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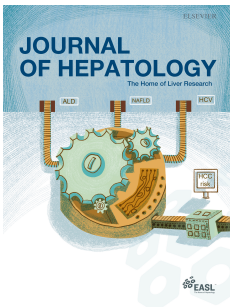

Prevention of NAFLD-associated HCC: role of lifestyle and chemoprevention

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Conflict of Interest

The authors have no potential conflicts (financial, professional, or personal) that are relevant to the manuscript to disclose.

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Brief summary

In many countries worldwide, the burden of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) is increasing and preventive strategies are needed to counteract this trend. This review provides an overview of the evidence on preventive strategies in NAFLD-associated HCC. We considered the impact of lifestyle factors such as weight loss, physical activity, smoking, dietary patterns and food items, including coffee and alcohol, on both HCC and NAFLD/NASH. Furthermore, evidence on chemopreventive treatments, including aspirin, anti-diabetic treatments and statins is summarized. The role of adjuvant therapies considered for tertiary prevention of HCC is briefly reviewed.

Key points

- Dietary factors, such as implementation of the Mediterranean diet, and regular physical activity may reduce the risk of NAFLD-associated HCC beyond the potential effect of weight loss and should be recommended to all NAFLD/NASH patients.
- Smoking and alcohol cessation should be considered important goals in the prevention of NAFLD-HCC.
- Several epidemiological studies found that coffee reduces the risk to develop HCC.
- Potential chemoprophylactic treatments that may be warranted in patients with associated comorbidities or certain circumstances include aspirin, metformin, and statins.
- Currently, no adjuvant treatment is approved for tertiary prevention of HCC recurrence.
- HCC prevention in NAFLD/NASH patients should embrace a multifactorial approach that includes optimization of lifestyle habits, management of metabolic comorbidities, and chemoprevention when appropriate.

1. Prevention of NAFLD-associated HCC

Carcinogenic processes and pathways leading to the development of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are complex and incompletely understood. While the progression to cirrhosis precedes the development of HCC in most etiologies of chronic liver disease, this is not necessarily the case with NAFLD-associated HCC, which may occur in the absence of cirrhosis (1). Several risk factors, that are associated with HCC in the NAFLD population, may be modified by lifestyle intervention or chemoprevention, although a beneficial effect of these measures likely extends beyond the modulation of risk factors (*Figure 1*). The following provides an overview of proposed preventive measures in the context of NAFLD-HCC.

2. Lifestyle factors

Metabolic diseases, most notably diabetes and obesity along with other dysmetabolic traits such as hypertension and dyslipidemia, are associated with an increased risk of HCC (2). To some extent, this risk may be mediated by a higher rate of progression to NAFLD/NASH cirrhosis, a precancerous condition, in the presence of these factors although NAFLD-associated HCC may arise in non-cirrhotic livers (1,3). Lifestyle-related modifiable factors such as certain food items, dietary patterns, and physical activity are associated with reduced risk of HCC, while alcohol consumption and smoking are associated with carcinogenesis in various tissues including the liver (4).

A study conducted in the prospective, population-based Singapore Chinese Health Study cohort, which included a population with a high prevalence of viral hepatitis B, found the highest composite score of healthy lifestyle factors, including normal body mass index, low alcohol consumption, abstaining from cigarette smoking, adherence to the Mediterranean diet, and sufficient sleep duration, to be associated with a markedly lower risk of HCC (HR 0.13, 95% CI 0.06-0.30) (5). This suggests that HCC risk may be reduced by the combined modification of these risk factors. Lifestyle interventions, which may be employed for this purpose, thus present an essential tool in HCC prevention and should be utilized in NAFLD patients.

2.1 Weight loss

Weight loss has not been directly proven to reduce NAFLD-associated HCC. Previous clinical studies, however, have shown beneficial effects of weight loss on NAFLD activity, with some findings indicating the possibility of fibrosis regression.

Combined lifestyle interventions in patients with metabolic comorbidities and NAFLD demonstrated significant histological improvements in steatosis, inflammation, ballooning injury, and overall NAFLD activity score, but not in fibrosis stage, in patients who achieved weight loss of at least 7% of body weight (6,7). In a more recent Cuban study with paired liver biopsies of 261 NAFLD patients, on the other hand,

reduction of 10% of body weight led to NASH resolution in 90% and fibrosis regression in 45% of patients after 52 weeks (8).

The effect of weight loss after bariatric surgery rather than lifestyle adjustments in patients with NAFLD and obesity was evaluated in a large meta-analysis (9). Histological resolution of steatosis, inflammation, and fibrosis was observed in 66%, 50%, and 40% of patients, respectively. 12% of patients, however, showed postoperative worsening of histological disease activity. It has been suggested that some cases of hepatic decompensation in post-bariatric patients occur in the setting of malnutrition and previously unrecognized significant alcohol intake (10), highlighting the importance of lifestyle monitoring and counseling beyond weight loss.

It should also be noted that the effects of bariatric surgery on disease severity in NAFLD/NASH may be mediated in part by post-interventional endocrine changes, particularly changes in levels of digestive peptide hormones and reproductive hormones (11). Concentrations of the incretin glucagon-like peptide-1 (GLP-1), for example, rise shortly after bariatric surgery, preceding weight loss (12). GLP-1 agonists have been shown in clinical trials to improve steatohepatitis in NASH (13,14), suggesting that increased GLP-1 levels may contribute to the beneficial effect of bariatric surgery.

2.2 Diet

Various dietary patterns, nutrients, and food groups have been examined in the context of NAFLD and HCC (15–17), although few studies have looked at HCC-risk specifically in NAFLD etiology. Recently, a systematic review identified 30 observational studies (17 cohort, 7 case-control, 6 cohort with nested case-control subset) that focus on the association of food groups and dietary patterns with primary liver cancer, with 23 studies specifying HCC as the main outcome (16). A summary of important findings regarding the impact of diet on the risk of HCC and NAFLD/NASH is provided in *Table 1*.

Among dietary patterns, higher index scores of adherence to the Mediterranean diet were significantly associated with decreased risk of HCC (OR [95% CI] 0.51 [0.34–0.75], HRs 0.62 [0.47–0.84] and 0.68 [0.51–0.90], respectively) in several studies (18–20), while no significant association was reported from a large US-American prospective cohort study (HR 0.75, 95% CI 0.49-1.15) (21). In NAFLD, additional beneficial effects of the Mediterranean diet beyond weight loss have been identified on glycemic indices, cardiovascular risk markers, anthropometric variables, lipid profile, intrahepatic fat (IHF) content, and markers of severity of liver injury (22–25). The Mediterranean diet is recommended by EASL European guidelines on NAFLD (26).

2.3 Physical activity

Evidence suggests that physical activity reduces HCC risk beyond the confounding effects of weight loss. Potential mechanisms include improvement of mitochondrial functions, such as mitochondrial biogenesis

and autophagy, attenuation of NAFLD/NASH activity, and modulation of carcinogenic signaling pathways (27–29).

HCC risk reduction in active individuals and those performing at least 2 hours of vigorous activity per week was recently demonstrated in the pan-European EPIC (European Prospective Investigation into Cancer and Nutrition cohort) study (HR [95% CI] 0.55 [0.38–0.80], and 0.50 [0.33–0.76], respectively), independently of body weight and other common risk factors for HCC (30). These findings were further corroborated in a meta-analysis of 14 prospective studies, which found a significantly lower risk in individuals with high physical activity compared to low physical activity (HR 0.75, 95% CI 0.63 - 0.89) (31). Physical activity might to some extend also attenuate the increased risk for alcohol-related cancers, including liver cancer, in individuals who consume alcohol regularly (32).

2.4 Coffee

One dietary item that has shown promising effects in both NAFLD/NASH and HCC is coffee. Coffee intake at least twice per day was associated with a significantly lower risk of liver cancer compared to non-drinkers (HR 0.40, 95% CI 0.20–0.79) (33). Findings from a meta-analysis of six Japanese cohort studies confirmed this observation, showing a pooled relative risk estimate of 0.50 (95% CI 0.38–0.66) for regular coffee consumption compared with non-coffee drinkers (34). This is in line with findings from a large meta-analysis of international case-control and prospective cohort studies, which found a pooled relative risk of 0.52 (95% CI 0.42-0.63) (35). In the context of NAFLD/NASH, this might be mediated by a reduced risk of fibrosis development, as a meta-analysis of observational studies demonstrated a pooled relative risk of 0.68 (95% CI 0.68–0.79) for fibrosis in NAFLD patients who consumed coffee regularly (36).

No conclusive data exist regarding the optimum type and dosage of coffee intake. Whether consumption of decaffeinated coffee is associated with equally beneficial effects is not entirely clear, as conflicting results exist and several studies fail to further specify the type of coffee consumed (34,36). A large meta-analysis including over 2 million participants from 18 cohort and 8 case-control studies, reported a non-significant risk reduction of 14% (RR 0.86, 95% CI 0.74-1.00) for intake of two cups of decaffeinated coffee daily (37). In this meta-analysis, the authors further examined the dose-response relationship between coffee consumption and HCC risk. Consumption of two cups per day was associated with a 35% risk reduction (RR 0.65, 95% CI 0.59-0.72) and the risk was halved with consumption of five cups per day (37). This is in line with findings from an updated meta-analysis, reporting a 15% liver cancer risk reduction (RR 0.85, 95% CI 0.82-0.88) for each cup of coffee consumed (35).

While an increase in cholesterol levels has been observed with consumption of unfiltered coffee, evidence from observational studies suggests that consumption of filtered coffee does not increase the risk of cardiovascular disease and has overall beneficial effects on metabolism and the cardiovascular system (38). Therefore, encouraging coffee consumption, as currently recommended by EASL guidelines in individuals with chronic liver disease (39), may also be applied in NAFLD patients.

2.5 Alcohol

Alcohol shares several pathophysiological processes with NAFLD/NASH, shows synergistic effects with metabolic risk factors for NAFLD-HCC, especially diabetes and obesity, while also driving specific carcinogenic mechanisms (40). While a threshold for non-harmful consumption has been debated in the context of NAFLD, mounting evidence suggests detrimental effects (41), especially in the presence of metabolic risk factors. Recently, a large study of well-characterized NAFLD patients in whom alcohol consumption was prospectively assessed found that even at low levels of alcohol consumption of 0-9 g/day, there was no benefit in terms of development of advanced liver disease and an increased risk of incident cancer (42).

One case-control study (43) and two longitudinal studies (44,45) from the USA and Taiwan have demonstrated a supra-additive interaction of alcohol consumption and obesity on HCC development (OR 5.5, HR 3.40 and 3.82, respectively), meaning that the synergistic risk of both factors exceeded the sum of the separate factors (OR 1.2, HR 0.64 and 1.17 for obesity; OR 2.6, HR 1.64 and 1.46 for alcohol consumption; reviewed in (46)). Similar findings were reported by two case-control studies that assessed the risk associated with diabetes and heavy alcohol consumption (defined as ≥80g/d and >4 drinks/d, respectively) in HCC patients compared to matched controls with other malignancies and healthy controls (OR 9.9 and 17.3 for concomitant diabetes and alcohol consumption; OR 2.4 and 2.5 for diabetes; OR 2.6 and 3.4 for alcohol consumption; (47,48), reviewed in (46)). Given the high prevalence of metabolic conditions among individuals living with NAFLD, these findings are especially relevant in this context.

Conclusive data regarding the effect of specific drinking patterns on liver cancer risk is lacking. In a cohort of patients undergoing liver biopsy for suspected NAFLD, moderate alcohol consumption was associated with a lower risk of advanced fibrosis compared to alcohol abstinence, but this pattern was not confirmed in patients who reported binge drinking (49). Another study found daily drinking to be associated with an increased risk of cirrhosis (50), thus indirectly increasing the risk of liver cancer. Among Japanese men who consumed alcohol at levels consistent with NAFLD diagnostic criteria, there was no difference in overall cancer-related mortality when stratified by drinking days per week (51). Whether this is also the case in patients with underlying NAFLD, however, is unknown.

2.6 Smoking

Smoking is associated with an increased risk of HCC in general, while data in NAFLD specifically is lacking. A meta-analysis of 81 studies reported pooled ORs for HCC development of 1.55 (95% CI 1.46–1.65) in current and 1.39 (95% CI 1.26–1.52) in former smokers compared to non-smokers (52). Data from the Liver Cancer Pooling Project demonstrated that the risk of patients who quit smoking >30 years ago was similar to never smokers (HR = 1.09, 95% CI 0.74-1.61) (53), suggesting a beneficial effect of smoking cessation on HCC risk.

Regarding the synergistic effect of smoking and metabolic comorbidities, few data exist. No synergistic effect of diabetes on HCC occurrence among smokers was observed in a US-American case-control study (48). Another case-control study, however, found a synergistic effect among individuals with obesity (43). Thus, it is not entirely clear whether the risk of HCC among NAFLD/NASH patients with metabolic conditions exposed to smoking may exceed the risk of patients with other etiologies of liver disease.

3. Chemoprevention

Several drugs have been shown to modulate risk factors and carcinogenic pathways in NAFLD/NASH-associated HCC, thereby suggesting potential for use in the development and implementation of prevention strategies. In this section, we review drugs that have demonstrated a preventive effect on HCC.

3.1 Aspirin

In a pooled analysis of two prospective cohort studies in the USA (N = 133'371), Simon et al. (2018) showed that regular use of at least 650 mg aspirin per week was associated with a 50% reduction in HCC risk (HR 0.51, 95% CI 0.34–0.77) (54). A Swedish, nationwide registry-based study confirmed that regular intake of less than 160 mg/d aspirin for at least 5 years, lowered the risk of HCC (HR 0.69, 95% CI 0.62–0.76), without increasing the risk of gastrointestinal bleeding (55). In a study of 361 patients with biopsy-confirmed NAFLD, daily aspirin use was shown to significantly lower the odds ratio of NASH and fibrosis (56).

Selective cyclooxygenase-2 (COX-2) inhibition was suggested as being responsible for the negative effect on fibrosis, portal hypertension, and proliferation of liver cancer cells. In addition, in animal models, aspirin demonstrated inhibitory features on platelet-derived growth factor, known as an important factor in the activation of hepatic stellate cells and promotion of fibrosis (57). Aspirin has also been shown to inhibit P4HA2, involved not only in collagen synthesis but also in HCC development (58). Moreover, recent evidence suggests that platelet recruitment and activation in the liver contribute to HCC development in mice, specifically via platelet glycoprotein Ibα (GPIbα) signaling (59).

Given the growing body of evidence regarding the association of NAFLD and cardiovascular disease, the use of aspirin in NAFLD patients may be an appropriate option for selected patients.

3.2 Antidiabetic drugs

3.2.1 Metformin

Several large population-based cohort studies reported that metformin, a first-line drug to treat type 2 diabetes, has a chemoprophylactic effect on HCC (*Table 2*).

In a sub-analysis of a meta-analysis evaluating 37 trials, the authors found a significant HCC risk reduction in metformin users for both incidence (78%) and mortality (77%), respectively (60). Another meta-analysis of 10 studies, with 22'650 HCC cases among 334'307 diabetic patients, showed that the use of metformin was associated with a 41% reduction in HCC incidence (61).

Metformin seems to exert anti-tumoral effects through multiple mechanisms such as decreasing the level of insulin-like growth factor-1, downregulating c-Jun N-terminal kinase (JNK)/mitogen-activated protein kinase (p38 MAPK), human epidermal growth factor receptor-2, and nuclear factor kappa-B pathways, activating AMP-activated protein kinase, inhibiting mammalian target of rapamycin (mTOR), and reducing endogenous production of reactive oxygen species (62).

The only trial that aimed to evaluate the chemoprophylactic effect of metformin in patients with viral hepatitis C (NCT02319200) was terminated early due to slow recruitment. No further randomized controlled trials to examine the effects of metformin on the development of HCC are currently planned.

3.2.2 Pioglitazone

Pioglitazone, an activator of peroxisome proliferator-activated receptor gamma (PPAR-γ) known for its insulin-sensitizing effects, reduced the incidence of HCC in a hospital-based case-control study and a population-based cohort study (63)(64)(65). In contrast with these findings, an Italian nested case-control study using healthcare databases failed to show a significant effect of pioglitazone on HCC risk (66). Since the antitumor effect of PPAR-γ ligands is dose-dependent, this might explain the conflicting findings (67).

In vitro studies suggested that the anti-carcinogenic properties of pioglitazone could be the result of suppression of hepatic stellate cell activation (68,69). This anti-fibrotic and anti-carcinogenic effect of low dose pioglitazone was confirmed in two rodent models (70). In addition, pioglitazone demonstrated a positive effect on adiponectin levels, which was associated with protection from carcinogenesis (71).

However, serious side effects such as weight gain, bone loss, and fracture risk, increased risk of myocardial infarction (rosiglitazone) and increased risk of bladder cancer (pioglitazone) limit the use of this drug class (72–74).

3.3 Statins

Several clinical trials have reported statins to be effective in reducing HCC risk (Table 3). The results of a recent meta-analysis of 24 studies showed a 46% decrease in HCC risk among statin users, suggesting that statins may be an option in chemoprophylaxis (75). According to a sub-analysis of another meta-analysis, the use of lipophilic statins was associated with a significantly reduced risk of HCC compared with hydrophilic statins (51% vs. 27%) (76). This finding could be explained by the greater lipid solubility and membrane permeability of lipophilic substances, enabling them to exert their cholesterol-dependent effects against HCC development (77).

Potential mechanisms include inhibition of MYC, Protein kinase B (AKT), and nuclear factor-kappa B (NF-κB) pathways, as well as decreased production of IL-6, TNF-α, and TGF-β1 (78). In addition, simvastatin has been shown to reduce tumor cell growth and impair tumor cell adhesion to endothelial cell monolayers, resulting in reduced tumor cell invasion (79).

Given that many NAFLD/NASH patients are prescribed statins, more data will likely become available in the future.

3.4 Anti-fibrotic therapies

Several drugs specifically targeting NASH pathogenesis are being tested, but to date obeticholic acid (OCA), a farnesoid X receptor agonist (FXR), is the only drug that showed improvement in fibrosis without worsening of NASH in an interim analysis of the phase 3 trial (REGENERATE; NCT02548351) (80). Whether this translates into a reduced risk of HCC is not yet known. Moreover, OCA has several side effects, including pruritus and elevated LDL cholesterol levels. The latter is of particular importance in the NAFLD population because it is associated with cardiovascular disease, which is the leading cause of death in this population (81). It has been reported, however, that the increase in LDL cholesterol was transient and managed with statins. Thus, LDL cholesterol should be followed up regularly and treated as necessary. Long-term safety and efficacy need to be evaluated in real-world populations, particularly with regard to tolerability and cardiovascular risk.

3.5 Pre- and Probiotics

A growing body of evidence suggests that intestinal dysbiosis increases the permeability of the intestinal barrier, which allows substances such as short-chain fatty acids, bile acids, bacterial components, choline, and endogenous ethanol to reach the liver, prompting the development of NAFLD and progression to NASH (82). Dietary factors interact with the gut-liver axis, but this ecosystem may also be targeted more specifically using pre- and probiotics (83).

In a diethyl nitrosamine (DEN) model of rat hepatocarcinogenesis, probiotics-treated rats were protected against acute hepatic injury, had a significantly lower rate of cell proliferation and less extensive leukocyte infiltration intrahepatically (84). Yoshimoto et al. showed that obesity-induced alterations in the gut microbiota of mice promote the development of HCC and that this effect may be mitigated by antibiotic therapy (85).

Possible mechanisms by which probiotics exert their anti-tumorigenic effects include their ability to bind carcinogens (e.g. aflatoxin B1), modulate gut microbiota and immune response, improve the intestinal barrier function and reduce the absorption of lipopolysaccharides (carcinogen-induced hepatocarcinogenesis) (86). All studies reviewed reported no adverse effects or issues of safety with the clinical use of probiotics in patients with NAFLD (87).

Theoretically, probiotics can be used alone or in conjunction with other NAFLD-targeted therapies. However, the identification of appropriate bacterial strains, potential interactions with other agents, and the risk of "relapse" after cessation of therapeutic intervention require further investigation.

3.6 Tertiary chemoprophylaxis - adjuvant therapies

A high rate of recurrence after curative therapies for HCC indicates the need for adjuvant treatment in selected cases.

3.6.1 Tyrosine kinases inhibitors

One drug class that has been investigated in this setting is tyrosine kinase inhibitors, which are currently being used in the systematic treatment of advanced HCC. Regarding their use in the adjuvant treatment of HCC, however, the phase 3 STORM study failed to show a benefit of sorafenib compared to placebo in terms of recurrence-free survival (33.3 vs 33.7, p=0.26), indicating that sorafenib is not an effective option in the adjuvant setting for HCC (88).

3.6.2 Immunotherapy

The encouraging results of immunotherapy, 15–20% rate of durable objective remissions (including complete response in 1–5%) in HCC patients, have raised hopes for effective adjuvant treatment of HCC. Currently, several studies on the use of immunotherapy as adjuvant therapy are ongoing (Table 4). However, a recent meta-analysis of three large randomized controlled phase 3 trials of immunotherapies in advanced HCC (CheckMate-45911, IMbrave1505, and KEYNOTE-24010) showed that non-viral HCC might be less responsive to these treatments compared to viral HCC (HR 0.92, 95% CI 0.77–1.1 and HR 0.64, 95% CI 0.48–0.94, respectively) (89). Moreover, Pfister et al. observed that prophylactic anti-PD1 treatment led to an increase in the incidence of NASH–HCC. These findings deem a critical evaluation of ongoing trials of anti-PD1 drugs in NASH populations.

4. Conclusion

Weight loss, dietary modifications, and increased physical activity remain the mainstays of HCC prevention in the NAFLD/NASH population. However, patients with diabetes, obesity and cardiovascular comorbidities may benefit from chemoprevention in addition to lifestyle modification.

Evidence for tertiary prevention of HCC is still inconclusive, and moreover, new emerging data on the possibly deleterious effect of anti-PD1 drugs on HCC warrant caution in the NAFLD/NASH population.

Overall, these findings need to be interpreted with caution as few data exist on HCC in the context of NAFLD specifically. Response of NAFLD-associated HCC to lifestyle factors and chemopreventive agents may

differ from other etiologies and - considering the heterogeneity of the NAFLD/NASH population - within clinical phenotypes of NAFLD/NASH. An increasing understanding of underlying pathophysiological mechanisms and disease phenotypes may in the future allow for targeted preventive strategies for NAFLD-associated HCC.

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Author names in bold designate shared co-first authorship

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Figure Legends

Figure 1. Modifiable and non-modifiable risk factors for HCC development in NAFLD have been identified. Lifestyle and chemoprevention strategies may target modifiable risk factors.

Table 1. Dietary patterns, food groups and nutrients, and association with risk of primary liver cancer, suggested mechanism of action in liver cancer and findings in NAFLD/NASH populations.

Nutritional item, group or dietary pattern	Primary liver cancer risk	Potential influences on other risk factors for liver cancer and suggested pathophysiological links	Findings regarding NAFLD/NASH
Dietary Patterns			
Mediterranean diet (MED)	Reduced	• **Beneficial**: Diet mainly containing food groups associated with reduced risk; favoring a high ratio of unsaturated to saturated fats; improvement of dysmetabolic traits and systemic inflammation. • **Adverse**: Unclear role of SSB (excluded from index scores); encourages light alcohol consumption; associated with higher levels of SHBG in women.	• Beneficial effects beyond weight loss, including improvement of glycemic indices, anthropometric variables, lipid profile, IHF (including NAFLD resolution) and markers of severity of liver injury (22–24). • Associated with reduced odds of developing advanced NAFLD (90). • Advantageous effect on cardiovascular markers (25). • Recommended by EASL European guidelines on NAFLD (26).
Dietary approaches to stop hypertension	Neutral	• **Beneficial**: Low intake of SSB, alcohol and sodium; containing several food groups associated with reduced risk; low glycemic index; improvement of hypertension and other dysmetabolic traits.	• No robust data exist (improvement of several markers, but likely confounded by weight loss (91)).
Food groups			
Vegetables	Reduced	• **Beneficial**: Source of vitamins, minerals, dietary fibers, and other bioactive compounds with anti-carcinogenic properties (e.g. flavonoid polyphenols).	• Studied mostly in the context of unrefined carbohydrates, plant-based protein and fiber content, and in MED. • Severe steatosis (FLI) was inversely associated with plant-based protein intake (92). • High insoluble fiber and fiber from fruit were associated with improvement of noninvasive scores and liver enzymes (93). • No benefit demonstrated for purely vegetarian diet (94). • "Green" MED (additional Mankai, nuts and tea as source of green plant-based proteins and polyphenols) doubled IHF loss compared to MED alone (22).
Wholegrains	Reduced	• **Beneficial**: Source of dietary fibers; lower glycemic index.	
Fruits	Neutral	• **Beneficial**: Source of vitamins, minerals, dietary fibers, and other bioactive compounds with anti-carcinogenic properties (e.g. flavonoid polyphenols). • **Adverse**: high glycemic index of certain foods.	
Nuts	Neutral	• **Beneficial:** Source of unsaturated fats, vegetable protein, vitamins, folate, fiber, and minerals.	
Fish	Reduced	• **Beneficial**: High content of n3 PUFAs.	• Studied mostly in the context of MED and PUFAs (e.g. fish oil supplement).
White meat (poultry)	Reduced	• **Beneficial**: Source of PUFAs. • **Adverse**: Contains BCAAs (mTORC1 activation).	• Largely studied in the context of dietary protein (animal vs. plant-based).

Dairy	Neutral	• **Beneficial:** Certain foods may contain probiotics (e.g. yogurt). • **Adverse**: Contains SFAs; high glycemic index of certain foods (e.g. milk, yogurt); increase of IGF-1 levels (low-fat dairy).	• Data not consistent: steatosis (presence and severity, latter by FLI) associated with protein intake from animal sources (92,95), while other data suggest improvement of steatosis with high protein diet irrespective of source (96).
(Processed) red meat	Increased	• **Adverse**: Contains carcinogens (e.g. heme iron, N-nitrous compounds, heterocyclic amines); increased generation of ROS (during iron reduction); contains high levels of cholesterol, SFAs, and BCAAs (mTORC1 activation).	• Often studied in context of dietary pattern ("Western" diet). • Processed meat consumption positively associated with liver iron content (97).
Tea	Neutral	• **Beneficial**: Contains bioactive compounds with anti-carcinogenic properties (e.g. flavonoids, caffeine).	• Reduction of liver enzymes in NAFLD for green tea (98).
Coffee	Reduced	• **Beneficial**: Contains antioxidants and phenolic compounds; inhibition the PI3K/Akt pathway by caffeine.	• Regular coffee consumption significantly associated with decreased risk of fibrosis development in NAFLD (36).
Sugar sweetened beverages (SSB)	Increased	• **Adverse**: High glycemic index, gut dysbiosis, generation of reactive oxygen species, activation of pro-inflammatory pathways (fructose).	• No deleterious effect of fructose in isocaloric trials; increase in liver enzymes and IHF in hypercaloric diet (99). • Reduction of IHF with SSB and free sugar reduction (100). • SSB containing fructose and sucrose, but not glucose, increased hepatic lipogenesis (101).
Nutrients			
Monounsaturated fatty acids (MUFA)	Reduced	• **Beneficial:** Effects of MED if primary source of MUFAs is plant-based (e.g. olive oil, nuts, fish). • **Adverse:** effects of red meat if primary source of MUFAs.	• Significant reduction in IHF, improvement in hepatic and overall insulin sensitivity with MUFAs from olive oil (102).
Saturated fatty acids (SFA)	Neutral	• **Adverse:** Promotion of adipose tissue inflammation, activation of hepatic lipogenesis, NF-κB activation, and JNK/AP-1 signaling.	• SFA-rich hypercaloric diet lead to marked increases in IHF and visceral adipose tissue (103).
Polyunsaturated fatty acids (PUFAs)	Neutral	• **Beneficial**: Anti-inflammatory properties (decreased IL-6, IL-1β, TNF); blocking of β-catenin and COX-2 by n3 PUFAs; improved insulin sensitivity and induction of adiponectin. • **Adverse**: Pro-inflammatory metabolites of n6 PUFAs.	• Reduction of IHF and liver enzymes with n3 PUFAs (104).

Abbreviations: PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; TNF, tumor necrosis factor; IL, interleukin; ROS, reactive oxygen species; COX, cyclooxygenase; IGF-1, insulin-like growth factor 1; SHBG, sex-hormone binding globulin; SSB, sugar-sweetened beverages; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; RCT, randomized controlled trial; IHF, intrahepatic fat; MED, Mediterranean diet; FLI, Fatty Liver Index; mTORC1, mammalian target of rapamycin complex 1; BCAA, branched chain amino acid; NF-κB, nuclear factor-kappa B; JNK/AP-1, c-Jun N-terminal kinase/activator protein 1.

Table 2. Chemopreventive effect of metformin on hepatocellular carcinoma.

Year	Study	Design	Sample size n	HCC cases n	Metformin users in HCC group (%)	Results HR (95%CI)
2010	Hassan et al. (63)	Hospital-based cohort	1'524	420	47.1	0.3 (0.2-0.6)
2010	Donadon et al. (105)	Hospital-based cohort	549	190	23.5	0.2 (0.1-0.4)
2010	Kawaguchi et al. (106)	Hospital-based cohort	241	138	3.7	0.6 (0.2-2.2)
2011	Nkontchou et al. (107)	Hospital-based cohort	100	39	26.0	0.2 (0.04-0.8)
2012	Lai et al. (64)	Retrospective cohort study	96'745	1'120	84	0.49 (0.37–0.66)
2012	Ruiter et al. (108)	Population-based cohort	85'289 with antidiabetic drug prescription	1'590	61.8	0.7 (0.5-0.9)
2011	Chen et al. (64)	Population-based cohort	162	162	39.6	0.24 (0.07-0.80)
2019	Vilar-Gomez et al. (62)	Cohort	307		57.6	0.25 (0.11-0.58)
2021	Cho et al. (109)	Retrospective cohort study	857	857	61.3	No protective effect

Abbreviations: HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; NAFLD, non alcoholic fatty liver disease; n, number; NA, not applicable.

Table 3. Summary of studies on the chemopreventive effect of statins on hepatocellular carcinoma.

Completed						
Year	Study	Study Design	Sample size (n)	HCC cases (n)	Statin users in HCC group (%)	Results AHR (95%CI)
2009	El-Serag HB et al.(110)	Cohort	6'515	1'303	26	0.7 (0.6-0.9)
2011	Chiu HF et al. (111)	Case-control	2'332	1'166	NA	0.6 (0.4-0.9)
2012	Tsan H et al. (112)	Cohort	33'413	1'021	5.6	0.5 (0.4-0.6)
2013	Tsan H et al. (113)	Cohort	260'864	27'883	5.2	0.5 (0.5-0.6)
2015	McGlynn et al. (114)	Case-control	5'835	1'544	19.5	0.55 (0.45–0.69)
2016	Simon TG et al. (115)	Cohort	9'135	233	31.3	0.51 (0.36–0.72)
2017	Kim G et al. (116)	Case-control	1'374	247	10.9	0.36 (0.22–0.60)
2018	Kim G et al. (117)	Case-control	9'852	1'642	6.7	0.44 (0.33–0.58)
Ongoing						
NCT02968810, USA		Randomized controlled trial, Phase 2	Ongoing	Arm 1: simvastatin QD Arm 2: placebo QD		
NCT03024684, Taiwan		Randomized controlled trial, Phase 4	Ongoing	Arm 1: atorvastatin 10mg QD Arm 2: placebo QD		

Abbreviations: QD, once daily.

Table 4. Ongoing clinical trials evaluating possible adjuvant agents in hepatocellular carcinoma.

Trial	Target population	Arms	Clinical trials governamental identifier
EMERALD-2	HCC at high risk of recurrence after curative hepatic resection or ablation	Arm 1: durvalumab (Q3W) + bevacizumab (Q3W) Arm 2: durvalumab (Q3W) + bevacizumab placebo (Q3W) Arm 3: durvalumab placebo (Q3W) + bevacizumab placebo (Q3W)	NCT03847428
JUPITER 0	Locally advanced HCC after curative hepatic resection	Arm 1: toripalimab arm 2: placebo	NCT03859128
IMbrave050	HCC at high risk of recurrence after surgical resection or ablation	Arm 1: atezolizumab plus bevacizumab Arm 2: active surveillance of participants	NCT04102098
CheckMate 9DX	HCC at high risk of recurrence after curative hepatic resection or ablation	Arm 1: nivolumab Arm 2: placebo	NCT03383458
KEYNOTE-937	HCC with complete radiological response after surgical resection or local ablation	Arm 1: pembrolizumab Arm 2: placebo	NCT03867084

Abbreviations: HCC, hepatocellular carcinoma.