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Chemopreventive strategies in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer. The incidence and mortality of HCC are increasing in most Western countries as a result of an ageing cohort infected with chronic hepatitis C, and are expected to continue to rise as a consequence of the obesity epidemic. Chemopreventive strategies aimed at decreasing the risk or delaying the onset of HCC are needed. Universal immunization against HBV and antiviral therapy against HBV and HCV in patients with established disease has consistently been associated with reduced HCC risk, especially in patients who achieve sustained virologic response. However, the cost-effectiveness of antiviral therapy for primary HCC prevention is not known. Several commonly prescribed medications seem promising as chemopreventive agents against HCC, including statins, antidiabetic medications and aspirin. Dietary agents such as coffee, vitamin E and fish oil as well as phytochemicals might also be associated with reduced risk of HCC. Though randomized controlled trials are ideally needed to firmly establish efficacy, such chemoprevention trials are logistically and ethically challenging. Well-designed, prospective, population-based cohort studies might provide the best evidence for chemopreventive efficacy of these agents.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide.[1,2] More than 80% of cases of HCC occur in East Asia and sub-Saharan Africa, where incidence rates are in excess of 20 per 100,000 persons.[2] Although the incidence of HCC in East Asia is stable and expected to decline with more widespread immunization against HBV, the incidence is rising in most Western countries that have a low or intermediate prevalence of HCC.[3] With the ageing of the 'baby boomers' (people born between 1946–1964), the incidence of hepatitis-C-associated HCC is expected to rise over the next two decades and, perhaps, continue to rise due to the burgeoning obesity epidemic and risk of NAFLD-associated

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HCC. Only 13% of HCCs diagnosed in the USA are detected early enough to be eligible for curative therapy such as surgical resection or liver transplantation.[4] The 5-year survival rate for patients with HCC in the USA is dismal at 15%, ranging from 28% for localized disease to 3% for metastatic disease.[5] This low rate is in part due to mortality from underlying chronic liver disease and cirrhosis; patients with HCC in the absence of cirrhosis who are able to undergo surgical resection have a 5-year survival rate of >50%.[5]

Hence, in light of the increasing incidence of HCC, especially in some Western countries, and the high mortality rate associated with the disease, chemopreventive strategies to prevent or delay the development of HCC are attractive. In this Review, we discuss advances in the field of HCC chemoprevention, with a particular focus on aetiology-specific interventions (such as antiviral therapy against HBV and HCV), the cancer-modifying effects of statins, antidiabetic medications and aspirin, as well as dietary strategies for prevention of HCC.

Risk factors and pathogenesis of HCC

The leading risk factors for HCC are chronic HBV and HCV infection, alcoholic cirrhosis and NAFLD. Chronic HBV infection is associated with a 5–100-fold increase in the risk of HCC, with estimated incidence rates (per 100 person-years) of 0.02–0.20 in inactive carriers, 0.3–0.6 in patients with chronic HBV infection without cirrhosis, and 2.2–3.7 in patients with compensated cirrhosis.[6] Although HCC can arise in the absence of cirrhosis in patients with HBV, the majority of these cases (70–80%) have underlying cirrhosis.[7] Several factors are associated with an increased risk of HCC in patients with HBV, including the following: specific demographic factors, such as advanced age, male sex, Asian or African descent with acquisition of HBV infection either perinatally or in early childhood, and family history of HCC; viral factors, including high viral load, active HBV replication, and specific HBV genotypes; and environmental exposures, including concomitant alcohol intake, smoking and aflatoxin exposure.[8]

HCV infection is associated with a 15–20-fold increased risk of HCC, with most cases arising in the setting of advanced fibrosis or cirrhosis 25–30 years after infection.[8] In patients with cirrhotic stage hepatitis C, the annual rate of developing HCC ranges from 1% to 7%.[8] High rates are associated with modifiable risk factors—such as concomitant alcohol use, diabetes, smoking and co-existing latent HBV infection—as well as non-modifiable risk factors, including male sex, advanced age and African-American ethnicity. Alcoholic liver disease is the second most common risk factor for HCC in the USA, after hepatitis C.[8] In 30–40% of cases of HCC diagnosed in Western countries, a clear aetiology for HCC is not identified—although it is increasingly being recognized that NAFLD and the metabolic syndrome might be responsible for some of these cases.[9] Several population-based cohort studies have shown a 1.5–2.0-fold increase in the risk of HCC among obese patients compared with nonobese patients;[10,11] likewise, the presence of diabetes is associated with a twofold increased risk of HCC.[12]

HCC is a prototype of inflammation-associated cancer; an environment of chronic inflammation results in continuous rounds of cell injury, necrosis and regeneration within a

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genotoxic milieu of oxidative stress that leaves the liver prone to the development of activating mutations in oncogenes and inactivating genetic and epigenetic suppression of tumour suppressor genes.[13–15] This process results in disruption of multiple signalling cascades, as shown in Figure 1. Receptor tyrosine kinase pathways induce the Ras–mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)–Akt kinase signalling pathways in >50% of HCCs.[16] Activation of these pathways results in downstream activation of the Ras–Raf–ERK (extracellular signal regulated kinase) pathway, which in turn activates proto-oncogene c-Fos and transcription factor AP-1 (also known as proto-oncogene c-Jun), which induce transcription of genes that drive cell proliferation.[16] Activation of the PI3K–Akt kinase signalling pathway through insulin receptors or insulin-like growth factor receptors (such as IGFR1) results in disruption of the mammalian target of rapamycin (mTOR) pathway, which is seen in 40–50% of cases of HCC, leading to inactivation of tumour suppressors such as PTEN, and promoting carcinogenesis.[17] Activating mutations in β-catenin, which activate the Wnt signalling pathway, occur in one-third of HCCs.[15] Wnts are involved in regulation of liver regeneration and in the maintenance and self-renewal of pluripotent stem cells and progenitor cells; activation of the Wnt signalling pathway promotes hepatocarcinogenesis.[18] The pathogenesis of HCC has been reviewed in detail elsewhere.[13–15]

Aetiology-specific chemoprevention

Hepatitis B vaccination

Implementation of universal HBV vaccination (adopted in >175 countries worldwide) has markedly reduced the rate of acquisition of new HBV infections, which in turn has resulted in a substantial decline in the risk of HBV-associated HCCs.[19] In Taiwan, after implementation of nationwide HBV vaccination in 1984, HCC incidence declined among children 6–19 years of age.[20] In their analysis, Chang and colleagues[20] observed an incidence rate of 0.17 per 100,000 person-years among children who received immunization, compared with 0.56 per 100,000 person-years among age-matched and sex-matched children who did not receive the HBV vaccine (RR 0.31).[20]

Antiviral therapy against HBV

The potential utility of antiviral therapy for chemoprevention in patients with chronic hepatitis B stems from its ability to control viral replication, a key risk factor for HBV-associated hepatocarcinogenesis.[14] Studies assessing the efficacy of IFN-α in decreasing the risk of HBV-associated HCC have shown varying results, and have been summarized by Lai and Yeun.[21] Briefly, IFN-α might decrease the risk of HCC in a subset of patients with HBV-associated cirrhosis who have sustained response to treatment (seen in ~35% of patients).[21] In a cohort of 313 patients with HBV-associated cirrhosis, the cumulative occurrence of HCC was significantly lower in patients treated intermittently with interferon, versus no therapy, at 5 years (7.0% versus 19.6%, respectively) and 10 years (17.0% and 30.8%, respectively) ($P = 0.01$).[22] However, the risk of hepatic decompensation is substantial with interferon therapy in patients with cirrhosis; therefore the risk:benefit ratio of treatment with interferon for chemoprevention in these patients needs to be carefully weighed.

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Compared with interferon, nucleos(t)ide analogues provide more potent suppression of viral replication and demonstrate a more consistent decrease in the risk of HBV-associated HCC at all stages of the disease. In the only prospective, placebo-controlled clinical trial of the efficacy of lamivudine in 651 patients with HBV and advanced fibrosis or cirrhosis, 3.9% of lamivudine-treated patients developed HCC, compared with 7.4% of patients treated with placebo ($P = 0.047$), at 2.8 years follow-up.[23] Subsequent historical case–control and cohort studies have consistently demonstrated a beneficial effect of lamivudine or adefovir in decreasing the risk of HCC (Supplementary Table 1 online). In a long-term prospective cohort study, patients treated with entecavir were significantly less likely to develop HCC than propensity-matched control patients who did not receive any treatment: the 5-year cumulative incidence of HCC in the entecavir-treated patients was 3.7%, compared with 13.7% in the control group ($P < 0.01$).[24] In a meta-analysis of five studies with 2,289 patients (1,267 treated with lamivudine and 1,022 patients with no treatment), the risk of HCC was 78% lower in the treated group (the proportion of patients who developed HCC was 2.5% and 11.7% for treated and untreated patients, respectively; $P = 0.01$).[25] The protective effect of lamivudine occurred regardless of the presence or absence of cirrhosis, and even in patients with drug resistance. In an updated systematic review of 21 studies, HCC occurred significantly less frequently in treated than untreated patients with HBV (2.8% versus 6.4%, respectively; $P < 0.01$).[26] In a subset of studies, the risk of HCC was considerably lower in those who achieved virologic response compared with those who did not respond adequately to treatment.[26]

Antiviral therapy against HCV

With the ageing of baby boomers in the USA, it is estimated that without intervention, HCV-related deaths will reach 35,000 per year in the USA within the next 15–25 years.[27] About 16% of patients with HCV develop cirrhosis after 20 years,[28] with increased rates after longer follow-up;[29] HCC occurs at an estimated annual rate of 1–7% in patients with cirrhosis.[2] Several observational studies and randomized controlled trials have shown that clearance of viraemia with achievement of sustained virologic response (SVR) using interferon-based therapy is associated with a marked decline in the risk of HCC (Supplementary Table 2 online). In a meta-analysis of nine randomized controlled trials in 1,614 patients with HCV, Zhang and colleagues[30] reported that patients treated with interferon had a decreased risk of HCC, compared with patients who did not receive treatment (RR 0.39; 95% CI 0.26–0.59); however, this decline in risk was significant only in patients who achieved SVR (RR 0.96; 95% CI 0.59–1.56).[30] In the pivotal Hepatitis C Antiviral Long Term Treatment against Cirrhosis (HALT-C) trial, the adjusted cumulative incidence of HCC 7.5 years after enrolment was 1.1%, 5.5% and 8.8% among those who achieved SVR, breakthrough or relapse after initial response, and nonresponders, respectively.[31] In a pooled analysis of 30 observational studies, among 25,906 patients with all-stage HCV followed up for 3.0–8.2 years, Morgan and colleagues[32] observed that the rate of HCC was 1.6% among patients who achieved SVR and 6.1% among patients who either failed therapy or did not receive treatment.[32] The estimated reduction in risk of HCC was 76% among patients who achieved SVR (adjusted HR 0.24; 95% CI 0.18–0.31); the risk reduction estimates were similar for studies that assessed HCC risk in patients with all-stages of HCV or only in those with advanced fibrosis. On the basis of these results, the

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authors estimated that successful eradication of chronic HCV would result in 14 fewer HCC cases per 1,000 persons per year with HCV at all stages or 23 fewer HCC cases per 1,000 persons per year with HCV with advanced fibrosis.[32]

Although interferon seems to have some direct anti-tumour effects, current evidence suggests that most of the risk reduction is attributable to clearance of viraemia. With the introduction of new direct-acting antiviral agents such as the NS3/4A protease inhibitors, telaprevir and boceprevir, increased SVR rates are being achieved in treatment-naive as well as prior nonresponders.[33] Multiple other highly effective agents are in development that offer interferon-free treatment regimens, which might result in a greater proportion of infected patients being treated.[34] Hence, it is widely anticipated that the rates of HCC attributable to chronic HCV infection will decline with widespread utilization of these regimens. However, the cost of these new direct-acting antiviral agents for primary prevention of HCC remains prohibitive.

Recognition that obesity and alcohol use might synergistically increase the risk of HCC in patients with chronic HBV and HCV infection is increasing.[35] Hence, mitigation of obesity-induced chronic inflammation and insulin resistance through the use of metformin, as well as statins, might potentiate the antineoplastic effects of antiviral therapy in these patients (discussed later). In their population-based study of patients with chronic HCV infection, Tsan and colleagues[36] observed a decrease in HCC risk with statin use even in patients treated with antiviral therapy (adjusted HR 0.27; 95% CI 0.07–1.09);[36] however, perhaps owing to the small number of HCC cases developing in patients with HCV who have received treatment, this association did not achieve statistical significance.

Generic chemoprevention strategies

Statins

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the second most commonly prescribed medications worldwide and are primarily used for primary and secondary prevention of cardiovascular diseases.[37] Besides their effect on cholesterol biosynthesis, statins also have antineoplastic properties through antiproliferative, proapoptotic, antiangiogenic, immunomodulatory and anti-infective effects.[38] Observational studies have shown that statins might be protective against inflammation-driven cancers, including oesophageal adenocarcinoma,[39] *Helicobacter pylori*-associated gastric cancer[40] and colitis-associated colorectal cancer.[41]

Mechanism of action—By blocking conversion of HMG-CoA into mevalonate through competitive inhibition of HMG-CoA reductase, statins inhibit several downstream products of the mevalonate pathway.[38] This inhibition prevents post-translational prenylation of signalling Ras/Rho proteins, which are key mediators of cell growth, differentiation and survival (Figure 1). Statins are also proapoptotic, by regulating the RAF–MAPK–ERK pathway, activating caspases and decreasing expression of *BCL-2*.[42,43] Statins inhibit the activation of the proteasome pathway, limiting the degradation of the cyclin-dependent kinase inhibitors p21 and p27, thus allowing these molecules to exert their growth-inhibitory effects.[44] In addition, statins also exert anti-inflammatory and immunomodulatory effects.[38]

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In hepatocarcinogenesis, atorvastatin has been shown to block Myc phosphorylation and activation, suppressing tumour initiation and growth through a HMG-CoA reductase-dependent pathway.[45–47]

Evidence from epidemiological studies—Several large population-based cohort studies in Asian and Western populations have shown a protective association between statin use and risk of incident HCC.[36,48–50] Using the Taiwanese National Health Insurance Research Database, Tsan and colleagues[49] followed 33,413 HBV-infected adult patients from 1997 to 2008 (8.3% statin users) and identified 1,021 incident cases of HCC.[49] The incidence rate (per 100,000 person years) of HCC in patients receiving statins was 210.9, compared with 319.5 in statin non-users (P <0.01). After adjusting for potential confounders, including age, sex, cirrhosis, diabetes and medications (such as anti-HBV treatments, aspirin and angiotensin-converting enzyme inhibitors), they observed that statin users had a 53% lower risk of HCC than statin non-users. Similar results were also observed in another study on the chemopreventive effect of statins in patients with chronic HCV.[36] Although preclinical studies have suggested that lipophilic statins (such as lovastatin and simvastatin) might have greater chemoprotective effects than lipophobic statins (such as pravastatin), due to their greater lipid solubility and membrane permeability,[51] Tsan *et al.*[49] observed that the reduction in HCC risk was a class effect, and not specific for particular formulations of statins.[49] Supplementary Table 3 online summarizes findings from key studies on the chemopreventive effect of statins against HCC.

In contrast to observational studies, randomized controlled trials of statins have failed to demonstrate a protective effect against HCC. In a *post hoc* analysis of 22 randomized controlled trials from the Cholesterol Treatment Trialists' collaboration, 68 cases of HCC were observed in ~135,000 patients; statin users were no less likely to develop HCC than patients receiving placebo (adjusted OR 1.06; 95% CI 0.66–1.71).[52] In a meta-analysis of 10 studies (7 observational studies, 3 randomized controlled trials) reporting 4,298 cases of HCC in ~1.5 million patients, we observed that statins users were 37% less likely to develop HCC (adjusted OR 0.63; 95% CI 0.52–0.76).[53] The risk reduction was greater in Asian populations (adjusted OR, 0.52; 95% CI, 0.42–0.64), but was also observed in Western populations (adjusted OR, 0.67; 95% CI, 0.53–0.85).

Limitations of evidence—Observational studies lack the experimental random allocation of the intervention necessary to test exposure–outcome hypotheses optimally. Despite adjusting for numerous confounding variables, it is not possible to exclude residual confounding, in particular, confounding by indication. Even though statins are safe in patients with chronic liver disease, anecdotal evidence suggests that primary care physicians might be less likely to prescribe statins to patients with cirrhosis, the group at highest risk of HCC. Hence, the protective effect of statins might be overestimated in observational studies. In addition, most of the observational studies failed to adjust for the concomitant use of antidiabetic medications, which have inherent cancer-modifying effects. It can be presumed that a substantial proportion of patients on statins would also be receiving metformin and/or thiazolidinediones. This factor might potentially overestimate the chemopreventive effect of statins on HCC. However, in the above-mentioned Taiwanese study, re-analysis of the data

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after adjusting for metformin, thiazolidinediones and sulphonylurea use showed a persistent independent protective effect of statins.[54]

In addition, *post hoc* analyses of randomized controlled trials performed in Western populations also have inherent limitations. The patients enrolled in these randomized controlled trials, which were designed primarily for cardiovascular end points, are at low risk of developing HCC. Thus, these studies are not adequately powered to detect a significant difference between the placebo and statin groups with regard to development of HCC.[53]

Antidiabetic medications

Several preclinical and epidemiological studies have suggested that conventional antidiabetic medications might modify the risk of cancer in patients with diabetes: metformin and thiazolidinediones might be associated with decreased risk of cancer,[55] whereas insulin and insulin secretagogues, such as sulphonylureas, might be associated with increased cancer risk.[56]

Mechanisms of action—Metformin activates adenosine monophosphate-activated protein kinase (AMPK), which inhibits the mTOR pathway (a downstream effector of growth factor signalling), and might thus decrease HCC risk (Figure 1).[57] In addition, metformin might also inhibit cell growth and promote cell death by inhibiting cyclin D1 expression and pRb (retinoblastoma-like protein) phosphorylation.[58] Metformin can also inhibit hepatocarcinogenesis by downregulating c-Myc through AMPK-signalling and miR-33a upregulation and by decreasing lipogenesis.[59] Insulin-sensitizing peroxisome proliferator activated receptor γ (PPAR-γ)-agonists, or thiazolidinediones, also exert anticancer effects through inhibition of the ubiquitin–proteasome system and the ERK pathway.[60,61] Thiazolidinediones have also been shown to have PPAR-γ-independent effects in preclinical models of HCC.[61]

Sulphonylureas, by increasing insulin secretion, and exogenous insulin itself, can promote oncogenesis either directly or indirectly by increasing insulin-like growth factor 1 (IGF-1) activity. This activity results in abnormal stimulation of multiple cellular signalling cascades, enhancing growth-factor-dependent cell proliferation and affecting cell metabolism (Figure 1).[62]

Evidence from epidemiological studies—Several observational studies have reported an association between metformin and decreased risk of HCC in patients with diabetes. In a large population-based, nested, case–control study of 22,047 cases of HCC and 25,773 controls from Taiwan, metformin use was associated with a 21% decrease in the risk of HCC, after adjusting for potential confounders including duration and control of diabetes as well as use of other antidiabetic agents.[58] This apparent chemopreventive effect of metformin was dependent on cumulative dose, with each incremental year increase in metformin use being associated with a 7% decrease in HCC risk.[58] In a population-based Dutch cohort study of >85,000 patients with diabetes receiving metformin or sulphonylurea monotherapy, Ruiter and colleagues[63] observed that metformin use was associated with a 33% lower risk of HCC than sulphonylurea use.[63] In a meta-analysis of eight studies, we

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observed that metformin use (ever used versus never used) was associated with a 50% lower risk of HCC, with risk estimates significantly stronger in Western populations (adjusted OR 0.42; 95% CI 0.24–0.76) than in Asian populations (adjusted OR 0.79; 95% CI 0.75–0.83).[64] This association was stable when the analysis was restricted to studies that adjusted for the concomitant effect of other antidiabetic medications, as well as in studies that adjusted for the duration and/or severity of diabetes.[64]

Although some studies have suggested a potential protective association between thiazolidinediones and HCC risk in patients with diabetes, these results are less consistent than for metformin. Utilizing the Taiwanese National Health Insurance Database, Chang and colleagues[65] observed that use of rosiglitazone or pioglitazone is associated with a 17–27% reduced risk of HCC, with a trend towards a cumulative dose and duration-of-use effect.[65] However, this decrease in risk was only significant in a cohort of diabetic patients with a history of chronic liver disease, but not in patients with no history of underlying liver disease. Other studies from Asian[66,67] and Western[66] populations have not shown a significant protective effect of thiazolidinediones against HCC.

Both insulin and sulphonylureas have been associated with an increased risk of HCC. Insulin use (as compared to non-use), in particular has been consistently associated with an increased risk of HCC. In a meta-analysis of seven observational studies, we observed that insulin use was associated with a 2.6-fold increased risk of HCC (adjusted OR 2.61; 95% CI 1.46–4.65).[64] Chen *et al.*[58] observed that each incremental year of insulin use was associated with a 13% increased risk of developing HCC. Similarly, sulphonylureas have also been associated with an increased risk of HCC. In a subset of patients with diabetes in a hospital-based case–control study, Hassan *et al.*[68] observed a sevenfold higher risk of HCC for sulphonylureas than with other antidiabetic agents. Overall, it seems that sulphonylureas are associated with a 62% increased risk of HCC based on a meta-analysis of observational studies (adjusted OR 1.62; 95% CI 1.16–2.24).[64] Supplementary Table 4 online provides details of key studies assessing the relationship between antidiabetic medications and risk of HCC in patients with diabetes.

Limitations of evidence—Though the association between individual antidiabetic medications and risk of HCC seem to be strong and consistent, especially for metformin, caution needs to be exercised when interpreting the results of these observational studies. Most patients with diabetes require multiple antidiabetic medications simultaneously for optimal glycaemic control. As a result, in the individual studies, the nature of the comparator group for each individual medication was composed of other antidiabetic medications, which have an inherent cancer-modifying effect. For example, compared with patients receiving metformin, patients not on metformin (the comparator group) were more likely to be on sulphonylureas and/or insulin. Hence, it is difficult to interpret how much the risk modification attributed to any one medication is real or confounded by exposures to other glucose-lowering medications. This factor also puts studies at-risk for immortal time bias and inherent time-lagging issues when comparing first-line treatment with metformin with second-line and third-line treatments with other agents.[69] Therefore, all the apparent risk estimates might be amplified and the actual cancer-modifying effects are probably smaller.

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The inherent limitations of observational studies as mentioned above apply to these studies as well.

Just as studies on the chemopreventive effective of statins fail to adjust for the chemopreventive effect of antidiabetic agents, most of these studies of antidiabetic agents fail to adjust for the potential chemopreventive effect of statins.[70] In a cohort of Taiwanese patients with HBV, Tsan *et al.*[49] initially observed that metformin use was associated with a chemoprotective effect against HCC after adjusting for age, sex, cirrhosis and diabetes (adjusted OR 0.73; 95% CI 0.54–0.98); however, this effect was no longer significant after adjusting for statin use (adjusted OR 0.76; 95% CI 0.49–1.20).

Aspirin

Antiplatelet agents such as aspirin have been shown to have anti-inflammatory effects through different mechanisms, including inhibition of cyclooxygenase-2. Aspirin has been shown to have antineoplastic effects against inflammation-mediated cancers, for example oesophageal adenocarcinoma arising in patients with Barrett oesophagus.[71]

Mechanism of action—As described above, host immune-mediated chronic inflammation in response to HBV infection predisposes to hepatocarcinogenesis; platelets are key facilitators of this immune-mediated injury as they promote the accumulation of $CD8^+$ T cells.[72] In an HBV transgenic mouse model of chronic immune-mediated liver disease that rapidly progresses to HCC, Sitia and colleagues[73] showed that aspirin decreased T-cell-mediated inflammation, the severity of fibrosis and progression to HCC.[73] However, the protective effect of aspirin was not observed in a nonimmunologically-mediated toxin-induced model of HCC. In addition to amelioration of immune-mediated chronic inflammation, aspirin might also decrease the risk of tumour formation and spread by inhibiting the cyclooxygenase-2 enzyme.[74]

Evidence from epidemiological studies—In a large population-based study of men and women aged 50–71 years in the NIH–AARP Diet and Health Study cohort, Sahasrabuddhe *et al.*[75] observed that aspirin use (as compared to non-use) was associated with a 41% lower risk of HCC. However, a cumulative dose-response or duration-response relationship between aspirin use and risk modification of HCC was not observed; risk reduction of HCC was similar among patients who reported monthly (≤2–3 times per month) (OR 0.55; 95% CI 0.40–0.78) or daily aspirin use (more than once a day) (OR 0.59; 95% CI 0.43–0.81). By contrast, other population-based case–control and cohort studies have not observed such an association between aspirin use and risk of HCC due to any cause, although these studies were not specifically designed to address this question.[48,50]

Limitations of evidence—Epidemiological and experimental studies on the long-term effects of chronic aspirin use on risk of HCC are lacking. The primary study by Sahasrabuddhe and colleagues[75] had several limitations, including limited one-time assessment of self-reported aspirin use with no verification from pharmacy databases, absence of a dose–response relationship, lack of adjustment for major confounding variables including concomitant use of other potential chemopreventive agents such as statins and

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metformin, and perhaps most importantly, confounding by severity of liver disease.[76] Patients with cirrhosis and portal hypertension with thrombocytopaenia, the group presumably at highest risk of HCC, are frequently advised to abstain from aspirin use due to the risk of gastrointestinal bleeding and renal failure. This factor decreases the propensity of physicians to prescribe aspirin in this population and might therefore spuriously overestimate the apparent chemopreventive effect of aspirin. To address this concern, a subsequent sensitivity analysis by Sahasrabuddhe and colleagues[75]—which excluded patients who developed HCC or died within 5 years of reported aspirin use—showed a persistent protective association between aspirin and HCC risk.[75]

Dietary agents for prevention of HCC

Coffee

Coffee consumption has been consistently associated with a reduced risk of HCC in both case–control[77] and cohort studies.[78] The effect of coffee is dose-dependent regardless of the aetiology of underlying chronic liver disease. In a meta-analysis of 14 studies (eight cohort studies and six case–control studies; 2,733 cases of HCC), Bravi and colleagues[79] observed a 43% decline in the risk of HCC in individuals who consumed coffee (OR 0.57; 95% CI 0.49–0.67). For each cup of coffee consumed per day, the risk of HCC decreased by 23%.[80] Coffee might exert its anti-neoplastic effects through compounds such as diterpenes, cafestol and kahweol, which modulate enzymes involved in carcinogen detoxification; caffeine also has antioxidant properties.[81] In addition, coffee has been shown to reduce the risk of advanced fibrosis and cirrhosis, and hence, might indirectly modify the risk of HCC.[82]

Vitamin E

Vitamin E intake has also been shown to decrease the risk of HCC. In two large population-based cohorts—the Shanghai Women's Health Study and the Shanghai Men's Health Study—Zhang and colleagues[83] observed a significantly lower risk of HCC among patients in the highest quartile of dietary vitamin E intake than in the lowest quartile (RR 0.60; 95% CI 0.40–0.89); similar results were seen in patients consuming supplemental vitamin E (RR 0.52; 95% CI 0.30–0.90).[83] Such a protective association was not seen for dietary consumption or supplemental use of other vitamins or calcium, arguing in favour of a vitamin-E-specific effect, rather than a healthy user effect. Vitamin E has a potent anti-oxidant effect, which prevents DNA damage, enhances DNA repair and promotes inactivation of carcinogens. Currently, vitamin E is a first-line pharmacotherapy for patients without diabetes but with biopsy-proven NASH.[84]

Fish consumption

Fish consumption has also been associated with a reduced risk of HCC. In a large Japanese population-based cohort study, Sawada and colleagues[85] observed that dietary consumption of fish rich in *n*-3 polyunsaturated fatty acids might also be associated with a 36% reduced risk of HCC (RR 0.64; 95% CI 0.42–0.96, compared with the lowest quintile of consumption) in a dose-dependent manner.[85]

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Phytochemicals

Several preclinical studies have shown that dietary phytochemicals, which possess potent antioxidant, anti-inflammatory and antineoplastic properties, might also modify the risk of HCC. Multiple agents have been explored for their role in chemoprevention of HCC, in particular aflatoxin-induced HCC.[86] A strong link exists between aflatoxin-contaminated food and HCC incidence. Various biomarkers such as urinary aflatoxin-N7-guanine and aflatoxin-serum albumin adducts have been associated with risk of HCC, and modulation of these biomarkers by various compounds have been used in trials as surrogate end points of chemopreventive efficacy.[87] Cruciferous vegetables, for example broccoli sprouts, might exert antineoplastic effects via glucosinolates and metabolites (such as sulphoraphane) that modulate Keap1/Nrf2 signalling and activate cytoprotective responses against oxidants.[88] In a placebo-controlled randomized trial in Qidong, China, broccoli sprout extracts were shown to decrease urinary excretion of sulphoraphane metabolites and aflatoxin-DNA adducts, suggesting a chemopreventive potential in aflatoxin-induced HCC.[89] In another trial in the same population, oral chlorophyllin (a chlorophyll derivative) consumption with each meal was also associated with a 55% reduction in urinary aflatoxin-N7-guanine excretion compared with placebo.[90]

Curcumin, which is found in turmeric, has pro-apoptotic, anti-inflammatory and antiangiogenic actions both *in vitro* and *in vivo*, and has been shown to have a protective effect in mouse models of aflatoxin-induced hepatocarcinogenesis.[91] Although no clinical trials have been performed with curcumin in patients with HCC, studies have shown that curcumin might protect against other cancers, such as oral, breast, prostate, pancreatic and colorectal cancers.[92] Resveratrol, a dietary polyphenol found in grapes, berries, peanuts and red wine, might also inhibit carcinogenesis by suppressing hepatic-carcinogen-activating enzymes such as cytochrome P450, and inducing oxidoreductases and glutathione S-transferase.[93] Resveratrol exerts its proapoptotic effect via p53 upregulation and has been shown to suppress proliferation in hepatoma cell lines.[94,95] *In vivo* studies have also demonstrated protective effects of resveratrol in diethylnitrosamine-initiated HCC.[96] A double-blind placebo-controlled study showed that 10 mg resveratrol per day for 4 weeks might improve insulin sensitivity, reduce oxidative stress and activate the Akt pathway in patients with type 2 diabetes;[97] however, these findings were not confirmed in another randomized controlled trial in obese but otherwise healthy patients.[98] By improving insulin sensitivity, resveratrol is hypothesized to decrease the risk of HCC. However, observational and clinical trial evidence for the efficacy of these phytochemicals in humans is lacking.

Secondary prevention of HCC

Cirrhosis and chronic HBV can induce field cancerization in the entire liver. Hence, despite curative resection or local ablative therapy, there is a high risk of recurrence of HCC of up to 75% by 5 years after surgical resection.[99] In patients with chronic HBV infection, nucleoside analogues have been shown to be effective in secondary prevention of HCC: in a nationwide cohort study of 4,569 patients who underwent curative resection of HBV-associated HCC, patients who received treatment with nucleoside analogues had a significantly lower 6-year HCC recurrence rate than patients who did not receive treatment

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(45.6% versus 54.6% respectively; P <0.01).[100] The relative risk of HCC recurrence was 0.67 (95% CI 0.55–0.81) in the treated cohort; the beneficial effects were seen in all stages of liver disease. In the same study, it was observed that recurrence was less frequent in statin users (adjusted HR 0.68; 95% CI 0.53–0.87) as well as aspirin or NSAID users (adjusted HR 0.80; 95% CI 0.73–0.88). Likewise, in a population-based, nested case–control study, Hsu and colleagues[101] observed a significantly lower risk of HCC recurrence after 5 years in 216 interferon and ribavirin-treated patients with chronic HCV than in 852 untreated patients with HCV (52.1% versus 63.9%, respectively; adjusted HR 0.64; 95% CI 0.50–0.83). In this study, use of statins, metformin or aspirin did not significantly modify postoperative recurrence of HCC in these patients. On the basis of pooled results from seven studies (including six randomized controlled trials), vitamin K2 analogue has also been shown to decrease risk of HCC recurrence at 3 years (RR 0.70; 95% CI0.58–0.85), but not at 1-year after curative therapy (RR 0.67; 95% CI 0.39–1.13).[102]

Future directions

With the rising incidence of HCC, especially in the Western population, and high morbidity and mortality rates associated with this cancer, strategies for chemoprevention merit closer attention. However, given the generally low incidence of HCC and the rate of progression to HCC, a randomized controlled trial to study the potential chemopreventive effect of these agents would be logistically and ethically challenging. Assuming a 4% annual rate of progression to HCC among patients with cirrhotic-stage HCV[2] and a 50% decline in the risk of HCC with the putative chemopreventive agent (for example, metformin) compared with placebo, 2,396 patients would need to be recruited and followed up for 1 year, with strict adherence to therapy. Factoring in patient dropout, progression of disease that requires additional therapies such as liver transplantation and the competing risk of mortality in patients with cirrhosis, the number of patients needed to perform such a chemoprevention trial is much higher. In addition, even if such a study would be logistically possible, it would be ethically impermissible as one would have to withhold antiviral therapy to minimize confounding. A similar study in patients with chronic HBV infection without cirrhosis would require ~3,776 patients, with complete prospective follow-up for 5 years, an enormous and potentially cost-prohibitive undertaking. A search of the WHO International Clinical Trials Registry Platform did not identify any registered clinical trials on chemoprevention using these agents against HCC. Two strategies that might help realize the potential for a chemoprevention trial in HCC could be considered: first, identify an enriched patient population at high risk of HCC; and second, use molecular markers of early HCC or perhaps pre-cancerous lesions as end points. Several predictive models incorporate demographic, biochemical, genetic and aetiology-specific risk factors to identify patients at high risk of HCC.[103,104] Identifying those at highest risk and applying chemopreventive strategies targeting this population might enhance the feasibility of a chemoprevention trial. Likewise, using surrogate markers for early HCC (such as high-grade preneoplastic lesions) as surrogate end points for a phase II chemoprevention trial might be more logistically feasible.[105]

Alternatively, it might be possible to construct a well-designed population-based prospective cohort study with high-rates of follow-up in a high-risk population to answer the question.

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However, any such study would require careful adjustment for known risk factors for HCC (such as age, sex, presence and severity of chronic liver disease, diabetes and use of other medications with putative chemopreventive effect), and should also account for the propensity to prescribe these medications (particularly in the case of aspirin). On the basis of the currently available evidence, we propose an algorithm for the use of potential chemopreventive agents against HCC (Figure 2).

Conclusions

Several promising agents have chemopreventive effects against HCC. Although antiviral therapies against HBV and HCV are consistently effective, their adverse effect profile and concerns regarding their cost-effectiveness remain a barrier to widespread use of these agents for the primary purpose of chemoprevention. By contrast, non-aetiology-specific medications, such as statins and metformin, are inexpensive, have a favourable adverse effect profile, and might have several extrahepatic metabolic benefits. These medications merit further exploration for their role as chemopreventive agents against HCC. It is quite possible, especially in light of the rising obesity epidemic and widespread use of these medications, that they might have already saved millions of people from cancer, unknown to the prescribing physician.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Antiviral therapies directed against HBV and HCV are universally effective in primary and secondary prevention of hepatocellular carcinoma (HCC), but are associated with substantial costs and adverse effects
- Statin use is associated with decreased risk of HCC, potentially by inhibiting Myc activation and through inhibition of the mevalonate pathway
- In patients with diabetes, the use of metformin might reduce the risk of HCC through mTOR inhibition, whereas insulin and insulin-secreting agents might increase the risk of HCC
- Aspirin has also been shown to decrease risk of hepatitis-B-associated HCC in animal models, with early epidemiological studies also showing a favourable association
- Dietary agents, such as coffee, vitamin E, fish rich in *n*-3 polyunsaturated fatty acids and dietary polyphenols, might also have antineoplastic effects against HCC
- Randomized controlled trials for chemopreventive agents are logistically and ethically challenging; prospective cohort studies that adjust for relevant confounders might be well-suited to inform us about these agents

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Review criteria

We performed a systematic literature search of PubMed, Embase and Web of Science, from inception until March 31, 2013, as well as review article bibliographies and abstracts of gastrointestinal/oncological society meetings for the years 2008–2012, for all relevant English language articles on chemopreventive strategies in hepatocellular cancer. The search terms included: “chemoprevention”, “prevention”, “statins”, “metformin”, “thiazolidinediones”, “sulfonylureas” “insulin”, “aspirin”, “antiviral therapy”, “interferon”, “lamivudine”, “entecavir”, “tenofovir”, “sustained virologic response”, “diet”, “coffee”, “phytochemicals”, “aflatoxin” in combination with “hepatocellular cancer”, “hepatoma” and “liver cancer”.

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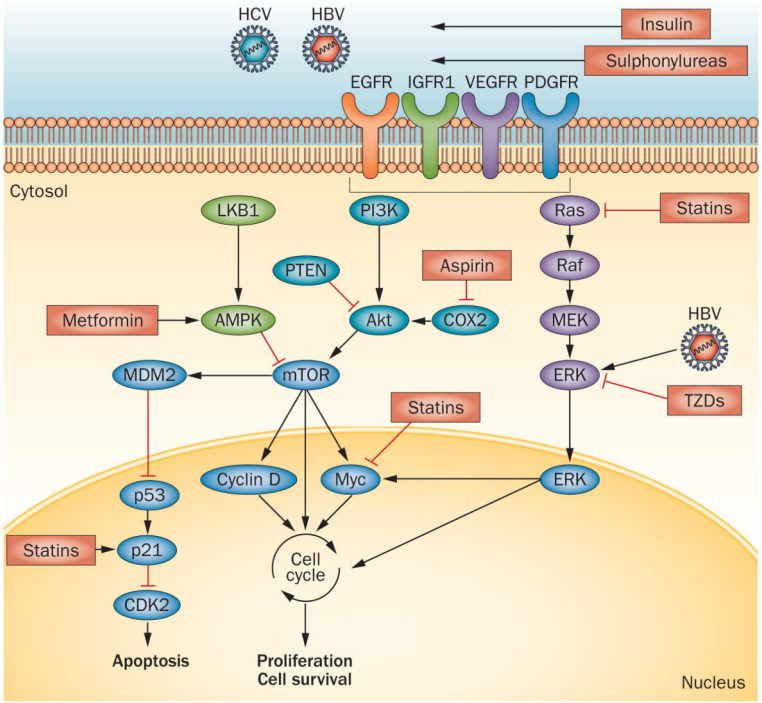

Figure 1.

Pathogenesis of HCC and targets for chemopreventive agents. Receptor tyrosine kinase pathways induce MAPK and PI3K–Akt kinase signalling pathways in >50% of HCCs. Activation of the PI3K–Akt kinase signalling pathway results in disruption of the mTOR pathway, which is seen in 40–50% of cases of HCC, leading to inactivation of tumour suppressors such as PTEN, and promoting carcinogenesis. Statins prevent post-translational prenylation of signalling Ras/ Raf proteins, inhibit the activation of the proteasome pathway, limiting the degradation of the cyclin-dependent kinase inhibitors p21 and p27, and block Myc phosphorylation and activation, suppressing tumour initiation and growth. Metformin activates AMPK, which inhibits the mTOR pathway. Thiazolidinediones also exert anticancer effects through inhibition of the ubiquitin-proteasome system and extracellular signal-regulated kinase pathway. Antiplatelet agents, such as aspirin, decrease T-cell-mediated inflammation through inhibition of cyclo-oxygenase-2, decreasing severity of fibrosis and progression to HCC. Insulin and sulphonylureas might promote hepatocarcinogenesis by increasing IGFR1 activity, resulting in abnormal stimulation of multiple cellular signalling cascades, enhancing growth-factor-dependent cell proliferation and affecting cell metabolism. Cirrhotic-stage HCV and HBV infection leaves the liver prone to the development of activating mutations in oncogenes and inactivating genetic and epigenetic suppression of tumour suppressor genes. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; HCC, hepatocellular carcinoma; IGFR1, insulin-like growth factor receptor 1; IR, insulin receptor; MAPK, Ras mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PPAR-γ, peroxisome proliferator activated receptor γ.

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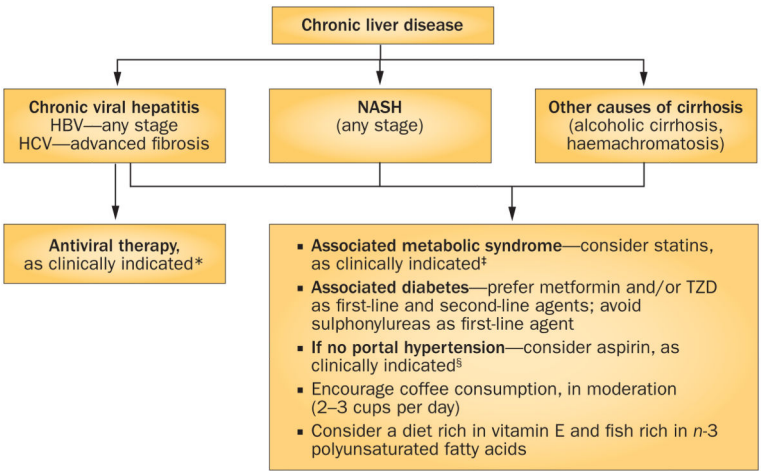

Figure 2.

Proposed algorithm for chemoprevention in patients at risk of hepatocellular carcinoma. *On the basis of AASLD guidelines;[106,107] ‡on the basis of ATP III guidelines for management of hyperlipidaemia;[108] §on the basis of USPSTF guidelines for prevention of cardiovascular disease.[109] Abbreviations: AASLD, American Association for the Study of Liver Diseases; ATP III, Adult Treatment Panel III; TZD, thiazolidinediones; USPSTF, United States Preventive Services Task Force.