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Chemoprevention in hepatocellular carcinoma

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Abstract

Purpose of Review The number of deaths due to hepatocellular carcinoma (HCC) continues to rise. Chemoprevention may be a useful strategy to prevent HCC.

Recent Findings We summarize recent clinical and translational studies on the chemoprevention of HCC from the aspects of etiology-specific and generic chemoprevention in the context of contemporary HCC etiologies.

Summary Use of safe and effective HCC chemopreventive agents may reduce the burden of HCC, but more data are required before these can be recommended in routine clinical practice.

Keywords Chemoprevention · Hepatocellular carcinoma · Etiology · Generic

Introduction

Hepatocellular carcinoma (HCC) accounts for more than 80% of primary liver malignancies and is the third leading cause of cancer-related deaths worldwide [1]. HCC is more prevalent in patients with hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol intake, and metabolic dysfunction–associated steatotic liver disease (MASLD)/metabolic dysfunction–associated steatohepatitis (MASH) [2]. Substantial changes in the etiology of HCC over the past decade have occurred, with a decline in HCV infection with the widespread use of new-generation anti-HCV drugs (direct-acting antivirals; DAAs). However, HCC risk post-HCV cure remains high for nearly a decade when cirrhosis is present [3]. HBV-induced HCC is currently the most prevalent etiology for HCC and the dominant cause in Southeast Asia and sub-Saharan Africa. However, the rates have been steadily declining owing to interferon-/nucleot(s)ide analogs (NAs)–based suppression of HBV replication and universal vaccination [4].

An emerging major cause of HCC has been attributed to MASLD/MASH with a pooled global prevalence of MASLD being approximately 30% [5, 6]. A recent analysis by Tan et al. found that the prevalence of MASLD-related HCC is rising, with an increased risk of HCC developing in people without cirrhosis [5]. Despite the current significant advances in the treatment of HCC, the prognosis for patients with HCC remains poor with a 5-year survival rate of <20% with a high recurrence rate [2]. As such, there has been an increased interest in HCC chemoprevention, particularly amongst patients with cirrhosis. Chemoprevention approaches aimed at preventing, delaying, or suppressing tumor development using synthetic or natural bioactive

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agents (as seen in Fig. 1). This review is based on the current status, limitations, and future directions of HCC chemoprevention, emphasizing the potency of phytochemicals as effective chemopreventives.

Etiology-Specific Chemoprevention

HBV

The implementation of universal HBV vaccination introduced in more than 180 countries worldwide has significantly reduced the rate of new HBV infections by substantially reducing neonatal HBV vertical transmission resulting in a lower risk of HBV-related HCCs [7, 8]. Taiwan was among the first to initiate nationwide neonatal HBV vaccination and national antiviral therapy programs in 1984 and 2003. Chiang et al. showed the percentage of chronic HBV infections in patients with HCC sharply decreased from 83.3% (born in 1980–1984) to 55.6% (born in 2000–2004) [9]. Another Taiwanese population-wide intervention study on the long-term effectiveness of HBV vaccination showed a reduction in HCC incidence by approximately 15% in the young and middle-aged groups [10]. Wong and colleagues observed HBV vaccination reduced HCC development from 0.4 to 0.1% in Hong Kong [11]. In patients who have already acquired HBV, advancements in the field of antiviral therapies have been shown to reduce the rate of HCC development, particularly with tenofovir [12•]. The potential utility of antiviral therapy for chemoprevention in patients with chronic hepatitis B stems from its ability to control viral replication, which is a major risk factor for HBV-related hepatocarcinogenesis. Although the current HBV therapeutics (e.g., pegylated-interferon-α and NAs) enabled potent viral suppression and improved prognosis in patients with chronic hepatitis B, they rarely achieve HBV cure and thus require long-term treatment to maintain a virologic response [13]. In addition, even though obtaining spontaneous hepatitis B surface antigen seroclearance, HCC continues to develop at an estimated rate of 0.86%/year in certain situations [14]. To reduce HBV-related HCC, several novel agents are currently under development including DAAs and immune modulators.

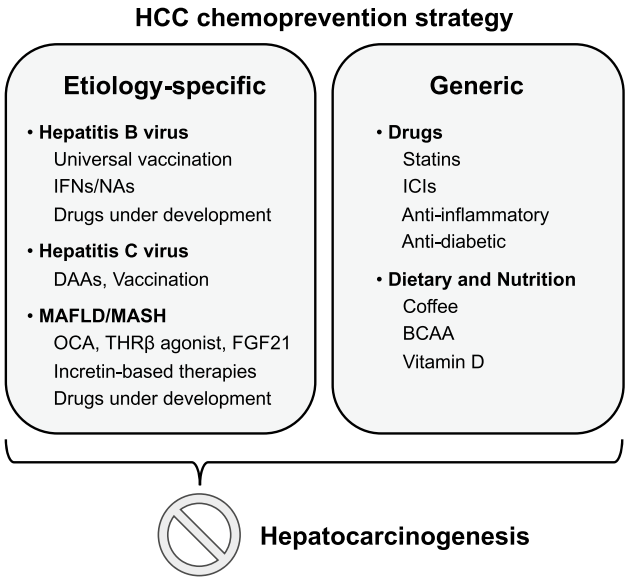

Fig. 1 Strategy for HCC chemoprevention. Abbreviations: IFN, interferon; NA, nucleot(s)ide analog; DAA, direct-acting antivirals; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; OCA, obeticholic acid; THR, thyroid hormone receptor; FGF, fibroblast growth factor; ICI, immune checkpoint inhibitor; BCAA, branched-chain amino acids

HCV

A recent modeling study estimated that 56.8 million (71 million in 2015) individuals are affected with viremic HCV infection globally [15]. While HCV clearance by DAAs can significantly reduce the risks of HCC incidence, the risk of HCC cannot be completely eliminated [3]. A recent systematic review and meta-analysis (44 studies, 107,548 person-years of follow-up) revealed the incidence of HCC was 2.1/100 person-years (95% confidence interval (CI), 1.9–2.4) among patients with cirrhosis and 0.5/100 person-years (95% CI, 0.3–0.7) among patients with F3 fibrosis, respectively [16]. The development of a prophylactic HCV vaccine is a promising primary prevention strategy for HCV-related HCC. Targeting host genes/proteins, such as viral entry factors, may be a candidate or complementary antiviral strategy [17]. Additionally, utilizing experimental rodent models such as an infection of rats by an HCV-related hepacivirus, a mechanistic platform for vaccine is being developed [18, 19]. Recently, several types of vaccines such as permuted HCV glycoprotein nanoparticle vaccine and subviral particle-based DNA vaccine were developed [20, 21]. Then, a phase I trial of a therapeutic DNA vaccine for preventing HCC from chronic HCV infection is currently underway [22].

MAFLD/MASH

With the growing population of HCC patients with a background of metabolic diseases such as MAFLD/MASH, many drugs that aim to ameliorate MAFLD/MASH have been tested in clinical trials. However, none has currently met regulatory approval [23]. Based on the interim analysis of a randomized global phase III trial (REGENERATE, NCT02548351), rapid and sustained improvements in various non-invasive tests were observed with obeticholic acid

(OCA) treatment [24]. A meta-analysis with 1878 individuals showed OCA could be used in chronic liver disease safety [25•]. A recent preclinical study uncovered that microbiota-induced lipid peroxidation impairs OCA-mediated antifibrotic effect towards MASH in mice [26]. In an ongoing phase III study of the MASH population, MAESTRO-NASH (NCT03900429) supported the efficacy and safety of resmetirom (MGL-3196), a thyroid hormone receptor β agonist, with significant reduction of hepatic fibrosis [27]. Recent experiment using MASH model mouse revealed that resmetirom could improve MASH by recovering RGS5 expression and subsequently inactivating the signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kappa B (NF-κB) signaling pathways [28].

Fibroblast growth factor 21 (FGF21) is a pleiotropic hormone with various beneficial effects on glucose metabolism, sugar intake, and preference, which can be regulated by a variety of mechanisms, such as adipose-derived circulating microRNAs, genetic polymorphism (rs838133), and the underlying protective effects of time-restricted feeding [29]. In rodent models, the lack of FGF21 is known to accelerate liver injury and the development of MASH and HCC [29]. A recent phase II trial of efruxifermin, a long-acting Fc-FGF21 fusion protein showed (NCT03976401) [30]. A recent prospective cohort study with 825 HCC individuals revealed that patients . A synthetic FGF21 protein, LY2405319, reduces transforming growth factor β1 (TGFβ1) and collagen I expression as well as NF-κB p65, c-Jun N-terminal kinase 1/2 (JNK1/2), and p38 phosphorylation, and inhibits MASH progression in diet-induced MASH mouse model, suggesting that FGF21 may play a role in the chemoprevention of HCC [31].

Incretin-based therapies (e.g., dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 (GLP-1) receptor agonists) might reduce HCC risk, especially in patients with MAFLD/MASH [32]. A phase III trial that semaglutide, a GLP-1 receptor agonist, with lifestyle intervention for overweight or obesity participants showed sustained and clinically relevant reduction in body weight [33]. However, in a recent phase II trial, semaglutide did not significantly improve fibrosis or achievement of MASH resolution for patients with MASH and compensated cirrhosis [34]. In a MASH mouse model, liraglutide, a GLP-1 receptor agonist, significantly ameliorated steatosis, inflammation, and hepatocyte ballooning of non-tumorous lesions, resulting prevention of HCC progression [35]. Using MASH-related HCC mouse model, Kawaguchi et al. showed that DDP-4i suppressed the pentose phosphate pathway by downregulating the p62/Keap1/Nrf2 pathway, or activating lymphocyte chemotaxis, and thereby preventing MASH-related HCC progression [36, 37]. Despite the promise of these novel agents for preventing HCC, clinical data remains limited, and prospective clinical studies are required.

Generic Chemoprevention for HCC

Anti-inflammatory Drugs

Chronic hepatic inflammation is a well-established driver of hepatocarcinogenesis; therefore, anti-inflammatory therapies may be effective strategies for HCC chemoprevention. Preclinical and clinical studies have suggested that aspirin use is associated with reduced risk of development and recurrence of several cancer types including HCC [38, 39]. An in vitro experiment showed that aspirin-induced ferroptosis through inhibited NF-κB p65-activated SLC7A11 transcription [40] and HCC cell proliferation via inducing cell cycle arrest and apoptosis [41]. As shown in multiple systematic reviews and meta-analyses, evidence is accumulating that aspirin, but not other non-steroidal anti-inflammatory drugs (NSAIDs), reduces the risk of developing HCC [42, 43••, 44]. Cyclooxygenase (COX)-2 promotes HCC initiation and progression through suppression of tumor suppressor genes, activation of oncogenic pathways, and impairment of antitumor immunity via various mechanisms that involve tet methylcytosine dioxygenase 1 (TET1), long non-coding RNA HULC and immunosuppressive cell populations such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) [45, 46]. Hepatic translocation of intestinal lipoteichoic and deoxycholic acids enhances COX-2-mediated suppression of antitumor immunity in a mouse model of obesity/MASLD-related HCC [47]. An in vitro experiment showed that COX-2 formed a regulatory loop with YAP to promote the proliferation and tumorigenesis of HCC [48]. A phase III trial of another COX-2 inhibitor, celecoxib, with or without metformin therapy for tertiary prevention in patients who have undergone curative HCC resection, is currently underway (NCT03184493). However, in the clinical setting, patients with cirrhosis are often complicated by thrombocytopenia and portal hypertension and are at higher risk for both HCC development and gastrointestinal bleeding.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) have been rapidly incorporated into the HCC treatment algorithm as a frontline treatment [49]. Recent early-phase clinical trials have shown promising antitumor efficacy of ICI-based regimens as neo/adjuvant therapies along with surgical treatment. In a study of atezolizumab plus bevacizumab versus active surveillance as adjuvant therapy in patients with HCC at high risk of recurrence after surgical resection or ablation, combination therapy showed that improvement in recurrence-free survival, meeting the primary end point of

the IMbrave050 study (NCT04102098) [50]. Cemiplimab (anti-programmed death receptor-1 (PD-1) antibody) as a neoadjuvant therapy before surgical resection achieved a tumor necrosis rate of 70% [51]. Nivolumab (anti-PD-1 antibody) with or without ipilimumab (anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) antibody) as neoadjuvant plus adjuvant therapy achieved an objective response rate of 30% [52]. In a recent systematic review and meta-analysis, Zhao et al. identified that neoadjuvant ICIs were well-tolerated in patients with resectable HCC and conferred therapeutic benefits [53].

Statins

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are primarily used for the primary and secondary prevention of cardiovascular diseases by inhibiting cholesterol biosynthesis. In addition, statins are known to have antineoplastic properties through antiproliferative, proapoptotic, antiangiogenic, immunomodulatory, and anti-infective effects [54, 55]. Cancer cells depend on the mevalonate metabolic pathway for growth and survival and HMG-CoA reductase is the rate-limiting enzyme in the pathway. Therefore, cancer cells may be susceptible to statin therapies that inhibit HMG-CoA reductase [56, 57]. Experimental studies have shown these effects multifaced as follow; statins inhibit oncogenesis drivers such as Myc, Akt, Rho-dependent kinase, NF-κB, tumor necrosis factor (TNF)–mediated interleukin (IL)6 production, the Hippo pathway, and extracellularsignal–regulated kinase 1/2 (ERK1/2) [58]. In addition, statins reduce liver fibrosis by inhibiting hepatic stellate cell activation via nitric oxide synthase and induction of peroxisome proliferator-activated receptors (PPARs) in diet/chemical-induced rodent models [59]. In addition to the accumulation of preclinical evidence, the chemopreventive efficacy of statins has been clarified in clinical settings. Although the existence of marked heterogeneity in the study population (e.g., etiology) and confounding factors, several meta-analyses, and nationwide cohort studies reproduced the trend that statin use is associated with reduced risk of HCC development by 42–48% compared with non-statin users [43••, 60, 61]. A phase II trial for verifying the chemopreventive effects of atorvastatin on HCC is also currently underway (TORCH; NCT05028829).

Antidiabetic Therapies

Type 2 diabetes is widely and clinically recognized as a predisposing factor for HCC, which approximately doubles the risk, suggesting that antidiabetic therapies may reduce the risk of HCC [62]. Aside from GLP-1 inhibitors which are currently undergoing evaluation in MASH, metformin, a traditional first-line pharmacological treatment for type 2 diabetes is well known to exert anticancer effects against HCC in experimental rodent models through upregulating hippo signaling pathway, AMPK-mediated inhibition of the Shh pathway or NF-κB signaling [63, 64]. Long-term metformin use may improve clinical outcomes in diabetic patients with MASH or post-cured HCV and bridging fibrosis or compensated cirrhosis [65]. Several meta-analyses showed that metformin use was associated with lowered HCC risk and all-cause mortality. However, in a recent meta-analysis by Zeng and colleagues, metformin use was not associated with reduced overall risk of HCC (HR, 0.57; 95% CI, 0.31–1.06) [43••, 65, 66]. One of the reasons why the discordant results between meta-analysis might be derived from the inability to rule out imbalances in baseline characteristics between study groups in some of the previous meta-analyses.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) also show a reduction in HCC development by inhibiting adenosine triphosphate-generating system [67]. From national database from Taiwan (31,215 patients received SGLT2i) showed that the overall HRs showed a significantly lower risk of HCC in SGLT2i users in comparison to a reference group of beta-blocker users with an adjusted HR of 0.27 (95% CI, 0.21–0.34) in patients with HBV/HCV infection and diabetes [68]. A territory-wide cohort study in Hong Kong showed SGLT2i use lowered the risk of incident HCC (HR, 0.54; 95% CI, 0.33–0.88) [69]. A national Surveillance, Epidemiology and End Results (SEER)-Medicare-linked data in the USA (3,185 patients) showed SGLT2i initiation was associated with significantly lower mortality risk after adjusting for potential confounders (HR, 0.68; 95% CI, 0.54–0.86) with a stronger association for a longer duration of use (HR, 0.60; 95% CI, 0.41–0.88) [70]. A nationwide study from Taiwan showed that dipeptidyl peptidase 4 inhibitor (DPP4i) users had a significantly lower risk of HCC, especially long-term its use >1.49 years also had significantly lower risks of HCC compared to DPP4i nonusers [71]. A recent retrospective cohort study revealed that DPP-4i users showed a significant reduction in HCC risk (adjusted HRs 0.53; 95% CI, 0.44–0.65) in type 2 diabetes patients with chronic HBV infection [72].

Molecular Targeted Agents

In rodent models, it has been shown that activation of epidermal growth factor receptor (EGFR) signaling in hepatic stellate cells and macrophages promoted HCC development [73]. Erlotinib, a small molecule EGFR inhibitor, reversed a high-risk liver transcriptome pattern and suppressed HCC development in rodent models of fibrosis-driven carcinogenesis [74]. Based on these animal studies, a phase I HCC chemoprevention trial was initiated using transcriptome signature as a companion biomarker (NCT02273362). In

addition, a phase II trial to evaluate the HCC chemopreventive effects of erlotinib is going (NCT04172779).

The phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is involved in cell survival, and AKT has been identified as a key HCC risk driver by a human hepatic transcriptome meta-analysis, therefore, this pathway is one of the candidates for HCC chemoprevention target [75]. In chemical/obesity-driven HCC animal models, sirolimus (rapamycin) reduced HCC development risks through inhibiting IL-6/STAT3 axis [76]. In the clinical setting, mTOR inhibitors, such as sirolimus and everolimus, are widely used after liver transplantation to exert their immunosuppressive effects. Sirolimus use for ≥3 months after liver transplantation for HCC independently benefited the most with regard to overall survival, disease-free survival, and HCC recurrence [77]. A systematic review and meta-analysis to investigate the potential survival benefits of mTOR inhibitors for liver transplantation recipients with HCC showed that the 1-, 2-, and 3-year overall survival and recurrence-free survival were improved with a lower risk of renal toxicity [78].

Dietary and Nutritional Agents

Coffee consumption is known to lower hepatic inflammation, liver stiffness, and incidence of HCC via inhibition of PI3K/AKT/mTOR pathway [79]. Although both caffeinated and decaffeinated coffee was associated with a reduction in HCC risk, caffeinated coffee and higher intake (>3 cups/day) have stronger associations with a reduction of HCC [80]. Based on the reproducible inverse association that several analyses [81, 82], the European Association for the Study of the Liver (EASL) practice guideline and American Association for the Study of Liver Diseases (AASLD) practice guidelines encourage coffee consumption [83, 84].

Branched-chain amino acids (BCAA) supplementation is widely used in cirrhotic patients with improvement of event-free survival and overall survival [85]. BCAA enhances mTOR signaling-mediated cellular senescence and reduces liver fibrosis and HCC [86]. In obese mouse models, BCAA increased the expression of PPAR, p21, and p27, whereas suppresses IL6, IL1β, IL18, and TNF expression, resulting reduction of inflammation and spontaneous hepatic carcinogenesis [87]. In a Japanese multicenter prospective observational study, BCAA supplementation was associated with less frequent HCC development and death [88]. A systemic review with meta-analysis with a short follow-up period (1–3 years) showed that no significant effect was found in occurrence rates of HCC; therefore, long-term BCAA supplementation administration and long-term observation is needed [85].

Vitamin D might help in cancer management by regulating cell proliferation and differentiation, as well as exerting anti-inflammatory, and antifibrotic effects [89, 90]. 1α,25-Dihydroxyvitamin D3 (calcitriol) supplementation attenuated HCC aggressive behavior by IL-6 expression reduction, suppressing epithelial-mesenchymal transition in vitro [91]. Vitamin D3 upregulated protein 1 (VDUP1) suppresses TNF and NF-κB signalling and protects mice from chemical-induced hepatocarcinogenesis [92]. 1,25-(OH)2D3, the active form of vitamin D, is involved in anti-fibrosis and partially improves liver function [93]. Administration of 1,25-(OH)2D3 exerted the anti-apoptotic effect via decrement of caspase-3 and MPST expression and abolished the MASLD changes in 4 weeks of high-fat diet (HFD)–fed rats, and markedly attenuated the changes in 12-week HFD-fed [94]. Lower 25-OH vitamin D levels are associated with the development of HCC [95]. A phase IV trial of vitamin D3 is planned to prevent HCC in patients with chronic hepatitis B receiving NA treatment (VDHCC trial; NCT02779465).

HCC Chemoprevention Recommendation in Academic Society Guidelines (AASLD, EASL, and APASL)

Based on the evidence previously described, several academic society guidelines including AASLD, EASL, and the Asian Pacific Association for the Study of the Liver (APASL), recommend HCC chemoprevention [83, 84, 96]. Vaccination for HBV infection and antiviral therapies for HCV and HBV infection are recommended in these guidelines [83, 84, 96]. Coffee consumption is recommended in AASLD and EASL practice guidelines [83, 84]. Whereas, solely usage of statins, aspirin, or metformin are not recommended in HCC chemoprevention in AASLD practice guideline [84].

Conclusion

With decreasing viral hepatitis-related HCC and increasing carcinogenesis based on MAFLD/MASH, half of the population is suffering from metabolic disorders. Available HCC chemopreventive agents are increasingly important to effectively control the HCC burden and mortality. Although experimental and retrospective studies have shown that commonly used drugs and/or lifestyle interventions are useful chemopreventive agents, no convincing evaluations have been made owing to the heterogeneity among studies and conflicting observations. The widespread use of safe and potent generic HCC chemopreventive agents could contribute to breakthroughs in improving the prognosis of patients with HCC.

Data availability All articles in this manuscript are available from the Medline and Embase.

Author Contributions HS drafted the manuscript. CHN, DQH, and TK critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

Declarations

Ethics Approval This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests Cheng Han Ng has serves as a consultant for the Boxer Capital. Takumi Kawaguchi received lecture fee from the Janssen Pharmaceutical K.K., Taisho Pharmaceutical Co., Ltd., Kowa Company, Ltd., Otsuka Pharmaceutical Co., Ltd., Eisai Co., Ltd., ASKA Pharmaceutical Co., Ltd., AbbVie GK., and EA Pharma Co., Ltd. Daniel Q. Huang has served as an advisory board member for Eisai and receives funding support from the Singapore Ministry of Health's National Medical Research Council under its NMRC Research Training Fellowship (MOH-000595-01). The rest of the authors have no conflicts of interest to declare.

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- • Of importance
- •• Of major importance

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