitamins & minerals

Vitamin E

There have been many animal studies that have suggested an anticarcinogenesis role for vitamin E. The rationale is based on its vast antioxidant properties, which would counter the oxidative stress required for hepatocytes to undergo malignant transformation. One of the earliest studies done in 1951 found that high levels of vitamin E supplementation decreased the incidence of liver tumors induced by 30-methyl-4-dimethylaminoazobenzene in mice [78]. More recent studies such as that by Kakizaki *et al.* examined whether deficiency or high levels of dietary vitamin E could influence hepatocarcinogenesis in transgenic mice. The mice receiving the control level of vitamin E (20 mg α -tocopheryl acetate/kg diet) developed the most tumors, while the mice receiving the highest level (500 mg/kg diet) had a significantly lower incidence [79]. Epidemiological studies have not shown a strong correlation between low vitamin E levels and the incidence of HCC. There are few randomized controlled trials that have looked solely at vitamin E supplementation. The Selenium and Vitamin E Cancer Prevention Trial study found no significant difference in the incidence of HCC in supplementation with either selenium or vitamin E [66]. One Chinese study looked at over 30,000 healthy volunteers using supplementation with several vitamin–mineral combinations over a period of 5.25 years. There were 151 cases of HCC in that period, but of note, the arm of the study looking at vitamin E also included a β -carotene (15 mg) and selenium (50 mg) supplement. No significant beneficial effect was found, and although it was not possible to examine the effect of vitamin E alone in that study, it can be inferred from the studies published to date that there is no significant chemopreventive role of vitamin E in HCC [80].

Vitamin E may have a role in delaying progression of some CLD, such as NAFLD, and therefore reducing the incidence of cirrhosis. Certainly, there is much evidence to suggest histological and biochemical improvement after the administration of vitamin E, but one of the largest studies of recent times, the Treatment of Non-alcoholic Fatty Liver Disease in Children, which compared Metformin, vitamin E or placebo in children gave largely disappointing results [81]. Similarly, in patients with chronic HCV, early biochemical improvement has been seen but no long-term benefits reported on survival [82]. An exhaustive review of vitamin E in CLD is beyond this review, but to date, there are no human studies that demonstrate a beneficial effect of vitamin E in delaying the development of cirrhosis.

There may, however, be a role for vitamin E in supportive treatment for HCC. A study that looked at trans-retinoic acid, tamoxifen and vitamin E found a significant increase in survival in the treatment group [83]. Although a small study, there was better toleration of Tamoxifen with the addition of vitamin E than in other studies with Tamoxifen alone. With the advent of many new drugs in the treatment of HCC, future studies could try and use vitamin E as an adjunct to treatment to improve tolerability of drugs and symptoms.

Conclusion: There are no data to support a role of vitamin E as chemopreventive agent against HCC occurrence. However, vitamin E may be used in supportive treatment of HCC and further studies are suggested.

Vitamin A

Vitamin A consists of retinol and the carotenes, α -carotene, β -carotene, γ -carotene as well as the xanthophyll β -cryptoxanthin. Deficiencies in vitamin A and other fat-soluble vitamins have been well documented in cirrhotics and in epidemiological studies. A prospective study of 107 consecutive patients who were assessed for liver transplantation found that there is a strong correlation between severity of liver disease and vitamin A deficiency [84]. Many animal and cell line studies have found that acyclic retinoid (a synthetic retinoid) could have important tumor suppressor abilities. As yet, no RCTs have demonstrated a clear benefit, but a meta-analysis by Chu *et al.* in 2010 found that progression-free survival was improved in post radiofrequency ablation and hepatectomy patients with acyclic retinoid although no studies demonstrated a benefit on overall survival [85].

β -carotene, in addition to its ability to be converted into vitamin A, is thought to have strong antioxidant properties. Many animal studies have suggested a protective role [86], but although no human data for HCC exist, in two large RCTs looking at retinol and carotene in Lung Cancer (CARET and ATBC studies), β -carotene was found to increase the incidence of lung cancer among smokers [87].

Conclusion: Based on current evidence, β -carotene supplementation cannot be advocated to prevent HCC.

Vitamin C

There is little convincing evidence for its use in chemoprevention in HCC. Animal and cell studies have provided conflicting results with some studies even showing an increase in tumor activity. A large population-based prospective study of 19,998 Japanese individuals found that vitamin C increased the risk of HCC in smokers with a HR of 3.58 (95% CI: 1.21–10.63), while no significant association was found in nonsmokers [88].

Conclusion: Based on the current evidence, vitamin C supplementation should not be recommended in high-risk patients.

Selenium

Selenium (Se) is an important trace element, and its dietary deficiency has been linked to various cancers. It forms a component of a series of proteins, which include glutathione peroxidases (GPx), thioredoxin reductases, iodothyronine deiodinases, selenophosphate synthetase, selenoprotein P and selenoprotein W [89]. GPx and thioredoxin reductase function as antioxidants, so increasing Se intake has been proposed as a way to prevent the development of some forms of cancer.

The liver is particularly affected under selenium deficiency because other organs such as brain, testes and endocrine tissues

are supplied preferentially with selenium [90]. Previous studies have suggested a lower concentration of selenium within focal areas of HCC compared with surrounding tissue [91]. A Taiwanese study looking at a cohort of 7342 men found an inverse association with selenium levels and HCC in patients with chronic viral hepatitis [92]. Growing epidemiological evidence for a potential chemopreventive role has led to many animal studies. In a study using a transplantable tumor model using HepG2 human hepatoma cells, mice were given drinking water containing sodium selenite or green tea extracts in which the tea had been grown with different levels of Se. Both selenite and high Se teas inhibited the growth of the transplantable tumors [93]. Another study by Bjorkhem-Bergman *et al.* found that 1 and 5 mg/kg Se administered to rats had no effect on the number and volume of hepatic nodules, but Se administered during either the selection or 6-month progression stages decreased liver volume occupied by the nodules in the liver [94].

Animal studies have provided conflicting results, and some have suggested that too high levels of selenium indeed promoted carcinogenesis. Randomized controlled trials with selenium supplementation took place in China almost 20 years ago, with the most striking study investigating the preventive effect of Se on primary liver cancer. This found that Se supplementation using table salt fortified with sodium selenite (30–50 mg Se/day) resulted in an almost 50% decrease in the primary liver cancer incidence [95]. These results have not been reproduced since, and larger clinical trials are lacking. The Selenium and Vitamin E Cancer Prevention trial using supplementation with vitamin E and Selenium looked at many different cancers and had largely disappointing results with regard to a chemopreventive role [80].

Previously, animal and cellular studies have focused on the antioxidant properties of the glutathione peroxidases and have presumed this to be the main factor in preventing carcinogenesis. However, this is likely to be an oversimplification with emerging evidence suggesting that certain forms of selenium might exclusively elevate the level of SBP1 rather than GPX1, thus increasing SBP1 expression and decreasing GPX1 activity which can promote pro-oxidant formation that can induce apoptosis and cell arrest of cancer cells [96]. These are certainly interesting developments and may explain the conflicting results seen in animal studies and clinical trials.

Conclusion: Selenium supplementation may exert chemopreventive effect, but more studies are needed, and certainly, a larger clinical trial of at-risk populations would be helpful in determining a potential role for selenium and a safe dose.

Vanadium

Vanadium is a trace element that is considered essential for animals, but it has not been yet established as an important micronutrient for humans [97]. Vanadium has been described to exert an insulin-mimetic action, and it improves hyperlipidemia and hypertension. Moreover, vanadium appears to exert inhibitory effects on various tumor cells of human origin through multiple biochemical and molecular pathways. Both *in vitro*

studies and animal have found vanadium to provide protection against all stages of carcinogenesis, initiation, promotion and progression. Vanadium could suppress the growth and spread of existing tumors by inhibiting tumor cell proliferation, inducing apoptosis and limiting the invasion and metastatic potential of neoplastic cells.

Several studies have examined the chemopreventive effects of vanadium in preclinical chemically induced models of primary HCC, and promising results have been described in terms of reduced risk of HCC. Moreover, the chemopreventive effect of vanadium may be increased by the combination with other chemopreventive agents such as vitamin D and β -carotene [98].

Conclusion: Vanadium has shown promising results as chemopreventive agent against HCC, but evidence from human studies is still lacking.

Aflatoxins

Aflatoxins are a group of mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, which cause liver cancer in many experimental animal models. Contamination of food stocks by these fungi occurs from improper storage of cereals, peanuts and other vegetables and is prevalent, in particular, in Africa, Southeast Asia and China. Aflatoxin B1 (AFB1) has been confirmed as an independent carcinogen in many animal studies and also found to interact with that exerted by HBV infection [99]. Although avoidance of contaminated foods is not practical in countries where food stocks are so vital, countries with a high prevalence of at-risk populations should have education programs designed to decrease exposure to aflatoxins using postharvest interventions. Other secondary measures that have been suggested include the drinking of green tea and hot water infusions of 3-day-old broccoli sprouts, containing high concentrations of glucosinolates that are a rich source of the anticarcinogen sulforaphane [100].

Conclusion: Aflatoxins are known to cause liver cancer, and countries with a high prevalence of at-risk populations should have education programs to decrease exposure to aflatoxins.

Probiotics

There is no direct evidence of the use of probiotics, such as lactobacilli and bifidobacteria, in the prevention of hepatocellular cancer. Animal studies have found chemopreventive properties in development of 'aflatoxin-induced' HCC [101]. There may be a role in use of probiotics in helping to normalize liver function after hepatectomy for HCC. A study conducted on 120 patients posthepatic resection found that the group supplemented with probiotics developed fewer postoperative complications, quicker normalization of liver function and lower serum tumor markers [102].

Conclusion: Based on the current evidence, probiotics cannot be advocated to prevent HCC.

Prebiotics

Prebiotics such as inulin and oligofructose promote functionally active bacteria, and their selective promotion of bifidobacteria

in particular has led to much interest in potential use as chemopreventative agents. To date, most of the research has centered on colorectal cancer, but one animal study found that transplanted tumor mice had an increase in lifespan of 16–18% in diets supplemented with inulin and oligofructose. Outside of colorectal cancer, there is little human evidence at present [103].

Conclusion: Prebiotics cannot be advocated in HCC due to lack of evidence in this specific setting.

Stichopus japonicus acid mucopolysaccharide

Stichopus japonicus acid mucopolysaccharide (SJAMP) is an important biologically active compound that is extracted from the body wall of the sea cucumber *Stichopus japonicus* and is made up of galactosamine, hexuronic acid, fructose and sulphuric acid [104]. SJAMP has shown antitumor, immunological regulation, anticoagulant and antiviral properties [101] and has been reported to exert anticancer effects through the induction of apoptosis of malignant cells [106].

Some studies suggested a close relationship between immune functional status and the occurrence and progression of tumors [107]. A recent study investigated the antitumor and immunomodulatory activities of SJAMP in a DEN-induced HCC rat model and showed that SJAMP effectively inhibited the growth of HCC through the stimulation of immune system and tissue proliferation [108]. Three doses of SJAMP (17.5, 35 and 70 mg/kg administered 5 days/week via oral lavage) were given to rats with DEN-induced HCC. SJAMP treatment reduced the number of DEN-induced HCC lesions and the volume of the largest nodules, and levels of serum α -fetoprotein. With regards the effect of SJAMP administration on immune system, SJAMP doses significantly increased serum IL-2 and decreased serum TNF- α . Moreover, SJAMP administration resulted in improved indices of spleen and thymus function, improved macrophage phagocytosis and NK cell-mediated anticancer activity.

Conclusion: SJAMP may exert anticancer effect, mainly through the regulation of the immune system, but further studies are needed.

Conclusion

Epidemiological and preclinical studies have suggested that nutrition plays an important role in the etiology of cancer, and dietary factors are strongly suspected to contribute to HCC risk. However, the results are often inconclusive and do not allow us to draw solid conclusions due to the paucity of large randomized clinical trials.

In our review, we explored those nutritional factors that might play a role in the development and progression of HCC (Box 1). Red meat intake, particularly processed meat, should be limited and should be replaced by the consumption of fish as it might reduce the risk of HCC. Fatty acids might exert anticancer effects although the exact mechanisms involved are still to be clearly elucidated. GL and particularly dietary sugar

intake should be monitored and controlled in at-risk populations to slow the development of cirrhosis and HCC.

High intake of coffee appears to exert a chemopreventive role in the development of HCC and indeed against progression of liver disease. Also green and black tea may be preventive against HCC, but further randomized control trials would be useful to determine optimum dosing. Other polyphenol-rich food (i.e., flavonoids, soya products and curcumin) as well as dietary fiber (i.e., cereals), fruits and vegetables have shown encouraging results and may have a potential protective effect against the development of HCC. Vitamin supplementation, probiotics and prebiotics cannot be advocated in HCC as there is still little human evidence at present, and available data are often conflicting. Selenium supplementation only showed some encouraging results, but again further studies are warranted.

Better preventive measures to control the spread of HCC are urgently needed. Large prospective randomized trials are recommended to elucidate the relationship between diet and the risk of HCC occurrence with the aim of both introducing nutrition approach in clinical practice and sensitizing public health policy to the importance of dietary factors in HCC development. However, in heterogeneous populations with different lifestyle, nutritional BMI and many other variable, it is difficult to design prospective randomized trials aimed at developing population-based prevention strategies for HCC.

Expert commentary

Due to the increasing incidence and high mortality rate of HCC, better preventive measures are required to potentially decrease the clinical burden of HCC.

Epidemiological and preclinical studies have suggested that nutrition plays an important role in the etiology of many cancers, and dietary factors are strongly suspected to contribute to HCC risk.

The results of many of these studies are often inconclusive, and large randomized clinical trials are required. However, from the data that are available, we can conclude that there is a need to highlight the importance of dietary factors in HCC development which can then be used to help develop public health policy.

According to available data, we recommend to limit red meat intake and increase the consumption of white meat and fish. Furthermore, dietary sugar intake should be monitored and controlled in at-risk populations, with greater education provided about the hidden sugars in many foods.

We also suggest increasing the daily consumption of coffee, cereals, fruits and vegetables, which have shown encouraging results and might exert a potential protective effect against the development of HCC.

With regards the role of nutritional supplements, including polyphenols, minerals and some vitamins, for example, vitamin E, data are limited but there appears to be a benefit without significant toxicity. Further randomized trials are needed.

Box 1. Summary of current evidence about the association between dietary factors and risk of hepatocellular carcinoma.

Main findings summarized: strongest evidence

- Red meat intake appears to be associated with increased risk of HCC
- Increased consumption of fish may decrease the risk of development of HCC
- Supplementation with branched chain amino acids may be helpful to reduce the risk of HCC
- Dietary sugar intake should be monitored and controlled in at-risk populations to attempt to slow down the development of cirrhosis and HCC
- There is strong epidemiological evidence that increasing coffee consumption may have a chemopreventive role in the development of HCC and indeed against progression of liver disease
- Dietary fiber, particularly that from cereals appears to reduce the risk of HCC
- Tomatoes and other lycopene-rich products are associated with a decreased risk of HCC and may slow down the development of metastases
- Aflatoxins are known to cause liver cancer, and countries with a high prevalence of at-risk populations should have education programs to decrease exposure to aflatoxins
- Based on the available evidence, Isoflavone supplementation should not be advocated
- Vitamin A supplementation in the form of B-Carotene should be avoided due to epidemiological evidence suggesting a possible increased risk of HCC

Limited evidence

- Some polyunsaturated fatty acids might exert an anticancer effect
- Green and black tea may be preventive against HCC, but further randomized control trials would be useful to determine optimum dosing
- Raspberries have shown promise, but evidence is only available from *in vitro* studies
- Cruciferous vegetables are likely to be beneficial, but few studies looking solely at a potential chemopreventive role in HCC have been published
- Resveratrol is likely to be a potent chemopreventive agent, but as the best source is from grapes and red wine, it is difficult to advocate increasing their intake to at-risk populations. Randomized control trials with resveratrol supplements may shed more light on its potential
- Fermented brown rice and rice bran have shown promise, but to date, the evidence is restricted to animal studies
- Curcumin has limited human studies, and the appropriate dosing is uncertain
- Vitamin E may be useful as supportive agent in patients receiving chemotherapy for HCC
- Vitamin C may be harmful and increase the incidence of HCC in some at-risk groups – the evidence is often contradictory
- Selenium is likely to be chemopreventive, but more studies are required to determine which isoform is beneficial
- Vanadium has shown a potential role in chemoprevention in animal studies, but further human studies are required

HCC: Hepatocellular carcinoma.

Five-year view

The increasing clinical burden of HCC is likely to continue worldwide and the shortage of organ donors, limited efficacy and tolerability of chemotherapy and even newer molecular-targeted therapies will lead to focus on preventative measures. The development of a nutrition-focused approach as part of the multidisciplinary management of CLD, involving greater education and enrolment into clinical trials will lead to greater awareness of its role and provide more convincing evidence for specific dietary modifications.

The impact of diet and nutritional supplements has been investigated in other tumor types and has led to the

development of clinical trials using dietary supplements alongside chemotherapy and we look forward to such studies in HCC.

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Key issues

- There is increasing evidence for a potential chemopreventive role of nutrition in hepatocellular carcinoma.
- The majority of the evidences are from large epidemiological studies, but both *in vivo* and *in vitro* studies have led to the development of interesting hypotheses.
- Increased fish intake, decreased red meat intake and dietary sugar could represent simple steps for diet modification in at-risk groups that may confer benefit.
- Nutritional supplements, including polyphenols and some vitamins, for example, vitamin E appear to be beneficial and randomized trials are needed.

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