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Pharmacological chemoprevention of hepatocellular carcinoma: hype, hope, or reality?

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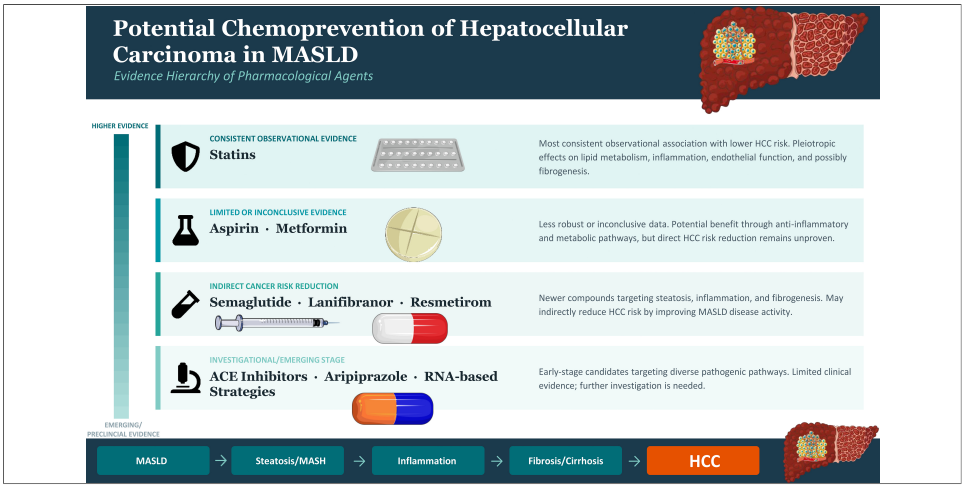

Abstract

Hepatocellular carcinoma (HCC) remains a major global health challenge and is increasingly linked not only to chronic viral hepatitis and alcohol exposure, but also to metabolic dysfunction-associated steatotic liver disease (MASLD), obesity, and dysglycemia. Advanced fibrosis and cirrhosis are the main precancerous conditions for hepatocarcinogenesis, making chemoprevention a rational strategy for individuals at risk of developing primary HCC or experiencing recurrence after treatment. However, fibrosis regression, steatohepatitis resolution, and steatosis reduction are biologically plausible but unvalidated surrogate endpoints for HCC chemoprevention. While antiviral therapy and hepatitis B vaccination have proven effective in preventing liver cancer, there is currently no established pharmacological approach for MASLD-related HCC. Among available agents, statins have shown the most consistent observational evidence of benefit, while data for aspirin and metformin are less robust or inconclusive. Newer compounds targeting key pathogenic pathways involved in steatosis, inflammation, and fibrogenesis are of significant interest. Semaglutide, lanifibranor, and resmetirom may indirectly reduce HCC risk by improving MASLD-related disease activity, although direct evidence for cancer

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prevention is still lacking. Other potential candidates, such as angiotensin-converting enzyme inhibitors, aripiprazole, and RNA-based strategies, are still in the investigational stages. Advances in this field will require improved risk assessment, validated biomarkers, and prospective trials to determine whether reducing fibrosis can lead to meaningful reductions in HCC incidence.

BACKGROUND - DEFINITION, BURDEN AND AIMS

Hepatocellular carcinoma (HCC), the main histological subtype of primary liver cancer, is the sixth most frequently diagnosed malignancy worldwide and the third leading cause of cancer-related mortality[1,2]. In addition to chronic viral hepatitis and excessive alcohol consumption, overweight/obesity and dysglycemia are increasingly recognized as major contributors to HCC, posing a significant burden on global public health, especially in countries with a high or middle sociodemographic index[3]. Advanced liver fibrosis and cirrhosis, regardless of their cause, are established risk factors for HCC, highlighting the importance of surveillance and preventive measures[4]. Hepatocarcinogenesis is a complex and interconnected set of events at the molecular, cellular, and tissue levels, offering potential targets for chemoprevention[5,6].

In this context, chemopreventive strategies, which involve the use of natural or synthetic agents to reduce cancer risk or prevent recurrence, are particularly relevant given the increasing incidence of HCC, especially in Western countries, and its high mortality rates[7,8]. Even after successful treatment of early-stage HCC, the carcinogenic environment may persist in the remaining diseased liver, potentially leading to new tumor formation. Preventing first and subsequent primary HCC in at-risk patients could confer substantial prognostic benefit[9], although no established strategy currently exists beyond HBV vaccination and antiviral therapy for chronic viral hepatitis.

This article focuses on the historical development, underlying mechanisms, and primary drug classes relevant to HCC pharmacological chemoprevention. Special attention is given to HCC occurring in the setting of metabolic dysfunction-associated steatotic liver disease (MASLD) due to its increasing prevalence. Key areas for future research in this field are also highlighted.

HISTORY OF HCC CHEMOPREVENTION

The history of HCC chemoprevention has evolved from a theoretical concept proposed in the 1970s into a multilayered clinical strategy aimed at blocking, reversing, or delaying liver carcinogenesis[10]. A major milestone in HCC prevention was the introduction of hepatitis B virus (HBV) vaccination in 1982[11]. Mass immunization programs, recommended by the WHO since 1991, have markedly reduced HCC incidence in younger populations[12]. More recently, effective therapies for chronic HBV and hepatitis C virus (HCV) infection have shown that sustained viral suppression substantially reduces long-term HCC risk[13]. As a result, the relative burden of MASLD-related HCC has increased, in parallel with the global rise in obesity and dysglycemia[14]. This has shifted research from "generic" approaches, including retinoids, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and metformin[9] to newer antidiabetic, cholesterol-lowering, anti-hypertensive, and other drug classes, which are the main focus of the present article.

PRINCIPAL MECHANISMS OF ACTION OF KEY DRUGS POTENTIALLY CONTRIBUTING TO HCC CHEMOPREVENTION THROUGH EFFECTS ON DISEASE PATHOBIOLOGY

HCC is driven by a chronic cycle of liver injury, inflammation, fibrosis, and unchecked cellular proliferation[10,15]. Key pharmacological agents are listed in Table 1[10,16-33]. Several key drugs may potentially affect HCC pathogenesis, thereby serving as candidate chemopreventive agents[10]. These are schematically illustrated in Figure 1.

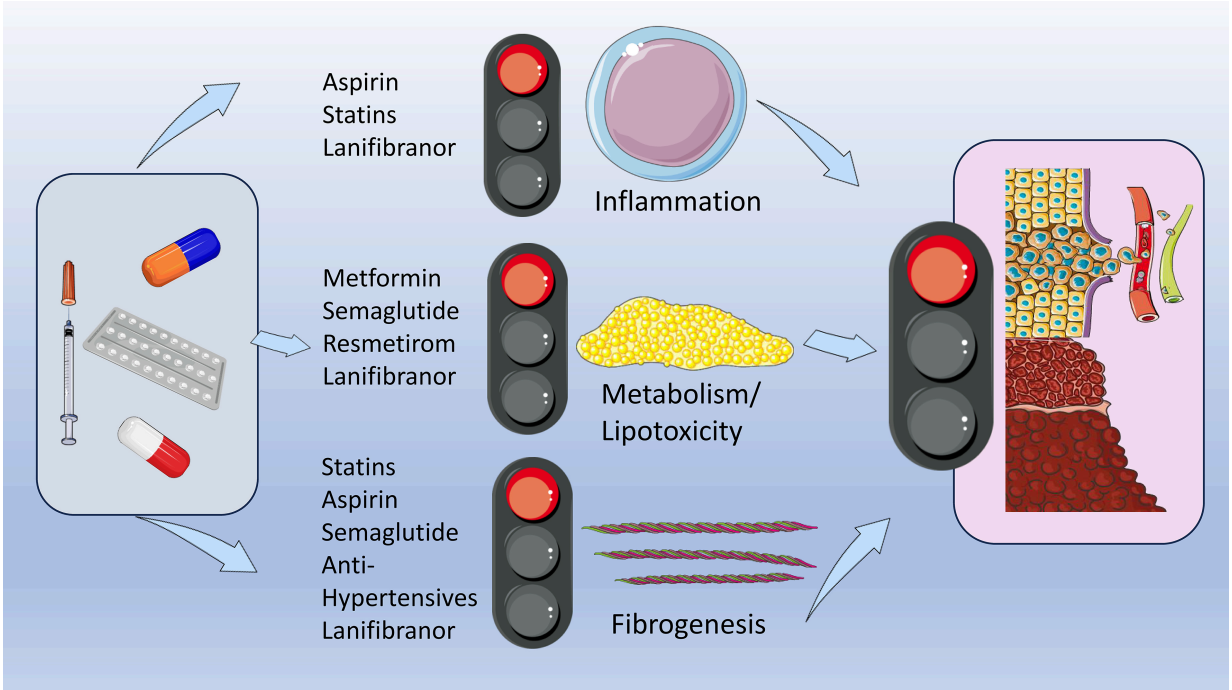

Figure 1. Principal pathways implicated in chemoprevention by selected pharmacological agents. Schematic representation, based on references cited in the text and Table 1, of liver histological changes induced by the main drug classes listed in Table 1 that may influence the pathobiology of metabolic dysfunction-associated steatotic liver disease and contribute to chemopreventive effects. Key molecular pathways involved include THR-β and the MDK/LRP1 axis for resmetirom, pan-PPAR α/δ/γ activation for lanifibranor, GLP-1R signaling for semaglutide, HMG-CoA reductase/mevalonate signaling for statins, COX/platelet signaling for aspirin, AMPK for metformin, and ACE/angiotensin II/EGFR transactivation for captopril and related agents. The traffic-light symbols indicate attenuation or blockade of pathological pathways rather than the strength of clinical evidence. Figure 1 provided by Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). ACE: Angiotensin-converting enzyme; AMPK: adenosine monophosphate-activated protein kinase; COX: cyclooxygenase; EGFR: epidermal growth factor receptor; GLP-1R: glucagon-like peptide-1 receptor; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; LRP1: low-density lipoprotein receptor-related protein 1; MDK: midkine; PPAR: peroxisome proliferator-activated receptor; THR-β: thyroid hormone receptor-beta.

CHEMOPREVENTION OF MASLD-HCC

Levels of evidence for HCC chemoprevention by drug class

The evidence hierarchy separates direct randomized clinical evidence for reduction of HCC incidence from indirect clinical evidence, surrogate histological evidence in MASLD/Metabolic Dysfunction-Associated Steatohepatitis (MASH) or fibrosis trials, and preclinical or mechanistic plausibility. At present, most chemoprevention signals for HCC are observational rather than randomized and should therefore be interpreted as hypothesis-generating unless supported by prospective HCC-endpoint trials. Figure 2 summarizes the levels of evidence in HCC chemoprevention by pharmacological class.

Metformin, aspirin, and statins

A meta-analysis updated as of 2022 found that both statin and aspirin use were associated with a reduced risk of HCC [statins: Hazard ratio (HR) 0.52, 95%CI: 0.37-0.72; 10 studies; 1,774,476 participants; aspirin: HR 0.48, 95%CI: 0.27-0.87; 11 studies; 2,190,285 participants][23]. This evidence is almost entirely observational, although higher-quality analyses increasingly restrict inclusion to propensity-score-matched or inverse probability-weighted cohorts to reduce confounding by indication, immortal-time bias, and differences in baseline liver disease severity. However, in subgroup analyses accounting for concurrent medications, only statin use remained significantly associated with lower HCC risk. By contrast, metformin use was not significantly associated with reduced HCC risk (HR 0.57, 95%CI: 0.31-1.06; 3 studies; 125,458 participants). Thus, these agents should not be interpreted as equivalent chemopreventive options: statins have the most

Table 1. HCC chemopreventive drugs at a glance

	Main mechanism	HCC reduction	Effect on liver histology	Clinical stage	Overall level for HCC chemoprevention	References
Metformin	AMPK activation; reduces IR and cell proliferation	Strongest data in viral hepatitis and diabetes	Minimal effect on existing fibrosis	Approved for T2D; used off-label for HCC prevention	Low to moderate: mechanistically plausible, but current adjusted clinical evidence is inconsistent	[16,17]
Aspirin	COX-1 inhibition and antiplatelet activity; COX-2 inhibition and anti-inflammatory activity; upregulates PPARδ, AMPK, and PGC-1α; suppresses NF-κB signaling and downregulates P4HA2	30% to 50% RRR in incident HCC among regular aspirin users compared with non-users. The protective effect is most pronounced and consistently observed in patients with chronic viral hepatitis (HBV/HCV)	Suppression of steatosis; blunting of fibrosis and collagen deposition; mitigation of necroinflammation	Aspirin's position in the clinical workflow for HCC prevention is not yet established	Moderate: consistent observational signal, but no direct randomized HCC endpoint evidence	[18-21]
Statins	HMG-CoA reductase inhibition; oncogenic pathway suppression; cell-cycle arrest and induction of apoptosis in malignant hepatocytes; impaired tumor vascularization and metastasis	43% to 48% overall reduction in HCC risk among statin users, with variable data according to the etiology and severity of CLD	Fibrosis and cirrhosis regression: reduced portal hypertension; diminished chronic hepatic necroinflammation; slower transition from steatohepatitis to cirrhosis	Investigational but approved for lipid/cardiovascular indications	Moderate to high observational evidence, but still not definitive without randomized HCC-endpoint trials	[22,23]
Anti-hypertensives	ACEIs, ARBs, and NSBBs have been studied in relation to HCC chemoprevention in patients with CLD	The effects of medication classes on inflammation, fibrosis, and angiogenesis may contribute to HCC chemoprevention	ACEIs and ARBs help reduce liver fibrosis, necroinflammation, and disease progression in patients with MASLD	Evidence for HCC chemoprevention with ACEIs, ARBs, and NSBBs remains limited. The AASLD recommends NSBBs in selected patients with CSPH as a promising candidate to prevent hepatic decompensation	Low to moderate (ARBs): suggestive observational and mechanistic evidence, not definitive. Low (ACEIs and NSBBs): biologically plausible but clinically unproven	[10,24,25]
Semaglutide	GLP-1 regulates glucose homeostasis, food intake, and reward-related processes. GLP-1RAs promote weight loss and reduce systemic inflammation	Observational evidence links semaglutide use with lower HCC risk, likely reflecting the 63% MASH resolution rate associated with the use of this drug	Improves MASH but has limited direct effect on advanced fibrosis	Approved for MASH (conditional) and obesity; primary HCC trials ongoing	Low to moderate: promising indirect evidence, but no direct HCC-prevention outcome data	[26-30]
Lanifibranor	Pan-PPAR agonist (α/δ/γ); direct liver-targeted metabolic and anti-fibrotic repair	Markedly reduces fibrosis, but mouse models showed no direct tumor reduction compared to semaglutide	In the Phase 2b NATIVE trial, lanifibranor demonstrated efficacy in achieving MASH resolution and improving fibrosis	In Phase III trials (NATiV3) for MASH and fibrosis	Moderate for disease-modifying MASH biology, but low for proven HCC chemoprevention	[31]

Resmetirom	Oral, liver-directed, THR-β selective agonist	Reduces steatosis by upregulating hepatic FA β-oxidation; inhibits the MDK pathway; modulates the tumor microenvironment and mitigates chronic inflammation	MASH resolution; fibrosis regression; and steatosis reduction	In animal models, resmetirom significantly inhibits tumor growth, reduces tumor burden, and acts synergistically with dedicated MDK inhibitors. Long-term follow-up is needed to determine the exact reduction rate of HCC in human cohorts	Moderate for surrogate MASH improvement, low for HCC chemoprevention	[32,33]

AASLD: American Association for the Study of Liver Diseases; ACEIs: angiotensin-converting enzyme inhibitors; AMPK: adenosine monophosphate-activated protein kinase; ARBs: angiotensin II receptor blockers; CLD: chronic liver disease; COX: cyclooxygenase; CSPH: clinically significant portal hypertension; FA(s): fatty acid(s); GLP-1: glucagon-like peptide-1; GLP-1RA: glucagon-like peptide-1 receptor agonist; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; IR: insulin resistance; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; MDK: midkine; NF-κB: nuclear factor-kappa B; NSBBs: non-selective beta-blockers; P4HA2: prolyl 4-hydroxylase subunit alpha 2; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPAR: peroxisome proliferator-activated receptor; RRR: relative risk reduction; THR-β: thyroid hormone receptor-beta; T2D: type 2 diabetes.

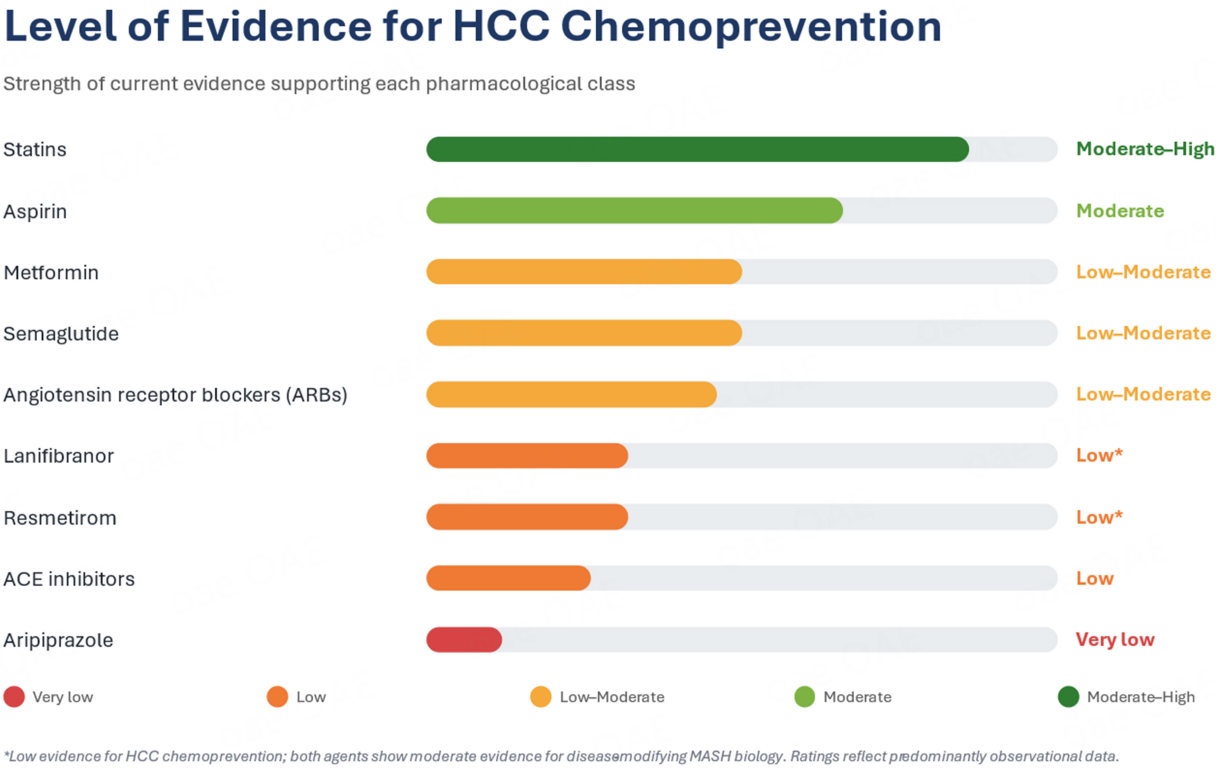

Figure 2. Level of Evidence for drug-based HCC chemoprevention. Semi-quantitative graphical summary of the relative strength of evidence supporting statins, aspirin, metformin, semaglutide, ARBs, lanifibranor, resmetirom, ACE inhibitors, and aripiprazole as candidate approaches for HCC chemoprevention. ACE: Angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; HCC: hepatocellular carcinoma.

consistent epidemiologic signal, aspirin has a plausible but more confounded association, and metformin has the weakest and most diabetes-dependent evidence base.

A more recent study evaluated whether metformin and statins may reduce HCC risk in patients with chronic hepatitis C from the T-COACH cohort who did not respond to antiviral therapy[34]. The findings suggest that both drugs may have a chemopreventive effect in this setting. Importantly, the higher HCC risk associated

with non-use of metformin was mainly observed in non-cirrhotic patients, whereas statins were associated with lower HCC risk in both cirrhotic and non-cirrhotic patients. These etiology- and stage-specific findings are important because the apparent benefit of metformin may be driven partly by metabolic risk modification in diabetic or insulin-resistant patients rather than by a direct antineoplastic effect across all causes of chronic liver disease. In HCV, particularly before sustained virologic response was widely achievable, residual inflammation and metabolic cofactors may have amplified any protective signal; in HBV, MASLD, and alcohol-related liver disease, evidence remains less uniform and is more dependent on cohort design, medication duration, and adjustment for diabetes, obesity, antiviral therapy, and cirrhosis.

Statins should be viewed not only as cholesterol-lowering agents, but also as drugs with the strongest retrospective evidence for HCC prevention. Meta-analyses of observational studies suggest that statin use is associated with an approximately 46% reduction in HCC risk[35-38]. The association has been reported across several high-risk populations, including chronic HBV, chronic HCV, cirrhosis, and MASLD, and appears more reproducible for lipophilic statins and for longer cumulative exposure. Nevertheless, causality has not been established, and the available data cannot fully exclude healthy-user bias, better cardiometabolic care among statin users, or differential surveillance for HCC.

The biologically plausible chemopreventive effect of statins against HCC is most evident in patients at high risk for liver cancer, particularly Asians, those with underlying cirrhosis, MASLD, or chronic viral hepatitis[21,39-41]. The risk reduction, which requires prospective evaluation, appears to be dependent on the chemical properties and dose of statins, with lipophilicity, long-term use, and higher cumulative daily doses conferring greater benefits[42-45].

The chemopreventive effect of aspirin in HCC is likely to vary by disease etiology, reflecting differences in the inflammatory, thrombotic, and carcinogenic pathways that drive viral, metabolic, alcohol-related, and other forms of chronic liver disease[10]. Low-dose aspirin is an appealing candidate for modifying MASLD pathobiology, but current data do not justify routine use, especially in cirrhosis. In a single-center phase 2 trial, daily 81 mg aspirin for 6 months reduced hepatic fat content *vs*. placebo in adults with non-cirrhotic MASLD, but the study was small, short, and not powered for fibrosis, decompensation, HCC, or bleeding outcomes[46]. Observational meta-analyses link aspirin exposure to lower HCC incidence, yet estimates remain vulnerable to confounding, immortal-time bias, heterogeneous exposure definitions, and residual differences in liver disease severity[47]. Benefit was not significant in cirrhosis, whereas bleeding risk increased; in compensated HBV-related cirrhosis, aspirin was associated with lower HCC risk but higher gastrointestinal bleeding risk[48]. Any chemopreventive signal must therefore be weighed against portal-hypertensive bleeding, thrombocytopenia, anticoagulant use, and decompensation risk pending adequately powered prospective trials. Statins are generally usable in compensated chronic liver disease when clinically indicated, but require caution in decompensated cirrhosis, frailty, interacting drug regimens, and patients at risk of myopathy or hepatotoxicity. Metformin remains attractive in type 2 diabetes, yet its preventive role is uncertain after adjustment for statin use, glycemic control, and liver disease stage, and it should be avoided or used cautiously in severe renal impairment, hypoxic illness, sepsis, or unstable decompensated cirrhosis. Overall, these agents support risk-stratified investigation, not routine prescription solely for HCC chemoprevention.

Semaglutide

Semaglutide is currently a major focus of HCC chemoprevention research, particularly for patients at risk of MASLD-HCC. Current evidence is confined largely to weight loss, metabolic improvement, MASH resolution, and observational class-level associations, with no prospective trials powered for HCC endpoints. While not yet Food and Drug Administration (FDA)-approved specifically for cancer prevention,

semaglutide may reduce HCC risk in patients with MASLD and type 2 diabetes based on recent observational evidence[49].

Several putative mechanisms may be involved, although current data should be distinguished as indirect risk-reduction evidence rather than evidence of direct anti-tumor effects. Phase III trials, such as the ESSENCE trial, have shown that semaglutide (2.4 mg) can lead to the resolution of steatohepatitis (MASH) in up to 63% of patients[50], potentially slowing the progression to cancer through this pathway. Moreover, a large-scale meta-analysis of over 2.3 million patients indicated that Glucagon-like peptide-1 (GLP-1) receptor agonists, a class that includes semaglutide, are associated with a 42% reduction in HCC risk in patients with type 2 diabetes[29]. The proposed "chemopreventive" effect is thought to be indirect, stemming from significant weight loss, improved insulin sensitivity, and reduced systemic inflammation rather than direct antitumor activity[51].

Preclinical findings

In preclinical Gubra Amylin NASH (GAN) diet-induced NASH-HCC mouse models, semaglutide significantly reduced both the number and size of liver tumors, leading to a notable decrease in overall tumor burden[30]. These encouraging preclinical findings now warrant rigorous validation in appropriately designed clinical trials.

Major caveats

Real-world discrepancies and fibrosis limitations should be considered when interpreting published studies. In a retrospective cohort of 71,612 individuals, semaglutide was not associated with a significant 10-year reduction in HCC risk[52]. This suggests that semaglutide's benefits may depend on treatment timing or cirrhosis status. Semaglutide is effective in reducing liver fat and inflammation[53]. However, its effect on advanced fibrosis remains uncertain and may not fully offset risk once cirrhosis is established[53].

Lanifibranor

Based on available research as of mid-2026, lanifibranor is an investigational antifibrotic MASH therapy with theoretical chemopreventive relevance but is not used or approved for HCC chemoprevention. However, it is a leading investigational drug for MASH. The Phase 2b NATIVE trial showed that lanifibranor improved liver histology in MASH patients, a population at potential risk for developing HCC[31,54]. Because MASH-related fibrosis and cirrhosis are major drivers of HCC, lanifibranor's ability to reverse fibrosis suggests it may reduce HCC risk, but it is not currently classified as a chemopreventive agent.

Resmetirom

Resmetirom is a MASH-directed agent with preclinical antitumor signals requiring long-term human validation. A recent study offers the first detailed preclinical assessment of resmetirom as a potential modifier of MASLD-associated hepatocarcinogenesis[55]. Using hydrodynamic tail-vein injection models driven by $NRas^{V12}$/Myr-AKT, ΔN90-β-catenin/c-Myc, or c-Myc/TP53 knockout, combined with a Western diet and low-dose CCl_4, Zhang *et al.* showed that resmetirom significantly reduced hepatic steatosis and HCC burden across oncogenic settings. To link these effects to disease progression, they developed a multistage Western diet/CCl_4 model recapitulating MASLD, MASH, advanced fibrosis, and overt MASLD/MASH-HCC, and performed single-cell RNA sequencing on 134,760 liver and tumor cells[55]. This integrative approach showed expansion of myeloid populations, particularly M2-like and MASH-associated macrophages ($TREM2^+GPNMB^+$), together with hepatic stellate cell activation and the emergence of dysplastic hepatocytes with copy-number alterations, closely recapitulating the cellular landscape of human MASLD/MASH-HCC. The limitations of this study include differences between animal models and humans, and the timing of drug administration, implying that these findings do not firmly establish resmetirom as an HCC therapy. However,

these authors provide a detailed Midkine/Low-density lipoprotein receptor-related protein 1 (MDK/LRP1)-centered framework to guide rational combination strategies and future clinical trial design[56]. Additionally, resmetirom should be tested as a potential chemopreventive agent given its ability to improve MASH histology while displaying antitumor effects by reversing steatosis, improving liver metabolism, and reducing immunosuppressive MDK/LRP1 interactions.

Targeting the angiotensin-converting enzyme and epidermal growth factor receptor signaling

Barone *et al*. conducted a systematic review to clarify the role of angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors in HCC[57]. Their meta-analytic evaluation indicated that, in humans, renin-angiotensin system inhibitors, whether administered alone or in combination, were associated with a significantly reduced cumulative incidence of HCC recurrence, although no improvement in overall survival was observed.

Crouchet *et al*. established a simplified human cell-based model incorporating a prognostic liver signature (PLS) predictive of liver disease progression and HCC risk. In their initial study, this platform was applied to screen more than 20,000 compounds, followed by experimental validation in a cell-based system, leading to the identification of captopril, an ACE inhibitor primarily used to treat hypertension, as a promising candidate for HCC chemoprevention[58]. In their subsequent study, these researchers further investigated ACE as a therapeutic target for HCC chemoprevention and demonstrated that captopril could attenuate liver fibrosis and delay progression toward HCC in both a diethylnitrosamine (DEN)-induced rat cirrhosis model and a diet-induced rat model of MASH-associated hepatocarcinogenesis[59]. RNA sequencing analysis of cirrhotic rat liver tissue demonstrated that captopril suppressed molecular pathways implicated in fibrogenesis, inflammation, and carcinogenesis, including epidermal growth factor receptor (EGFR) signaling. Complementary mechanistic studies in liver disease models further indicated angiotensin-mediated transactivation of the EGFR pathway.

Further supporting the translational relevance of this strategy, captopril significantly reversed the high-risk HCC status defined by the PLS in liver tissue obtained from patients with advanced fibrosis. Collectively, these findings suggest that captopril may represent a safe and cost-effective candidate for HCC chemoprevention and may delay progression of fibrotic liver disease toward HCC in preclinical settings.

Based on available evidence, it remains premature to recommend ACE inhibitors (ACEIs) as primary chemopreventive agents in MASLD/nonalcoholic steatohepatitis (NASH)[60,61]. However, a strong rationale supports further basic and translational research to clarify the pathogenic mechanisms underlying the effects of ACEIs and, more importantly, randomized controlled trials evaluating their impact on HCC chemoprevention.

SGLT2 inhibitors as emerging metabolic partners

SGLT2 inhibitors (SGLT-2i) are gaining attention as metabolic partners in MASLD, with potential implications for lowering HCC risk through indirect pathways rather than proven antitumor effects. By improving glycemic control, promoting modest weight loss, reducing visceral adiposity, and ameliorating hepatic steatosis, these agents may attenuate insulin resistance, lipotoxicity, oxidative stress, and inflammatory signaling that contribute to fibrogenesis and hepatocarcinogenesis[62]. Emerging clinical data also suggest favorable effects on aminotransferases, liver fat, fibrosis markers, and broader cardiometabolic outcomes. In their nationwide cohort study, Bea *et al.* found that SGLT-2i were associated with a reduced risk of hepatic decompensation events in patients with MASLD compared with TZDs and showed similar effectiveness to GLP-1RA[63]. The hepatic effectiveness of SGLT-2i was greater in female patients and patients younger than 65 years. However, whether these metabolic improvements translate into clinically meaningful

HCC chemoprevention remains uncertain; direct protective effects against HCC have not yet been demonstrated in prospective trials.

Aripiprazole

Recent investigations have identified aripiprazole, an oral atypical antipsychotic, as a potential candidate for HCC chemoprevention[64]. Clinical analysis of liver tissue has shown that aripiprazole targets are expressed in various liver cell compartments, including fibroblasts, macrophages, and epithelial cancer cells, and are linked to fibrotic liver disease and HCC. In a rat model of MASH-driven HCC induced by a choline-deficient L-amino acid-defined high-fat diet, aripiprazole slowed the progression of liver disease and the development of HCC by altering fibrogenic and inflammatory pathways. Mechanistically, it exerted antifibrotic and anti-inflammatory effects by changing fibroblast and macrophage phenotypes. Cancer cell studies demonstrated reduced tumor initiation and proliferation through the inhibition of c-Met encoding the hepatocyte growth factor receptor (HGFR)' and extracellular sginal-regulated kinase (ERK) signaling and disruption of mitochondrial function. In patient-derived tumor spheroids, aripiprazole also affected immune responses in the tumor microenvironment[64]. These findings collectively support aripiprazole as a potentially promising candidate for HCC chemoprevention, although clinical experience is limited, and further observational studies and trials in high-risk populations are necessary.

Can sex differences in HCC pathobiology be exploited for HCC chemoprevention?

A robust body of published evidence, summarized elsewhere[65], pinpoints sex disparities in HCC, with men having a higher risk approximately 2.5 times that of women. Sex, reproductive status, and gender also modify several other aspects of HCC pathobiology, ranging from disease stage at presentation to treatment outcomes[65]. Reproductive and hormonal factors appear to modify HCC risk in women: higher parity, later natural menopause, and hormone replacement therapy (HRT) were associated with lower risk, whereas premenopausal oophorectomy before age 50 was associated with increased risk[66]. Hormone replacement therapy is associated with reduced HCC risk and improved survival among postmenopausal women with hepatitis B[67]. However, menopausal HRT is not indicated for the chemoprevention of HCC[68,69].

Combined chemopreventive approaches

Statin combination

Large-scale studies of patients with failed antiviral therapy or diabetes show that combining metformin and statins can reduce HCC risk by up to 50% compared with non-users[34].

GLP-1 combinations

New research is exploring the potential synergy of GLP-1 receptor agonists, such as semaglutide, with older drugs. Combination therapies, such as GLP-1 receptor agonists plus metformin, have shown a significantly lower risk of hepatic decompensation and HCC compared with using either drug class alone[70].

Acyclic retinoid and branched-chain amino acids

Acyclic retinoid (ACR) and branched-chain amino acids (BCAAs) have shown cooperative inhibitory effects on HCC cell growth and obesity-related liver tumorigenesis in experimental studies, but their role in clinical HCC chemoprevention remains uncertain[71,72]. These approaches are less well integrated into contemporary MASLD-HCC prevention strategies, and their validity remains uncertain compared with more modern drugs.

Antifibrotic and antiviral/metabolic agents

Combining agents such as captopril with antioxidants such as vitamins E and C, or other agents, can reduce liver fibrosis, a potentially important step in limiting progression from steatohepatitis to HCC[59]. These

strategies, supported only by small or preclinical studies, require validation in prospective randomized controlled trials.

siRNA-based therapies

N-acetylgalactosamine (GalNAc)-conjugated siRNAs targeting multiple genes, such as *CDK1* and *ANLN*, have shown potential in preventing HCC development across various models, including MASH and chemically induced injury[73].

CANDIDATE PATIENT POPULATIONS FOR FUTURE CHEMOPREVENTION TRIALS

In HCC, prevention is most clearly established when directed at the underlying cause of liver injury. Core evidence-based strategies include universal and risk-based HBV vaccination, nucleos(t)ide analog treatment for chronic HBV infection, curative direct-acting antiviral therapy for HCV infection, reduction of alcohol exposure, weight loss and control of metabolic risk in MASLD, avoidance of tobacco, and semiannual surveillance in patients with cirrhosis or selected high-risk patients with non-cirrhotic HBV infection[69,74].

Current guidelines identify HBV vaccination and antiviral therapy as disease-modifying interventions that reduce HCC incidence, but do not support prescribing statins, aspirin, or metformin solely for HCC prevention. No pharmacological agent is approved specifically for chemoprevention of MASLD-related HCC[35,75]. Future prevention trials should therefore be enriched for populations with sufficiently high event rates and measurable benefit-risk trade-offs, including male and postmenopausal female patients with compensated cirrhosis, advanced MASH fibrosis, persistent viral risk despite viral suppression or cure, hereditary hemochromatosis, previous curative-intent resection or ablation, and a family history of HCC[76].

CONCLUSION AND RESEARCH AGENDA

Additional effective pharmacological strategies to prevent HCC are still lacking[64]. This urgent unmet need has driven research on HCC chemoprevention for decades. Chronic fibrotic liver disease of viral or metabolic origin is associated with a substantial HCC risk. Even after curative treatment of early-stage HCC, the carcinogenic microenvironment persists in the residual diseased liver and may foster *de novo* recurrence. Accordingly, preventing HCC in patients at risk of both first and second primary tumors may confer the greatest prognostic advantage. However, no established therapy is currently available for this purpose beyond HBV vaccination and antiviral therapy for chronic viral hepatitis.

Importantly, although biologically plausible, fibrosis regression, resolution of MASH, and attenuation of steatosis remain unvalidated surrogate endpoints for HCC chemoprevention until proven by randomized controlled trials.

A major challenge lies in identifying clinically relevant targets, which may be facilitated by reverse-engineering approaches integrating omics data from clinical cohorts with completed cancer follow-up. Candidate compounds could subsequently be evaluated cost-effectively in conjunction with HCC risk biomarkers to identify the patients most likely to derive benefit. These include (a) cirrhosis of any etiology[10]; (b) uncontrolled chronic viral hepatitis[77]; (c) selected patients with MASH, for example, those with F3/F4 fibrosis and/or type 2 diabetes[10]; (d) individuals with hereditary hemochromatosis[78]; (e) post-resection or post-ablation patients[10]; and (f) individuals with a family history of HCC[10]. Nontoxic, generic agents may offer broad applicability across HCC etiologies and clinical settings and could contribute to improving the persistently poor prognosis of HCC[9]. Nevertheless, the administration of these pharmacological classes in patients with compromised hepatic function should be undertaken with the utmost caution.

In conclusion, despite decades of research, there is still no single gold-standard approved chemopreventive drug, largely due to the long latency of the disease and the difficulty of conducting long-term, ethically sound trials. Future studies should focus on identifying PLS[59] to identify high-risk patients who would benefit most from chemoprevention. Moreover, new agents targeting liver fibrosis, the primary precursor to HCC, are being tested in randomized controlled trials[79] to provide proof-of-concept evidence on whether targeting liver fibrosis effectively prevents HCC onset.

DECLARATIONS

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Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Weiskirchen R, Lonardo A

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool OpenAI (GPT-5.5, released 2026-04-23) was used solely for language editing and Microsoft 365 Copilot (last updated on 2026-08-04) for the creation of Figure 2. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

Weiskirchen R is the Guest Editor of the special issue entitled "*Fibrosis Driven Hepatocarcinogenesis in MASLD/MASH: Mechanisms, Biomarkers and Therapeutic Horizons*" in *Hepatoma Research*. Lonardo A is an Associate Chief Editor of *Hepatoma Research*. Weiskirchen R and Lonardo A were not involved in any steps of editorial processing, notably including reviewer' selection, manuscript handling, and decision making.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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