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EDITORIAL

Dietary factors can protect against liver cancer development

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Abstract

Liver cancer is the third leading cause of cancer mortality worldwide with hepatocellular carcinoma (HCC) representing more than 90% of primary liver cancers. Most HCC patients are also suffering from chronic liver disease (CLD). Evidence is emerging that the composition of diet plays an important role in HCC and CLD development and may also have a chemoprotective role. In contrast to other types of cancer, there are few studies investigating the role of diet in hepatocarcinogenesis. From the available data it is evident that high intakes of red meat and dietary sugar positively correlate with HCC occurrence. On the contrary, high consumption of white meat, fish, vegetables, fruits and cereals are inversely associated with HCC risk. This letter discusses the potential role of dietary interventions in the prevention of hepatocarcinogenesis. The increasing HCC incidence and its high fatality are making HCC prevention an urgent matter. Dietary modifications are found to offer protection against HCC, however, new studies from well-designed and large prospective trials are required to confirm these results.

Key words: Cancer prevention; Diet; Hepatitis virus; Meat; Hepatocellular carcinoma

Core tip: Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality. Evidence shows that diet relates to HCC risk and may also have a protective role. Several dietary factors such as vegetables, cereals, fruits, white meat and fish have been found to be inversely associated with HCC risk, whereas a positive correlation has been found with red meat and dietary sugar intakes. The increasing HCC incidence makes its prevention an urgent matter and diet intervention represent an attractive potential. Dietary modifications are found to protect against HCC, however, new studies from well-designed and large prospective trials are required to confirm these results.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is third leading cause of cancer mortality worldwide and accounts for about 90% of primary liver cancers. The major risk factors for HCC occurrence include chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), excess of alcohol consumption, non-alcoholic fatty liver disease (NAFLD), dietary aflatoxin exposure, obesity, smoking and diabetes mellitus[1]. Exposure to these factors can injure the liver leading to chronic liver disease (CLD) and patients with CLD are at high risk of developing HCC. A substantial proportion of HCC, however, occurs in patients without exposure to these risk factors[2], suggesting the existence of additional factors.

For the past few decades, epidemiological evidence has shown that diet-related factors are closely related with cancer. A healthy diet is known to reduce the development of some types of cancer, while a poor diet increases cancer risk[3]. However, there is no current definition of healthy eating. Observational studies have indicated a protective role of vegetables, fruits and cereals in cancer prevention. In contrast to other types of cancer, there are relatively few studies that investigated the association of diet and HCC risk. Although studies have reached conflicting results, consistent evidence suggests that high intakes of red meat[4,5] and dietary sugar[6] should be avoided in at-risk populations. Higher intakes of white meat or fish[7-10], vegetables[10-16], fruits[10,14,17,18], cereals[6], eggs[10,17,18], milk[18] and yogurt[10] have been reported to decrease HCC development. Dietary patterns can capture interactions between dietary components and other risk factors providing a better understanding of the association between dietary intakes and HCC risk. Here the impact of dietary patterns on the prevention of HCC is being discussed.

RED MEAT

Red meat is an important dietary source of saturated and monounsaturated fatty acids and iron. A number of studies associated meat, especially red and processed meat, with gastrointestinal cancers, including HCC[5,10,13,17-23]. Nanji *et al*[24] was the first to report in 1985 that high pork intake correlated with liver cancer mortality and since then significant associations between total red meat and an increased risk of CLD and HCC have been found[4,25,26] (Table 1). A large prospective study by Freedman *et al*[4] with a United States cohort revealed an association between total fat, monounstaturated fat, and saturated fat with both CLD and HCC incident and another smaller study from Greece observed that that high saturated fat intake correlated with liver cirrhosis and HCC[26]. One study of daily beef, pork and poultry intake found a statistically significant positive association between red meat and HCC risk in an age- and sex-adjusted analysis[5]. On the contrary, Polesel *et al*[27] reported no direct association of HCC risk with saturated fat intake and results from a Greek case-control study showed no association with any fat type[20]. Notably, Polesel *et al*[27] did report a positive association between iron intake and HCC. Furthermore, a recent meta-analysis study by Luo *et al*[28] as well as the multicenter prospective EPIC cohort study, which associates diet with various types of cancer, reported no association between different kinds of meats (red and processed meats or poultry) and increased HCC risk[7,28,29]. The EPIC study, however, found that a 20 g/d substitution of fish with meat results in a 16% decrease in HCC risk.

The link between red meat and liver cancer is biological plausible, since red meat contains high amounts of known carcinogens including heme iron, N-nitroso compounds (NOC) and heterocyclic amines (HCA) that are produced when meat is cooked in high temperatures[30]. Red meat contains high amounts of bioavailable heme iron while reactive oxygen species are being formed when iron undergoes reduction. Interestingly, individuals with hereditary hemochromatosis, an iron overload disease, have substantially increased HCC occurrence[31]. Also excess dietary iron has been shown to contribute to HCC risk in several parts of Africa, and treatment with chelating agents, repeated phlebotomy and low iron diet appear to reduce the HCC incident[32]. Freedman *et al*[4] 2010 observed that meat processing, its heme iron and NOCs associated with CLD but not with HCC. A case-control study with an Italian cohort revealed a significant positive association between dietary iron intake and HCC risk but did not investigate the role of heme iron[27]. HCA and polycyclic aromatic hydrocarbons, carcinogens are generated during high-temperature cooking, and NOCs compounds have been shown to induce liver tumour development[30] while high doses of HCAs cause liver tumours in primates[30]. The higher fat content of red meat could also explain the harmful effect. Red meat and processed meat contain high levels of cholesterol and saturated fat, and correlate with high risk of obesity and diabetes, which are known as cancer risk factors. In addition, fat intake may play a role in insulin resistance, which relates with liver disease and cancer. Fatty acid deposition in the liver can result in NAFLD therefore increasing the risk of CLD and HCC[33].

Although conflicting results, it can be suggested that red meat intake positively associates with CLD and HCC risk. The observed discrepancies between the studies can be attributed to the limitations of the studies, including differences in the dietary patterns of the various countries studied. However, further large prospective randomized trials investigating the relationship between meat intake and HCC risk are required to reach conclusive results.

WHITE MEAT AND FISH

Evidence from case control and prospective studies from the NIH-AARP Diet and Health study, Italy and Japan reported an inverse association of white meat, including chicken, turkey and fish, with HCC development[4,7,8,10,29] (Table 1). In the EPIC study, the subgroup analyses revealed that lean fish, fatty fish, crustaceans and

Table 1 Main characteristics of studies on dietary factors and hepatocellular carcinoma risk

Conclusions	Study details	Location	Ref.
Inverse association of vegetable and fruit intake with HCC and upper digestive cancers risk	Study design: Case-control Cases: 285 Controls: 6147 Duration: 1983-1990 Intake: Vegetables and fruit	Italy	Negri *et al*[14], 1991
No association between meat and vegetable intake and HCC risk	Study design: Case-control Cases: 97 Controls: 128 Duration: 1995-1998 Intake: Total meat, fruit and vegetables	Greece	Kuper *et al*[44], 2000
Association of red meat intake and HCC risk *NAT2* gene polymorphisms play a role in the effect of meat in HCC development	Study design: Case-control Cases: 185 Controls: 185 Duration: 1999-2001 Intake: Red and white meat, vegetables and fruits	China	Huang *et al*[23], 2003
Inverse association of white meat, coffee and vegetables with HCC mortality Association of egg intake with HCC mortality	Study design: Cohort Cases: 401 Controls: 110688 Duration: 1988-1999 Intake: Fish, red meat, processed meat, chicken, vegetables	Japan	Kurozawa *et al*[17], 2004
Inverse association of white meat, milk, yogurt, eggs, and fruits with HCC risk	Study design: Population based case-control Cases: 185 Controls: 412 Duration: 1999-2002 Intake: Milk, yogurt, white meats, eggs, fruits, vegetables	Italy	Talamini *et al*[10], 2006
Association of red and processed meat intake with HCC risk	Study design: Case-control Cases: 403 Controls: 567169 Duration: 1995-2006 Type of meat: Processed meat	United States	Cross *et al*[25], 2007
Association of dietary iron intake and HCC risk Inverse association of linoleic acid (white meat) intake and HCC risk	Study design: Case-control Cases: 185 Controls: 412 Duration: 1999-2002 Intake: Total meat	Italy	Polesel *et al*[27], 2007
Association of red meat and saturated fat intake with CLD and HCC risk Inverse association of white meat with HCC and CLD risk	Study design: Case-control Cases: 338 Controls: 495006 Duration: 1995-2006 Intake: White and red meat	United States	Freedman *et al*[4], 2010
Inverse association of fish or n-3 PUFAs intake and HCC risk	Study design: Cohort Cases: 398 Controls: 90296 Duration: 1990-2008 Intake: Fish	Japan	Sawada *et al*[9], 2012
Inverse association of vegetables intake and HCC risk	Study design: Case control Cases: 267 Controls: 132837 Duration: 1997-2006 Intake: Meat	China	Zhang *et al*[41], 2013
Inverse association of fish intake and HCC risk HCC risk decreases by 16% for 20 g/d substitution of fish with meat	Study design: Cohort Cases: 157 Controls: 35628 Duration: 1992-2000 Intake: Dietary flavonoids	World-wide	Zamora-Ros *et al*[46], 2013
Inverse association of fish intake and HCC risk No association of meat and poultry intake and HCC development	Study design: Cohort Cases: 191 Controls: 477206 Duration: 1992-2010 Intake: Total meat, fish, red and white meat	Europe	Fedirko *et al*[7], 2013
HCC risk decreases by 8% for every 100 g/d increase in vegetable intake	Study design: Meta-analysis Cases: 3912 Controls: 1290045 Duration: 1956-2014 Intake: Vegetables and fruits	World-wide	Yang *et al*[43], 2014

HCC: Hepatocellular carcinoma; CLD: Chronic liver disease.

molluscs independently associated with low HCC risk[7]. In a large population-based prospective Japanese cohort, Sawada *et al*[9] revealed that the consumption of fish or n-3 polyunsaturated fatty acids (n-3 PUFA) protects against the HCC development even among subjects with HBV and/or HCV infection, and Freedman *et al*[4] reported an inverse association between fish intake and CLD risk.

The finding that both fish and white meat reduce HCC risk is unforeseen. Nutritionally, fish and white meat are a rich source of PUFA and have less cholesterol and saturated fat compared with red meat. Substantial evidence indicates that n-3 PUFA possess anti-inflammatory activity by inhibiting IL-1 and TNF synthesis[34], which can contribute in HCC prevention, considering that chronic inflammation plays a central role in HCC development. PUFA might exert anticancer effects also through their ability to induce apoptosis, to modulate cell cycle and eicosanoid production[35]. In particular, n-3 PUFAs have been shown to inhibit HCC growth *in vitro* through the blockage of β-catenin and cyclooxygenase-2[36]. It is observed that n-3 PUFA supplementation can improve hepatic steatosis in patients with NAFLD in a pilot study[37]. All of this evidence support a possible chemoprotective effect for fish and white meat on HCC development and suggest a molecular mechanism of n-3 PUFA in HCC prevention. However, some fatty acids themselves can also have harmful effects, particularly the saturated fats and trans fatty acids since their increased consumption is strongly linked with the development of non-alcoholic steatohepatitis and its progression to cirrhosis and fibrosis[38]. As there is significant heterogeneity in fat subtypes within most foods, increasing fatty acid consumption should not be encouraged in at-risk populations at least until more studies prove the potential benefits of specific PUFA supplements.

MILK AND EGGS

High intake of milk, yogurt and eggs was found to reduce liver cancer risk in a case control study[10]. Decreased risk of HCC with highest milk intakes was also reported in another case-control study from Italy[18], while a Japanese case-control study revealed a higher risk with greater than average milk consumption[19]. Saturated fat from dairy products was also independently associated with CLD and HCC risk[4]. However, two other studies from China and Japan did not find such associations[17,39]. An inverse correlation between egg and HCC has been observed in two Italian case-control studies[10,18], while a Japanese study reported an increased risk of HCC for high egg consumption in men only[19]. Such discrepancies, however, may be attributed to different dietary habits between the studied populations, such as the use of fat for cooking. Notably eggs are a different diet indicator in Italy and Japan. The inverse association with dairy products and eggs could be explained by their retinol content, since serum retinol levels have been inversely related to HCC risk in a case-control study from China[40].

VEGETABLE, FRUIT AND CEREALS

The association of vegetable and fruit intakes with HCC incidence has been investigated by a number of observational studies since Negri *et al*[14] revealed in a case-control study in the 1990s that high intake of vegetables and fruit was inversely associated with risk of upper digestive cancers, including HCC. The majority of studies reported inverse associations between high vegetable consumption and liver cancer risk[1,10,11,13-15,17,41] (Table 1). In the large prospective study of a US cohort and two European cohorts it was revealed that adherence to the high vegetable content diets of the dietary recommendations and the Mediterranean diet decreases HCC risk[42,43]. This observation was confirmed by Yang *et al*[43] in a meta-analysis on 19 published studies where it was reported that HCC risk decreases by 8% for every 100 g/d increase in vegetable intake. On the contrary, two case-control studies from Greece reported no association, although they involved a small number of cases[20,44]. The role of fruit consumption in HCC risk is more controversial. Three case-control studies reported a decreased liver cancer risk with higher fruit intake[10,13,18], while other four studies found no such association[19,20,28,41]. Another case-control study in northern Italy found that the population attributable-risk for liver cancer was as high as 40% for low vegetable and fruit consumptions[11].

Vegetables and fruits are major sources of vitamins, minerals, dietary fibres, and other bioactive compounds, including flavonoids. Several *in vitro* studies have shown an anti-tumour effect of flavonoids in some hepatocarcinoma cell lines[45,46] while in animal models, flavonoids have been shown to modulate mechanisms involved in proliferation, invasion, angiogenesis, survival and metastasis[47]. According to the EPIC study and a case-control study from Greece an inverse association exists between the flavonoids subclass, flavones, and HCC occurrence[46,48]. Therefore, flavonoids may explain the favorable effects of vegetables and fruits against liver cancer. In addition, evidence is emerging from cell culture and animal model experiments that phytochemicals and other bioactive components found in vegetables, such as diallyl sulphides, lentinan, apigenin and luteolin, have cancer-inhibitory effects through their anti-oxidative properties, stimulation of the immune system, or inhibition of mutagenesis[41]. An animal study on effects of dietary dry bean on hepatic gene expression in rats, found that the expression of six genes was significantly altered after high bean intakes suggesting that these genes may exert cancer preventive effects in liver[49].

A protective role of dietary fiber has been also suggested in HCC development[6]. High intake of fiber from cereals and cereal derivatives was found to be statistically significantly inverse associated with HCC risk. Consumption of fiber from vegetables or other sources (but not fruits)

was also revealed to have a chemoprotective role in HCC development although a statistical significance was not reached[6]. Diets with a high fiber content, like cereals, could lower HCC occurrence by decreasing subjective appetite and energy intake and hence contributing to the maintenance of normal body weight as well as exerting beneficial effects on postprandial glucose level and blood lipid profile. Further research is needed to understand the mechanisms underlying these associations.

DIETARY SUGAR

Dietary glycemic load (GL) estimates how much the food will raise a person's blood glucose level after eating it and is therefore the extent to which carbohydrate-rich foods increase the concentration of glucose in the blood to represent the total glycemic effect of a diet. GL has been associated with diabetes mellitus and with several types of cancer. The mechanism for the role of high GL in carcinogenesis is thought to be *via* increased insulin concentrations, glucose intolerance and insulin resistance, even in the absence of diabetes mellitus. Foods such as added sugars, syrups, sweets, white bread and soft drinks are the main culprits. One case control study from Italy showed a positive association between GL and HCC overall and interestingly a stronger association was observed in patients with HBV and HCV[50]. On the contrary, the EPIC study reported that GL and total carbohydrate intakes did not correlate with HCC risk[6]. However, when specific carbohydrates were analysed, a positive association was found for total sugar. Increased fructose intake is known to underlie NAFLD and may therefore provide a possible explanation for the positive association seen in HCC[51].

DIET IN VIRAL HEPATITIS-INDUCED HCC

HBV and HCV infections are major risk factors for the development of CLD and HCC. Three studies in the United States and Italy agree that the risk estimates for meat and fish consumption were similar between subjects with or without HBV and/or HCV infection[4,7,10,27]. The association of n-3 PUFA, fibers and flavonoids with HCC risk has also been found to exist independently of the HBV and/or HCV status[6,9,46,48]. However, the positive correlation of GL and HCC was observed to be stronger in patients with HBV and HCV in one case control study from Italy[50]. This evidence indicates that the dietary patterns, possibly except the GL, do not appear to affect HCC outcome in chronically HBV or HCV infected individuals. However, the possibility that dietary intakes can protect against the HCC progression in viral hepatitis infection cannot be excluded.

CONCLUSION

Considering the increasing trend of HCC incidence and its high fatality, prevention of HCC is an urgent matter. At present attempts to prevent HCC mainly include the control of HBV or HCV infection, reduction of alcohol consumption, and reducing the prevalence of obesity and diabetes. It is of great importance to discover novel strategies to prevent HCC and dietary factors represent an attractive potential.

Up to date the results from studies investigating the impact of dietary factors in HCC development are conflicting and often inconclusive. Notably, there are several limitations in the methodology of most studies, including selection bias, errors in diet assessment and insufficient adjustment for potential confounders such as HBV/HCV status, diabetes, alcohol and energy intake. Since both case control and prospective studies include data that comes from questionnaires, which are based on self-reported food intakes it is important to consider the dietary habits. Food consumption categories are different across the studies and this can contribute to the heterogeneity of the results. In addition, the case-control studies assessed diet after HCC diagnosis, at which stage the health of individuals has already been compromised, affecting the accuracy of dietary recall. Indeed, a major problem of the case-control studies on HCC is reverse causation because HCC precedes chronic hepatitis and cirrhosis. Furthermore, in the large prospective EPIC study, the diet was assessed only at baseline without considering any potential dietary changes during the follow-up, the period of exposure to cancer initiation was not taken into account and also that dietary patterns of different European countries may have not been fully accounted. It is therefore possible that dietary errors may have occurred that might underestimate the true associations described in the EPIC study.

Nevertheless from the available data it is evident that dietary factors play an important role in CLD and HCC occurrence and their identification can be used for the development of new public health diet recommendations. In particular, consistent associations indicate that higher consumption of vegetables, white meat, fish, milk and cereals have beneficiary effects in liver cancer development. It should be noted that increased consumption of fatty acids correlates with the progression of cirrhosis and fibrosis. The potential benefits of fat subtypes, deriving from white meat, fish and milk, should not be encouraged until more well designed studies prove their chemoprotective effect. Furthermore, it can be inferred that red meat and dietary sugar consumption intake associates with CLD mortality and HCC risk and hence their intake should be monitored and controlled in at-risk populations to attempt to slow down HCC development. Flavonoids appear to reduce the risk of HCC, but pharmacological doses might be required in order to effectively protect against carcinogenesis. Although current studies on infections with HBV and HCV suggest that the effect of diet is independent of viral hepatitis infection, an association between diet and hepatitis virus related HCC progression is possible.

To prevent disease progression to CLD or HCC it is crucial to investigate the impact of diet and subsequently to lead to the development of clinical trials using new

dietary patterns. Evidence from well designed prospective interventional studies with large sample sizes and long-term follow-up are required to develop diet modifications to lower HCC incidence or to prolong survival in HCC patients. Additional experimental and molecular research is also needed to explore the possible mechanisms involved.

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