Lifestyle and Environmental Approaches for the Primary Prevention of Hepatocellular Carcinoma

Tracey G. Simon, MD, MPH[a,b,c], Andrew T. Chan, MD, MPH[a,b,c,d,e,f,*]

KEYWORDS

• Cancer prevention • Hepatocellular carcinoma • Chemoprevention • Lifestyle
• Modifiable risk factor

KEY POINTS

- Cancer chemoprevention approaches can include primordial, primary, or secondary prevention strategies; primary prevention strategies include modification of behaviors or high-risk exposures in order to eliminate risk factors for chronic liver disease.
- Epidemiologic data show that modifiable lifestyle factors contribute to the pathogenesis of hepatocellular carcinoma (HCC), including an unhealthy diet, alcohol use, obesity, type 2 diabetes, and nonuse of certain medications, including aspirin and statins.
- Lifestyle modification or the repurposing of medications used for other conditions, including statins, aspirin, and metformin, represent novel and important strategies for the primary prevention of HCC.
- Research to define the molecular determinants of HCC could help elucidate much-needed prognostic biomarkers and thereby facilitate the design of more efficient, biomarker-driven HCC chemoprevention trials.

INTRODUCTION

Hepatocellular carcinoma (HCC) represents the third leading cause of cancer-related mortality worldwide, and is a major cause of death among patients with cirrhosis.[1] In

Grant support: NIH K24 DK098311 (A.T. Chan), NIH K23 DK122104 (T.G. Simon). Dr T.G. Simon is supported by the Harvard University Center for AIDS Research (Career Development Award). Dr A.T. Chan is a Stuart and Suzanne Steele MGH Research Scholar.
[a] Division of Gastroenterology, GRJ-825C, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA; [b] Harvard Medical School, Boston, MA, USA; [c] Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA, USA; [d] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; [e] Broad Institute, Boston, MA, USA; [f] Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA, USA
* Corresponding author. Division of Gastroenterology, GRJ-825C, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114.
E-mail address: achan@mgh.harvard.edu

Clin Liver Dis 24 (2020) 549–576
https://doi.org/10.1016/j.cld.2020.06.002
liver.theclinics.com

the United States, the incidence of HCC has tripled over the past 30 years, and mortalities from HCC are increasing at an alarming pace.[2,3] At present, it is recommended that patients at high risk for developing HCC undergo regular surveillance ultrasonography with assessment of alpha fetoprotein.[4] This approach has a sensitivity of 84% (95% confidence interval [CI], 76%–92%) for the detection of any-stage HCC; however, the sensitivity of ultrasonography for detecting early-stage HCC is only 47% (95% CI, 33%–61%).[5] Moreover, the accuracy of ultrasonography varies widely with body habitus and operator expertise,[6] and it is underused among high-risk populations.[7] Thus, HCC is often diagnosed at a late stage, when treatment options are limited and prognosis is poor.[8] Despite recent advances in treatment, patients diagnosed with HCC have a 5-year survival rate of less than 15%, and 70% of patients experience tumor recurrence within 5 years.[1,3] Given these alarming trends, an urgent need remains to develop effective primary prevention strategies that improve patient outcomes by preventing the development of HCC.

HCC risk varies according to the underlying cause of chronic liver disease, the severity of liver fibrosis, and individual clinical and demographic factors. Major risk factors for HCC include chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, alcohol-related liver disease, and nonalcoholic fatty liver disease (NAFLD).[9,10] Most HCC tumors arise within cirrhotic livers; however, HCC may also arise in the absence of cirrhosis, particularly in patients with chronic HBV infection and NAFLD.[11–13] There are also well-established disparities in the incidence of HCC, with the highest rates observed in men and in racial and ethnic minorities.[14,15] In addition, patients with HCC are often clustered in areas of high poverty and unemployment, relative to the general population.[16] In addition, an increasing body of literature now shows that environmental and lifestyle factors play a key role in the pathogenesis of HCC, including diabetes, obesity, diet, and use of certain medications[17–21] (**Fig. 1**). Thus, developing comprehensive strategies for HCC prevention requires a thorough assessment of risk, based on these diverse clinical, demographic, lifestyle, and environmental factors.

Given the limited treatment options and poor prognosis of HCC, strategies focused on preventing the development of HCC would likely carry the most impact. This article outlines recent advances in understanding of modifiable HCC risk factors that could inform the development of much-needed biomarker-based strategies for HCC prevention.

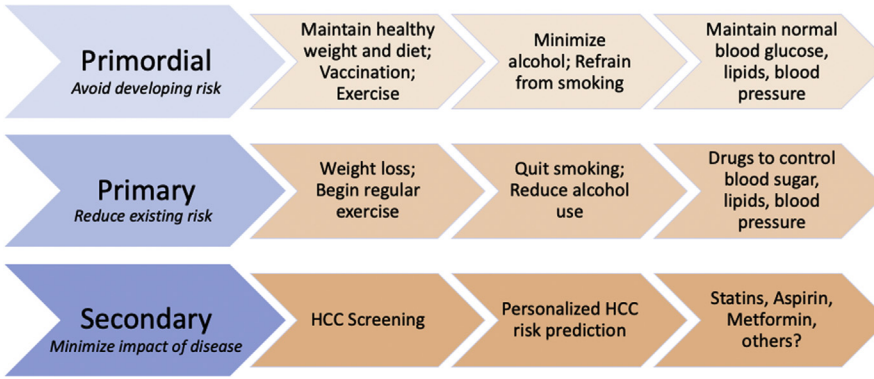

Fig. 1. Overview of HCC prevention strategies.

OVERVIEW OF HEPATOCELLULAR CARCINOMA PREVENTION STRATEGIES

HCC prevention strategies can be applied before or during the natural history of chronic liver disease, and may be categorized as primordial, primary, secondary, and tertiary prevention strategies. Primordial prevention includes behaviors and actions that maintain overall health and thereby prevent the development of risk factors for liver disease. Primary prevention is defined as the modification of behaviors or high-risk exposures in order to reduce risk factors for liver disease. Secondary and tertiary prevention includes screening and surveillance procedures that accurately identify and diagnose existing disease, facilitate early detection and timely interventions for HCC, or that minimize risk of HCC recurrence, among patients with established disease (Fig. 2).

When this framework is applied to HCC prevention, primordial prevention involves maintenance of a healthy body weight, eating a healthy diet with minimization of alcohol use, vaccination against HBV infection, avoiding smoking, and maintaining normal circulating blood glucose and cholesterol levels. Primary prevention of HCC includes lifestyle and behavioral modification, including making changes to adopt a healthy diet; quit smoking or reduce alcohol consumption; weight loss; or taking medications to control or reduce risk factors, including diabetes, obesity, hypertension, and/or dyslipidemia. Among patients with HBV or chronic HCV infection, the initiation of antiviral therapy is also considered primary prevention, because the control of HBV DNA or the eradication of HCV infection can control these risk factors and thereby reduce long-term HCC risk. In addition, secondary prevention for patients with high-risk disease or cirrhosis includes engagement in regular HCC surveillance, every 6 months.

HCC risk can be reduced with cause-specific treatments, which include the use of antiviral therapy to suppress HBV DNA levels or to eradicate HCV infection, among patients with chronic viral hepatitis. These cause-specific strategies have been reviewed in detail elsewhere.[22] However, even with such therapies, excess HCC risk may nevertheless persist, particularly in high-risk patients or in those with cirrhosis.[9,23] Furthermore, as the prevalence of lifestyle-related liver diseases grows, it is increasingly recognized that primary prevention strategies focused on lifestyle modification are likely to provide the most impactful benefits.[11,22] However, to date, the optimal strategy for primary HCC prevention remains undefined.

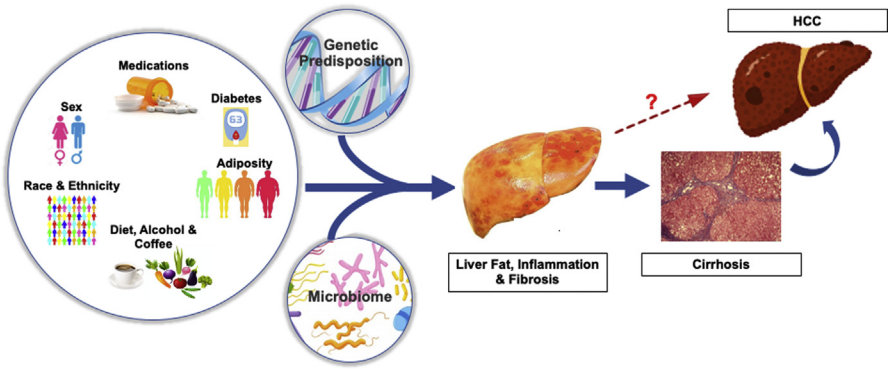

Fig. 2. Emerging risk factors for hepatocellular carcinoma (HCC).

ESTABLISHED AND EMERGING LIFESTYLE RISK FACTORS FOR HEPATOCELLULAR CARCINOMA

Accumulating preclinical, clinical, and epidemiologic evidence shows that modifiable environmental and lifestyle factors play a key role in the pathogenesis of HCC, including diet, alcohol use, obesity, type 2 diabetes, and medications (**Table 1**). Accordingly, lifestyle modification has emerged as an important strategy for the primary prevention of HCC.

Alcohol

Alcohol use represents a major underlying cause of HCC. Worldwide, approximately one-third of incident HCC cases are attributable to alcohol, although these rates vary markedly between regions.[24,25] For example, the proportion of HCC cases attributable to alcohol is estimated to be 6% in the Middle East, 14% in northern Africa, 20% in southern Europe, and as high as 63% in some eastern European countries.[26] According to the Global Burden of Disease study, approximately 854,000 new primary liver cancers were diagnosed in 2015, and there were 815,000 liver cancer–related deaths.[26] Of these recorded cases of new primary liver cancer, 245,000 cases (30%) were attributable to alcohol use, with a strong male predominance (204,000 cases).[26] In longitudinal cohort studies from France, Spain, Belgium, and Japan, the annual incidence of HCC among adults with alcoholic cirrhosis ranged between 2.1% and 5.6%.[27–30] Although prior studies have developed strategies to predict future HCC risk in this population,[27,28] large-scale validation studies are still needed. This topic represents a research area of important unmet need, for it is projected that the proportion of HCC cases attributable to alcohol is likely to increase in the coming decades, because of the improved efficacy of antiviral therapies for chronic viral hepatitis, HBV vaccination strategies, and the increasing per capita consumption of alcohol that has been recorded in regions of northern Europe, eastern Europe, and in the United States.[24,31]

Epidemiologic studies show that heavy alcohol use is independently associated with a 1.2-fold higher risk of developing incident HCC, compared with nondrinking.[32] In a meta-analysis of 19 cohorts and 4445 incident cases of HCC, alcohol consumption contributed to HCC risk in a dose-dependent manner, with 46% higher risk observed with 50 g of alcohol consumption per day, and 66% higher risk with 100 g of alcohol consumption per day.[32] This excess risk is compounded in patients with underlying liver fibrosis,[24,33,34] and alcohol contributes synergistically to the development of HCC in patients with obesity, diabetes,[33,34] and chronic HCV infection.[34] Notably, even after alcohol cessation, the excess observed HCC risk related to alcohol use seems to last for many years.[35] In a meta-analysis of 4 studies, HCC risk declined by approximately 6% per year with abstinence from alcohol; the investigators found that, for patients with cirrhosis, it takes approximately 23 years before an individual achieves the same HCC incidence rates as a nondrinker.[35]

NONALCOHOLIC FATTY LIVER DISEASE, OBESITY, AND DIABETES

Worldwide, approximately 25% of adults are affected by nonalcoholic fatty liver disease (NAFLD).[17] Closely linked to obesity and diabetes, NAFLD is thought to represent the hepatic manifestation of the metabolic syndrome. Although most patients with NAFLD have nonprogressive disease, nearly 30% of adults with NAFLD develop nonalcoholic steatohepatitis (NASH) and fibrosis, and, among those patients, between 10% and 20% progress to cirrhosis.[36] NAFLD represents the most rapidly growing

Table 1
Summary of prior studies relating lifestyle factors with hepatocellular carcinoma risk

Risk Factor	Relative Risk Estimates[a]	Proposed Mechanisms for HCC Prevention
Obesity	HR 1.95, 95% CI 1.46–2.46 for BMI >30 (vs BMI <25)[38]; HR 1.59, 95% CI 1.38–1.83 for increased WC vs normal WC[193]	Hyperinsulinemia; lipotoxicity; adipokine disruption; alterations in the gut microbiome and gut-derived metabolites[47,194–196]
Diabetes	RR 2.01, 95% CI 1.61–2.51 for diabetes (vs no diabetes)[39]	Insulin resistance, hyperglycemia cause ROS formation, lipotoxicity and increased IGF-I and IGF-II levels, which activate Wnt signaling through PI3K/B-catenin pathways[197,198]
Alcohol use	HR 1.16, 95% CI 1.01–1.34 for 3 or more drinks/d (vs nondrinking)[32]	DNA adducts alter DNA repair mechanisms and change protein structure and function; induction of the CYP2E1 enzyme, mitochondrial dysfunction, and ROS lead to cellular toxicity[199]
Diet	HR 0.68, 95% CI 0.51–0.90 for the highest quintile of the AMED score (vs the lowest quintile)[56]	Healthy diet reduces ROS formation and lipotoxicity, inhibits synthesis of proinflammatory cytokines and blocks B-catenin and COX-2 signaling pathways[75,200]
Coffee	RR 0.71 for consumption of >2 cups of coffee/d (vs none)[66]	Induction of UDP glucuronosyltransferase genes may have antioxidant and cytoprotective effects; caffeine inhibits CTGF and TGF-β[201,202]
Aspirin	HR 0.69, 95%CI 0.62–0.76 for low-dose (<163 mg/d) aspirin use (vs nonuse)[166]	Inhibition of COX-2 and proinflammatory prostaglandins may reduce angiogenesis and tumor cell proliferation,[137] by blocking protein kinase 3 and NF-kB pathways[140,141]
Statins	OR 0.63, 95%CI 0.52–0.76 for statin use (vs nonuse)[120]	Blockade of diverse carcinogenic pathways governed by Myc, PI3K-Akt, integrins, Rho-dependent kinase, NF-kB, and the Hippo signaling pathway[102–109]
Metformin	OR 0.52, 95%CI 0.40–0.68[170] for metformin use (vs nonuse)	AMPK-mediated inhibition of VEGF and HIF1A, preventing angiogenesis and cell signaling,[167,203] and suppression of hepatic progenitor cells[168]

Abbreviations: Akt, protein kinase B; AMED, Alternative Mediterranean Diet; AMPK, adenosine monophosphate-activated protein kinase; BMI, body mass index; COX-2, cyclooxygenase-2; CTGF, connective tissue growth factor; CYP2E1, cytochrome P450 2E1; HIF1A, hypoxia-inducible factor 1-alpha; HR, hazard ratio; IGF, insulinlike growth factor; NF-kB, nuclear factor kappa B; OR, odds ratio; PI3K, phosphatidylinositol 3 kinase; ROS, reactive oxygen species; RR, relative risk; TGF, transforming growth factor; UDP, uridine 5′-diphospho; VEGF, vascular endothelial growth factor; WC, waist circumference.

[a] Relative risk estimates were selected from meta-analyses (if available) or from the largest published cohort studies to date.

cause of cirrhosis in the United States, and it is also the fastest growing indication for liver transplant, among adults with HCC.[37]

Obesity and diabetes are present in 51% and 23% of patients with NAFLD,[17] and both conditions represent independent risk factors for the development of HCC. Epidemiologic studies have linked excess adiposity (defined by total body weight, body mass index [BMI], waist circumference, and so forth) to an increased risk of incident HCC,[18–20] and to a nearly 2-fold higher risk of HCC-related mortality.[38] Similarly, type 2 diabetes is significantly and independently associated with excess HCC risk.[20,39–42] In a meta-analysis of 23 cohort studies, diabetes was associated with a 2-fold higher pooled relative risk of incident HCC.[39] Furthermore, recent evidence shows that this risk increases with longer duration of type 2 diabetes,[42] with additional metabolic comorbidities,[32,42] and also that diabetes compounds HCC risk among patients with chronic viral hepatitis.[43]

There is increasing awareness of a link between NAFLD and HCC; however, clinical data are limited and conflicting regarding the precise magnitude of this risk. In a 2011 meta-analysis, the 5-year to 10-year risk estimates of HCC incidence ranged from 0% to 38% and showed marked heterogeneity, caused by the small sample sizes and limited numbers of cases of incident HCC, among the included studies.[44] This limitation was partially addressed by a 2018 retrospective cohort study of 296,707 US veterans with NAFLD and matched non-NAFLD controls, which found that a diagnosis of NAFLD was associated with a modest but statistically significant increased risk of developing HCC (incidence rate difference, 0.02 per 1000 person-years), and the highest excess risk was observed with NAFLD cirrhosis (incidence rate difference, 10.6 per 1000 person-years).[12] However, this cohort was primarily male (94%), with NAFLD and cirrhosis identified by administrative codes and/or by surrogate serum fibrosis scores; thus, future studies are still needed in unselected, population-based cohorts, including those with NAFLD histology, to establish more precise and generalizable estimates of HCC risk across the complete NAFLD histologic spectrum.

Recent evidence has also suggested that HCC risk might be increased in patients with NAFLD who do not have cirrhosis.[45] Although prospective studies are still needed to fully define this relationship, it suggests that the mechanisms that underpin NAFLD-related hepatocarcinogenesis may depend less on liver fibrosis, compared with other causes of liver disease. It has been hypothesized that these mechanisms might relate to gut microbial dysbiosis, changes in circulating gut microbiota-derived metabolites (ie, secondary bile acids or short-chain fatty acids), oxidative stress, disruption of circadian rhythms, or dysregulation of circulating and hepatic adipokines and proinflammatory cytokines.[46–50] Further research is needed in animal models and in human studies to more precisely characterize these pathways and to translate these findings to novel preventive therapies.

DIETARY PATTERNS

A growing body of clinical and epidemiologic evidence suggests that dietary patterns may influence HCC risk. Dietary patterns reflect complex combinations of nutrients and individual compounds that act synergistically within whole foods and across combinations of foods to exert biological effects, which may affect long-term health outcomes.[51] In one of the earliest observational studies of dietary patterns and incident HCC risk, male and female participants in the Shanghai Men's and Women's Health Studies who adhered to a vegetable-based dietary pattern had a significantly reduced risk of developing incident HCC.[52]

More recently, the National Cancer Institute launched the Dietary Patterns Methods Project, which compares validated indices of overall diet quality in relation to incident cancers.[53] These indices were selected based on their established associations with cancer and cardiovascular disease,[54] and include the Alternative Healthy Eating Index (AHEI), the Healthy Eating Index, the Dietary Approaches to Stop Hypertension (DASH), and the Alternate Mediterranean Diet (AMED). Since that time, 3 observational cohort studies have evaluated index-based dietary patterns in relation to HCC incidence.[21,55,56] Two of those studies were conducted in 3 large, prospective US cohort studies (the National Institutes of Health [NIH]/AARP Diet and Health Study, the Nurses' Health Study, and the Health Professionals Follow-up Study), and these found significantly lower HCC risk in participants with higher AHEI-2010 and AMED dietary scores.[21,55] The third study included 169,806 adults enrolled in the prospective Multiethnic Cohort study, and found that higher AMED dietary scores were associated with significantly lower risk of incident HCC (adjusted hazard ratio for the highest quintile vs the lowest quintile, 0.68; 95% CI, 0.51–0.90).[56] However, published evidence is not yet sufficiently robust to recommend 1 particular diet for HCC primary prevention.

INDIVIDUAL FOODS, NUTRIENTS, AND DIETARY COMPOUNDS

Fruit, Vegetables, Meat, and Fat

Consumption of fruits and vegetables has also been studied in relation to HCC incidence. In a 2014 meta-analysis of 19 studies (1.29 million subjects and 3912 cases of incident HCC), each 100-g increase in daily vegetable intake was associated with an 8% lower risk of incident HCC, among the included cohort studies (OR, 0.92; 95%CI, 0.88–0.95).[57] In contrast, a null association was found for fruit consumption and incident HCC risk.[57] Observational cohort studies and case-control studies have also evaluated the intake of red meat, white meat, and fish, in relation to incident HCC. In a meta-analysis pooling results from 9 studies, the highest category of daily red meat intake was not significantly associated with increased HCC incidence, compared with the lowest category (pooled OR, 1.10; 95% CI, 0.85–1.42).[58] In contrast, both white meat and fish consumption were significantly associated with reduced HCC risk, when the highest versus the lowest categories of consumption were compared (pooled OR for white meat and fish, 0.69; 95% CI, 0.58–0.81).[58]

Although human data regarding dietary fat intake and HCC risk are more limited, a notable study included 495,006 older adults enrolled in the prospective NIH-AARP cohort, and observed that a higher daily intake of saturated fat at baseline was associated with a significant, 1.9-fold increased risk of incident HCC (hazard ratio [HR], 1.87; 95% CI, 1.23–2.85).[59] In contrast, the prospective European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study did not find a significant association between saturated fats and incident HCC risk (HR, 1.08; 95% CI, 0.88–1.34), whereas monounsaturated fats were inversely associated with HCC risk (per each 5 g/d: HR, 0.71; 95% CI, 0.55–0.92).[60]

Coffee

Coffee contains well-described antiinflammatory, antioxidant, and antifibrotic properties, and it has been observed that coffee drinkers tend to have lower risk of developing advanced liver disease, including liver fibrosis,[61] cirrhosis, and incident HCC.[62,63] Both the World Cancer Research Fund and the International Agency for Research on Cancer have also published reports supporting the beneficial effects of coffee for the prevention of HCC.[64,65]

A recent meta-analysis of 26 studies and 1825 incident HCC cases showed that consumption of at least 2 cups/d of coffee was associated with significantly reduced risk of incident HCC, with a pooled relative risk of 0.71.[66] Per each additional 2 cups of coffee consumed per day, the magnitude of observed benefit was significantly greater with caffeinated coffee (27% relative risk reduction) than with decaffeinated coffee (14% relative risk reduction).[66] Overall, the strength and consistency of the epidemiologic associations for coffee have led to recommendations for moderate coffee consumption for HCC prevention in the 2018 guidelines from the European Association for the Study of the Liver (EASL).[67] However, several important questions remain unanswered, including the optimal "dose" and preparation of coffee (ie, espresso vs drip coffee, type of coffee bean, or roasting process), the optimal timing of initiation, and the necessary duration of consumption during the natural history of liver disease to achieve meaningful risk reduction. Thus, high-quality, prospective studies are needed in well-phenotyped populations that include more specific details regarding coffee consumption.

Green Tea

Two meta-analyses have evaluated green tea consumption in relation to HCC incidence.[68,69] The most recent 2016 meta-analysis included 11 Asian cohort studies of more than 460,000 individuals and 3694 cases of liver cancer, and showed a pooled relative risk for incident HCC of 0.88 (95% CI, 0.81–0.97) when the highest category of green tea intake was compared with the lowest category.[68] In a dose-response analysis, each additional 1 cup of daily green tea was associated with a 3% reduction in HCC risk (95% CI, 0.95–1.00). In contrast, data from European cohort studies have been mixed: in the EPIC cohort, persons in the highest quintile of green tea consumption had a 59% lower risk of developing HCC (adjusted HR, 0.41; 95% CI, 0.22–0.78) compared with the lowest quintile,[70] whereas 2 prior Italian case-control studies found null associations.[71,72]

Green tea is produced by heating or steaming fresh tea leaves at high temperatures, in processes that result in minimal oxidation and thus preservation of the polyphenols (ie, catechins) within the tea. Between 50% and 75% of the primary catechins in green tea are epigallocatechin-3-gallate (EGCG), whereas the remainder include epigallocatechin, epicatechin-3-gallate, and epicatechin. In preclinical studies, EGCG inhibits carcinogenesis at numerous sites, including within the liver, albeit with potential risk of hepatotoxicity at high levels.[73] However, in an epidemiologic cohort study, higher levels of urinary catechins were associated with increased HCC risk among subjects with positive HBV surface antigens, and this excess risk was magnified in patients with low circulating retinol levels (adjusted odds ratio, 2.62; 95% CI, 1.25–5.51).[74] Given that green tea is the primary source of catechins, these data indicate that further research is needed to understand the relationship between green tea consumption and HCC risk, particularly among patients with chronic HBV infection.

Omega-3 Polyunsaturated Fatty Acids

Preclinical data suggest that intake of the omega-3 (n-3) polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexanoic acid (DHA), could prevent hepatocarcinogenesis by inhibiting the proinflammatory cyclooxygenase (COX)-2 enzyme, which in turn inhibits endogenous biosynthesis of prostaglandins and β-catenin signaling pathways,[75] while simultaneously stimulating the endogenous biosynthesis of proresolution lipid mediators. When fat-1 transgenic mice (which endogenously form n-3 PUFAs) were compared with wild-type pairs, both the size and number of hepatic tumors was reduced after

diethylnitrosamine treatment, and hepatic COX-2 expression was significantly reduced, whereas levels of circulating n-3 PUFA–derived proresolution lipid mediators were significantly increased.[76] These proresolution lipid mediators, which include lipoxins, resolvins, maresins, and protectins, are also stimulated by aspirin and have been shown in murine models to mediate antitumor activity (**Fig. 3**).[77]

In a large, prospective, cohort study of 90,296 Japanese adults, consumption of an n-3 PUFA–rich diet and individual n-3 PUFA supplements was significantly and inversely associated with reduced HCC risk, in a dose-dependent manner.[78] Specifically, compared with the lowest quintiles of n-3 PUFA intake, the adjusted HRs in the highest quintiles were 0.64 for n-3 PUFA–rich fish, 0.56 for EPA, 0.64 for DPA, and 0.56 for DHA.[78] These findings are also supported by prior cohort studies that have similarly shown significant inverse associations between intake of diets rich in n-3 PUFA–rich fish or white meat, and reduced HCC risk.[79–81]

Vitamin D

Both preclinical and clinical studies have linked higher levels of vitamin D (25-hydroxyvitamin D [25(OH)D]), to reduced HCC incidence. In vitro, administration of 1-alpha,25$(OH)_2$D has proapoptotic and antiproliferative effects on numerous cancer cells,[82–84] and inhibits growth of HCC cell lines,[85] by modulating cell cycle growth via induction of p21 and p27 tumor suppressor genes and suppression of cyclins and cyclin-dependent kinases.[86,87] In humans, higher 25(OH)D levels have been associated with reduced HCC risk, with a relative risk of 0.51[88]; in contrast, low 25$(OH)D_3$ levels have been linked to excess HCC risk in patients with chronic HBV infection (adjusted HR, 1.90).[89]

Several carcinogenic signaling pathways are hypothesized to be responsive to vitamin D and its metabolites. First, 1-alpha,25$(OH)_2$D has been shown to downregulate epidermal growth factor receptor expression, which inhibits cell growth and promotes cell division, through mitogen-activated protein kinase (MAPK)–dependent pathways.[90] Second, vitamin D_3 might inhibit vascular endothelial growth factor–mediated endothelial cell proliferation and angiogenesis.[91,92] In addition, it has been

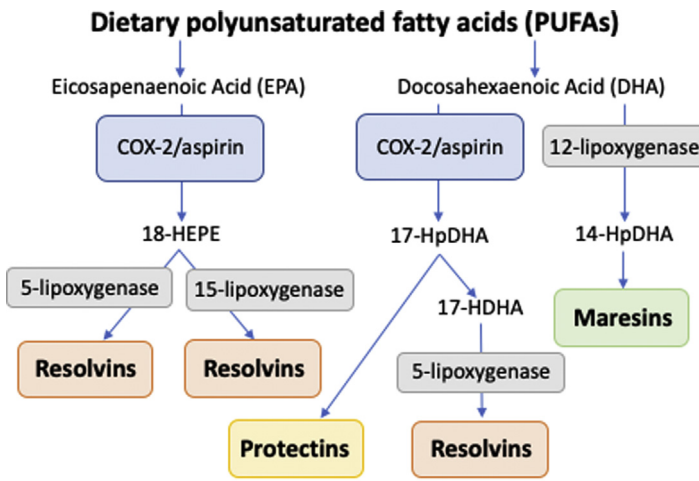

Fig. 3. Polyunsaturated fatty acids promote the endogenous biosynthesis of antiinflammatory, proresolution lipid mediators. HDHA, hydroxydocosahexanoic acid; HEPE, hydroxyeicosapentaenoic acid; HpDHA, hydroperoxydocosahexanoic acid.

posited that vitamin D might act on insulinlike growth factor (IGF) I and II signaling pathways,[93] which may in turn affect liver cancer cell proliferation.

Branched-Chain Amino Acids

Preclinical data suggest that increased circulating branched-chain amino acid (BCAA) levels might protect against hepatocarcinogenesis. In vivo, BCAA treatment enhances mammalian target of rapamycin (mTOR) signaling, which reduces both liver fibrosis and HCC.[94,95] In HCV-transgenic mice, BCAA administration reduces hepatic iron deposition and decreases reactive oxygen species (ROS) formation,[96] and, in high-fat diet–fed mice with NASH, BCAA therapy represses profibrogenic gene expression in hepatic stellate cells and protects hepatocytes from apoptosis.[97] Furthermore, in vivo, BCAA therapy suppresses expression of interleukin (IL)-6, IL-1b, IL-18, and tumor necrosis factor, reducing inflammation in both the liver and white adipose tissues, and inhibiting spontaneous HCC development.[98]

BCAA therapy has historically been used as a treatment of hepatic encephalopathy, and clinical evidence linking BCAA supplementation to HCC incidence is sparse. In a prospective study of 299 Japanese patients with cirrhosis, those provided with BCAA supplementation (5.5–12.0 g/d) had a significantly lower risk of developing incident HCC (relative risk, 0.45)[99] compared with controls. In a meta-analysis of 11 studies, oral BCAA supplementation in patients with established HCC was associated with improved mortality among Child-Pugh class B patients and among those with higher levels of albumin (standardized mean difference, 0.234), and lower rates of ascites (relative risk, 0.55).[100] More recently, in an observational study of 166 patients undergoing evaluation for liver transplant, reduced plasma levels of valine and the valine to phenylalanine ratio were significantly associated with increased overall mortality.[101]

Other Dietary Compounds

Numerous additional dietary components and phytochemicals have been examined for their potential role in HCC chemoprevention, including curcumin, resveratrol, flavonoids (including silymarin), and carotenoids. However, to date, robust clinical evidence supporting HCC preventive effects from these compounds in humans is still lacking.

STATINS

Statins, or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are prescribed for the reduction of low-density lipoprotein cholesterol levels. Beyond their cholesterol-lowering effects, statins also exert a diverse array of pleiotropic anti-inflammatory and antineoplastic effects. Both in vitro and in vivo studies show that statins block numerous carcinogenic signaling pathways, including those governed by Myc, protein kinase B (Akt), integrins, Rho-dependent kinase, nuclear factor kappa B (NF-kB), IL-6, and the Hippo pathway.[102–109] By curtailing mevalonate synthesis, statins also inhibit downstream posttranslational modification of Ras/Rho signaling proteins, which regulate cellular survival and growth, and they inhibit the cellular breakdown of p21 and p27, thereby permitting these molecules to exert potent growth-inhibitory effects.[106,110]

Statins also seem to exert direct antifibrotic actions within the liver, which may potentiate their anti-HCC benefits. Liver fibrosis is driven by the activation of hepatic stellate cells (HSCs), which undergo a phenotypic change from a quiescent state to become proliferative myofibroblasts. In preclinical studies, statins inhibit the activation and proliferation of HSCs[111–113] by upregulating Kruppel-like factor 2, a transcription

factor that promotes HSC quiescence and thereby limits collagen production.[114] The administration of statins has also been shown to reduce pressures in the portal circulation, which may further limit hepatic fibrogenesis,[115] potentially through noncanonical Hedgehog signaling pathways.[116]

Observational studies largely support a link between statin use and reduced HCC risk. The authors observed a dose-dependent, inverse association between statin use and reduced risk of cirrhosis and incident HCC among US veterans with chronic HCV infection,[117] and also in a posthoc analysis of a randomized controlled trial.[118] Kaplan and colleagues[119] studied a different cohort of US veterans with new diagnoses of cirrhosis and found significant HCC risk reduction with statin use for at least 90 days, compared with nonuse. These findings have been confirmed in several large meta-analyses,[120–122] which have shown a significant, inverse association between statin use and reduced HCC risk. The observed benefits of statins were most apparent among observational studies, whereas, in contrast, posthoc analyses of prior randomized controlled trials (RCTs) of statins for cardiovascular disease have failed to show significant HCC risk reduction. However, those prior RCTs were not designed or powered to evaluate the long-term effect of statins on HCC incidence. Further, because they excluded patients with cirrhosis, they comprised study populations at very low risk for developing incident HCC.[120,121]

Emerging evidence further suggests that statin class may also influence HCC risk. Specifically, statins can be broadly divided into lipophilic and hydrophilic subclasses, and it has been hypothesized that lipophilic statins (ie, atorvastatin, simvastatin, fluvastatin, and lovastatin) may confer more potent anti-HCC effects than hydrophilic statins (ie, pravastatin, rosuvastatin). This hypothesis based on 4 lines of evidence. First, in preclinical studies, lipophilic statins suppress viral replication, potentiate antiviral therapy, and stimulate antitumor immunity to a greater degree than is observed with hydrophilic statins.[123–126] Second, in the setting of progressive liver fibrosis, the expression of organic anion transporter proteins on the surface of hepatocytes is markedly reduced, and this may prevent hydrophilic statins from entering hepatocytes, whereas lipophilic statins can passively diffuse across cell membranes.[127,128] Third, lipophilic statins limit cell growth and promote cellular apoptosis by inducing cell cycle arrest via regulation of Ras/Raf/MEK/ERK signaling.[108] Further, administration of simvastatin to hepatocyte cell lines enhances expression of the proapoptotic BAX gene and suppresses expression of the antiapoptotic BCL-2 gene, indicating that lipophilic statins can induce apoptosis by acting at the pretranslational level, as well.[129]

Epidemiologic data comparing lipophilic and hydrophilic statins are both limited and conflicting. Specifically, 2 prior studies did not identify differences in HCC risk with use of lipophilic compared with hydrophilic statins[121,130]; however, in a large, population-based cohort study of Swedish adults, the authors recently showed significantly reduced HCC risk among lipophilic statin users, compared with nonusers, whereas the relationship between hydrophilic statin use and incident HCC risk was null.[131] Although future studies are still needed to confirm these findings, such data suggest that the observed benefits associated with statin use in prior studies may have been driven by the unique, class-specific benefits of lipophilic statins.

To date, evidence supporting the use of statins for HCC chemoprevention is not yet sufficient to be incorporated into guidelines. First, published data derive primarily from observational studies, which lack the benefits of randomization and are prone to selection or confounding by indication bias. Among prior studies, only a few have appropriately balanced the prevalence of underlying HCC risk factors (such as HBV and HCV infection, alcohol-related liver disease, diabetes, obesity, and smoking status) between exposure groups.[119,131] Such imbalances could introduce confounding by

indication, particularly because physicians historically have avoided prescribing statins to patients with liver disease out of concern for hepatotoxicity. Second, high-quality, prospective data are scarce regarding the optimal statin type, necessary duration of use, and the durability of statin-related treatment response, nor are sufficient data available regarding the impact of statins in patients with NAFLD or alcohol-related liver disease. In addition, it remains unknown whether there might be potential additive benefits from the concomitant use of statins together with other medications with putative anti-HCC effects, such as aspirin or metformin. Although some prior data suggest that the relationship between statin use and reduced HCC risk is not significantly modified by concurrent aspirin or antidiabetic medication use,[131] confirmatory studies are needed to validate these findings.

ASPIRIN

Preclinical evidence supports a role for aspirin in the prevention of HCC. Although the precise mechanisms remain undefined, both COX-dependent and COX-independent actions have been proposed. Specifically, the inducible, proinflammatory COX-2 enzyme is overexpressed in many cancers associated with obesity and chronic inflammation,[132,133] including HCC,[134,135] and aspirin irreversibly inhibits COX-2 expression in a dose-dependent manner.[136] COX-2 expression in hepatocytes promotes the spontaneous development of HCC in mice, by reducing tet methylcytosinedioxygenase 1 (TET1) expression, silencing tumor suppressor genes, and activating oncogenic pathways.[134] Hepatocarcinogenesis has also been linked to hepatic translocation of 2 gut microbial metabolites, lipoteichoic acid and deoxycholic acid, which promote cellular senescence and upregulate COX-2 expression, driving the production of prostaglandin E2 and suppressing antitumor immunity.[47] Moreover, by stimulating production of prostaglandins, COX-2 overexpression also promotes angiogenesis and cellular proliferation,[137–139] by activating the proinflammatory protein kinase 3, mTOR, and NF-kB signaling cascades.[134] In contrast, aspirin inhibits NF-kB activation and protein kinase 3 signaling,[140–142] and, in preclinical models, pharmacologic inhibition of COX-2 or prostaglandin E2 prevents the proliferation of liver cancer cells[135] and promotes the resolution of liver fibrosis.[143–145]

The benefits of aspirin in the liver may also derive from the inhibition of platelet activity, which has been shown to limit hepatic inflammation, fibrosis, and hepatocarcinogenesis.[146] Platelets play a central role in promoting accumulation of $CD8^+$ T cells in the liver during chronic viral infection. They also generate platelet-derived growth factor-beta, which activates HSCs and promotes fibrosis progression in rodent models.[147] Recently, Malehmir and colleagues[148] showed in murine models that antiplatelet therapy with aspirin prevented the development of NASH and subsequent HCC via inhibition of platelet-derived glycoprotein 1b alpha, which subsequently reduced intrahepatic platelet accumulation, activation, and immune cell trafficking. Together, these lines of evidence provide additional promising mechanistic explanations for the observed hepatoprotective effects of aspirin.

Clinical evidence regarding the impact of aspirin use on HCC incidence derives exclusively from observational studies.[149–166] Although some investigators have reported conflicting results, most of these observational studies have found a significant, inverse association between aspirin use and reduced risk of incident HCC (**Table 2**). For example, within 2 prospective cohorts of US women and men, the authors showed that regular aspirin use was associated with a significant, 49% lower risk of developing incident HCC (adjusted HR, 0.51; 95% CI, 0.34–0.77), and these

Table 2
Observational studies of aspirin use and risk of hepatocellular carcinoma

Study (Author, Year)	Region	Study Design	HCC Cases (N)	Aspirin Users (N)	Total (N)	HCC Risk (OR, RR, HR; 95% CI)
Simon et al,[149] 2020	Sweden	Retrospective cohort	1612	14,205	50,275	0.69 (0.62–0.76)
Du et al,[161] 2019	China	Retrospective cohort	41	59	264	0.16 (0.04–0.71)
Lee et al,[150] 2019	Korea	Retrospective cohort	697	2123	10, 615	0.70 (0.58–0.86)
Tsoi et al,[151] 2019	Hong Kong	Retrospective cohort	9370	204,170	612,509	0.49 (0.45–0.53)
Hwang et al,[152] 2018	Korea	Prospective cohort	2336	64,782	460,755	0.87 (0.77–0.98)
Simon et al,[165] 2018	United States	Prospective cohort	108	58,855	133,371	0.51 (0.34–0.77)
Lin et al,[154] 2018	Taiwan	Retrospective cohort	110	3576	18,243	0.67 (0.42–1.08)
Tseng et al,[155] 2018	Taiwan	Retrospective cohort	1750	23,112	43,800	0.83 (0.69–0.99)
Lee et al,[157] 2017	Korea	Retrospective cohort[a]	63	343	14,392	0.34 (0.15–0.77)
Lee et al,[156] 2017	Taiwan	Retrospective cohort	NR	5602	18,080	0.70 (0.37–1.36)
Kim et al,[153] 2017	Korea	Case control	229	390	1374	0.34 (0.15–0.78)
Yang et al,[162] 2016	United Kingdom	Case control	1195	1670	5835	1.11 (0.86–1.44)
Petrick et al,[164] 2015	United States	Prospective cohort	679	477,470	1,084,133	0.68 (0.57–0.81)
Sahasrabuddhe et al,[163] 2012	United States	Prospective cohort	250	89,585	300,504	0.51 (0.35–0.75)
Chiu et al,[158] 2011	Taiwan	Case control	1166	162	2332	1.0 (0.73–1.38)
Friis et al,[160] 2003	Denmark	Retrospective cohort	21	29,470	29,470	1.0 (0.60–1.50)
Coogan et al,[159] 2000	United States	Case control	51	491	7101	0.90 (0.30–2.90)

[a] Estimates provided are from the propensity score-matched cohort.

benefits were both dose and duration dependent.[165] More recently, we confirmed these associations in a nationwide, unselected population of Swedish adults with chronic HBV or HCV infection, in whom low-dose aspirin use (<163 mg) was associated with significant, duration-dependent reductions in risk of developing incident HCC (adjusted HR, 0.69; 95% CI, 0.62–0.76) and in the risk of liver-related mortality (adjusted HR, 0.73; 95% CI, 0.67–0.81).[166] Similarly, a pooled analysis of 10 US-based prospective cohorts (with nearly 1.1 million adults, and 679 incident HCC cases) reported a pooled HR for incident HCC of 0.68 with aspirin use, compared with nonuse.[164] Although these lines of evidence are promising, additional prospective data are still needed to more fully characterize the potential benefits of aspirin across the complete spectrum of chronic liver disease, and also to quantify the potential risks of bleeding associated with aspirin use.

METFORMIN

Antidiabetic medications have also been explored as potential agents for HCC chemoprevention. Among them, the best studied is metformin, a biguanide derivative that blocks gluconeogenesis and enhances peripheral insulin sensitivity. Metformin exerts diverse antiangiogenic, antiinflammatory, and antineoplastic effects; by activating adenosine monophosphate-activated protein kinase (AMPK), metformin inhibits hypoxia-inducible factor 1 alpha and vascular endothelial growth factor signaling, which serve to block angiogenesis.[167] Metformin also suppresses hepatic progenitor cell activation[168] and can inhibit cellular proliferation by suppressing NF-kB and reducing the expression of cyclin D1.[167] Furthermore, in murine models, metformin prevents HSC activation and attenuates fibrosis,[169] and it also seems to reduce HCC development, particularly when it is initiated before the development of cirrhosis.[168]

In humans, several prior meta-analyses have shown that metformin use is associated with reduced HCC incidence. The most recent meta-analysis included 19 studies and more than 550,000 patients with diabetes, and found a 48% lower risk of incident HCC with metformin use, compared with nonuse (pooled OR, 0.52; 95% CI, 0.40–0.68).[170] Notably, the investigators found no significant reduction in HCC incidence in a subanalysis of 2 posthoc studies of prior RCTs of metformin use among patients with diabetes (pooled OR, 0.84 with metformin use vs nonuse; 95% CI, 0.10–6.83); however, those 2 prior RCTs were limited by very few cases of liver cancer, and they were not designed or powered to assess HCC end points, thus their findings should be interpreted with caution.[171]

Pioglitazone, which stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma, has shown efficacy for reducing liver fat levels and inflammation in patients with established NASH[172]; however, whether this translates to reduced HCC risk is still unknown. To date, 1 case-control study reported significantly reduced HCC risk with use of pioglitazone, compared with nonuse (OR, 0.83; 95% CI, 0.72–0.95),[173] and 2 studies have found significant risk reduction with use of any thiazolidinedione medication, compared with nonuse,[174,175] although others have shown null associations.[176,177] In addition, although glucagonlike peptide-1 (GLP-1) receptor agonists have shown short-term efficacy for the resolution of NASH,[178] little is currently known about the long-term impact of GLP-1 receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors on HCC incidence.

OTHER POTENTIAL CHEMOPREVENTIVE DRUGS

Although published data are limited, several other medications could represent plausible agents for HCC chemoprevention, including angiotensin-converting enzyme

inhibitors and menopausal hormone therapy. The renin-angiotensin axis participates in liver fibrogenesis and hepatocarcinogenesis,[179] and, by activating NF-kB, angiotensin II can promote the survival of hepatic myofibroblasts, but this effect is reversed with captopril treatment.[180] Moreover, telmisartan, an angiotensin II type 1 receptor blocker (ARB), can prevent fibrosis and HCC development in rodents.[181] In addition, it is well established that there are marked sex disparities in the incidence of HCC, with men being affected more frequently than women, leading to the hypothesis that estrogen may protect against HCC incidence. In support of this, a case-control study of 234 women with treated HCC and 282 healthy controls showed that menopausal hormone therapy use was associated with reduced odds of developing HCC.[182] A meta-analysis of 87 studies also found that variants in the estrogen receptor 1 (ESR1) gene were associated with excess HCC risk.[183] Moreover, in a large consortium of prospective US cohort studies, bilateral oophorectomy was significantly associated with increased HCC incidence (HR, 2.67; 95% CI, 1.22–5.85), after accounting for other lifestyle and clinical factors and duration of exposure to exogenous hormone therapy.[184,185]

THE POTENTIAL IMPACT OF LIFESTYLE MODIFICATION FOR HEPATOCELLULAR CARCINOMA RISK REDUCTION

Given the growing prevalence of chronic liver disease attributable to an unhealthy lifestyle, and the significant associations between high-risk lifestyle factors and excess HCC risk, HCC prevention strategies focused on adopting a low-risk lifestyle would likely offer substantial benefits. However, in order to identify priorities for public health interventions, it is important to quantify the magnitude of contribution of lifestyle factors to HCC risk. Using 2 nationwide, prospective US cohort studies, the authors recently showed that more than 80% of HCC cases could theoretically have been prevented with adherence to low-risk lifestyles. Such data underscore the enormous potential impact of primary HCC prevention efforts focused on lifestyle modification. Nevertheless, important knowledge gaps still remain. In order to translate such data into meaningful recommendations, well-designed, prospective studies are needed to define the optimal approaches to lifestyle modification to achieve clinically meaningful and durable HCC risk reduction in patients who are at high risk of developing incident HCC.

CHALLENGES AND FUTURE DIRECTIONS

Progress in the development and clinical translation of HCC prevention strategies has thus far been limited by 4 important barriers. First, despite promising associations between low-risk lifestyle factors and reduced HCC risk, data are lacking regarding the optimal approaches to lifestyle modification that might translate to effective and durable HCC risk reduction in high-risk populations. Second, the molecular mechanisms of hepatocarcinogenesis remain largely uncharacterized[11,186] because of the genetic heterogeneity of HCC tumors[187] and also suboptimal animal models,[188] which limit the ability to translate hypotheses from preclinical studies to humans. Third, research into other cancers benefits from ready access to tumor biospecimens, precursor lesions, and adjacent normal tissues, which facilitates the discovery and validation of targeted, molecular chemoprevention strategies.[189] In contrast, access to HCC specimens is more difficult, because HCC tumors may be diagnosed without confirmatory pathologic specimens. Although there have been promising recent developments in molecular tools for HCC risk prediction and in the use of liquid biopsy, the clinical utility of these approaches is not yet established.[11]

In addition, a major challenge has been the need for large numbers of subjects and prolonged follow-up times in HCC chemoprevention trials. It has been hypothesized that these requirements for large populations and prolonged follow-up are caused by the inclusion of heterogeneous study populations, which dilute potential treatment effects. For example, 2 large chemoprevention trials of low-dose interferon therapy for patients with advanced fibrosis or cirrhosis failed to show significant HCC risk reduction with treatment.[189–191] However, among patients with cirrhosis (the subgroup at highest risk of developing HCC), a significant treatment benefit was found. Thus, it is plausible that enrollment of an enriched, high-risk study population might maximize the potential to detect a treatment effect, which in turn would enable the design of more feasible and efficient clinical trials, requiring smaller numbers of patients and shorter follow-up times.[186]

In addition to risk-stratified enrollment, biomarker-based HCC chemoprevention trials are needed. To achieve this goal, such biomarkers must (1) predict future risk of HCC development, (2) predict response to chemoprevention therapy, and (3) provide insight into drug pharmacokinetics. Recently, molecular biomarkers of HCC risk have been developed and are undergoing rigorous validation for these purposes.[11] For example, liver tissue–derived transcriptomic signatures have been validated for predicting incident HCC risk among patients with cirrhosis of any cause, including chronic HBV or HCV infection, alcohol-related liver disease, and NAFLD.[192] Based on these results, enrollment was recently completed for a phase I/II clinical trial of erlotinib for the prevention of HCC in patients with cirrhosis (NCT02273362); this trial used a liver tissue transcriptomic prognostic signature as a selection factor for study enrollment and as a surrogate, biomarker-based end point. Showing that a high-risk transcriptomic signature predicts meaningful HCC risk reduction with erlotinib would form a strong scientific rationale for future biomarker-driven HCC chemoprevention trials that use molecular-based risk-stratified enrollment procedures and validated, surrogate biomarker end points for HCC.[186] Such trials would have enhanced feasibility, overcoming many of the barriers outlined earlier, and would therefore enable more rapid translation of preclinical discoveries to humans.

SUMMARY

Given the diversity of HCC and its underlying risk factors, strategies for primordial and primary HCC prevention are likely to have broad clinical applicability for patients with chronic liver disease. Lifestyle modification or the repurposing of medications such as statins, aspirin, or metformin could be readily combined with cause-specific HCC prevention strategies and might offer synergistic benefits. In parallel, research to better characterize the molecular determinants of HCC will help elucidate much-needed prognostic biomarkers and thereby enable the design of more efficient, biomarker-based HCC chemoprevention trials. Ultimately, combining lifestyle modification strategies with the use of safe, generic compounds and targeted biomarkers for predicting HCC risk could provide a robust and cost-effective strategy for HCC chemoprevention among at-risk patients with chronic liver disease.

DISCLOSURES AND CONFLICTS OF INTEREST

Dr A.T. Chan has previously served as a consultant for Bayer Pharma AG, Janssen Pharmaceuticals, Pfizer Inc, and Boehringer Ingelheim for unrelated work. Dr T.G. Simon has no disclosures and no conflicts of interest to disclose.

REFERENCES

1. Bertuccio P, Turati F, Carioli G, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol 2017;67:302–9.
2. Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C, et al. Trends and patterns of disparities in cancer mortality among US Counties, 1980-2014. JAMA 2017;317:388–406.
3. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53.
4. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–80.
5. Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154:1706–1718 e1.
6. Simmons O, Fetzer DT, Yokoo T, et al. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. Aliment Pharmacol Ther 2017;45:169–77.
7. Singal AG, Yopp AC, Gupta S, et al. Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res (Phila) 2012;5:1124–30.
8. Parikh ND, Singal AG, Hutton DW. Cost effectiveness of regorafenib as second-line therapy for patients with advanced hepatocellular carcinoma. Cancer 2017;123:3725–31.
9. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet 2008;371:838–51.
10. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol 2013;47(Suppl):S2–6.
11. Fujiwara N, Friedman SL, Goossens N, et al. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018;68:526–49.
12. Kanwal F, Kramer JR, Mapakshi S, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterology 2018;155:1828–37.e2.
13. Lim J, Singal AG. Surveillance and diagnosis of hepatocellular carcinoma. Clin Liver Dis (Hoboken) 2019;13:2–5.
14. Kim AK, Singal AG. Health disparities in diagnosis and treatment of hepatocellular carcinoma. Clin Liver Dis (Hoboken) 2014;4:143–5.
15. Yu L, Sloane DA, Guo C, et al. Risk factors for primary hepatocellular carcinoma in black and white Americans in 2000. Clin Gastroenterol Hepatol 2006;4:355–60.
16. Shebl FM, Capo-Ramos DE, Graubard BI, et al. Socioeconomic status and hepatocellular carcinoma in the United States. Cancer Epidemiol Biomarkers Prev 2012;21:1330–5.
17. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
18. Hagstrom H, Tynelius P, Rasmussen F. High BMI in late adolescence predicts future severe liver disease and hepatocellular carcinoma: a national, population-based cohort study in 1.2 million men. Gut 2018;67:1536–42.
19. Hassan MM, Abdel-Wahab R, Kaseb A, et al. Obesity early in adulthood increases risk but does not affect outcomes of hepatocellular carcinoma. Gastroenterology 2015;149:119–29.

20. Campbell PT, Newton CC, Freedman ND, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for U.S. Adults. Cancer Res 2016;76:6076–83.
21. Ma Y, Yang W, Simon TG, et al. Dietary patterns and risk of hepatocellular carcinoma among U.S. men and women. Hepatology 2019;70:577–86.
22. Singh S, Singh PP, Roberts LR, et al. Chemopreventive strategies in hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2014;11:45–54.
23. Loomba R, Yang HI, Su J, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. Am J Epidemiol 2013;177:333–42.
24. Pimpin L, Cortez-Pinto H, Negro F, et al. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. J Hepatol 2018;69:718–35.
25. Schutze M, Boeing H, Pischon T, et al. Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. BMJ 2011;342:d1584.
26. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol 2017;3:1683–91.
27. Mancebo A, Gonzalez-Dieguez ML, Cadahia V, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. Clin Gastroenterol Hepatol 2013;11:95–101.
28. Ganne-Carrie N, Chaffaut C, Bourcier V, et al. Estimate of hepatocellular carcinoma incidence in patients with alcoholic cirrhosis. J Hepatol 2018;69:1274–83.
29. Kodama K, Tokushige K, Hashimoto E, et al. Hepatic and extrahepatic malignancies in cirrhosis caused by nonalcoholic steatohepatitis and alcoholic liver disease. Alcohol Clin Exp Res 2013;37(Suppl 1):E247–52.
30. Torisu Y, Ikeda K, Kobayashi M, et al. Diabetes mellitus increases the risk of hepatocarcinogenesis in patients with alcoholic cirrhosis: a preliminary report. Hepatol Res 2007;37:517–23.
31. Haughwout Sarah P, Slater ME. Apparent per capita alcohol consumption: national S, and regional trends, 1977-2016; national Institute on alcohol abuse and alcoholism, surveillance report #110. Available at: https://pubs.niaaa.nih.gov/publications/surveillance110/CONS16.htm. Accessed May 17, 2020.
32. Turati F, Galeone C, Rota M, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. Ann Oncol 2014;25:1526–35.
33. Grewal P, Viswanathen VA. Liver cancer and alcohol. Clin Liver Dis 2012;16:839–50.
34. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–13.
35. Heckley GA, Jarl J, Asamoah BO, et al. How the risk of liver cancer changes after alcohol cessation: a review and meta-analysis of the current literature. BMC Cancer 2011;11:446.
36. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–85.
37. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014;59:2188–95.

38. Gupta A, Das A, Majumder K, et al. Obesity is independently associated with increased risk of hepatocellular cancer-related mortality: a systematic review and meta-analysis. Am J Clin Oncol 2018;41:874–81.
39. Wang C, Wang X, Gong G, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer 2012;130:1639–48.
40. Lai SW, Chen PC, Liao KF, et al. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. Am J Gastroenterol 2012;107:46–52.
41. Chen HF, Chen P, Li CY. Risk of malignant neoplasms of liver and biliary tract in diabetic patients with different age and sex stratifications. Hepatology 2010;52:155–63.
42. Simon TG, King LY, Chong DQ, et al. Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: results from two prospective cohort studies. Hepatology 2018;67:1797–806.
43. Tan Y, Zhang X, Zhang W, et al. The influence of metabolic syndrome on the risk of hepatocellular carcinoma in patients with chronic hepatitis B infection in mainland China. Cancer Epidemiol Biomarkers Prev 2019;28:2038–46.
44. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol 2012;10:1342–1359 e2.
45. Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016;14:124–131 e1.
46. Loo TM, Kamachi F, Watanabe Y, et al. Gut microbiota promotes obesity-associated liver cancer through PGE2-mediated suppression of antitumor immunity. Cancer Discov 2017;7:522–38.
47. Yoshimoto S, Loo TM, Atarashi K, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 2013;499:97–101.
48. Kettner NM, Voicu H, Finegold MJ, et al. Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. Cancer Cell 2016;30:909–24.
49. Park EJ, Lee JH, Yu GY, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 2010;140:197–208.
50. Gomes AL, Teijeiro A, Buren S, et al. Metabolic inflammation-associated IL-17A causes non-alcoholic steatohepatitis and hepatocellular carcinoma. Cancer Cell 2016;30:161–75.
51. Tapsell LC, Neale EP, Satija A, et al. Foods, nutrients, and dietary patterns: interconnections and implications for dietary guidelines. Adv Nutr 2016;7:445–54.
52. Zhang W, Xiang YB, Li HL, et al. Vegetable-based dietary pattern and liver cancer risk: results from the Shanghai women's and men's health studies. Cancer Sci 2013;104:1353–61.
53. National Cancer Institute. Applied research: cancer control and population sciences. Dietary patterns methods Project. Rockville (MD): MNCI; 2018.
54. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–18.
55. Li WQ, Park Y, McGlynn KA, et al. Index-based dietary patterns and risk of incident hepatocellular carcinoma and mortality from chronic liver disease in a prospective study. Hepatology 2014;60:588–97.

56. Bogumil D, Park SY, Le Marchand L, et al. High-quality diets are associated with reduced risk of hepatocellular carcinoma and chronic liver disease: the multiethnic cohort. Hepatol Commun 2019;3:437–47.
57. Yang Y, Zhang D, Feng N, et al. Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: a meta-analysis. Gastroenterology 2014;147:1031–42.
58. Luo J, Yang Y, Liu J, et al. Systematic review with meta-analysis: meat consumption and the risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2014;39:913–22.
59. Freedman ND, Cross AJ, McGlynn KA, et al. Association of meat and fat intake with liver disease and hepatocellular carcinoma in the NIH-AARP cohort. J Natl Cancer Inst 2010;102:1354–65.
60. Duarte-Salles T, Fedirko V, Stepien M, et al. Dietary fat, fat subtypes and hepatocellular carcinoma in a large European cohort. Int J Cancer 2015;137:2715–28.
61. Alferink LJM, Fittipaldi J, Kiefte-de Jong JC, et al. Coffee and herbal tea consumption is associated with lower liver stiffness in the general population: the Rotterdam study. J Hepatol 2017;67:339–48.
62. Saab S, Mallam D, Cox GA 2nd, et al. Impact of coffee on liver diseases: a systematic review. Liver Int 2014;34:495–504.
63. Bravi F, Tavani A, Bosetti C, et al. Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. Eur J Cancer Prev 2017;26:368–77.
64. Loomis D, Guyton KZ, Grosse Y, et al. Carcinogenicity of drinking coffee, mate, and very hot beverages. Lancet Oncol 2016;17:877–8.
65. World Cancer Research Fund International/American Institute for Cancer Research. Continuous update Project report: diet N, physical activity and liver cancer 2015. Available at: https://wcrf.org/sites/default/files/Liver-Cancer-2015-Report.pdf. Accessed May01, 2020.
66. Kennedy OJ, Roderick P, Buchanan R, et al. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. BMJ Open 2017;7:e013739.
67. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
68. Huang YQ, Lu X, Min H, et al. Green tea and liver cancer risk: a meta-analysis of prospective cohort studies in Asian populations. Nutrition 2016;32:3–8.
69. Fon Sing M, Yang WS, Gao S, et al. Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis. Eur J Cancer Prev 2011;20:157–65.
70. Bamia C, Lagiou P, Jenab M, et al. Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: multicentre, prospective cohort study. Int J Cancer 2015;136:1899–908.
71. Montella M, Polesel J, La Vecchia C, et al. Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. Int J Cancer 2007;120:1555–9.
72. La Vecchia C, Negri E, Franceschi S, et al. Tea consumption and cancer risk. Nutr Cancer 1992;17:27–31.
73. Lambert JD, Kennett MJ, Sang S, et al. Hepatotoxicity of high oral dose (-)-epigallocatechin-3-gallate in mice. Food Chem Toxicol 2010;48:409–16.
74. Butler LM, Huang JY, Wang R, et al. Urinary biomarkers of catechins and risk of hepatocellular carcinoma in the Shanghai Cohort Study. Am J Epidemiol 2015;181:397–405.

75. Lim K, Han C, Dai Y, et al. Omega-3 polyunsaturated fatty acids inhibit hepatocellular carcinoma cell growth through blocking beta-catenin and cyclooxygenase-2. Mol Cancer Ther 2009;8:3046–55.
76. Weylandt KH, Krause LF, Gomolka B, et al. Suppressed liver tumorigenesis in fat-1 mice with elevated omega-3 fatty acids is associated with increased omega-3 derived lipid mediators and reduced TNF-alpha. Carcinogenesis 2011;32:897–903.
77. Gilligan MM, Gartung A, Sulciner ML, et al. Aspirin-triggered proresolving mediators stimulate resolution in cancer. Proc Natl Acad Sci U S A 2019;116:6292–7.
78. Sawada N, Inoue M, Iwasaki M, et al. Consumption of n-3 fatty acids and fish reduces risk of hepatocellular carcinoma. Gastroenterology 2012;142:1468–75.
79. Yu SZ, Huang XE, Koide T, et al. Hepatitis B and C viruses infection, lifestyle and genetic polymorphisms as risk factors for hepatocellular carcinoma in Haimen, China. Jpn J Cancer Res 2002;93:1287–92.
80. Wang MP, Thomas GN, Ho SY, et al. Fish consumption and mortality in Hong Kong Chinese–the LIMOR study. Ann Epidemiol 2011;21:164–9.
81. Talamini R, Polesel J, Montella M, et al. Food groups and risk of hepatocellular carcinoma: a multicenter case-control study in Italy. Int J Cancer 2006;119:2916–21.
82. Chiang KC, Chen TC. Vitamin D for the prevention and treatment of pancreatic cancer. World J Gastroenterol 2009;15:3349–54.
83. Chiang KC, Persons KS, Istfan NW, et al. Fish oil enhances the antiproliferative effect of 1alpha,25-dihydroxyvitamin D3 on liver cancer cells. Anticancer Res 2009;29:3591–6.
84. Flanagan JN, Zheng S, Chiang KC, et al. Evaluation of 19-nor-2alpha-(3-hydroxypropyl)-1alpha,25-dihydroxyvitamin D3 as a therapeutic agent for androgen-dependent prostate cancer. Anticancer Res 2009;29:3547–53.
85. Pourgholami MH, Akhter J, Lu Y, et al. In vitro and in vivo inhibition of liver cancer cells by 1,25-dihydroxyvitamin D3. Cancer Lett 2000;151:97–102.
86. Caputo A, Pourgholami MH, Akhter J, et al. 1,25-Dihydroxyvitamin D(3) induced cell cycle arrest in the human primary liver cancer cell line HepG2. Hepatol Res 2003;26:34–9.
87. Hager G, Formanek M, Gedlicka C, et al. 1,25(OH)2 vitamin D3 induces elevated expression of the cell cycle-regulating genes P21 and P27 in squamous carcinoma cell lines of the head and neck. Acta Otolaryngol 2001;121:103–9.
88. Fedirko V, Duarte-Salles T, Bamia C, et al. Prediagnostic circulating vitamin D levels and risk of hepatocellular carcinoma in European populations: a nested case-control study. Hepatology 2014;60:1222–30.
89. Wong GL, Chan HL, Chan HY, et al. Adverse effects of vitamin D deficiency on outcomes of patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2015;13:783–790 e1.
90. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer 2007;7:684–700.
91. Chung I, Wong MK, Flynn G, et al. Differential antiproliferative effects of calcitriol on tumor-derived and matrigel-derived endothelial cells. Cancer Res 2006;66:8565–73.
92. Iseki K, Tatsuta M, Uehara H, et al. Inhibition of angiogenesis as a mechanism for inhibition by 1alpha-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 of colon carcinogenesis induced by azoxymethane in Wistar rats. Int J Cancer 1999;81:730–3.

93. Scharf JG, Dombrowski F, Ramadori G. The IGF axis and hepatocarcinogenesis. Mol Pathol 2001;54:138–44.
94. Cha JH, Bae SH, Kim HL, et al. Branched-chain amino acids ameliorate fibrosis and suppress tumor growth in a rat model of hepatocellular carcinoma with liver cirrhosis. PLoS One 2013;8:e77899.
95. Nakano M, Nakashima A, Nagano T, et al. Branched-chain amino acids enhance premature senescence through mammalian target of rapamycin complex I-mediated upregulation of p21 protein. PLoS One 2013;8:e80411.
96. Korenaga M, Nishina S, Korenaga K, et al. Branched-chain amino acids reduce hepatic iron accumulation and oxidative stress in hepatitis C virus polyprotein-expressing mice. Liver Int 2015;35:1303–14.
97. Takegoshi K, Honda M, Okada H, et al. Branched-chain amino acids prevent hepatic fibrosis and development of hepatocellular carcinoma in a non-alcoholic steatohepatitis mouse model. Oncotarget 2017;8:18191–205.
98. Terakura D, Shimizu M, Iwasa J, et al. Preventive effects of branched-chain amino acid supplementation on the spontaneous development of hepatic preneoplastic lesions in C57BL/KsJ-db/db obese mice. Carcinogenesis 2012;33:2499–506.
99. Kawaguchi T, Shiraishi K, Ito T, et al. Branched-chain amino acids prevent hepatocarcinogenesis and prolong survival of patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12:1012–1018 e1.
100. Chen L, Chen Y, Wang X, et al. Efficacy and safety of oral branched-chain amino acid supplementation in patients undergoing interventions for hepatocellular carcinoma: a meta-analysis. Nutr J 2015;14:67.
101. Kinny-Koster B, Bartels M, Becker S, et al. Plasma amino acid concentrations predict mortality in patients with end-stage liver disease. PLoS One 2016;11:e0159205.
102. Higashi T, Hayashi H, Kitano Y, et al. Statin attenuates cell proliferative ability via TAZ (WWTR1) in hepatocellular carcinoma. Med Oncol 2016;33:123.
103. Wang J, Tokoro T, Higa S, et al. Anti-inflammatory effect of pitavastatin on NF-kappaB activated by TNF-alpha in hepatocellular carcinoma cells. Biol Pharm Bull 2006;29:634–9.
104. Relja B, Meder F, Wang M, et al. Simvastatin modulates the adhesion and growth of hepatocellular carcinoma cells via decrease of integrin expression and ROCK. Int J Oncol 2011;38:879–85.
105. Roudier E, Mistafa O, Stenius U. Statins induce mammalian target of rapamycin (mTOR)-mediated inhibition of Akt signaling and sensitize p53-deficient cells to cytostatic drugs. Mol Cancer Ther 2006;5:2706–15.
106. Cao Z, Fan-Minogue H, Bellovin DI, et al. MYC phosphorylation, activation, and tumorigenic potential in hepatocellular carcinoma are regulated by HMG-CoA reductase. Cancer Res 2011;71:2286–97.
107. Yang PM, Liu YL, Lin YC, et al. Inhibition of autophagy enhances anticancer effects of atorvastatin in digestive malignancies. Cancer Res 2010;70:7699–709.
108. Sutter AP, Maaser K, Hopfner M, et al. Cell cycle arrest and apoptosis induction in hepatocellular carcinoma cells by HMG-CoA reductase inhibitors. Synergistic antiproliferative action with ligands of the peripheral benzodiazepine receptor. J Hepatol 2005;43:808–16.
109. Kah J, Wustenberg A, Keller AD, et al. Selective induction of apoptosis by HMG-CoA reductase inhibitors in hepatoma cells and dependence on p53 expression. Oncol Rep 2012;28:1077–83.

110. Rao S, Porter DC, Chen X, et al. Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent of hydroxymethyl glutaryl-CoA reductase. Proc Natl Acad Sci U S A 1999;96:7797–802.
111. Trebicka J, Hennenberg M, Odenthal M, et al. Atorvastatin attenuates hepatic fibrosis in rats after bile duct ligation via decreased turnover of hepatic stellate cells. J Hepatol 2010;53:702–12.
112. Miyaki T, Nojiri S, Shinkai N, et al. Pitavastatin inhibits hepatic steatosis and fibrosis in non-alcoholic steatohepatitis model rats. Hepatol Res 2011;41:375–85.
113. Wang W, Zhao C, Zhou J, et al. Simvastatin ameliorates liver fibrosis via mediating nitric oxide synthase in rats with non-alcoholic steatohepatitis-related liver fibrosis. PLoS One 2013;8:e76538.
114. Marrone G, Maeso-Diaz R, Garcia-Cardena G, et al. KLF2 exerts antifibrotic and vasoprotective effects in cirrhotic rat livers: behind the molecular mechanisms of statins. Gut 2014;64(9):1434–43.
115. Abraldes JG, Albillos A, Banares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology 2009;136:1651–8.
116. Uschner FE, Ranabhat G, Choi SS, et al. Statins activate the canonical hedgehog-signaling and aggravate non-cirrhotic portal hypertension, but inhibit the non-canonical hedgehog signaling and cirrhotic portal hypertension. Sci Rep 2015;5:14573.
117. Simon TG, Bonilla H, Yan P, et al. Atorvastatin and fluvastatin are associated with dose-dependent reductions in cirrhosis and hepatocellular carcinoma, among patients with hepatitis C virus: results from ERCHIVES. Hepatology 2016;64:47–57.
118. Simon TG, King LY, Zheng H, et al. Statin use is associated with a reduced risk of fibrosis progression in chronic hepatitis C. J Hepatol 2015;62:18–23.
119. Kaplan DE, Serper MA, Mehta R, et al. Effects of hypercholesterolemia and statin exposure on survival in a large national cohort of patients with cirrhosis. Gastroenterology 2019;156:1693–1706 e12.
120. Singh S, Singh PP, Singh AG, et al. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. Gastroenterology 2013;144:323–32.
121. Shi M, Zheng H, Nie B, et al. Statin use and risk of liver cancer: an update meta-analysis. BMJ Open 2014;4:e005399.
122. Pradelli D, Soranna D, Scotti L, et al. Statins and primary liver cancer: a meta-analysis of observational studies. Eur J Cancer Prev 2013;22:229–34.
123. Syed GH, Amako Y, Siddiqui A. Hepatitis C virus hijacks host lipid metabolism. Trends Endocrinol Metab 2010;21:33–40.
124. Kapadia SB, Chisari FV. Hepatitis C virus RNA replication is regulated by host geranylgeranylation and fatty acids. Proc Natl Acad Sci U S A 2005;102:2561–6.
125. Xia Y, Xie Y, Yu Z, et al. The mevalonate pathway is a druggable target for vaccine adjuvant discovery. Cell 2018;175:1059–73.e21.
126. Bader T, Korba B. Simvastatin potentiates the anti-hepatitis B virus activity of FDA-approved nucleoside analogue inhibitors in vitro. Antiviral Res 2010;86:241–5.
127. Kato S, Smalley S, Sadarangani A, et al. Lipophilic but not hydrophilic statins selectively induce cell death in gynaecological cancers expressing high levels of HMGCoA reductase. J Cell Mol Med 2010;14:1180–93.

128. Thakkar N, Slizgi JR, Brouwer KLR. Effect of liver disease on hepatic transporter expression and function. J Pharm Sci 2017;106:2282–94.
129. Spampanato C, De Maria S, Sarnataro M, et al. Simvastatin inhibits cancer cell growth by inducing apoptosis correlated to activation of Bax and down-regulation of BCL-2 gene expression. Int J Oncol 2012;40:935–41.
130. Tsan YT, Lee CH, Wang JD, et al. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. J Clin Oncol 2012;30:623–30.
131. Simon TG, Duberg AS, Aleman S, et al. Lipophilic statins and risk for hepatocellular carcinoma and death in patients with chronic viral hepatitis: results from a nationwide Swedish population. Ann Intern Med 2019;171:318–27.
132. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007;356:2131–42.
133. Singh B, Berry JA, Shoher A, et al. COX-2 overexpression increases motility and invasion of breast cancer cells. Int J Oncol 2005;26:1393–9.
134. Chen H, Cai W, Chu ESH, et al. Hepatic cyclooxygenase-2 overexpression induced spontaneous hepatocellular carcinoma formation in mice. Oncogene 2017;36:4415–26.
135. Kern MA, Schubert D, Sahi D, et al. Proapoptotic and antiproliferative potential of selective cyclooxygenase-2 inhibitors in human liver tumor cells. Hepatology 2002;36:885–94.
136. Patrono C, Garcia Rodriguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373–83.
137. Kim AK, Dziura J, Strazzabosco M. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma: the egg of columbus or another illusion? Hepatology 2013;58:819–21.
138. Hossain MA, Kim DH, Jang JY, et al. Aspirin enhances doxorubicin-induced apoptosis and reduces tumor growth in human hepatocellular carcinoma cells in vitro and in vivo. Int J Oncol 2012;40:1636–42.
139. Fajardo AM, Piazza GA. Chemoprevention in gastrointestinal physiology and disease. Anti-inflammatory approaches for colorectal cancer chemoprevention. Am J Physiol Gastrointest Liver Physiol 2015;309:G59–70.
140. Chan TA, Morin PJ, Vogelstein B, et al. Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis. Proc Natl Acad Sci U S A 1998;95:681–6.
141. Leng J, Han C, Demetris AJ, et al. Cyclooxygenase-2 promotes hepatocellular carcinoma cell growth through Akt activation: evidence for Akt inhibition in celecoxib-induced apoptosis. Hepatology 2003;38:756–68.
142. Fodera D, D'Alessandro N, Cusimano A, et al. Induction of apoptosis and inhibition of cell growth in human hepatocellular carcinoma cells by COX-2 inhibitors. Ann N Y Acad Sci 2004;1028:440–9.
143. Kanai S, Ishihara K, Kawashita E, et al. ASB14780, an Orally Active Inhibitor of Group IVA phospholipase A2, is a pharmacotherapeutic candidate for nonalcoholic fatty liver disease. J Pharmacol Exp Ther 2016;356:604–14.
144. Hu X, Cifarelli V, Sun S, et al. Major role of adipocyte prostaglandin E2 in lipolysis-induced macrophage recruitment. J Lipid Res 2016;57:663–73.
145. Paik YH, Kim JK, Lee JI, et al. Celecoxib induces hepatic stellate cell apoptosis through inhibition of Akt activation and suppresses hepatic fibrosis in rats. Gut 2009;58:1517–27.
146. Sitia G, Aiolfi R, Di Lucia P, et al. Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. Proc Natl Acad Sci U S A 2012;109:E2165–72.

147. Yoshida S, Ikenaga N, Liu SB, et al. Extrahepatic platelet-derived growth factor-beta, delivered by platelets, promotes activation of hepatic stellate cells and biliary fibrosis in mice. Gastroenterology 2014;147:1378–92.
148. Malehmir M, Pfister D, Gallage S, et al. Platelet GPIbalpha is a mediator and potential interventional target for NASH and subsequent liver cancer. Nat Med 2019;25:641–55.
149. Simon TG, Duberg A, Aleman S, et al. Association of Aspirin with Hepatocellular Carcinoma and Liver-Related Mortality. N Engl J Med 2020;382(11):1018–28.
150. Lee TY, Hsu YC, Tseng HC, et al. Association of daily aspirin therapy with risk of hepatocellular carcinoma in patients with chronic hepatitis B. JAMA Intern Med 2019;179:633–40.
151. Tsoi KKF, Ho JMW, Chan FCH, et al. Long-term use of low-dose aspirin for cancer prevention: a 10-year population cohort study in Hong Kong. Int J Cancer 2019;145:267–73.
152. Hwang IC, Chang J, Kim K, et al. Aspirin Use and risk of hepatocellular carcinoma in a national cohort study of Korean adults. Sci Rep 2018;8:4968.
153. Kim G, Jang SY, Han E, et al. Effect of statin on hepatocellular carcinoma in patients with type 2 diabetes: a nationwide nested case-control study. Int J Cancer 2017;140:798–806.
154. Lin YS, Yeh CC, Huang SF, et al. Aspirin associated with risk reduction of secondary primary cancer for patients with head and neck cancer: a population-based analysis. PLoS One 2018;13:e0199014.
155. Tseng CH. Metformin and risk of hepatocellular carcinoma in patients with type 2 diabetes. Liver Int 2018;38:2018–27.
156. Lee TY, Wu JC, Yu SH, et al. The occurrence of hepatocellular carcinoma in different risk stratifications of clinically noncirrhotic nonalcoholic fatty liver disease. Int J Cancer 2017;141:1307–14.
157. Lee M, Chung GE, Lee JH, et al. Antiplatelet therapy and the risk of hepatocellular carcinoma in chronic hepatitis B patients on antiviral treatment. Hepatology 2017;66:1556–69.
158. Chiu HF, Ho SC, Chen CC, et al. Statin use and the risk of liver cancer: a population-based case–control study. Am J Gastroenterol 2011;106:894–8.
159. Coogan PF, Rosenberg L, Palmer JR, et al. Nonsteroidal anti-inflammatory drugs and risk of digestive cancers at sites other than the large bowel. Cancer Epidemiol Biomarkers Prev 2000;9:119–23.
160. Friis S, Sørensen HT, McLaughlin JK, et al. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. Br J Cancer 2003;88:684–8.
161. Du ZQ, Zhao JZ, Dong J, et al. Effect of low-dose aspirin administration on long-term survival of cirrhotic patients after splenectomy: a retrospective single-center study. World J Gastroenterol 2019;25:3798–807.
162. Yang B, Petrick JL, Chen J, et al. Associations of NSAID and paracetamol use with risk of primary liver cancer in the Clinical Practice Research Datalink. Cancer Epidemiol 2016;43:105–11.
163. Sahasrabuddhe VV, Gunja MZ, Graubard BI, et al. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma. J Natl Cancer Inst 2012;104:1808–14.
164. Petrick JL, Sahasrabuddhe VV, Chan AT, et al. NSAID use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the liver cancer pooling project. Cancer Prev Res (Phila) 2015;8:1156–62.

165. Simon TG, Ma Y, Ludvigsson JF, et al. Association between aspirin use and risk of hepatocellular carcinoma. JAMA Oncol 2018;4:1683–90.
166. Simon TG, Duberg AS, Aleman S, et al. Association of aspirin with hepatocellular carcinoma and liver-related mortality. N Engl J Med 2020;382:1018–28.
167. Zheng L, Yang W, Wu F, et al. Prognostic significance of AMPK activation and therapeutic effects of metformin in hepatocellular carcinoma. Clin Cancer Res 2013;19:5372–80.
168. DePeralta DK, Wei L, Ghoshal S, et al. Metformin prevents hepatocellular carcinoma development by suppressing hepatic progenitor cell activation in a rat model of cirrhosis. Cancer 2016;122:1216–27.
169. Shankaraiah RC, Callegari E, Guerriero P, et al. Metformin prevents liver tumourigenesis by attenuating fibrosis in a transgenic mouse model of hepatocellular carcinoma. Oncogene 2019;38:7035–45.
170. Ma S, Zheng Y, Xiao Y, et al. Meta-analysis of studies using metformin as a reducer for liver cancer risk in diabetic patients. Medicine (Baltimore) 2017; 96:e6888.
171. Home PD, Kahn SE, Jones NP, et al. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A diabetes outcome progression trial) and RECORD (rosiglitazone evaluated for cardiovascular outcomes and regulation of glycaemia in diabetes) clinical trials. Diabetologia 2010;53:1838–45.
172. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–307.
173. Chang CH, Lin JW, Wu LC, et al. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. Hepatology 2012;55: 1462–72.
174. Hassan MM, Curley SA, Li D, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer 2010;116: 1938–46.
175. Huang MY, Chung CH, Chang WK, et al. The role of thiazolidinediones in hepatocellular carcinoma risk reduction: a population-based cohort study in Taiwan. Am J Cancer Res 2017;7:1606–16.
176. Kasmari AJ, Welch A, Liu G, et al. Independent of cirrhosis, hepatocellular carcinoma risk is increased with diabetes and metabolic syndrome. Am J Med 2017;130:746 e1–7.
177. Kawaguchi T, Taniguchi E, Morita Y, et al. Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection. Liver Int 2010;30:479–86.
178. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–90.
179. Hoshida Y, Fuchs BC, Tanabe KK. Prevention of hepatocellular carcinoma: potential targets, experimental models, and clinical challenges. Curr Cancer Drug Targets 2012;12:1129–59.
180. Oakley F, Teoh V, Ching ASG, et al. Angiotensin II activates I kappaB kinase phosphorylation of RelA at Ser 536 to promote myofibroblast survival and liver fibrosis. Gastroenterology 2009;136:2334–2344 e1.
181. Tamaki Y, Nakade Y, Yamauchi T, et al. Angiotensin II type 1 receptor antagonist prevents hepatic carcinoma in rats with nonalcoholic steatohepatitis. J Gastroenterol 2013;48:491–503.

182. Hassan MM, Botrus G, Abdel-Wahab R, et al. Estrogen replacement reduces risk and increases survival times of women with hepatocellular carcinoma. Clin Gastroenterol Hepatol 2017;15:1791–9.
183. Sun H, Deng Q, Pan Y, et al. Association between estrogen receptor 1 (ESR1) genetic variations and cancer risk: a meta-analysis. J BUON 2015;20:296–308.
184. McGlynn KA, Sahasrabuddhe VV, Campbell PT, et al. Reproductive factors, exogenous hormone use and risk of hepatocellular carcinoma among US women: results from the Liver Cancer Pooling Project. Br J Cancer 2015;112:1266–72.
185. Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut 2013;62:606–15.
186. Bode AM, Dong Z. Cancer prevention research - then and now. Nat Rev Cancer 2009;9:508–16.
187. Cancer Genome Atlas Research Network. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. Cell 2017;169:1327–41.e23.
188. Le Magnen C, Dutta A, Abate-Shen C. Optimizing mouse models for precision cancer prevention. Nat Rev Cancer 2016;16:187–96.
189. Maresso KC, Tsai KY, Brown PH, et al. Molecular cancer prevention: current status and future directions. CA Cancer J Clin 2015;65:345–83.
190. Bruix J, Poynard T, Colombo M, et al. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. Gastroenterology 2011;140:1990–9.
191. Lok AS, Everhart JE, Wright EC, et al. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology 2011;140:840–9 [quiz: e12].
192. Nakagawa S, Wei L, Song WM, et al. Molecular liver cancer prevention in cirrhosis by organ transcriptome analysis and lysophosphatidic acid pathway inhibition. Cancer Cell 2016;30:879–90.
193. Rahmani J, Kord Varkaneh H, Kontogiannis V, et al. Waist circumference and risk of liver cancer: a systematic review and meta-analysis of over 2 million cohort study participants. Liver Cancer 2020;9:6–14.
194. Esposito K, Capuano A, Giugliano D. Metabolic syndrome and cancer: holistic or reductionist? Endocrine 2014;45:362–4.
195. Vanni E, Bugianesi E. Obesity and liver cancer. Clin Liver Dis 2014;18:191–203.
196. Farrell G. Insulin resistance, obesity, and liver cancer. Clin Gastroenterol Hepatol 2014;12:117–9.
197. Michelotti GA, Machado MV, Diehl AM. NAFLD, NASH and liver cancer. Nat Rev Gastroenterol Hepatol 2013;10:656–65.
198. Gehmert S, Sadat S, Song YH, et al. The anti-apoptotic effect of IGF-1 on tissue resident stem cells is mediated via PI3-kinase dependent secreted frizzled related protein 2 (Sfrp2) release. Biochem Biophys Res Commun 2008;371:752–5.
199. Sidharthan S, Kottilil S. Mechanisms of alcohol-induced hepatocellular carcinoma. Hepatol Int 2014;8:452–7.
200. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265–71.
201. Gressner OA, Lahme B, Rehbein K, et al. Pharmacological application of caffeine inhibits TGF-beta-stimulated connective tissue growth factor

expression in hepatocytes via PPARgamma and SMAD2/3-dependent pathways. J Hepatol 2008;49:758–67.
202. Kalthoff S, Ehmer U, Freiberg N, et al. Coffee induces expression of glucuronosyltransferases by the aryl hydrocarbon receptor and Nrf2 in liver and stomach. Gastroenterology 2010;139:1699–710, 1710.e1-2.
203. Zhou X, Chen J, Yi G, et al. Metformin suppresses hypoxia-induced stabilization of HIF-1alpha through reprogramming of oxygen metabolism in hepatocellular carcinoma. Oncotarget 2016;7:873–84.