Dickinson *et al. Hepatoma Res* 2024;10:37
DOI: 10.20517/2394-5079.2024.81

Hepatoma Research

Review

Open Access

Chemoprevention of hepatocellular carcinoma associated with metabolic dysfunction-associated steatotic liver disease: an updated review

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How to cite this article: Dickinson A, Dinani A, Wegermann K. Chemoprevention of hepatocellular carcinoma associated with metabolic dysfunction-combined with steatotic liver disease: an updated review. *Hepatoma Res* 2024;10:37. https://dx.doi.org/10.20517/2394-5079.2024.81

Received: 15 Jun 2024 **First Decision:** 13 Aug 2024 **Revised:** 2 Sep 2024 **Accepted:** 19 Sep 2024 **Published:** 23 Sep 2024

Academic Editor: Amedeo Lonardo **Copy Editor:** Pei-Yun Wang **Production Editor:** Pei-Yun Wang

Abstract

With the predicted rise in metabolic dysfunction-associated steatotic liver disease (MASLD) prevalence over the next decade, strategies to prevent hepatocellular carcinoma (HCC), which is the third most common cause of cancer-related death, are paramount. In this narrative review, we present recent clinical and translational studies from 2020-2024, providing an updated overview of the literature on chemoprevention of HCC associated with MASLD. We specifically focus on statins, aspirin, metformin, and newer diabetes medications. These agents target specific steps in the development of HCC in MASLD, including steatosis resulting in oxidative stress, inflammation, and eventually fibrosis. All offer promising avenues for HCC chemoprevention, although statins have the strongest data at present. Further ongoing prospective studies are needed.

Keywords: MASLD, statins, aspirin, semaglutide, liver-related events

INTRODUCTION

Liver cancer is the third leading cause of cancer-related deaths globally, with hepatocellular carcinoma (HCC) representing 77% of all primary liver cancers in the United States (US)[1]. Unfortunately, the prognosis of HCC is extremely poor. According to the National Cancer Institute's Surveillance,

Epidemiology and End Results (SEER) database, HCC has a 5-year survival rate in the US of 19.6%, dropping as low as 2.5% in metastatic disease[2]. HCC arises in patients with chronic liver disease of multiple etiologies, including viral hepatitis, alcohol-associated liver diseases, genetic and autoimmune liver diseases. Exposure to environmental agents such as aflatoxins and tobacco contributes in some patients. This review focuses on metabolic dysfunction-associated steatotic liver disease (MASLD), formally known as non-alcoholic fatty liver disease (NAFLD). Our ultimate goal is to identify the most effective strategies for preventing MASLD-associated HCC. Consequently, articles exclusively examining alcohol-associated liver disease or viral hepatitis are not covered. Moving forward, we reference literature using the updated terminology MASLD instead of NAFLD and metabolic dysfunction-associated steatohepatitis (MASH) instead of non-alcoholic steatohepatitis (NASH).

MASLD affects approximately 30% of the global population and is now one of the leading causes of chronic liver disease worldwide[3]. The prevalence of MASLD is forecasted to increase by 21% in the US by 2030. This steep increase in cases parallels the rapid rise in the worldwide incidence of obesity and diabetes[4]. The global prevalence of MASLD has risen from 25% in 2006 to 38% in 2019, resulting in an increase of 50.4% by 2023[5]. Unsurprisingly, the incidence of MASLD-associated HCC is rising significantly. It is projected that MASLD-associated HCC will increase by 137% in the US between 2015 and 2030[6]. Given the striking increase in MASLD-associated HCC cases, it is imperative to focus on preventative measures to address this growing public health concern.

Mechanisms of MASLD-associated HCC

Understanding the cellular mechanisms of carcinogenesis in MASLD-associated HCC is crucial to isolate effective chemoprevention. MASLD is characterized by the abnormal accumulation of fat, primarily triglycerides, in hepatocytes. MASLD encompasses a spectrum of liver diseases that can ultimately progress to HCC.

The progression begins with simple hepatic steatosis, in which fat accumulates in the liver. If the fat results in oxidative stress, this can then advance to MASH, formerly known as NASH, which is characterized by inflammation, hepatocyte injury, and liver fibrosis[7]. Approximately 20% of patients diagnosed with simple steatosis progress to MASH, and of these, 2.6% may further progress to HCC[8]. Complicating the picture, MASLD is not a linear disease trajectory; the rates of progression vary significantly, and disease regression is possible under certain circumstances.

Recent studies have extensively investigated the pathogenesis and development of HCC. There is a proposed "two-hit hypothesis" for MASLD progression to MASH, then HCC. The first hit involves the sensitization of hepatocytes to inflammation and resistance to insulin, while the second hit involves increased inflammation resulting in fibrosis [Figure 1][9]. Oxidative stress in the liver may produce DNA damage and trigger a wound healing response, both of which contribute to hepatocarcinogenesis[10].

Chronic liver disease prevention and cure

We briefly mention HCC chemoprevention specific to viral hepatitis, given the potential for this to dramatically influence the global burden of HCC. The incidence of viral hepatitis-associated HCC has significantly decreased due to the implementation of early screening, universal vaccination programs, and effective antiviral therapies. Since the recommendation for universal newborn vaccination for hepatitis B vaccine in 1991, there has been a marked decline in viral-related HCC, especially in the US[11]. Although there is no approved vaccine for hepatitis C virus (HCV), HCV-associated HCC has decreased with the advent of potent direct-acting antivirals (DAAs), though it has not completely been eliminated. Addressing the obesity and alcohol use disorder epidemics through public health interventions would be expected to dramatically reduce HCC incidence as well.

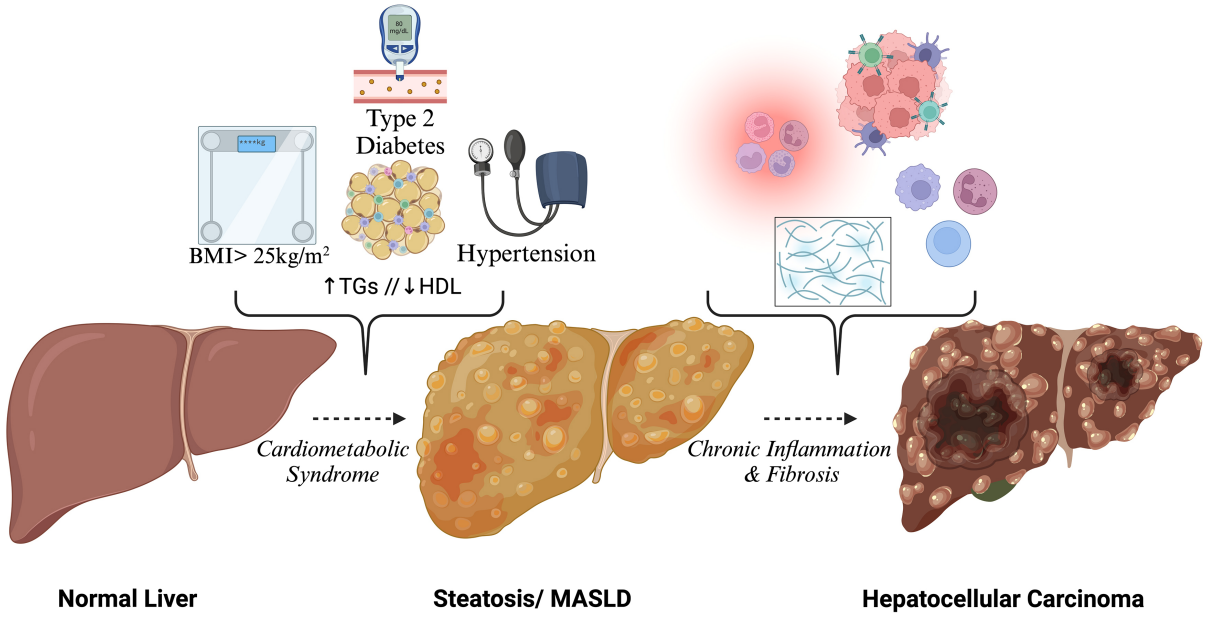

Figure 1. MASLD-associated HCC. Illustrating the pathogenesis of HCC, first with cardiometabolic risk factors contributing to the formation of steatosis. Then, chronic inflammation and fibrosis ultimately leading to HCC. Created with BioRender.com. TG: Triglycerides; HDL: high-density lipoprotein; BMI: body mass index; MASLD: metabolic dysfunction-associated steatotic liver disease; HCC: hepatocellular carcinoma.

The importance of fibrosis

Despite the reduction in viral hepatitis cases, the overall incidence of HCC continues to rise, attributable to the increase in MASLD-associated HCC. Fibrosis is a critical factor in liver cancer development, as shown by recent data findings that 80%-90% of HCCs are preceded by cirrhosis[12]. In exploring chemoprevention strategies, a key focus is on agents that actively reduce hepatic fibrosis or promote fibrosis regression. Therefore, as expected, most drugs discussed in this article help reduce liver fibrosis and, in turn, have a potential preventative effect against HCC.

ASPIRIN

Mechanisms

Non-steroidal anti-inflammatory drugs (NSAIDS) such as Aspirin have been extensively studied for their chemoprotective effects against various malignancies, including but not limited to colorectal, prostate, and ovarian cancer[13,14]. Chronic inflammation acts as a catalyst for the development of fibrosis, which is the primary driver of HCC. Moreover, data in animal models suggest that platelets may facilitate the accumulation of T lymphocytes in the liver in acute viral hepatitis, thereby contributing to inflammation and potentially fibrosis in the liver[15]. Consequently, both aspirin's anti-inflammatory and anti-platelet properties may contribute to its ability to protect against the development of HCC. Specifically, in patients with MASLD, there is enhanced intrahepatic prostaglandin synthase-2 (COX-2) and prostaglandin E2. This promotes lipid droplet formation and further activates hepatic stellate cells, leading to fibrosis[16]. One proposed mechanism by which aspirin prevents fibrosis is through its antagonism and irreversible inhibition of proinflammatory COX-2 isozymes[16]. Studies have shown that COX-2 overexpression is present in many patients with HCC, suggesting its causative role in hepatocarcinogenesis[17]. One study demonstrated that enhancing COX-2 expression in mice was sufficient to induce HCC[18]. Conversely,

COX-2 expression is not detected in normal liver tissue without chronic inflammatory diseases[19]. Furthermore, COX-2 single nucleotide polymorphisms (SNPs) have been associated with the presence of HCC in humans[20].

Literature review of aspirin chemoprevention

In alignment with previous literature, recent studies continue to affirm that aspirin is an effective chemoprevention for HCC. A 2023 meta-analysis involving over 2.2 million patients demonstrated that aspirin use was associated with a 30% reduction in the risk of developing HCC[21]. This protective effect was observed with aspirin use in both patients with cirrhosis (HR 0.78; 95%CI: 0.69-0.88) and those without cirrhosis (HR 0.86; 95%CI: 0.78-0.94)[21]. Yan *et al.* reported a reduced risk of HCC with daily aspirin use in their meta-analysis (HR 0.64; 95%CI: 0.56-0.75), with the most significant benefit observed in patients with cirrhosis (HR 0.60; 95%CI: 0.45-0.81)[22]. Additionally, a 2021 meta-analysis by Tan *et al.* found that aspirin use not only reduced the incidence of HCC (HR 0.51; 95%CI: 0.36-0.72), but also improved liver-related mortality (OR 0.32; 95%CI: 0.15-0.70)[23]. Another proposed mechanism by which aspirin may act against hepatocarcinogenesis is through the reduction and prevention of hepatic fat accumulation. In a 2024 randomized control trial, Simon *et al.* demonstrated that six months of daily aspirin use led to a significant reduction in hepatic fat quantity in MASLD patients. The study reported a mean absolute change in hepatic fat content of -6.6% in the aspirin group compared to 3.6% in the placebo group, resulting in a mean difference of -10.2% (95%CI: -27.7% to -2.6%)[24]. Overall, these findings underscore the potential and promising use of aspirin as a valuable agent in the chemoprevention of HCC.

Dose- and time-dependent aspirin use

A dose- and time-dependent risk reduction in HCC has been observed, with one study showing the greatest benefits seen in high-dose aspirin (100 mg/day) used for more than three years[22]. Similarly, Ma *et al.* found a higher dose response with the risk of HCC decreasing by 10% for each 50 mg/day increment in aspirin use and reduction by 6% with each additional year of aspirin exposure[25]. These findings are consistent with our current understanding that while low-dose aspirin (75-100 mg) is sufficient to irreversibly inhibit COX-1, higher doses (> 100 mg) are required to completely inhibit COX-2, thereby exerting optimal anti-inflammatory effects[26-28]. Although low-dose aspirin does not act through the conventional COX pathway, it exhibits anti-inflammatory properties by reducing the accumulation of polymorphonuclear leukocytes and macrophages[29] which are implicated in the development of steatohepatitis.

Conversely, Abdelmalak *et al.* found that aspirin reduced the risk of HCC by approximately 30% (HR 0.70, 95%CI: 0.60-0.81). However, only low-dose aspirin (< 163 mg/day) led to significant HCC risk reduction (HR 0.39; 95%CI: 0.17-0.91), as opposed to high-dose (HR 0.67; 95%CI: 0.42-1.08)[30]. Additionally, a 2022 meta-analysis by Wang *et al.* reported a significant inverse association between aspirin dose and liver cancer risk, with effective doses hitting a limit up to ~100 mg/day; doses higher than this threshold did not show a significant impact on reducing HCC incidence[31]. These findings highlight the complexity behind using aspirin for HCC chemoprevention and the mixed results of prior studies. There is also a reasonable concern regarding the risk of gastrointestinal bleeding associated with the use of higher doses of aspirin. Overall, while both high- and low-dose aspirin may offer protective benefits, confirming this effect with prospective studies and determining the optimal dosage for maximizing efficacy while minimizing risks require further investigation [Table 1][21-23,25,27,30-38].

STATINS

Statin medications are well-known for their cholesterol-lowering effects; however, they also possess antifibrotic and anti-inflammatory properties that make them valuable as chemopreventive agents against

Table 1. Summary of articles on aspirin chemoprevention of HCC

Study	Year	Design	Sample size, *n*	Results (HR/OR/RR, 95%CI)
Wang *et al.*[21]	2023	Meta-analysis/systemic review	2,217,712	0.70 (0.63-0.76)
Yan *et al.*[22]	2022	Meta-analysis	2,531,742	0.64 (0.56-0.75)
Tan *et al.*[23]	2021	Meta-analysis/systemic review	147,283	0.51 (0.36-0.72)
Ma *et al.*[25]	2022	Meta-analysis/systemic review	3,273,524	0.75 (0.71-0.80)
Zhou *et al.*[27]	2022	Meta-analysis/systemic review	2,781,100	0.56 (0.46-0.69)
Abdelmalak *et al.*[30]	2023	Meta-analysis/systemic review	2,404,876	0.70 (0.60-0.81)
Wang *et al.*[31]	2020	Systematic review	2,604,319	0.59 (0.47-0.75)
Lee *et al.*[32]	2023	Case control	35,898	0.57 (0.37-0.87)
Liu *et al.*[33]	2022	Meta-analysis/systemic review	2,659,629	0.53 (0.43-0.65)
Memel *et al.*[34]	2021	Meta-analysis/systemic review	2,389,019	0.61 (0.51-0.73)
Singh *et al.*[35]	2022	Retrospective	521	0.35 (0.12-0.98)
Tan *et al.*[36]	2023	Meta-analysis/systemic review	71,211	0.46 (0.31-0.67)
Wang *et al.*[37]	2021	Meta-analysis	3,000,000+	0.54 (0.44-0.66)
Zeng *et al.*[38]	2022	Meta-analysis	2,190,285	0.48 (0.27-0.87)

HCC: Hepatocellular carcinoma; HR: hazard ratio; OR: odds ratio; RR: relative risk.

HCC. Statins reduce the expression of transforming growth factor-beta, a potent cytokine that promotes the activation of hepatic stellate cells[39]. The anti-inflammatory effects of statins are evident through their reduction of macrophage activity, cytokine production, and inflammatory markers such as soluble CD40 ligand[40,41]. Additionally, statins activate peroxisome proliferator-activated receptors (PPAR-α, PPAR-γ), which leads to a reduction in inflammation and fibrosis[42]. Given that inflammation precedes fibrosis and hepatocarcinogenesis, inhibiting inflammation is a crucial step in preventing the development of HCC.

Literature review of statin chemoprevention

In a recent meta-analysis with over 1.7 million patients, Zeng *et al.* found that the use of statins was associated with a significantly reduced overall risk of HCC compared to non-users (HR 0.52; 95%CI: 0.37-0.72). This study also revealed a reduced risk of HCC in MASLD patients using statins (HR 0.68; 95%CI: 0.59-0.77)[38]. Additionally, among 272,431 adults diagnosed with MASLD, Zou *et al.* found that statin users exhibited a 53% diminished risk of HCC development in contrast to non-users (HR 0.47; 95%CI: 0.36-0.60)[43]. Similar protective effects of statins in preventing HCC were observed in another study focusing on patients with chronic liver disease (OR 0.52; 95%CI: 0.40-0.68)[44]. Sung *et al.* further highlighted that the overall HCC incidence was 2.8 times higher in the non-statin cohort compared to the statin cohort[45]. Although the above meta-analyses have found a chemopreventive effect of statins, it should be noted that not every individual study found such effects. In fact, multiple large studies of individual patient data from randomized controlled trials (e.g., Matsushita *et al.* 2010, Emberson *et al.* 2012) have not found such effects[46,47]. Therefore, ongoing investigation with prospective studies, as discussed below, will be important to confirm these findings.

Hydrophilic *vs.* lipophilic statin use

Hydrophilic and lipophilic statins appear to have different effects on HCC risk. According to Zeng *et al.*, only lipophilic statins exhibited a preventive effect against HCC (HR 0.46; 95%CI: 0.37-0.57), whereas hydrophilic statins did not (HR 0.48; 95%CI: 0.18-1.27)[38]. Similarly, Wang *et al.* reported that lipophilic statins could prevent HCC (OR 0.51; 95%CI: 0.40-0.68), while hydrophilic statins could not (OR 0.77; 95%CI: 0.58-1.02)[44]. Facciorusso *et al.* found that all lipophilic statins tested (atorvastatin, lovastatin, simvastatin) were associated with reduced HCC incidence (HR 0.49; 95%CI: 0.39-0.62), with atorvastatin showing the greatest magnitude of protection (HR 0.43; 95%CI: 0.28-0.65)[48]. When looking exclusively at

MASH patients, one retrospective study showed that statin use was linked to a lower risk of developing HCC (HR 0.40; 95%CI: 0.24-0.67)[49]. Specifically, patients using lipophilic statins had a significant HCC risk reduction (adjusted HR 0.31; 95%CI: 0.17-0.56), in contrast to those who used hydrophilic statins (aHR 0.85; 95%CI: 0.42-1.72)[49].

The higher efficacy of lipophilic statins in reducing HCC risk is likely related to the difference in the ease with which they can enter cells. Lipophilic stains enter cells through passive diffusion (because of their ability to cross cell membranes) and are thus widely distributed within tissues, including hepatocytes. In contrast, hydrophilic statins require a specific carrier-mediated mechanism in order to enter the hepatocytes[28]. Lipophilic statins are thought to have more pleiotropic and off-target effects as well. A recent study on MASLD patients found a reduced risk of HCC development with both the use of lipophilic statins (HR 0.49; 0.37-0.65) and hydrophilic statins (HR 0.40; 0.21-0.76)[43].

Future directions

Statins have other beneficial effects, including a reduction in portal hypertension and liver-related events. Multiple prospective studies of statins in patients with cirrhosis are ongoing. The RESCU Trial in the Liver Cirrhosis Network (NCT05832229) will evaluate rosuvastatin 40 mg daily in patients with compensated cirrhosis. The SACRED Trial (NCT03654053) will evaluate simvastatin in patients with cirrhosis followed in the Veterans Affairs Health Care System. The STAT NASH Trial (NCT04679376) is evaluating statins in the treatment of MASH specifically. Hopefully, these will provide valuable insights into the safety, and optimal types and dosing of statins. The challenge in performing clinical trials for chemoprevention is low event rates and the need for long-term follow-up. One way to address this is to use biomarkers as surrogate endpoints. PLS-NAFLD, a blood-based signature developed to predict HCC in patients with MASLD and validated in multiple independent cohorts, is modified by statins and may serve as a surrogate endpoint [Table 2][37,38,43-45,48-59].

METFORMIN

Type 2 diabetes mellitus (T2DM) is a leading predisposing factor for HCC, with studies indicating that it doubles the risk of developing HCC[60]. This risk then increases tenfold in patients with both cirrhosis and T2DM[61]. The exact mechanism by which T2DM leads to HCC is not fully understood, but it is believed to involve the excessive production of reactive oxygen species, which activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and hepatic stellate cells, thereby promoting hepatocarcinogenesis [Figure 2][62]. A recent study by Ribback *et al.* showed that ballooned hepatocytes, a distinct diagnostic feature of MASLD, were present in 43.8% of cirrhotic livers[63]. Ballooned hepatocyte formation is attributed to dysregulation of the glycogen metabolism, resulting in highly pronounced glycogenosis, which is often associated with the development of steatosis. Therefore, ballooned hepatocytes may link insulin resistance to MASLD. Additionally, insulin resistance in T2DM leads to elevation in levels of insulin growth factor-1, which stimulates hepatocyte proliferation and also inhibits cellular apoptosis, contributing to fibrosis[62]. This then raises the question of whether antidiabetic drugs such as metformin can help reduce HCC risk.

Metformin is thought to exert anti-cancer effects on the liver by suppressing the mTOR pathway through the activation of AMPK, thereby affecting protein synthesis and growth[64]. It also decreases hepatic triglyceride accumulation, which is especially helpful in MAFLD patients as this assists in the reduction of obesity-induced inflammation[64]. In a mouse model study, metformin intervention inhibited hepatic stellate cell activation, reduced liver fibrosis, decreased lipid accumulation in hepatocytes, and halted the progression to cirrhosis and HCC development[65].

Table 2. Summary of articles on statin chemoprevention of HCC

Study	Year	Design	Sample size, *n*	Results (HR/OR/RR, 95%CI)
Wang *et al.*[37]	2021	Meta-analysis	1,772,463	0.57 (0.49-0.65)
Zeng *et al.*[38]	*2022*	Meta-analysis	1,774,476	0.52 (0.37-0.72)
Zou *et al.*[43]	2023	Retrospective study	272,431	0.47 (0.36-0.60)
Wang *et al.*[44]	2022	Meta-analysis	4,963,518	0.58 (0.51-0.67)
Sung *et al.*[45]	2022	Cohort study	1,545,671	0.36 (0.35-0.38)
Facciorusso *et al.*[48]	2020	Meta-analysis	1,925,964	0.73 (0.69-0.76)
Pinyopornpanish *et al.*[49]	2021	Retrospective study	1,072	0.40 (0.24-0.67)
Azit *et al.*[51]	2021	Matched case-control study	424	0.37 (0.21-0.65)
Chang *et al.*[52]	2020	Systemic review/meta-analysis	1,611,596	0.54 (0.42-0.66)
German *et al.*[53]	2020	Retrospective case-control study	103	0.20 (0.07-0.60)
Hashemi Rafsanjani *et al.*[54]	2024	Systemic review/meta-analysis	5,732,948	0.56 (0.50-0.63)
Islam *et al.*[55]	2020	Meta-analysis	59,073	0.54 (0.47-0.61)
Khazaaleh *et al.*[56]	2022	Systemic review/meta-analysis	2,668,497	0.57 (0.49-0.67)
Vell *et al.*[57]	2023	Cohort study	1,785,491	0.58 (0.35-0.96)
Wong *et al.*[58]	2021	Systemic review/meta-analysis	1,742,260	0.57 (0.52-0.62)
Zhang *et al.*[59]	2023	Systemic review/meta-analysis	684,363	0.59 (0.39-0.89)

HCC: Hepatocellular carcinoma; HR: hazard ratio; OR: odds ratio; RR: relative risk.

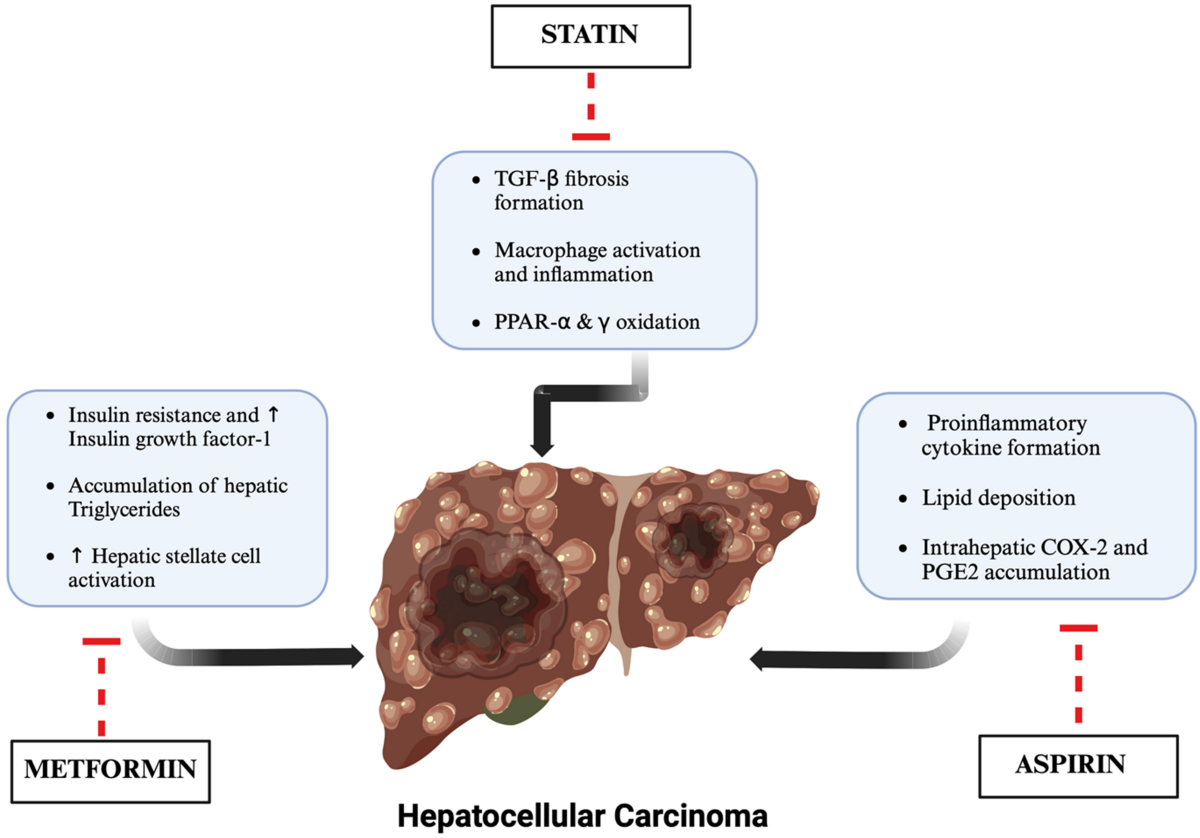

Figure 2. HCC chemoprevention drug mechanisms. Created with BioRender.com. HCC: Hepatocellular carcinoma.

Literature review of metformin chemoprevention

Compared to statin and aspirin, there is less literature on metformin's effects on HCC prevention. Further, the available literature is mixed with regard to the presence and degree of chemoprevention seen with metformin. In a retrospective study involving 1,061 cirrhotic patients with T2DM, the five-year incidence of HCC was lower in the metformin exposure group, compared to the non-exposure group (HR 0.42; 95%CI: 0.33-0.54) [Table 3][62]. Another study by Li *et al.* reported a decreased risk of HCC in T2DM patients with daily metformin use (OR/RR 0.59; 95%CI: 0.51-0.68), along with an overall reduction in HCC-related mortality (HR 0.74; 95%CI: 0.66-0.83)[64]. In a large cohort of patients with T2DM and NAFLD, metformin use was associated with a 20% reduction in HCC risk (HR 0.80; 95%CI: 0.93-0.98) compared to insulin use alone which did not have any effect on HCC risk (HR 1.02; 95%CI: 0.85-1.22)[66].

The difference between HCC risk reduction with metformin compared to insulin raises the question of whether improved glycemic control, independent of the specific drug, is what is truly protective against HCC. Indeed, good glycemic control (A1c < 7% for > 80% of the time) was associated with a 32% lower risk of HCC (HR 0.69; 95%CI: 0.60-0.77)[66]. Among T2DM patients with MASH cirrhosis, metformin use was associated with significant HCC risk reduction (aHR 0.78; 95%CI: 0.69-0.96)[67]. Another study of 3,358 patients with T2DM and MASH cirrhosis found that dual therapy with metformin and a sodium-glucose cotransport 2 inhibitor (SGLT2i) significantly reduced HCC risk (HR 0.43; 95%CI: 0.21-0.88), whereas metformin monotherapy did not[68]. While the potential of metformin as a chemopreventive agent against HCC is encouraging, the limited number of studies and variability in their results both indicate a critical need for further research to fully establish its efficacy.

NEWER DIABETES MEDICATIONS

While available data point to the beneficial effects of multiple diabetes medications on MASLD histology and progression, it is unclear whether these have chemopreventive effects on HCC beyond their influence on the natural history of MASLD. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), which increase insulin secretion and slow gastric emptying, have gotten attention in the field of MASLD due to the substantial weight loss they produce, and associated beneficial effects on liver histology. GLP-1RAs including semaglutide, liraglutide, and dulaglutide may be associated with reduced risk of HCC as well. A recent study from 2024 of 1,890,020 patients with T2DM found that GLP-1RAs were associated with a lower risk of HCC compared to insulin (HR 0.20; 95%CI: 0.14-0.31) and sulfonylureas (HR 0.39; 95%CI: 0.21-0.69). There was no statistically significant difference between GLP-1RA and metformin[69]. Another very recent retrospective cohort study from 2024 involving MASLD cirrhosis patients with type 2 diabetes found that GLP-1RAs were associated with a lower risk of liver-related events including decompensation (HR 0.74; 95%CI: 0.61-0.88) and HCC (HR 0.37; 95%CI: 0.20-0.63)[70].

SGLT2is are another newer class of diabetes medications that result in increased glucose excretion in the kidneys. In both human and animal studies, SGLT2is have been associated with reductions in steatosis and fibrosis[71]. Two large claims database studies from Korea, both published in 2024, found associations between SGLT2i use and HCC incidence or survival. In one study, SGLT2i use in patients with T2DM without chronic liver disease ($N \sim 4$ million) was associated with a lower incidence of HCC compared to the use of dipeptidyl peptidase-4 inhibitors[72]. The other study, which included patients with T2DM and MASLD ($N = 201,542$), found that among 4,936 patients with both MASLD and chronic viral hepatitis, SGLT2i use was associated with a lower risk of HCC even after matching for propensity scores (adjusted HR 2.32; 95%CI: 1.06-5.06)[73]. Although the authors found that the risk of HCC was also lower among patients with T2DM and MASLD only who took SGLT2i, the association was not statistically significant after matching for propensity scores (HR 0.88; 95%CI: 0.62-1.25).

Table 3. Summary of articles on metformin chemoprevention of HCC

Study	Year	Design	Sample size, *n*	Results
Huynh *et al.*[68]	2023	Retrospective study	36,626	No protective effect with metformin monotherapy Metformin + SGLT2i: HR 0.43; 95%CI: 0.21-0.88
Kramer *et al.*[66]	2021	Retrospective cohort study	85,962	HR 0.80; 95%CI: 0.93-0.98
Li *et al.*[64]	2022	Meta-analysis	1,452,265	OR/RR 0.59; 95%CI: 0.51-0.68
Tangjarusritaratorn *et al.*[62]	2021	Retrospective study	719	HR 0.48; 95%CI: 0.36-0.61
Vilar-Gomez *et al.*[67]	2021	Cohort study	299	aHR 0.78; 95%CI: 0.69-0.96
Zeng *et al.*[38]	2022	Meta-analysis	125,458	No protective effect. HR 0.57; 95%CI: 0.31-1.06

HCC: Hepatocellular carcinoma; SGLT2i: sodium-glucose cotransport 2 inhibitor; HR: hazard ratio; OR: odds ratio; RR: relative risk.

Studies of the association between GLP-1RA and SGLT2i and HCC are generally limited by a lack of data on the magnitude of associated changes in weight and diabetes control. These agents require further study, including in prospective cohorts with systematic measurement of improvement in metabolic parameters. Overall, whether observed effects are products of improved glycemic control is not known.

CONCLUSION

The cascade of steatosis to oxidative stress to inflammation to fibrosis is key in the development of HCC in patients with MASLD. Aspirin, statins, and metformin all address key parts of this pathway, offering promising avenues for HCC chemoprevention.

Aspirin's anti-inflammatory and anti-platelet properties help prevent HCC; however, optimal dosing and long-term bleeding risks remain unclear. Statins have demonstrated efficacy in reducing fibrosis and hepatocarcinogenesis, yet further research is needed to determine the most effective dosage and types of statins. Overall, statins have the strongest evidence of the agents we discuss, and momentum is gathering for the use of statins to prevent liver-related complications in patients with MASLD and cirrhosis. Metformin's role in mitigating insulin resistance and reducing hepatic triglycerides build-up is reassuring, though the current body of research is limited, warranting additional studies. Several key questions remain unanswered: how specifically is each agent mediating reduction in HCC risk? Is combination therapy beneficial? Is all glycemic control or lipid lowering the same, or are the pleiotropic properties of these agents unique?

Future research should focus on both existing and emerging therapies, including newer antidiabetic medications, immunotherapies, various selective COX inhibitors, and antifibrotic therapies. In addition, studies specifically targeting MASLD patients are essential. With numerous clinical trials and studies currently underway, significant advancements in HCC chemoprevention are anticipated. In the next 5-10 years, especially with the projected rise in MASLD prevalence, we expect to have more definitive guidance on effective treatments.

DECLARATIONS

Authors' contributions

Manuscript drafting: Dickinson A
Manuscript review and critical revision: Dinani A
Conceptualization, supervision, manuscript review and critical revision: Wegermann K

Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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