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Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine

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Summary

Chronic fibrotic liver disease caused by viral or metabolic etiologies is a high-risk condition for developing hepatocellular carcinoma (HCC). Even after complete HCC tumor resection or ablation, the carcinogenic tissue microenvironment in the remnant liver can give rise to recurrent de novo HCC tumors, which progress into incurable, advanced-stage disease in the majority of patients. Thus, early detection and prevention of HCC development is, in principle, the most impactful strategy to improve patient prognosis. However, practice guideline-recommended "one-size-fits-all" HCC screening for early tumor detection is utilized in less than 20% of the target population, and performance of screening modalities, i.e., ultrasound and alpha-fetoprotein is suboptimal. Furthermore, optimal screening strategies for emerging at-risk patient populations such as chronic hepatitis C after viral cure and non-cirrhotic non-alcoholic fatty liver disease remain controversial. New HCC biomarkers and imaging modalities may improve sensitivity and specificity of HCC detection. Clinical and molecular HCC risk scores will enable precise HCC risk prediction followed by tailored HCC screening for individual patients to maximize its cost-effectiveness and optimize allocation of limited medical resources. Several etiology-specific and generic HCC chemoprevention strategies are evolving. Epidemiological and experimental studies have identified candidate chemoprevention targets and therapies, including statins, anti-diabetic drugs, and selective molecular targeted agents, although their clinical testing has been limited by the lengthy process of cancer development that requires long-term, costly studies. Individual HCC risk prediction is expected to overcome the challenge by enabling personalized chemoprevention targeting high-risk patients to achieve precision HCC prevention and substantially improve the dismal prognosis of HCC.

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Introduction

Liver cancer, predominantly hepatocellular carcinoma (HCC) arising in the context of cirrhosis, is the second most lethal cancer worldwide with persistently increasing mortality in Europe, North/South America, and Africa in contrast to the decreasing trend in East Asia.[1-3] Cirrhosis is estimated to cause over 1.2 million deaths (2% of global incidences) in 2013, increased by 47% since 1990.[4] Cirrhosis and HCC are the major life-limiting consequences of progressive fibrotic liver diseases mainly caused by viral, i.e., hepatitis B virus (HBV) and hepatitis C virus (HCV), and metabolic, i.e., alcohol abuse and non-alcoholic fatty liver disease (NAFLD), etiologies.[5] In the U.S., HCC is the fastest rising cause of cancer-related deaths; HCC mortality rate has been increasing across almost all counties over the past three decades particularly in HCV-infected white men aged 55 to 64 years old and Hispanics affected with NAFLD in the Texas region.[6-8] In a model-based simulation forecasting until 2030, HCC incidence rate will continue increasing in the 1950-1959 birth cohorts, Hispanic men, and black women.[9]

HCC is highly refractory to therapeutic interventions. Even after surgical resection or ablation, 70% of patients experience tumor recurrence within 5 years,[10] and once the tumors progress into advanced stage, currently available medical therapies yield only marginal survival benefit and are not cost-effective.[11] Furthermore, the highly complex and heterogeneous genetic aberrations in HCC tumors hamper identification of therapeutic strategies despite the emerging breadth of molecular targeted anticancer agents.[12] Thus, it seems sensible to consider preventing HCC development and progression in patients at risk rather than treating advanced-stage disease with limited health benefit. However, despite the clinical unequivocal predisposing factors for liver disease progression toward cirrhosis and HCC, cancer prevention in this setting remains a daunting task as evidenced by the still dismal HCC prognosis (5-year survival rate <15%[13]). In this review, we overview limitations of the currently available measures of HCC prevention and opportunities to develop individual cancer risk-based tailored preventive strategies in the era of precision medicine.

HCC prevention strategies

Cancer prevention encompasses a wide variety of medical interventions. Primary prevention focuses on preventing exposure to cancer-predisposing factors or eliminating them at an early stage by vaccination, lifestyle modification, or environmental interventions in an etiology specific manner. Secondary or tertiary prevention covers early detection and chemoprevention of HCC occurrence or recurrence, respectively, in patients already exposed to etiological agents.[14] Tertiary prevention after radical HCC treatment aims to reduce either recurrence arisen from dissemination of residual tumor cells (disseminative recurrence) or de novo carcinogenesis in remnant fibrotic/cirrhotic livers (de novo recurrence).

Cancer chemoprevention discovery and development has been challenging and there has been scarce progress over the past decades due to elusive mechanisms of human carcinogenesis.[15] It is not feasible to verify mechanisms of cancer initiation in patients that are inferred from pre-clinical studies, because it is ethically and logistically difficult to monitor cancer-free individuals with molecular assessment for long durations until a cancer develops. To overcome this challenge, a “reverse-engineering” approach has been proposed, in which clinically relevant targets are first identified in clinical cohorts with completed long-term follow-up, and subsequently validated in experimental systems.[10] Another factor limiting chemoprevention development is the suboptimal animal models that may not resemble human disease, leading to false discovery of chemoprevention targets and biomarkers; these approaches may be improved by more sophisticated modeling strategies.[16,17] Relatively difficult access to liver biospecimens is another limiting factor, contrasting with easier access to specimens from other tissues (for example skin, cervix, and gastrointestinal tract cancers) that have enabled more advanced chemoprevention development.[18] Utilization of liquid biopsy may resolve the issue of sampling, although it is still uncertain whether any informative biomolecules are present in the circulation.[19]

A major difficulty is the design and conduct of chemoprevention clinical trials, which are generally very resource-intensive. Chemoprevention trials typically require large sample sizes and long observation periods for several reasons: suboptimal potency of chemoprevention agents that meet high safety requirements, insufficient enrichment of high-risk patient populations, and lack of reliable surrogate endpoints of definitive long-term clinical outcomes.[18] For instance, two large HCC chemoprevention trials, enrolling patients with advanced fibrosis in Europe and the U.S., failed to demonstrate an effect of maintenance low-dose interferon on HCC incidence in the whole study subjects.[20,21] However, in subgroup analyses of patents with more advanced disease (i.e., cirrhosis or portal hypertension), HCC incidence was reduced, supporting the concept of enrichment by identifying high-risk patients in chemoprevention trials to better capture their effects with smaller sample sizes compared to conventional “all-comer” enrollment. Interestingly, in retrospective and prospective assessments of interferon and other agents in HCV-infected patients, an HCC preventive effect started to emerge approximately 2 years after enrollment.[20-23] This observation may indicate that the duration of the latent period in order for subclinical neoplastic clones to become clinically recognizable needs to be accounted for when designing HCC chemoprevention trials.[24]

Regular biannual HCC screening is recommended based on current HCC guidelines,[25] but its implementation in clinical practice is far from satisfactory, as detailed in the next section. Furthermore, there is no established HCC chemoprevention therapy to date. Various precipitants of chronic liver diseases, for example hepatitis virus infection, hepatic inflammation and fibrosis, and metabolic syndrome, may serve as chemoprevention targets. However, the obstacles reviewed above hamper the discovery of such chemoprevention targets and biomarkers. In addition, these challenges obscure the optimal timing and duration of chemopreventive interventions during the lengthy natural history of fibrotic liver disease progression towards HCC, which typically lasts for decades (Figure 1). In addition, clinical validation of the findings could easily extend beyond the scope and timeframe of

typical research studies and clinical trials, and may be less appealing for the pharmaceutical industry engagement, who may favor a faster return on investment.[26]

HCC screening

Screening is a vital component of cancer prevention. Current practice guidelines recommend regular HCC screening by biannual ultrasound with or without α-fetoprotein (AFP) in clinically identifiable population with HCC risk exceeding a certain threshold.[25] A series of cohort studies and model-based simulation indicate that HCC screening is cost-effective and associated with improved early tumor detection, curative treatment rates, and survival, when it is available to more than 34% of patients at risk.[27-31] However, the real-world utilization rate is below 20% due to multiple patient- and provider-related factors.[32] Population-based interventions such as mailed outreach could improve the utilization rate to up to 50%.[33] With the currently available resources, the vast size of the target population is another obstacle given that cirrhosis is estimated to affect 1-2% of global population and cause over 1.2 million (and 2% of total) deaths in 2013, increased by 47% since 1990.[4] The magnitude of HCC risk for emerging populations, i.e., patients with non-cirrhotic NAFLD as well as after HCV cure, is yet to be determined, and screening strategies for these populations have not been established.[32] These issues highlight the limitation of the current one-size-fits-all approach, which assumes uniform HCC risk across all patients with the same clinical condition (e.g., HCV cirrhosis) and results in often harmful over-or under-estimation of HCC risk for each patient. [34,35] Thus, prediction of individual HCC risk is critical to implementing effective and feasible HCC screening.

Clinical HCC risk scores

Combination of readily available clinical symptoms and laboratory variables have been evaluated to develop HCC risk-predictive scores, although their performance is somewhat limited and yet to be adopted in clinical practice (Table 1).[32] Semi-quantitative histological fibrosis stage has been associated with future HCC risk, although sampling variability in liver biopsy hampers its robust determination.[36] Quantification of collagen proportionate area may enable more reliable estimation of HCC risk.[37-39] Hemodynamic measurement of portal hypertension, hepatic venous pressure gradient (HVPG), has been associated with HCC risk.[40] Liver stiffness measurement (LSM) by ultrasound- or magnetic resonance imaging (MRI)-based elastography, by presumably capturing fibrotic and inflammatory tissue contents, has been associated with increased risk of HCC mostly in viral hepatitis, including cured HCV infection.[41-44] Smoking has been associated with increased HCC risk (relative risk [RR], 1.51) in a meta-analysis of 38 cohort and 58 case-control studies,[45] and incorporated in several HCC risk scores. The population attributable fraction (PAF) of smoking for HCC was 9% in the U.S.[46] Passive smoking was also associated with HCC development (odds ratio [OR] at home, 4.86; OR at work, 2.44).[47] Association of metabolic HCC risk factors is affected by smoking (interaction p=0.004).[48] Alcohol exposure may also enhance risk, as suggested by characteristic somatic DNA aberrations.[12]

Molecular HCC risk scores

Molecular biomarkers of HCC risk have been actively explored as overviewed below. Some of them were combined with clinical prognostic factors to develop integrative HCC risk scores to complement clinical scoring systems to refine HCC risk prediction (Table 2). Several germline single nucleotide polymorphisms (SNPs) have been identified as indicators of elevated HCC risk with odds ratios of around 1.5 in prospective and retrospective cohorts: *EGF* (in HBV- or HCV-infected patients), *MPO*, *DEPDC5*, and *MICA* (in HCV-infected patients), region in 1p36.22, *STAT4*, and *HLA-DQ* (in HBV-infected patients), and *PNPLA3* and *TM6SF2* (in alcoholic liver disease and NAFLD patients).[49-57] Shorter telomeres and germline mutations in *TERT* gene were observed in NAFLD-related HCC patients.[58]A SNP in *MBOAT7* gene was linked to HCC in non-cirrhotic NAFLD patients.[59]A recent genome-wide association study identified a SNP in *TLL1* gene associated with HCC risk after HCV cure.[60] A 7-gene SNP panel (Cirrhosis Risk Score) was associated with fibrosis progression in HCV-infected individuals.[61] Liver tissue-derived transcriptome signatures have been associated with HCC risk,. For example, a 32-gene signature in fibrotic liver has been validated as a pan-etiology HCC risk indicator in patients with chronic hepatitis B/C, alcohol abuse, and NASH.[10] Abundance of serum/plasma proteins such as insulin-like growth factor 1 (IGF1) and osteopontin (OPN/*SPP1*) has also been associated with HCC risk in cirrhosis.[62,63] The N-glycosylation pattern of total serum protein (GlycoHCCRiskScore) has identified a subset of compensated cirrhosis patients at HCC risk.[64] Body fluid (e.g., blood, urine)-based biomarkers will enable less-invasive and more flexible prognostic prediction given the decrease of liver biopsies in clinical practice, although tissue acquisition will help ensure their relevance to liver disease at least during the process of establishing such assays. Scientifically rigorous biomarker validation following the predefined phases of biomarker development will help ensure clinical validity of the biomarkers.[65] These biomarkers are promising candidates for clinical translation, although assay development and implementation, regulatory approval, and reimbursement are challenging obstacles.[66]

HCC screening modalities

Abdominal ultrasound and serum AFP have been widely used as the main HCC screening modalities. The suggested minimal sensitivity for an HCC screening test to be cost-effective is 42% assuming a screening access rate of 34%.[31] The sensitivity of ultrasound and AFP for detection of early-stage HCC tumor exceeds the threshold (approximately 60%), although it is still considered suboptimal.[67] Operator dependency and patient-related factors such as obesity are the major sources of variation in ultrasound sensitivity, which can be as low as 32%.[68-70] Serum AFP levels can non-specifically rise due to chronic hepatitis-related liver regeneration, which raises concern about its clinical utility as a screening modality.[71] New serum/plasma biomarkers have been explored as possible replacements for AFP, and some of them are awaiting larger clinical validation for further development and deployment (Table 3). Integrative scores combining serum biomarkers with clinical variables have been proposed to improve diagnostic performance.[72,73] In addition, identification of specific clinical contexts (e.g., HCV cirrhosis with normal serum alanine aminotransferase [ALT] level) has been suggested as a strategy to achieve improved performance of AFP.[74]

Computed tomography (CT) and MRI may serve as alternatives to ultrasound with better performance, and are free from inter-operator variability. Indeed, CT and MRI can double the lesion-based sensitivity for small HCC tumors (up to 86%), although the high costs and irradiation (for CT) preclude their use as practical widespread options for HCC screening.[75-77] An abbreviated contrast-enhanced MRI (AMRI) has been developed as an option that is specifically designed for regular HCC screening at half the cost of a full MRI, while maintaining a high sensitivity (81%) and specificity (96%).[78]

Individual risk-based tailored HCC screening

The heterogeneous individual HCC risk among the patients captured by clinical and/or molecular scores will enable rational allocation of the limited HCC screening resources to the high-risk patients who most need the intervention, and avoid ineffective and wasteful distribution of the demanding screening efforts to low-risk individuals. The currently recommended HCC screening interval of 6 months was determined based on estimated tumor volume doubling time.[79,80] Uniformly longer or shorter intervals did not improve HCC detection.[81,82] However, given that high-risk subjects likely develop HCC at a high frequency and in a multicentric manner, altering HCC screening intensity according to estimated individual HCC risk may enable more efficient early tumor detection (Figure 2).[34] Such a personalized risk-based cancer screening strategy has been successfully implemented in other tumor types such as colorectal and breast cancers.[83,84] In addition, education programs targeting high-risk communities with specific HCC risks based on etiology, for example African-born immigrants in New York City with a high prevalence of HBV infection, may efficiently improve uptake of high-risk individuals to HCC screening.[85]

The net benefit of HCC screening is determined as a function of multiple factors, including screening interval, performance of screening modalities, HCC incidence in the target population, and screening access rate, which has been evaluated by model-based cost-effectiveness analysis. A recent comprehensive assessment of individual risk-based tailored HCC screening strategies indeed revealed superior cost-effectiveness of personalized screening compared to the currently recommended uniform biannual screening of all patients.[86] For instance, exclusive screening of high-risk subjects using AMRI is a robustly cost-effective strategy. More frequent screening, i.e., four times per year, is cost-effective when annual HCC incidence is greater than 3%. Although these results need to be clinically verified, testing of such strategies is now technically feasible with the HCC risk tests and new screening modalities already available in the clinical setting.

Etiology-specific HCC prevention

Hepatitis B

Chronic HBV infection has been the dominant etiology in Southeast Asia and sub-Saharan Africa, although the incidence of HBV-induced HCC is declining.[87] Co-infection with hepatitis delta virus, food contamination with aflatoxin B1, microcystins, and metabolic risk factors facilitate fibrosis and/or HCC development.[48,88-90] HBV DNA integration into the host genome is a unique feature that may lead to direct *cis*/*trans* activation of oncogenic signals and carcinogenesis without requiring a fibrotic tissue microenvironment.[91] Serum

HBV DNA levels, certain HBV strains (e.g., genotype C in Asian and genotype F in Alaskan), and mutations in the HBV genome (e.g., pre-Core and basal core promoter regions) are associated with increased HCC risk.[91-94]

Universal HBV vaccination is effective as a primary HCC prevention measure by reducing neonatal HBV vertical transmission.[95] In a 20-year follow-up of a national vaccination program, the annual HCC incidence was significantly lower among vaccinated children, aged 6-19 years, compared with unvaccinated cohorts (RR, 0.31).[96] Antiviral therapies have been evaluated as secondary prevention. In a meta-analysis of 12 clinical trials, involving 2,082 patients, interferon-based regimens decreased cirrhosis and HCC development (RRs, 0.65 and 0.59, respectively).[97] Suppression of HBV replication by nucleot(s)ide analogs (NAs) reduced HCC incidence from 7.4% to 3.9% (hazard ratio [HR], 0.49) in a prospective trial enrolling 651 Taiwanese patients, and from 13.3% to 1.1% in a retrospective survey of 2,795 Japanese patients.[98-100] Retrospective studies conducted mainly in Asia reported HCC risk reduction with newer generation first-line NAs, entecavir and tenofovir, by approximately 30% in cirrhotic and 80% in non-cirrhotic patients, although evidence in Western patients is still limited.[101-103] A cohort study of 330 Taiwanese patients suggested that interferon may better prevent HCC development than NAs.[104] In the setting of tertiary prevention (i.e., adjuvant therapy after curative resection or ablation of primary HCC tumors), a meta-analysis of 13 trials with 6,350 patients reported that use of NAs is associated with lower recurrence-free survival (HR, 0.66),[105] which was confirmed in a more recent clinical trial (HR, 0.65).[106] Of note, the HCC incidence after achieving virologic response with HBV DNA level consistently < 2,000 IU/mL to NAs was significantly higher than the HCC incidence in inactive chronic hepatitis B, indicating residual cancer risk not eliminated by current antiviral therapies.[107] Even a low-level viremia (<2,000 IU/mL) during entecavir treatment increases HCC risk (HR, 1.98), especially in patients with cirrhosis (HR, 2.20) compared to patients with undetectable HBV DNA.[108]

Hepatitis C

Globally, 71 million individuals are affected with viremic HCV infection (prevalence, 1%).[109] The incidence and mortality of HCV-related HCC keep rising in specific subpopulations such as the 1945-65 birth cohort (baby boomers) and veterans in the U.S.[110] HCV clearance by antiviral therapies with a sustained virologic response (SVR) significantly reduces HCC incidence.[111] However, interferon-based regimens had no impact on the incidence at a population level due to low treatment uptake (1-3% annually) and a modest SVR rate (50%) in a regional study in Australia.[112] Despite the improved SVR rate with direct-acting antivirals (DAAs), HCC incidence is predicted to further increase until 2035 unless the treatment uptake rate is increased more than five-fold by 2018.[113,114] HCV elimination is hampered by the high DAA costs and lack of comprehensive HCV screening linked to treatment programs.[115] Undiagnosed HCV infection is estimated to represent 50% or more of the whole infected pool. In addition, high-risk populations such as inmates and injection drug users contribute to the 3-4 million new infections each year, and serves as a reservoir that maintains the pool of HCV-infected subjects via new and re-infection, and will lead to a sustained high disease burden in the next decade even in developed countries.[114,116,117]

Development of a prophylactic HCV vaccine as primary prevention has been challenging due to the high viral genetic variability, although there is promising progress.[118] New experimental models such as HCV-related hepacivirus-infected rats may facilitate vaccine development.[119] Targeting host genes/proteins such as viral entry factors may be an alternative or complementary strategy.[120] In cirrhotic patients, DAA treatment to prevent re-infection after transplantation is cost-effective according to disease severity.[121] HCV screening targeting high-risk populations is expected to boost uptake to antiviral treatment and subsequent HCC screening as needed.[122]

Secondary/tertiary chemoprevention could be achieved by antiviral therapies as suggested by retrospective studies consistently reporting reduction of annual HCC incidence from 1-8% to 0.07-1.2% by interferon-based SVR.[111] Recent trials have shown that DAAs are better-tolerated compared to interferon even in compensated and decompensated cirrhotic patients.[123,124] HCC incidence and recurrence rates after DAA-induced SVR are yet to be fully determined.[111] Recent large cohort studies reported a comparable magnitude of reduction in HCC incidence between interferon- and DAA-induced SVR (HR, 0.28-0.29).[124,125] Our understanding of post-SVR HCC risk drivers is still limited to several host factors, including advanced liver fibrosis, older age, accompanying metabolic diseases such as diabetes, persisting hepatic inflammation, and elevated AFP, and viral factors, including core protein variants and genotype 3.[111] A liver transcriptome signature may enable more precise post-SVR HCC risk prediction.[10,126] Clinical and experimental observations suggest there are DAA-specific modulations of host immunity and oncogenesis, for example reactivation of co-infected viruses, remission of follicular lymphoma, and rapidly restored function/differentiation of HCV-specific CD8+ T cells, memory T cells, and normalized NK cells.[111] A cell culture-based study reported restoration of p53 function and ER stress response by interferon, but not by DAA.[127] Further studies are needed to determine clinical utility and underlying mechanisms of action of DAAs as an HCC chemoprevention strategy.

Alcohol

Alcohol abuse remains a major and rising HCC etiology in several regions such as northern and central Europe, whereas alcohol consumption and HCC mortality are decreased in some countries such as France.[128] A meta-analysis of 19 cohort studies showed a dose-dependent increase of HCC risk (HR, 1.16).[129] Excessive alcohol drives hepatocarcinogenesis by increasing a mutagenic ethanol metabolite, acetaldehyde, oxidative stress, and DNA damage, and by generating a carcinogenic tissue microenvironment, which can synergize with viral hepatitis and metabolic syndrome.[130-132] HCC genome DNA sequencing has identified recurrent mutations in genes encoding alcohol metabolizing enzymes, e.g., *ADH1B*.[133] The magnitude of risk reduction by abstinence has not yet been established due to limited evidence. A meta-analysis of four cohort studies showed that abstinence reduced HCC risk by 6-7% annually, despite a large uncertainty in the estimate and more than two decades required to normalize the risk to the level of never drinkers when cirrhosis is present.[134-136]

NAFLD, obesity, and metabolic syndrome

One-fourth of the global population is affected by NAFLD, and among biopsied NAFLD patients, approximately 60% have non-alcoholic steatohepatitis (NASH), developing HCC

annually at a rate of 5.29 per 1,000 person-years.[137] Obesity, diabetes, and the metabolic syndrome are present in 51%, 23%, and 43% of NAFLD patients, respectively, suggesting highly heterogeneous pathogenesis across patients.[137] Obesity and type 2 diabetes with insulin resistance are independent risk factors of HCC. In 5.24 million individuals registered in the Clinical Practice Research Datalink, high body-mass index (BMI) was significantly associated with liver cancer risk (HR, 1.19 per BMI 5 kg/m^2).[138] In a meta-analysis of 13 case-control and 13 cohort studies, diabetes was associated with increased HCC risk (OR, 2.5 and HR, 2.5, respectively).[139] A more recent meta-analysis of 23 cohort studies reported a pooled RR of 2.0.[140] Metabolic risk factors also increase HCC risk in viral hepatitis patients.[48] The absence of established cirrhosis is more frequently associated with HCC in NAFLD compared to other etiologies such as HCV and alcohol abuse, which suggests NAFLD-specific mechanisms of carcinogenesis that are less dependent on hepatic fibrosis.[141] Dysregulated hepatic and circulating pro-inflammatory cytokines and adipokines, oxidative and endoplasmic reticulum stress, and changes in intestinal microbiota (dysbiosis) are likely associated with obesity-related hepatocarcinogenesis.[142-145] Bacterial metabolite (deoxycholic acid)-induced senescence-associated secretory phenotype (SASP)-mediated hepatic stellate cell activation that promotes tumors,[146] disruption of circadian rhythm,[147] depletion of anti-tumor CD4+ T-cells by linoleic acid from hepatocytes,[148] induction of metabolic inflammation-associated interleukin 17A (IL17A),[149] and prostaglandin E2 (PGE2)-mediated suppression of antitumor immunity by gut microbiota[150] are all potential mechanisms of NAFLD carcinogenesis. Clinically relevant animal models of NAFLD fibrosis and/or HCC will allow more reliable preclinical assessment of experimental therapies.[10,151-153]

Lifestyle intervention may serve as secondary prevention as suggested by observational studies. A meta-analysis of 19 studies, involving 1,290,045 individuals, reported that increased intake of vegetables, but not fruits, may reduce HCC risk (RR, 0.72).[154] In a prospective cohort of 428,584 subjects (HBV and HCV were positive in 15.7% and 2.6%, respectively), higher physical activity (metabolic equivalent tasks ≥ 7.5/hr) was associated with lower HCC risk (HR, 0.69).[155]

Statins

In experimental systems, statins elicit a variety of pleotropic anti-neoplastic, in addition to cholesterol-lowering, effects. Statins inhibit oncogenic pathways, including Myc,[156] Akt,[157,158] integrin and Rho-dependent kinase,[159] nuclear factor κB (NF-κB), and tumor necrosis factor (TNF)-mediated IL6 production,[160] and Hippo pathway effector TAZ, and extracellular signal–regulated kinase 1/2 (ERK1/2),[161] whereas adenosine monophosphate-activated protein kinase (AMPK) and p38/mitogen-activated protein kinase (MAPK) pathways are activated,.[162,163] and p53-dependent apoptosis is induced[164] (Figure 3). Statins also limit fibrogenic hepatic stellate cell activation via nitric oxide synthase,[165] paracrine signals from hepatocytes[166] and endothelial cells,[167] induction of sterol regulatory element-binding protein 1 (SREBP-1) and peroxisome proliferator-activated receptor (PPAR)-γ,[168] and reduce portal hypertension via non-canonical hedgehog signaling.[169]

A dose-dependent reduction of HCC incidence was observed in Korean diabetic patients (ORs, 0.32 to 0.53)[170] as well as Taiwanese patients infected with HBV (HR, 0.34 to 0.66) and HCV (HR, 0.33 to 0.66).[171,172] In 7,248 HCV-infected persons in the U.S. ERCHIVES database, statin use was associated with less frequent progression to cirrhosis (HR, 0.6) and HCC (HR, 0.51).[173] Fibrosis progression was reduced in the HALT-C cohort,[174] and decompensation, mortality, and HCC were reduced in Taiwanese patients with HBV-, HCV-, and alcohol-related cirrhosis (HRs, 0.39, 0.46, and 0.52, respectively).[175]. In 18,080 non-cirrhotic NAFLD patients, even higher HCC suppressive effects were suggested (HR, 0.29).[176] However, the protective effect was not observed in meta-analyses of 27 prospective studies involving 175,000 individuals in multiple cancer types including HCC.[177,178] Differential effects between statins have also been suggested. In a systematic pair-wise comparison, fluvastatin was shown to be more effective in reducing HCC risk (RR, 0.55) compared to other statins.[179] Atorvastatin and fluvastatin were associated with more significant anti-fibrotic effects compared to lovastatin, pravastatin, rosuvastatin, and simvastatin.[173] Randomized clinical trials are currently ongoing to determine the role of statins in HCC chemoprevention (Table 4). Secondary preventive effect of simvastatin in patients with cirrhosis is being tested in a phase 2 trial, seeking for a change in AFP-L3% (NCT02968810). Atorvastatin is being evaluated for tertiary prevention after complete HCC resection or ablation (Statin for preventing HCC recurrence after curative treatment [SHOT] trial, NCT03024684).

Metformin

Given the elevated HCC risk in association with type 2 diabetes, anti-diabetic therapies may be rational HCC chemopreventive strategies. Metformin, a biguanide derivate, inhibits gluconeogenesis and improves peripheral tissue insulin sensitivity, and also elicits various anti-neoplastic effects. Metformin inhibits the mammalian target of rapamycin (mTOR) pathway via activation of AMPK and its upstream regulator, LKB1,[180] inhibits angiogenesis via suppression of hypoxia inducible factor 1 α (HIF1A) and vascular endothelial growth factor (VEGF),[181] blocking cell cycle by decreasing cyclin D1 expression,[182] suppresses cell survival-conferring NF-κB signaling by upregulating IκBα,[180] and induces apoptosis via p53-independent mechanism[183] and CCAAT/enhancer-binding protein δ (CEBPD)-induced autophagy[184] (Figure 3) Metformin suppresses progenitor/stem cell activation and reduces HCC burden in a rat model of cirrhosis-driven carcinogenesis, although the HCC preventive effect is observed only when metformin treatment is started before development of cirrhosis.[185]

A meta-analysis of 19 studies involving 550,882 diabetic subjects suggested that metformin use reduced HCC incidence (OR, 0.52) compared to non-users.[186] In exploratory subgroup analysis, metformin remained protective in patients with HBV/HCV infection (OR, 0.50), cirrhosis (OR, 0.49), and obesity (OR, 0.42). However, pooled results of two randomized controlled trials enrolling 8,798 patients found no significant difference in HCC risk according to metformin use (OR, 0.84; p=0.87). A phase 3 trial was initiated to evaluate secondary HCC chemopreventive effect of metformin in compensated HCV cirrhosis and insulin resistance in France, however the trial was terminated by the decision of investigator

(NCT02319200). A phase 2 trial is planned to evaluate change in liver fibrosis by metformin in HCV-infected patients with or without HIV (NCT02306070).

Fibroblast growth factor 21 (FGF21)

FGF21 is a pleiotropic hormone with various beneficial effects on glucose metabolism and sugar intake and preference, which can be regulated by a variety of mechanisms such as adipose-derived circulating miRNAs and genetic polymorphism (rs838133).[187-189] Lack of FGF21 accelerates the development of NASH and HCC in diabetic mice.[190] FGF21 inhibits mTOR and improve insulin resistance as a candidate treatment for type 2 diabetes.[191] 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 NASH progression in leptin-deficient ob/ob mice fed methionine-and choline-deficient (MCD) diet, suggesting that FGF21 may have a role in chemoprevention of NAFLD cirrhosis and/or HCC.[192]

Generic chemoprevention strategies

Anti-inflammatory and immunomodulatory therapies

Chronic hepatic inflammation is a well-established driver of hepatocarcinogenesis.[14] The HCC preventive effect of low-dose maintenance interferon therapy in HCV cirrhosis patients[20,21] is likely due to reduced hepatic inflammation, so called “biochemical response”, instead of viral clearance, although the drug's intolerability hampers its wider use.[24] Hepatic expression of an interferon-stimulated gene, retinoic acid-inducible gene-I (RIG-I), and downstream STAT1 signaling are suppressed in association with increased HCC risk, which possibly contributes to the higher HCC incidence in men compared to women.[193] There is somewhat conflicting epidemiological evidence about the HCC preventive effect of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin.[194] A pooled analysis of 10 U.S.-based cohorts (679 HCC cases among 1,084,133 individuals) suggested a protective effect of aspirin use (HR, 0.68).[195] Intestinal microbiota can induce innate immune signaling via Toll-like receptor 4 (TLR4) and support promotion of transformed neoplastic cells in the liver, which can be inhibited by gut sterilization in mice.[196] Overexpression of cyclooxygenase 2 (COX2) has been implicated in hepatocarcinogenesis in experimental models.[197] COX2 expression in hepatocytes is sufficient to induce HCC through inducing promoter hypermethylation by reducing tet methylcytosine dioxygenase 1 (TET1) expression, silencing tumor suppressor genes and activating oncogenic pathways.[198] Hepatic translocation of lipoteichoic and deoxycholic acids from gut microbiota enhances SASP of hepatic stellate cells to upregulate COX2-mediated PGE2 production via TLR2, and suppresses anti-tumor immunity in a mouse model of obesity/NAFLD-associated HCC.[150] lncRNA HULC stabilizes COX2 protein and promotes HCC cell growth.[199] Activated hepatic stellate cells enhance immunosuppressive cell populations, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) via COX2-PGE2-EP4 signaling.[200] Co-administration of a COX2 inhibitor, NS398, and simvastatin synergistically reduces proliferation and enhances apoptosis of HCC lines.[201]

In a clinical trial enrolling 232 patients who underwent curative HCC resection or ablation (i.e., tertiary prevention), a COX2 inhibitor, meloxicam, did not reduce overall and disease-free survival, although subgroup analyses suggested a possible chemopreventive effect in non-viral HCC.[202] A phase 3 trial of another COX2 inhibitor, celecoxib, with or without metformin for tertiary prevention in patients who underwent curative HCC resection is now recruiting participants (NCT03184493). In a phase 3 trial conducted in Korea, adjuvant immunotherapy with activated cytokine-induced killer (CIK) cells (a natural killer [NK] cell subset incubated with patient-derived peripheral blood mononuclear cells, IL2, and CD3 antibody) reduced recurrence-free survival (HR, 0.63) and overall death (0.21) in HCC patients treated with resection or ablation.[203] Thymalfasin, an immune modulator with pleiotropic activities towards T cells, NK cells, and dendritic cells, prolonged the time to HCC recurrence and survival as adjuvant therapy in HBV HCC patients in several pilot studies.[204] A multicenter clinical trial is planned to evaluate the effect of thymalfasin 2-year recurrence-free survival rate and tumor immune microenvironment in patients with curatively treated HBV HCC (NCT02281266).

Anti-fibrotic therapies

Anti-fibrotic therapies may serve as HCC chemoprevention by halting progression of fibrotic liver diseases toward carcinogenesis as suggested by experimental studies and recent clinical trials.[5] Hepatocyte apoptosis due to chronic injury leads to release of inflammation-mediating damage-associated molecular patterns (DAMPs), including TNF, IL6, IL1β, reactive oxygen species (ROS), and hedgehog ligands, and triggers fibrogenic hepatic stellate cell activation.[5] Apoptosis signal-regulating kinase 1 (ASK1) activates JNK and p38 MAPK in response to various cellular stresses. A phase 2 trial of ASK1 inhibitor, selonsertib (GS-4997), reduced liver fibrosis (> 1 stage) in 43% of NASH patients (NCT02466516). Cenicriviroc, a dual inhibitor of fibrosis-promoting CCR2/CCR5 reduced liver fibrosis in a phase 2 trial (CENTAUR trial),[205] and is now being tested in a follow-up phase 3 trial (AURORA, NCT03028740). PPARs, nuclear receptors for various fatty acids and derivatives, transcriptionally regulate metabolic processes to maintain energy homeostasis.[5] A dual PPARα/δ agonist, elafibranor, stopped fibrosis progression in non-cirrhotic NASH in a phase 2 trial,[206] and a follow-up phase 3 trial has been initiated (RESOLVE-IT, NCT02704403). Despite the promising results, the framework to assess anti-fibrotic therapies for clinically meaningful HCC chemopreventive effects is not yet established. Therapeutically amenable cancer risk biomarkers such as HCC risk gene signatures may serve as surrogate endpoints to complete clinical trials within a realistic time frame and with an achievable trial size. In addition, drug development pipelines are largely designed to assess either anti-fibrotic or anti-cancer effects but not both in the same trial, posing a logistical difficulty in justifying evaluation of agents from anti-fibrotics pipeline in the context of cancer.

Dietary and nutritional agents

In large-scale cohort or population-based studies, intake of unsaturated fat (HR, 0.71), n-3 polyunsaturated fatty acids (PUFAs) (HR, 0.64), eicosapentaenoic acid (EPA) (HR, 0.56), docosapentaenoic acid (DPA) (HR, 0.64), and docosahexaenoic acid (DHA) (HR, 0.56) are associated with lower HCC risk.[207,208] Omega-3 PUFAs, DHA, and EPA inhibit HCC

growth through inhibition of COX2 and GSK-3β-mediated β-catenin degradation.[209] PUFA-forming Fat-1 transgenic mouse is protected from diethylnitrosamine (DEN)-induced hepatocarcinogenesis with reduced TNF and COX2 expression.[210] Intake of white meat (chicken, turkey, and fish) was associated with a lower risk of HCC (HR, 0.52), whereas red meat (beef and pork) was associated with a higher risk (HR, 1.74) in the NIH-AARP cohort.[211]

Higher vitamin D, 25(OH)D, levels have been associated with reduced risk of HCC (RR, 0.51).[212] Low serum levels of 25(OH)D3 are associated with adverse outcomes, including HBV-related HCC (HR, 1.90).[213] Vitamin D3 up-regulated protein 1 (VDUP1) suppresses TNF and NF-κB signaling, and protects mice from DEN-induced hepatocarcinogenesis.[214] Expression of KLF4 sensitizes HCC cells to the anti-proliferative effects of 25(OH)D3.[215] p62/SQSTM1 promotes heterodimerization of the vitamin D receptor (VDR) with retinoid X receptor (RXR), and inhibits liver fibrosis and HCC.[216] A clinical trial of vitamin D3 is planned for prevention of HCC in chronic hepatitis B patients on nucleos(t)ide analog treatment (VDHCC trial, NCT02779465).

Excessive dietary iron and/or genetic polymorphisms such as *HFE* C282Y and H63D variants can induce oxidative DNA damage and inflammation that increase HCC risk independently or with other etiologies, including HCV and alcohol.[14] Liver-specific β-catenin knockout increases susceptibility to dietary iron and steatohepatitis, fibrosis, and HCC via AKT, ERK, and NF-κB pathways in mice, which is protected by N-Acetyl-L-(+)-cysteine (NAC).[217] Long-term phlebotomy can lower serum ALT level and incidence of HCV-related HCC.[218] An oral iron chelator, deferasirox, suppresses N-nitrosodiethylamine-induced murine liver carcinogenesis, and upregulates expression of hepcidin, transferrin receptor 1, and hypoxia inducible factor-1α, but its use in humans is limited by dose-limiting toxicities.[219]

Branched-chain amino acid (BCAA), used for hepatic encephalopathy, enhances mTOR signaling-mediated cellular senescence, and reduces liver fibrosis and HCC in DEN-treated rats.[220,221] In HCV-transgenic mice, BCAA reduces hepatic iron and reactive oxygen species with elevated hepcidin-25, which is also observed in HCV fibrosis patients.[222] In high-fat diet-fed atherogenic NASH mice, BCAA represses TGFβ1-stimulated pro-fibrogenic gene expression in hepatic stellate cells, protects hepatocytes from apoptosis, and reduces transformation of WB-F344 rat liver epithelial stem-like cells in an mTOR-dependent manner.[223] In C57BL/KsJ-*db/db* obese mice, BCAA increases expression of PPARγ, $p21^{CIP1}$, and $p27^{KIP1}$, suppresses expression of IL6, IL1β, IL18, and TNF, reduces inflammation in both liver and white adipose tissues, and inhibits spontaneous hepatic carcinogenesis.[224] In an observational study of 299 Japanese cirrhotic patients, BCAA supplementation was associated with less frequent HCC development (RR, 0.45).[225]

Coffee consumption (>2 cups/day) has been associated with reduced HCC risk in a meta-analysis of 18 cohorts, involving 2,905 HCC cases (RR, 0.71) and 8 case-control studies, involving 1,825 HCC cases (RR, 0.53).[226] Caffeinated and decaffeinated coffee was associated with 27% and 14% reduced HCC risk, respectively. The reduced HCC risk was partly attributed to reduced hepatocellular injury measured by IL6, ALT, aspartate

aminotransferase (AST), and γ-glutamyltransferase (GGT).[227,228] In a European prospective cohort including 201 HCC cases, tea intake was also associated with reduced HCC risk to a lesser extent (HR, 0.41) than coffee (HR, 0.28).[229] A caffeine analog, CGS 15943, inhibits HCC cell growth by targeting phosphoinositide 3-kinase (PI3K)/AKT pathway.[230] A phase 1 trial of caffeine is planned to assess its effect on serum vascular adhesion protein 1 (VAP-1) linked to hepatic inflammation and fibrosis in NASH[5] (NCT02098785).

Dietary phytochemicals such as curcumin (turmeric extract), resveratrol (polyphenol in grapes, red wine, and berries), silymarin (herbal flavonoid), and carotenoids have been evaluated as potential HCC chemoprevention agents by activating cytoprotective mechanisms such as Keap1/Nrf2 pathway in mostly carcinogen-induced rodent models, although supporting clinical evidence is lacking.[14] This class of compounds may need careful assessment given the recent classification of curcumin as pan-assay interference compound (PANIS) that likely shows false experimental activity.[231] Reduction of DNA damage biomarkers such as urine 8-hydroxydeoxyguanosine (8-OHdG) was observed for epigallocatechin gallate (EGCG, green tea polyphenol) and broccoli sprout in human, although their HCC-preventive effect is undetermined.[14] Glycyrrhizin, licorice root extract, reduced HCC incidence when ALT was normalized (HR, 0.39).[232] S-adenosylmethionine (SAMe), a ubiquitous major methyl donor, is reduced in rodent HCC models, and SAMe treatment suppresses HCC development.[14] In a phase 2 trial, 24 weeks of SAMe treatment in 87 HCV cirrhosis subjects did not alter AFP level and biomarkers of liver injury and oxidative stress.[233]

Molecular targeted therapies

PI3K/AKT/mTOR pathway is involved in cell cycle and proliferation, and is an appealing candidate HCC chemoprevention target.[14] AKT was indeed identified as a key HCC risk driver in a human liver transcriptome meta-analysis.[10] Retrospective studies and their meta-analysis suggest that mTOR inhibitor-based immunosuppression reduces post-transplant HCC recurrence,[234] but adverse effect of an mTOR inhibitor, sirolimus, including hepatic artery thrombosis and decreased patient and graft survival have been noted.[235] In animal models of chemical- and obesity-driven HCC development, sirolimus activates IL6/STAT3 and enhances HCC development, despite a transient reduction of steatosis.[236] To determine the benefit or harm of mTOR inhibition, sirolimus and everolimus, have been tested in prospective trials for prevention of post-transplantation HCC recurrence.[237] A phase 3 trial of sirolimus after transplantation enrolling 525 patients (viral hepatitis, 48%; alcoholic, 31%) did not improve recurrence-free survival beyond 5 years (HR, 0.84), although subgroup analyses suggested that patients with less advanced HCC tumors within Milan criteria or younger age may benefit from the therapy (SiLVER trial).[238]

Bioactive lipids, e.g., lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P), transmit cellular signals via G-protein-coupled receptors, and regulate cell survival, differentiation, proliferation, and migration.[239] In liver, expression of autotaxin (ATX), which converts lysophosphatidylcholine into LPA, increases HCV replication and is elevated in serum of HCV-infected patients in association with hepatic fibrosis and HCC.[240] In NAFLD, lipotoxic lipids, including LPA, are generated from excess dietary fat and sugars,

and induce phenotypic manifestation of NASH, fibrosis, and HCC in the Substrate Overload Lipotoxic Liver Injury (SOLLI) model of NAFLD pathogenesis.[142] In a transcriptome-based meta-analysis of 523 human fibrotic livers, LPA receptor 1 (LPAR1) signaling was identified as a pan-etiology HCC risk driver, and Rho kinase and Ras/MAPK/ERK, but not PI3K/AKT/mTOR signaling, were identified as its downstream effector pathways in cirrhotic livers.[10] Genetic knockout of ATX as well as pharmacological inhibition of ATX or LPAR1 ameliorates liver fibrosis and HCC in multiple rodent models,[10,241] reinforcing the LPA pathway as a promising chemoprevention target.

The renin-angiotensin system is involved in liver fibrosis and carcinogenesis.[14] Angiotensin II-mediated NF-kB activation promotes fibrogenic myofibroblast survival, which can be inhibited by an angiotensin-converting enzyme (ACE) inhibitor, captopril.[242] Hepatic stellate cell-targeted delivery of an angiotensin II type 1 receptor blocker (ARB), losartan, reduce liver fibrosis by inhibiting expression of NADPH oxidase and collagen type I.[243] An ARB, telmisartan, prevents hepatic carcinoma in CDAA-induced NASH fibrosis and HCC in rats.[244] In a retrospective single center clinical study, the use of ARBs was associated with longer time to HCC recurrence and increased survival after radiofrequency ablation.[245] An ACE inhibitor, perindopril, combined with vitamin K2 reduced HCC recurrence after curative therapy.[246] A clinical trial of perindopril in combination with BCAA reduced serum VEGF level and post-ablation HCC recurrence in 54 patients with insulin resistance.[247]

A synthetic acyclic retinoid (vitamin A analogue), peretinoin, inhibits multiple cellular signaling, including Wnt and platelet-derived growth factor (PDGF) pathways; it also induces differentiation and apoptosis of hepatic stem cells, and is assumed to suppresses neoplastic clones.[248-250] Peretinoin also inhibits HCV replication and infectious virus release in cultured cells.[251] In atherogenic high-fat diet-fed mice, peretinoin activates autophagy and suppresses NASH and HCC development.[252] In a phase 3 trial of peretinoin in 377 patients with curatively treated HCV-related HCC, a lower trend of HCC recurrence was observed for the entire study period (HR, 0.73), and also after 2 years of randomization (HR, 0.27).[23] A follow-up survey reported a longer overall survival of patients treated with higher dose of peretinoin compared to untreated controls (HR, 0.58; p=0.03).[253] Prospective trials in cured HBV-related HCC patients are ongoing.[248]

Several kinase inhibitors initially developed and evaluated for treatment of advanced-stage cancers have also been tested as adjuvant therapies in HCC. Activation of epidermal growth factor receptor (EGFR) signaling in hepatic stellate cells and macrophages promotes HCC development in rodent models.[254,255] A small molecule EGFR inhibitor, erlotinib, reversed a high-risk pattern of the liver transcriptome and suppressed HCC development in rodent models of fibrosis-driven carcinogenesis.[256] Based on these animal studies, a phase 1 HCC chemoprevention trial was initiated using the transcriptome signature as a companion biomarker (NCT02273362). A multi-kinase inhibitor, sorafenib, did not alter recurrence-free survival (HR, 0.94) after complete resection or ablation of primary HCC tumors in a phase 3 trial.[257]

The estrogen pathway is deemed to play a key role in the sex disparity in HCC risk.[258] In a meta-analysis of 87 studies, variations in estrogen receptor 1 (ESR1) gene were associated

with increased HCC risk.[259] In a case-control study of 234 female patients with treated HCC and 282 healthy controls, estrogen replacement (as menopause hormone therapy) was associated with a reduced risk of HCC (OR, 0.53, 0.32) and prolonged survival (HR 0.55).[260] Systemic delivery of mi-R101, down-regulated in HCC tissue, inhibits some of the candidate HCC chemoprevention targets, e.g., COX2 and Rho-GTPase, and suppresses tumorigenesis in mice.[261]

Conclusions

Clinical evaluation and implementation of HCC preventive strategies, encompassing HCC screening and chemopreventive intervention, will not be successful and/or feasible without individual risk-based tailored approaches. Comprehensive, multi-omics, and multi-cell type characterization of diseased liver tissue microenvironment at risk of cancer development will facilitate cataloging of candidate chemoprevention targets. Such coordinated efforts will lead to tailored intervention for each individual according to specific molecular risk mechanism and chemoprevention targets. However, requirement of large sample size and long observation period are the major logistical challenges in chemoprevention clinical trials that diminish physicians' motivation to engage asymptomatic individuals and adhere to the protocol. Diversity in HCC incidence according to etiology, patient race/ethnicity, and clinical context (e.g., post-SVR cirrhosis) needs to be taken into account in assessing clinical utility and real-world effectiveness of preventive interventions. Drug safety in cirrhotic patients is another critical factor. The precision medicine approaches rely on molecular information derived from biospecimens. Although liver tissue is deemed as the most reliable source to interrogate pathogenic molecular dysregulation, transition to less invasive types of biospecimen during the process of clinical translation will help its wider applicability. Sampling bias and robustness in molecular readout should also be determined in preclinical and clinical studies. Once these issues are resolved and the preventive strategies are clinically implemented, the tailored approach will enable more cost-effective and precise preventive intervention in the clinical care of patients at HCC risk, which will substantially improve the dismal prognosis of HCC.

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Key points

- HCC mortality keeps increasing in several regions in Europe, Africa, and the U.S. in contrast to a decreasing trend in traditionally endemic areas such as East Asia.
- Patients with active or cured HCV infection and individuals with NAFLD or metabolic disorders are emerging populations for HCC development, awaiting customized HCC screening strategies.
- Regular HCC screening is significantly underutilized due to multiple patient- and provider-related barriers. This challenge may be overcome by multi-level clinical and community-based interventions as well as individual risk-based personalized HCC screening.
- New HCC screening modalities, including serum biomarkers, integrative scores, and imaging techniques, are under development or clinical evaluation for improved early HCC tumor detection.
- A variety of etiology-specific and independent interventions are evolving as potential HCC chemopreventive measures, although the framework of their clinical testing and implementation needs to be developed.
- Anti-viral therapies can be effective etiology-specific HCC chemopreventive interventions, although viral cure does not eliminate HCC risk, and therefore requires continued risk assessment, screening, and/or additional chemopreventive interventions.
- Anti-inflammatory, immunomodulatory, anti-fibrotic, metabolic, dietary, physical, and molecular targeted interventions may serve as generic HCC chemoprevention therapies.

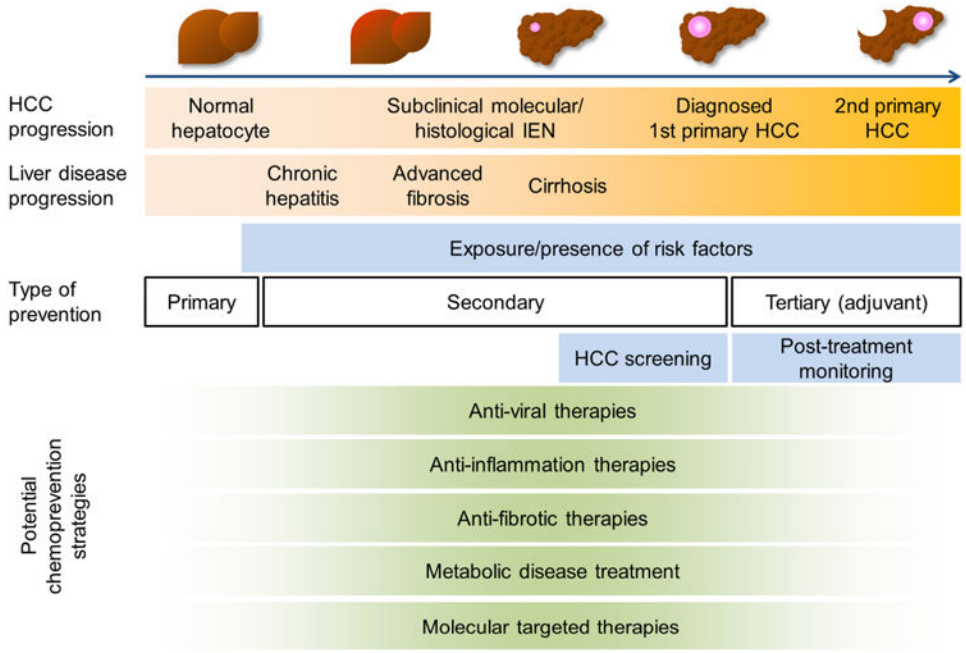

Figure 1. HCC-preventive interventions in the natural history of HCC development in progressive fibrotic liver diseases

HCC-preventive strategy targeting each specific clinical context (i.e., etiology-specific or independent primary, secondary, and tertiary prevention) should be developed to ensure its clinically meaningful impact on the course of fibrotic liver disease progression toward HCC. IEN, intraepithelial neoplasia; HCC, hepatocellular carcinoma.

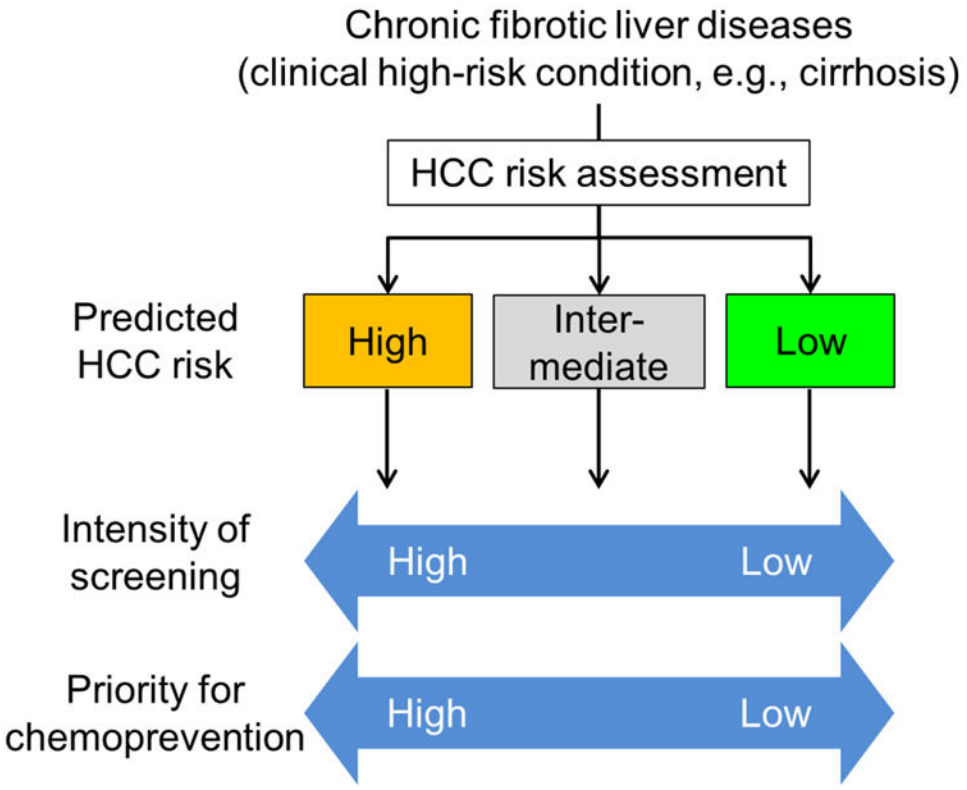

Figure 2. Individual risk-based tailored HCC screening and chemoprevention

Individual HCC risk assessment with clinical and/or molecular risk indicators (see Tables 1 and 2) will enable personalized HCC screening and chemoprevention strategies to optimize allocation of limited medical resources and maximize cost-effectiveness of the interventions by tailoring intensity of screening (i.e., frequency and choice of modalities) and prioritizing a subset of patients with higher HCC risk for chemopreventive therapies.

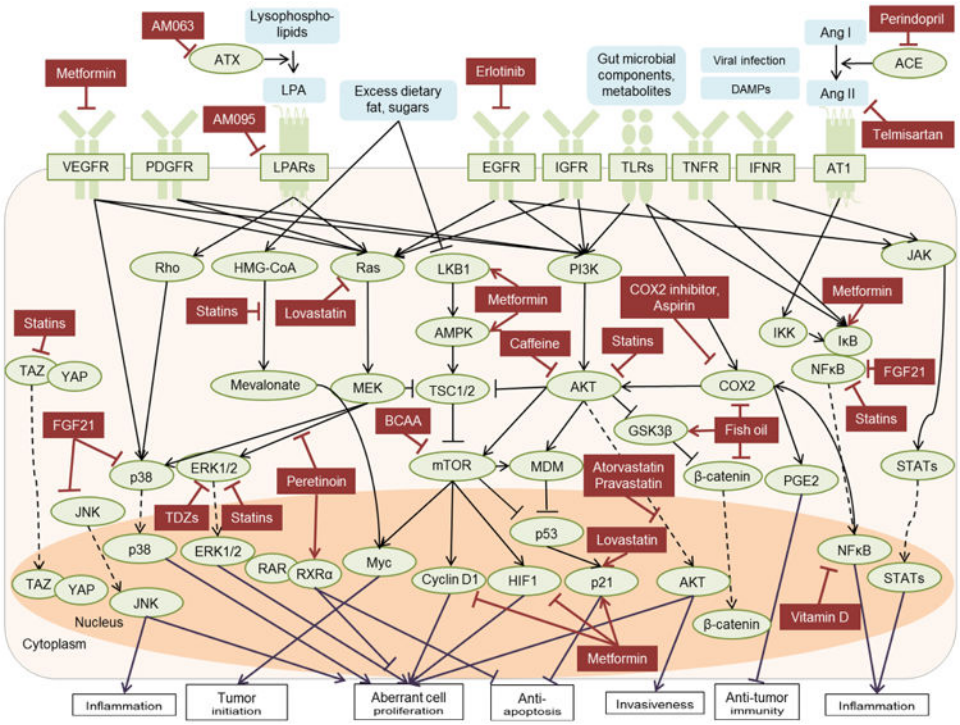

Figure 3. Molecular targets of potential HCC chemoprevention therapies

Intra- and extracellular targets of potential HCC chemopreventive therapies are summarized. Solid line with arrowhead or bar indicates activation or inhibition, respectively. Dotted line with arrowhead indicates translocation between intracellular compartments.

ACE, angiotensin-converting enzyme; AMPK, adenosine monophosphate-activated protein kinase; Ang, angiotensin; ASK1, apoptosis signal-regulating kinase 1; AT1, angiotensin type 1 receptor; CCR, C-C chemokine receptor; COX2, cyclooxygenase 2; DAMPs, damage-associated molecular pattern; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; ERK, extracellular signal–regulated kinase; FGF21, fibroblast growth factor 21; GSK3, glycogen synthase kinase 3; HIF, hypoxia inducible factor; HMG-CoA, 3-hydroxy-3nethyl-glutaryl-coenzyme A; IFNR, interferon receptor; IGFR, insulin-like growth factor 1 receptor; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LKB1, liver kinase B1; LPAR, lysophosphatidic acid receptor; MDM, mouse double minute; mTOR, mammalian target of rapamycin; NFκB, nuclear factor-kappa B; PDGFR, platelet-derived growth factor receptor; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; RAR, retinoic acid receptor; ROS, reactive oxygen species; RXR, retinoid X receptor; STAT, signal transducers and activator of transcription; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; TSC, tuberous sclerosis complex; VEGFR, vascular endothelial growth factor receptor; YAP, Yes-associated protein.

Table 1

Clinical HCC/fibrosis risk indicators

Risk indicator	Study design	Endpoint	Major etiology	No. subjects	Major race/ethnicity	Cirrhosis	Variables	Validation	Reference
LSM-H CC score	Prospective, cohort	HCC (3/5y)	HBV	1,035 + 520 *	Asian	32% + 31% *	LSM, age, albumin, HBV DNA	Internal	262
REACH-B	Prospective-retrospective, cohort	HCC (3/5/10y)	HBV	3,584 + 1,505 *	Asian	0% + 18% *	Sex, age, ALT, HBeAg, HBV DNA	External	263
CU-HCC	Prospective-retrospective, cohort	HCC (5y)	HBV	1,005 + 424 *	Asian	38% + 16% *	Age, albumin, bilirubin, HBV DNA, cirrhosis	External	264
Yang, et al.	Prospective-retrospective, cohort	HCC (5/10y)	HBV	2,435 + 1,218 *	Asian	n.a.	Sex, age, HCC family history, alcohol, ALT, HBeAg, HBV-DNA, HBV genotype C	Internal	265
Hung, et al.	Retrospective, cohort	HCC (10y)	HBV	8,252 + 4,125 *	Asian	n.a.	Age, sex, ALT, previous liver disease, HCC family history, smoking, HBV, HCV	External	266
PAGE-B	Retrospective, cohort	HCC (5y)	HBV	1,325 + 490 *	White	20% + 48% *	Age, sex, platelet	External	267
Sohn, et al.	Retrospective, cohort	HCC (5y)	HBV	990 + 1,071 *	Asian	39% + 35% *	Age, sex, cirrhosis	Internal	268
FIB-4	Retrospective, cohort	HCC	HBV	986	Asian	9.9%	AST, ALT, platelet, age	No	269
GAG-HCC	Retrospective, cohort	HCC (5/10y)	HBV	820	Asian	15%	Age, sex, HBV DNA, core promoter mutations, cirrhosis	No	270
Shin, et al.	Retrospective, cohort	HCC (5y)	HBV	227	Asian	50.3%	LSM, spleen diameter, platelet	No	43
Kim, et al.	Retrospective, cohort	HCC	HBV	2,878	Asian	10%	LSM	No	271
Singal, et al.	Prospective-retrospective, cohort	HCC (3/5y)	HCV	442 + 1,050 *	White, black, Hispanic	100% + 41% *	23 clinical variables	External	272
REVEAL-HCV	Prospective-retrospective, cohort	HCC (5y)	HCV	1,095 + 572 *	Asian	1.4% + 7.0% *	Age, ALT, AST/ALT, HCV RNA, cirrhosis, HCV genotype	External	273
Ganne-Carrié, et al.	Prospective-retrospective, cohort	HCC (3y)	HCV	720 + 360 *	n.a.	100%	Age, past alcohol abuse, platelet, GGT, SVR	Internal	274
Lok, et al.	Prospective-retrospective, cohort	HCC (5y)	HCV	1,005	White, black, Hispanic	40% (Ishak 5/6)	Age, race, platelet, ALP, esophageal varices, smoking	No	275
El-Serag, et al.	Retrospective, cohort	HCC	HCV	5,586 + 5,760 *	White, black	100%	AFP, ALT, platelet, age	Internal	276
Huang, et al.	Retrospective, cohort	HCC	HCC	533	n.a.	7%	CPA	No	38
Motosugi, et al.	Retrospective, case-control	HCC	HCV	66:66 §	Asian	n.a.	LSM by MRE	No	41

Risk indicator	Study design	Endpoint	Major etiology	No. subjects	Major race/ethnicity	Cirrhosis	Variables	Validation	Reference
Chang, et al.	Retrospective, cohort	HCC (5y)	HCV after interferon	1,252 + 627*	Asian	45% (F3/4)	Age, sex, platelet, AFP, advanced fibrosis, HCV genotype 1b, SVR	Internal	277
Ikeda, et al.	Retrospective, cohort	HCC	HCV after SVR	1,056	Asian	10%	Age, AST, platelet before interferon treatment	No	278
$score_{HCC}$	Retrospective, cohort	HCC	HCV after SVR	871	Asian	30%	Age, AFP, platelet, advanced fibrosis	No	279
Wang, et al.	Retrospective, case-control	HCC	HCV after SVR	21:355§	Asian	33.8% (F3/4)	LSM, advanced fibrosis, diabetes	No	44
ADRESS-HCC	Retrospective, cohort	HCC (1y)	HCV, alcohol, NASH/cryptogenic	17,124 + 17,808*	White, Hispanic	100%	Age, diabetes, race, etiology, sex, Child-Pugh score	External	280
Velázquez, et al.	Prospective, cohort	HCC (4y)	Alcohol, HCV	295 + 168*	n.a.	100%	Age, HCV, prothrombin time, platelet	Internal	281
VFMAP	Retrospective, cohort	HCC (5y)	Non-viral, HCV	1,808	Asian	13%	LSM, fast plasma glucose, sex, age, AFP	No	282
Wen, et al.	Retrospective, cohort	HCC (10y)	General population	428,584	Asian	n.a.	Smoking, alcohol, physical activity, diabetes, AST, ALT, AFP, HBV, HCV	Internal	155
Singh, et al.	Meta-analysis of 9, 6 studies	HCC, fibrosis (decompensation)	HCV, HBV, Alcohol, NASH	4,038, 2,410	n.a.	n.a.	LSM by TE, MRE	n.a.	42
Konerman, et al.	Prospective-retrospective, cohort	Fibrosis (>2 Ishak score, 1.5/3.5y)	HCV	184	White	0%	25 clinical variables	Internal	283
Lens, et al.	Prospective-retrospective, cohort	Fibrosis (F4, 5/7/10y)	HCV	832 + 457*	White	8.9% + 12.7% (F3)*	Advanced fibrosis, age, AST, GGT, Forns score	Internal	284
FILI score	Prospective-retrospective, cohort	Fibrosis after lifestyle intervention (1y)	NASH	261	n.a.	0%	HbA1c change, platelet, ALT normalization	No	285
ELF score	Prospective-retrospective, cohort	Fibrosis (F3-4)	HCV, HBV	300	n.a.	25% (F3/4)	Hyaluronic acid, TIMP1, PIIINP	No	286
Tsochatz is, et al.	Retrospectiv e, cohort	Fibrosis (decompensation)	Alcohol, HCV	69	n.a.	100%	CPA	No	37

Validation: “Internal”, validation in patients from the same institution(s); “External”, validation in patients from independent institution(s).

*Training + validation.

§Case:control. n.a., not available/applicable.

“Prospective-retrospective” indicates retrospective analysis of prospectively collected cohort in the past.[287] HCC, hepatocellular carcinoma; REACH-B, Risk estimation for hepatocellular carcinoma in chronic hepatitis B; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; LSM, liver stiffness measurement; ALT, alanine aminotransferase; HCV, hepatitis C virus; AST, aspartate aminotransferase; REVEAL-HCV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HCV; GGT, γ-glutamyltransferase; SVR, sustained virologic response; ALP, alkaline phosphatase; AFP, α-fetoprotein; CPA, collagen proportionate area; MRE, magnetic resonance elastography; ADRESS-HCC, age, diabetes, race, etiology of cirrhosis, sex and severity of liver dysfunction-HCC; NASH, non-alocholic steatohepatitis; VFMAP, virtual touch quantification, fast plasma glucose, sex, age, and AFP; TE, transient elastography; FILI, fibrosis improvement after lifestyle interventions; HbA1c, glycosylated hemoglobin, type A1c; ELF, enhanced liver fibrosis; TIMP1, tissue inhibitor of metalloproteinase-1; PIIINP, propeptide of type III procollagen.

Table 2

Molecular feature-based HCC/fibrosis risk indicators

Risk indicator	Study design	Endpoint	Major etiology	No. subjects	Major race/ethnicity	Cirrhosis	Combined clinical variables	Validation	Reference
Circulating microRNA signature	Prospective-retrospective, cohort	HCC	HBV	373	Asian	34.6%	n.a.	No	288
IGF 1 (serum protein)	Prospective, cohort	HCC	HCV	104	White	100%	n.a.	External	63
EGF 61 *G (SNP, rs4444903)	Prospective-retrospective, cohort	HCC	HCV	816	White, black	15.4%	Age, sex, smoking history, ALP, platelet	External	289
MPO -463 *G (SNP, rs2333227)	Prospective-retrospective, cohort	HCC	HCV	205	White	100%	n.a.	No	50
GlycoHCCRiskScore (serum glycome)	Prospective-retrospective, case-control	HCC	HCV	125	n.a.	100%	n.a.	No	64
TLL1 (SNP, rs17047200)	Retrospective, case-control	HCC	HCV after SVR	123:333 + 130:356 *§	Asian	24.6% + 20.1% * (F3-4)	Age, albumin, AFP after SVR	External	60
PNPLA3 444 *G (SNP, rs738409)	Prospective, cohort	HCC	Alcohol HCV	532	White	100%	Age, sex, BMI	External	290
HFE C282Y (SNP, rs1800562)	Prospective, cohort	HCC	Alcohol HCV	301	White	100%	n.a.	External	291
Osteopontin (serum protein)	Prospective-retrospective, nested case-control	HCC (2y)	Non-viral	100:194§	White	n.a.	AFP, AST, ALT, GGT	No	62
186/32-gene signature (liver tissue transcriptome)	Prospective-retrospective, cohort	HCC, HCC recurrence	HCV, HBV, Alcohol, NASH	82 + 225/216/145/263 *	Asian + n.a./white/white/Asian *	52.4% + n.a./100%/100%/43% *	AFP, vascular invasion, bilirubin, platelet, Child-Pugh class, AJCC stage	External	10,292-294
HSC signature (liver tissue transcriptome)	Experiment + retrospective, cohort	HCC, HCC recurrence	HCV, HBV	Mouse + 216/82	White/Asian	100%/100%	Bilirubin, platelet	No	295
Activated HSC signature (liver tissue transcriptome)	Retrospective, cohort	HCC recurrence	HBV	247+ 226/72 *	Asian	90.7%	n.a.	External	296
HIR signature (liver tissue transcriptome)	Retrospective, cohort	Late HCC recurrence	HBV	72 + 96/228 *	Asian	50% + 62.5%/92.5% *	n.a.	External	297
65-gene signature (HCC tissue transcriptome)	Retrospective, cohort	Early HCC recurrence	HBV	72 + 96/228 *	Asian	50% + 62.5%/92.5% *	n.a.	External	297
Cirrhosis Risk Score (serum glycome)	Retrospective, case-control	Fibrosis (5y)	HCV	205:66§	n.a.	21.8% (F2)	n.a.	No	298

Validation: “Internal”, validation in patients from the same institution(s); “External”, validation in patients from independent institution(s).

* Training + validation.

§Case:control.

"Prospective-retrospective" indicates retrospective analysis of prospectively collected cohort in the past.[287] Biomarkers evaluated in prospective patient series and/or externally validated in >100 patients are included. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; IGF 1, insulin-like growth factor 1; HCV, hepatitis C virus; ALP, alkaline phosphatase; SVR, sustained virologic response; AFP, α-fetoprotein; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; NASH, non-alcoholic steatohepatitis; AJCC, American Joint Committee on Cancer; HSC, hepatic stellate cell; HIR, hepatic injury and regeneration.

Table 3

HCC diagnostic biomarkers and scores

Biomarker	Study design	Major etiology	HCC stage	Major race/ethnicity	Sensitivity	Specificity	AUROC	Validation	Reference
- Biomarker in clinical use									
AFP	Meta-analysis (20 studies)	HCV	n.a.	Asian	4-71%	29-100%	0.65	n.a.	299
AFP-L3	Meta-analysis (8 studies)	HCV	n.a.	Asian	21-49%	93-100%	0.69	n.a.	299
DCP	Meta-analysis (16 studies)	HCV	n.a.	Asian	7-56%	72-100%	0.70	n.a.	299
- Integrative score									
GALAD model	Prospective, case-control	Alcohol, HCV, HBV	25% + 22% *	n.a.	94%	83%	0.95	External	73
Doylestown algorithm	Prospective-retrospective, nested case-control	HBV/HCVC + HCV/HBV/HCV *	54%/79% + 48%/100%/33% *	n.a.	53/58/63%	Fixed to 95%	0.84/0.89/0.88	External	72
- Experimental biomarker									
GPC3	Meta-analysis (19 studies)	HBV, HCV	n.a.	n.a.	55%	84%	0.76	n.a.	300
microRNA panel	Retrospective, case-control	HBV	78% + 75% (BCLC 0/A) *	Asian	81%	84%	0.89	External	301
DKK1	Retrospective, case-control	HBV	67.2% + 31.1% (BCLC 0/A) *	Asian	71%	87%	0.86	External	302
MDK	Retrospective, case-control	HBV	49.2% + 100% (BCLC 0/A) *	Asian	86%	90%	n.a.	External	303
Annexin A2	Retrospective, case-control	HBV	81.7% (AJCC I/II)	Asian	83%	68%	0.79	No	304
GlycoHCC Test	Retrospective, case-control	HBV	34.7% (AJCC I/II)	Asian	57%	88%	0.81	No	305
Osteopontin	Prospective-retrospective, case-control	HCV + HBV *	60% (BCLC 0/A) + n.a. *	n.a. + Asian *	93%	61%	0.93	External	306
GP73	Prospective-retrospective, case-control	HCV	48% (UNOS TNM 1/2)	White	69%	86%	0.79	No	307
GlycoHCC RiskTest	Prospective-retrospective, case-control	HCV	n.a.	n.a.	n.a.	n.a.	0.73	No	64
Fucosylated kininogen	Prospective-retrospective, case-control	HCV	60% (UNOS TNM 1/2)	n.a.	n.a.	n.a.	0.88	No	308

Diagnostic performance measures (sensitivity, specificity, AUROC) were derived from meta-analysis or validation studies.

* Training + validation. “Prospective-retrospective” indicates retrospective analysis of prospectively collected cohort in the past.[287] HCC, hepatocellular carcinoma; AUROC, area under the receiver operating characteristic curve; AFP, α-fetoprotein; HCV, hepatitis C virus; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; DCP, des-gamma-carboxy prothrombin ; GALAD, gender, age, AFP-L3, AFP, des-carboxy prothrombin; HBV, hepatitis B virus; GPC3, glypican 3; BCLC, Barcelona Clinic Liver Cancer; DKK1, Dickkopf-1; MDK, midkine; AJCC; American Joint Committee on Cancer; GP73, Golgi protein-73; UNOS, United Network of Organ Sharing.

Table 4

Ongoing clinical trials of HCC chemoprevention

Trial number	Agent/intervention	Type of agent/intervention	Phase	Type of prevention	Target population	Primary endpoint	No. planned subjects	Estimated completion data
NCT02224456	Tenofovir disoproxil fumarate	Anti-viral	4	Secondary	CHB with advanced fibrosis	HCC development	240	1/2021
NCT02968810	Simvastatin	Statin	2	Secondary	Cirrhosis	Change in AFP-L3	80	1/2020
NCT02306070	Metformin	Anti-diabetic	2	Secondary	CHC with diabetes	Change in LSM	60	9/2017
NCT02779465	Vitamin D3	Nutritional supplement	4	Secondary	CHB on anti-viral	Change in serum levels of 25(OH)D	1,500	12/2026
NCT02098785	Caffeine	Nutritional supplement	1	Secondary	Healthy	VAP-1 serum levels	63	9/2018
NCT02273362	Erlotinib	Kinase inhibitor	1	Secondary	Cirrhosis	Safety, pEGFR, 186-gene signature	45	1/2018
NCT03024684	Atorvastatin	Statin	4	Tertiary	HCC (BCLC 0/A) after curative ablation or hepatectomy	HCC recurrence	240	1/2022
NCT03184493	Metformin, celecoxib	Anti-inflammation, Anti-diabetic	3	Tertiary	HCC after hepatectomy	HCC recurrence	200	6/2021
NCT02281266	Thymalfasin	Immune modulator	4	Tertiary	HBV-HCC after hepatectomy	DFS	360	10/2018
NCT02686372	HBV antigen specific TCR redirected T cell	Immune modulator	1	Tertiary	CHB after transplantation	Safety	10	11/2020
NCT01924624	Thalidomide	Immune modulator, anti-angiogenesis	4	Tertiary	HCC after hepatectomy	DFS	140	12/2019
NCT02447679	Thalidomide, tegafururacil	Immune modulator, anti-angiogenesis, cytotoxic agent	2	Tertiary	HCC after hepatectomy	HCC recurrence	40	Completed, not reported
NCT03178929	SAMe	Nutritional supplement	n.a.	Tertiary	HCC (BCLC 0/A) after radical treatment	HCC recurrence	207	8/2020
NCT01770431	Huaier granule	Traditional herbal medicine	4	Tertiary	HCC (BCLC A/B) after hepatectomy	HCC recurrence, metastasis	1,080	12/2016
NCT02399033	Xihuang Capsules	Traditional herbal medicine	4	Tertiary	HCC (BCLC 0-B) after hepatectomy	HCC recurrence	1,000	12/2019
NCT01717066	Ginsenoside Rg	Chemo-sensitizer, anti-angiogenesis	3	Tertiary	HCC (BCLC A) after hepatectomy	HCC recurrence	480	Completed, not reported
NCT00116454	131 I-lipiodol	Cytotoxic agent	3	Tertiary	Viral/alcohol-HCC after hepatectomy or ablation (≤2 tumors)	HCC recurrence	73	Completed, not reported
NCT02767375	Hepatic arterial infusion chemotherapy	Cytotoxic agent	2~3	Tertiary	HCC after DFS hepatectomy	DFS	192	12/2018

HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; AFP-L3, lens culinaris agglutinin-reactive fraction of α-fetoprotein; CHC, chronic hepatitis C; LSM, liver stiffness measurement; 25(OH)D, 25-hydroxy vitamin D; VAP-1, vascular adhesion protein 1; BCLC, Barcelona clinic liver cancer; HBV, hepatitis B virus; DFS, disease-free survival; TCR, T cell receptor; SAMe, S-adenosylmethionine.