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Screening and interventions to prevent nonalcoholic fatty liver disease/nonalcoholic steatohepatitis-associated hepatocellular carcinoma

Simona Cernea, Danusia Onișor

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Abstract

Liver cancer is the sixth most commonly diagnosed cancer worldwide, with hepatocellular carcinoma (HCC) comprising most cases. Besides hepatitis B and C viral infections, heavy alcohol use, and nonalcoholic steatohepatitis (NASH)-associated advanced fibrosis/cirrhosis, several other risk factors for HCC have been identified (*i.e.* old age, obesity, insulin resistance, type 2 diabetes). These might in fact partially explain the occurrence of HCC in non-cirrhotic patients without viral infection. HCC surveillance through effective screening programs is still an unmet need for many nonalcoholic fatty liver disease (NAFLD) patients, and identification of pre-cirrhotic individuals who progress to HCC represents a substantial challenge in clinical practice at the moment. Patients with NASH-cirrhosis should undergo systematic HCC surveillance, while this might be considered in patients with advanced fibrosis based on individual risk assessment. In this context, interventions that potentially prevent NAFLD/NASH-associated HCC are needed. This paper provided an overview of evidence related to lifestyle changes (*i.e.* weight loss, physical exercise, adherence to healthy dietary patterns, intake of certain dietary components, *etc.*) and pharmacological interventions that might play a protective role by targeting the underlying

causative factors and pathogenetic mechanisms. However, well-designed prospective studies specifically dedicated to NAFLD/NASH patients are still needed to clarify the relationship with HCC risk.

Key Words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Hepatocellular carcinoma; Risk stratification; Lifestyle interventions; Prevention

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Core Tip: Nonalcoholic fatty liver disease (NAFLD) is a public health problem, especially in developed countries. This condition, depending on certain associated risk factors, can ultimately lead to liver cirrhosis and hepatocellular carcinoma (HCC). Having the necessary tools and knowing the characteristics of patients in whom the disease progresses more quickly, effective monitoring programs can be developed. Primary prevention of NAFLD/nonalcoholic steatohepatitis (NASH)-associated HCC relies on controlling the main modifiable risk factors. Some pharmacological (*e.g.*, metformin, statins, aspirin) and non-pharmacological interventions (weight loss, physical exercise, healthy diet, avoiding heavy drinking and smoking) might have protective effects. Herein, we emphasized the need for continued investigations to find the optimal methods for NAFLD/NASH-associated prevention.

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INTRODUCTION

Primary liver cancer was estimated to be the fourth leading cause of cancer-related deaths and the sixth most commonly diagnosed cancer in 2018 worldwide, with hepatocellular carcinoma (HCC) comprising most cases (75%-85%)[1]. The main risk factors for HCC are chronic infection with hepatitis C virus (HCV) and hepatitis B virus (HBV), and non-viral factors, such as heavy alcohol drinking or nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) and associated metabolic disorders [like type 2 diabetes mellitus (T2DM), obesity], which have emerged as important determinants of the disease[2]. In fact, while the incidence and mortality rate related to viral-associated HCC is decreasing lately, NAFLD/NASH has become a major cause of cirrhosis and HCC[3]. This is relevant considering the increased prevalence of NAFLD, which affects about one-quarter of the adult population worldwide[4]. Even if the HCC risk is lower in NAFLD patients compared to the HCV-infected patients, it is still seven times higher in comparison with the general population[5,6].

Besides NASH/advanced fibrosis and cirrhosis, several other risk factors for HCC have been identified (Figure 1). Among these, T2DM appears to be strongly and independently associated with both NAFLD/NASH and HCC[7]. In fact, the prevalence of NAFLD in patients with T2DM is twice as high, and the prevalence of NASH is about seven-ten times higher, while the risk of HCC is 2.0-2.5 fold higher than in the general population[4,8,9]. Some studies suggest that a longer duration of diabetes can increase the risk of HCC[10]. The underlying mechanisms that link T2DM to HCC are complex and not fully elucidated, but insulin resistance, chronic inflammation, lipotoxicity, and oxidative stress may play a substantial role by promoting DNA damage, angiogenesis, cellular growth and proliferation, and decreasing cellular apoptosis[11-13]. In fact, insulin resistance seems to play an important role in HCC development (through associated proinflammatory, vasoactive, and pro-oxidative environment), and it might explain in part the occurrence of HCC in non-cirrhotic NAFLD patients[6,13].

Although not unanimous, the overall evidence is suggestive of an increased risk of HCC in individuals with obesity [as evaluated by the body mass index (BMI)][7,14,15]. A case-control study performed in the United States has identified obesity in early adulthood (mid-20s to mid-40s) as a significant HCC risk factor [odds ratio (OR): 2.6, 95% confidence interval (CI): 1.4-4.4], as each unit of increased BMI was associated with a 3.89-mo decrease in age of HCC diagnosis ($P < 0.001$)[16]. Moreover, obesity in childhood (ages 7-13-years-old) was reported to be associated with higher HCC risk later in life in a retrospective cohort comprising 285884 Danish children[17]. Visceral obesity appears to be particularly significant as an HCC risk, regardless of BMI[18,19]. The gut-liver axis seems to play an important role in the obesity-associated HCC, as gut microbiota creates a tumor-promoting microenvironment by transferring its metabolites/components, which further trigger the release of proinflammatory cytokines (like tumor necrosis factor alpha, interleukin-1 β , interleukin-6, *etc.*), suppress the anti-tumor immunity, and modify the bile acid metabolism[20-22].

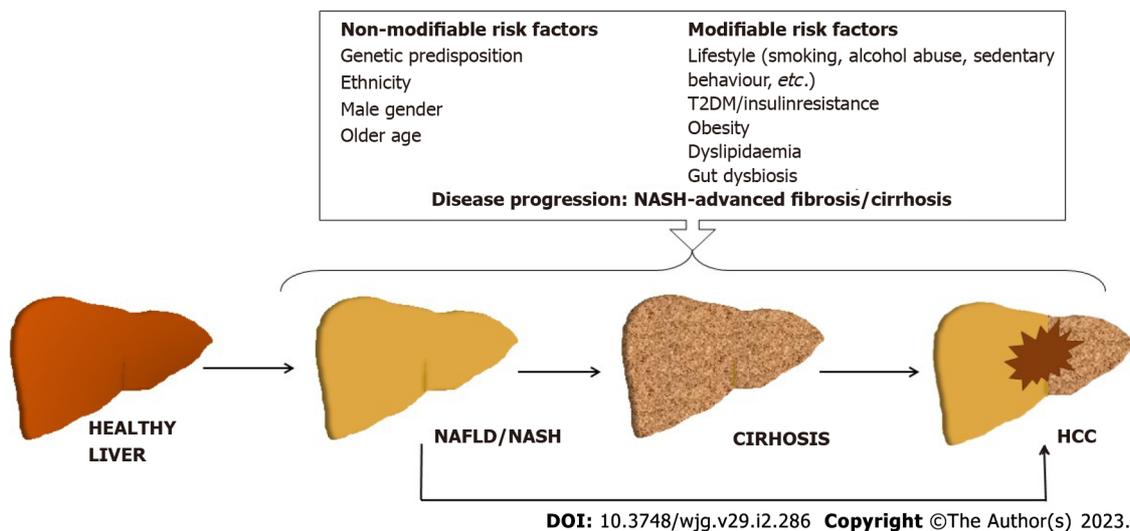


Figure 1 Risk factors for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis -associated hepatocellular carcinoma. HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus.

Other risk factors for NAFLD-related HCC are male sex, older age, smoking, genetic predisposition (*i.e.* PNPLA3 polymorphism, *etc.*) (Figure 1)[6,23-27]. In addition, dyslipidemia, ethnicity, intestinal dysbiosis, and sedentary lifestyle may also contribute (Figure 1)[3,6,26,28-30]. Apparently, the presence of multiple risk factors increases the risk of liver cancer synergistically[6].

In fact, multiple hits drive the development of the NAFLD/NASH-associated HCC through activation of various metabolic, endocrine, and immunological pathways (*i.e.* increased free fatty acids levels/impaired lipid metabolism, hyperinsulinemia, oxidative stress, endoplasmic reticulum stress, and hyperleptinemia and increased production of proinflammatory cytokines, altered immune response, release of pro-fibrinogenic mediators, *etc.*) on a background of genetic/epigenetic alterations [31].

RISK STRATIFICATION AND PREDICTION

The goal of HCC surveillance in NAFLD/NASH patients is to reduce the HCC-related mortality by promoting early tumor detection[32]. Controversy still exists regarding which NAFLD patients would benefit most from the HCC surveillance[6]. In NAFLD patients, the risk of liver-related and all-cause mortality raises exponentially with higher fibrosis stage (from F1 to F4)[33]. The meta-analysis by Dulai *et al*[33] indicated that compared to F0, the rate ratio of the all-cause mortality was 1.58 (in stage 1), 2.52 (in stage 2), 3.48 (in stage 3), and 6.40 (in stage 4), and the same trend was seen for liver-related mortality. However, it should be noted that the evolution of fibrosis is not linear, as it progresses and regresses in about 20%-30% of patients over 5 years[34]. Among patients with NAFLD, those with cirrhosis are at greatest risk, with an annual HCC incidence rate of 10.6/1000 person-years (PY) compared to 0.08/1000 PY in patients without cirrhosis[5]. Furthermore, HCC incidence rates are higher in patients with decompensated cirrhosis than in those with compensated cirrhosis[28].

Nevertheless, NAFLD patients without cirrhosis are still at risk of developing HCC. The analysis of data obtained from a cohort of 1500 patients with HCC showed that about 13% of them did not have cirrhosis, and patients with NAFLD had a five-fold increased risk of developing HCC in the absence of cirrhosis compared with those with HCV-related HCC[35]. A lower proportion of patients with NAFLD-associated HCC presented cirrhosis than patients with HCV- or alcohol-related HCC (58% *vs* 85.6% and 72.4%, respectively)[35]. The same was basically shown by the meta-analysis by Tan *et al*[36] (61 studies; 94636 patients). They reported that NAFLD-related HCC patients were more likely to be non-cirrhotic (38.5% *vs* 14.6%, $P < 0.0001$) and had larger tumor diameters ($P = 0.0087$)[36]. Moreover, these patients had undergone surveillance in a lower proportion than patients with HCC secondary to other causes (32.8% *vs* 55.7%, $P < 0.0001$)[36].

Poor HCC surveillance is a significant problem for patients with NAFLD, and in fact, identification of pre-cirrhotic NAFLD individuals with high HCC risk remains a significant challenge at the moment. A prospective multicenter study performed in Italian secondary care centers that included 756 patients with NAFLD- or HCV-related HCC has shown that HCC was diagnosed though regular ultrasound/specific surveillance in a lower proportion of NAFLD patients compared to HCV patients (47.7% *vs* 63.3%, $P < 0.0001$), resulting in a more advanced HCC burden at diagnosis in the former group[37]. Similarly, the analysis of data from the United States Veterans Administration HCC cohort study

showed that more patients with NAFLD-HCC did not benefit from HCC surveillance 3 years before diagnosis (43.3%) compared to patients with alcohol abuse- or HCV-related HCC (40.2%, and 13.3%, respectively)[38].

Solid data and guidance regarding risk stratification in non-cirrhotic NAFLD patients who might benefit from HCC surveillance are limited, and specific recommendations in this area are urgently needed due to the growing epidemic of NAFLD[39].

How to perform the screening?

Liver biopsy remains the “gold standard” for the diagnosis of NASH, but it cannot be routinely used in practice as a screening method to diagnose NAFLD, given its multiple limitations: It is expensive, the procedure is subject to interpretation errors, and it is potentially associated with adverse effects such as pain, bleeding, and infection[40,41]. The emergence of non-invasive methods for quantifying fibrosis and their validation has led to a decrease in the need for liver biopsies[42-44]. The Asia-Pacific and the American Gastroenterology Association guidelines agree that the combined use of serum tests and imaging tools may provide more reliable information than using either method alone[30,45]. The American Association for the Study of Liver Diseases guideline also consider the non-invasive methods as first-line tests for the investigation of fibrosis, but it does not recommend a specific diagnostic algorithm or follow-up strategies[43].

Identification of fibrosis and risk stratification is an essential step for HCC surveillance, as the guidelines clearly recommend screening in patients with cirrhosis, while patients with advanced fibrosis (F3) might also undergo surveillance based on individualized evaluation.

Currently, the primary imaging method for HCC detection is ultrasound (US)[40,46,47]. However, recent studies have highlighted the limitations of this examination[28]. For example, a study comprising 941 patients with cirrhosis who underwent ultrasonography reported that 20% of examinations had an inadequate quality to exclude images showing possible focal points[48]. Therefore, other methods (computer tomography, magnetic resonance imaging) might be used[45,47]. For these two investigations, the follow-up interval is not clearly established nor are the benefits of the association with measurement of alpha-fetoprotein (AFP) levels[49].

It has been questioned whether the addition of AFP quantification to routine biannual US examinations would increase the detection rate of HCC during screening. However, only about three-quarters of HCC patients are AFP positive[50]. In fact, the probability of having elevated AFP levels (*i.e.* > 10 ng/mL) in patients with early NAFLD-associated HCC without cirrhosis and normal transferase levels was only 17.5%-24.0% compared with 86.5%-90.5% in patients with viral-associated cirrhosis and advanced HCC with increased transaminases values, as showed in an Italian study that included 4123 HCC patients[51]. The use of AFP measurement as a screening tool for HCC might result in earlier diagnosis, but it does not seem to improve the mortality rate[52]. The European guidelines do not currently recommended AFP as a surveillance parameter for the detection of HCC in patients with NAFLD. The American guidelines recommend ultrasound screening with or without AFP, while Asia Pacific Society guidelines recommend screening with AFP[30,47,53]. Other biomarkers such as microRNAs (*e.g.*, miR-34a, miR-221) are under investigation for early detection of HCC but need further validation[54].

HCC screening in low risk NAFLD-patients

Most patients screened in a primary care setting have a low risk of clinically significant liver fibrosis, defined as having a Fibrosis-4 (FIB-4) score < 1.3, liver stiffness measurement (LSM) < 8.0 kPa on transient elastography, or a liver biopsy fibrosis stage of F0-F1[44,55-57]. Systematic HCC screening may not be prudent and is currently not recommended by the American Association for the Study of Liver Diseases, American Gastroenterology Association, and the European Association for the Study of the Liver in non-cirrhotic NAFLD patients (Figure 2)[42-44].

HCC screening in indeterminate risk-NAFLD patients

An estimated 30%-40% of screened patients have an indeterminate risk of clinically significant (advanced) liver fibrosis, defined as FIB-4 score of 1.3-2.67 and/or a LSM of 8.0-12.0 kPa on transient elastography[44,55-57]. The estimated incidence of HCC in non-cirrhotic NASH seems to be too low to justify systematic screening[58]. Apparently, non-cirrhotic NAFLD patients with multiple features of metabolic syndrome are at higher risk of HCC development and need special attention[5,35]. It is argued that additional triggers (such as active inflammation and fibrosis) are needed to promote carcinogenesis[6].

The current guidelines recommend the referral of these patients to a hepatologist for further evaluation by magnetic resonance elastography or liver biopsy[30,42,43]. The decision should be taken by mutual agreement and on the basis of an individual assessment (presence/absence of comorbidities, degree of fibrosis, *etc.*)[44]. The European Association for the Study of the Liver guidelines recommend that patients with liver disease and advanced fibrosis (F3) might be considered for HCC surveillance based on the individual risk, while the Asian Pacific and American Association for the Study of Liver Diseases clinical practice guidelines do not provide a specific recommendation for surveillance in

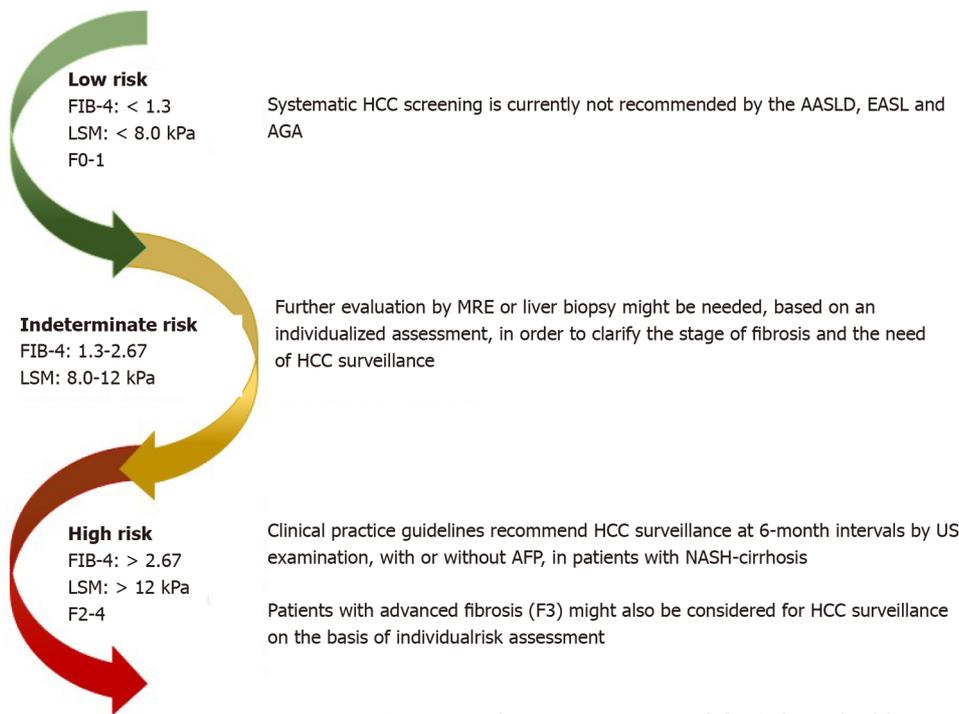


Figure 2 Recommended hepatocellular carcinoma screening approach in nonalcoholic fatty liver disease/nonalcoholic steatohepatitis patients according to the risk category. AASLD: the American Association for the Study of Liver Diseases; AFP: Alpha-fetoprotein; AGA: American Gastroenterology Association; EASL: The European Association for the Study of the Liver; FIB-4: Fibrosis-4; HCC: Hepatocellular carcinoma; LSM: Liver stiffness measurement; NASH: Nonalcoholic steatohepatitis; MRE: Magnetic resonance elastography; US: Ultrasonography.

patients with NAFLD without cirrhosis[30,43].

HCC screening in high risk-NAFLD patients

Nearly 10% of screened patients have a high risk of advanced liver fibrosis, defined as a FIB-4 score > 2.67, LSM > 12.0 kPa, or a liver biopsy showing clinically significant liver fibrosis (≥ F2)[44,55-57]. Patients with cirrhosis are at the highest risk for HCC. The meta-analysis and meta-regression by Orzi *et al*[59] involving 470404 patients showed that the incidence rate of HCC was 0.03/100 PY in patients with NAFLD at a pre-cirrhotic stage and 3.78/100 PY in those with cirrhosis, while in patients with cirrhosis undergoing regular screening for HCC, it was 4.62/100 PY.

Some data suggested that HCC surveillance might not be associated with improved clinical outcomes. For example, a matched case-control study from the United States Veterans Affairs health system failed to find an association between screening (by US, AFP, either test, or both tests) and rate of HCC-related mortality[60]. However, the lack of benefit may have not been related to the failure of surveillance but rather to other causes, such as underuse of HCC treatment or applying surveillance in patients who were not candidates for HCC treatment. On the other hand, a meta-analysis of 59 cohort studies indicated that HCC surveillance was associated with improved early HCC detection, receiving curative therapy, and survival in patients with cirrhosis but with heterogeneity in pooled estimates[32]. Thus, available data is in favor of HCC surveillance in patients with cirrhosis, although it still needs further confirmation[32].

Surveillance programs by regular US (and AFP) in patients with compensated cirrhosis are cost effective[61]. In fact, cost-effectiveness analyses indicate that HCC screening should be considered for patients with Child-Pugh A and B (compensated) cirrhosis and decompensated liver cirrhosis patients waiting for liver transplantation[47].

In patients with NASH-cirrhosis, all three liver study societies recommend the use of an HCC surveillance program at 6-mo intervals, with US exams, with or without AFP[30,42,43]. The same was endorsed by the recommendations of American Gastroenterology Association Clinical Practice[40].

INTERVENTIONS TO PREVENT NAFLD/NASH-ASSOCIATED HCC

The NAFLD/NASH-associated HCC primary prevention relies on controlling the main modifiable risk factors, *i.e.* obesity, T2DM/insulin resistance, gut dysbiosis, disease activity/fibrosis (disease progression), that have been associated with activation of various oncogenic pathways finally leading to

hepatocarcinogenesis[62]. There is no clearly effective intervention for HCC prevention available for NAFLD/NASH patients at the moment, although some pharmacological and non-pharmacological approaches might indeed be useful by addressing the predisposing factors/causes and underlying pathogenetic mechanisms (Table 1)[63].

Weight loss and bariatric surgery

Weight loss through lifestyle intervention represents the cornerstone for NAFLD management, as it has been associated with the regression of steatosis, steatohepatitis, and even fibrosis (for > 10% weight loss) [64]. The analysis of two randomized controlled trials (RCTs) indicated that each lost kg was associated with a 7% increase in odds of obtaining NASH resolution without worsening of fibrosis, and a 5% increase in odds of obtaining fibrosis improvement without worsening of NASH[65]. The meta-analysis by Koutoukidis *et al*[66], which included 2588 NAFLD subjects who underwent weight loss interventions (through behavioral programs, pharmacotherapy, or bariatric surgery), indicated that these interventions were associated with the improvement of liver steatosis, histologic NAFLD activity score (NAS) and presence of NASH (OR: 0.14, 95%CI: 0.04-0.49) but not of fibrosis.

Preliminary results from a retrospective analysis of a database containing 72 million unique patients reported that weight loss medications reduced the risk of HCC in obese populations (OR: 0.07), with orlistat and liraglutide showing statistically significant decreases (OR: 0.13, and 0.35, respectively)[67]. In addition, the meta-analysis by Ramai *et al*[68], which included data from major databases, indicated that bariatric surgery was associated with a reduced risk of HCC (pooled unadjusted OR: 0.40), although with high heterogeneity (I²: 79%).

Although there is limited evidence regarding the impact of weight loss on the risk of developing HCC, it is intuitive and reasonable to encourage overweight/obese patients to decrease their weight. Weight loss is associated with the improvement of metabolic health (or indirect outcomes, such as the decrease of insulin resistance, inflammation, oxidative stress, *etc.*), which may translate into liver health benefits[69-72]. However, a recent RCT in patients with NAFLD demonstrated that a modest weight loss (-4 kg) through a calory-restricted diet was accompanied by reduction in transaminases, but the liver steatosis grade or the markers of oxidative stress were not significantly changed in comparison with the controls[73]. Thus, the liver benefits still have to be demonstrated by prospective data, which should clarify the direct effect of weight loss on long-term NAFLD/NASH progression and primary HCC prevention.

The effects of bariatric surgery on liver outcomes might be explained in part by weight loss, although other contributing mechanisms cannot be excluded [*e.g.*, increase in glucagon-like peptide-1 (GLP-1) concentrations after intervention][74]. The meta-analysis by Lee *et al*[75], which analyzed the data of 32 cohort studies ($n = 3093$ liver biopsies from NAFLD patients with obesity that underwent bariatric surgery) showed that surgical intervention resulted in an absolute percentage BMI reduction of 24.98% (from 48.68 ± 2.92 to 34.2 ± 3.53 kg/m²). This was accompanied by steatosis resolution in 66% of patients as well as the resolution of inflammation (in 50% of patients), ballooning degeneration (in 76%), and fibrosis (in 40%)[75]. However, 12% of the subjects presented new or worsening fibrosis after the intervention[75].

The more recent meta-analysis by Ramai *et al*[68] included nine studies (19514750 patients) and reported that bariatric surgery was associated with a reduced risk of HCC (pooled unadjusted OR: 0.40, 95%CI: 0.28-0.57 and adjusted OR: 0.63, 95%CI: 0.53-0.75). So far there is no clear indication regarding the type of surgical intervention that would be most beneficial in terms of liver health.

Lifestyle changes

A large prospective cohort study has demonstrated the association of unhealthy lifestyle (assessed by a composite score comprising BMI, alternative Mediterranean diet, alcohol intake, smoking, and sleep duration) with the risk of HCC: Higher composite scores (5, 6, 7, 8) representing healthier lifestyle were associated with a lower risk of HCC (0.67, 0.61, 0.49, and 0.13, respectively; $P_{\text{trend}} < 0.0001$) compared with lower scores (0-4) over a mean follow-up of 17.7 years[76]. As unhealthy lifestyle is associated with a higher risk of NAFLD/NASH and HCC, it is reasonable to assume that correcting these behaviors will potentially protect against the development of HCC.

However, there is insufficient direct evidence to indicate that changes in lifestyle reduce the risk of HCC in NAFLD/NASH patients. A meta-analysis of 30 RCTs in NAFLD patients ($n = 3280$), which evaluated the effect of diet, exercise, or their combination on the liver and metabolic markers, reported that a combination of diet and exercise resulted in a greater decrease of ALT [mean difference (MD): -13.27], AST (MD: -7.02) and Homeostatic Model Assessment for insulin resistance (MD: -2.07) compared to either of them[77]. However, no histological or imaging data were available. Moreover, an umbrella review of evidence from observational studies and RCTs looking at the association between lifestyle and NAFLD with regards to risk and treatment (41 meta-analysis from observational studies and 81 meta-analysis from RCTs) suggested that some interventions [*i.e.* green tea, omega 3 polyunsaturated fatty acids (PUFA), and exercise] were associated with some improvement in metabolic and hepatic markers, but more robust RCTs are needed to investigate the effect of lifestyle changes on liver outcomes[78]. In addition, the network meta-analysis by Buzzetti *et al*[79] (59 RCTs, 3631 participants; 2-24 mo of follow-up) could not draw a definite conclusion regarding the effect of the lifestyle interventions on any of the

Table 1 Summary of lifestyle and pharmacological intervention with potential preventive effects against developing nonalcoholic fatty liver disease/nonalcoholic steatohepatitis-associated hepatocellular carcinoma

Interventions with potential protective effects	
Lifestyle interventions	Weight loss
	Dietary changes
	Adherence to healthy eating patterns: Mediterranean diet, traditional Cantonese dietary pattern; Chinese Healthy Eating Index
	Reduced intake of: Saturated fats, sugar-sweetened beverages, alcohol
	Increased intake of: Vegetables, coffee; possibly fiber, white meat and fish, omega-3 polyunsaturated fatty acids, vitamin E
	Physical exercise
	Smoking cessation
Pharmacological interventions	Metformin
	Statins
	Aspirin
	Possibly also: Pioglitazone, GLP-1 RA, vitamin E (in nondiabetic individuals?), obeticholic acid

GLP-1 RA: Glucagon-like peptide-1 receptor agonists.

clinical liver outcomes (including HCC), as the number of events was too low (probably due to short duration of follow-up).

Diet: There is limited information regarding the impact of diet/dietary components on liver histology in patients with NAFLD/NASH and on the risk of progression to HCC. Most studies report data related to liver biomarkers/fat content or risk of liver cancer in overall population/patients with chronic liver diseases, regardless of etiology. The relationship between HCC and several nutrients, foods, and dietary patterns has been evaluated mostly in observational studies, but few data exist exclusively in patients with NAFLD/NASH[80]. There is a lack of high-quality data from large RCTs in this population, but it should be noted that it is quite challenging to evaluate dietary determinants of the disease in the context of multiple confounding effects of other lifestyle factors[81].

Dietary patterns represent a complex combination of foods/nutrients and beverages that are habitually consumed, and their evaluation may capture in a more integrated way the effect of diet on health outcomes[82]. A recent systematic review of 30 observational studies (5222534 participants from Asia, America, and Europe) investigated the association between diet and risk of HCC and found differences with regards to geographical regions and dietary patterns[83]. Specifically, the Mediterranean diet appeared to be protective for the European and American populations, while the Chinese Healthy Eating Index and the Cantonese Dietary Pattern seemed to be associated with lower risk of HCC in Asian countries[83].

Analysis of combined data from two case-control studies demonstrated that better adherence to the Mediterranean diet was associated with a lower risk of HCC (ORs: 0.66 and 0.51, $P < 0.001$ for trend) [84]. In addition, the Alternate Mediterranean diet score (an adaptation of the original Mediterranean diet score) was associated with a decreased risk of HCC [hazard ratio (HR): 0.68; $P = 0.02$], as indicated by a multiethnic cohort prospective study[85]. Another study has shown a suggestive but nonsignificant association with lower risk (HR: 0.75; $P_{\text{trend}} = 0.18$)[86]. The Singapore Chinese Health Study data also indicated that higher Alternate Mediterranean diet scores as well as higher scores of Alternative Healthy Eating Index-2010 (AHEI-2010) and Dietary Approaches to Stop Hypertension, representing a better dietary quality, were associated with a lower risk of HCC ($P_{\text{trend}} < 0.05$)[76]. The results were in agreement with the report of the National Institutes of Health-AARP Diet and Health study, indicating that higher HEI-2010 and Alternate Mediterranean diet score were significantly associated with lower HCC risk (HR: 0.72; $P_{\text{trend}} = 0.03$ and HR: 0.62; $P_{\text{trend}} = 0.0002$, respectively)[87].

Similarly, better adherence to the Chinese Dietary Guidelines, as assessed by the Chinese Healthy Eating Index, was shown to be associated with a lower risk of HCC (OR: 0.43; $P < 0.001$), even in the stratified analysis by risk factors[88]. The study by Lan *et al*[89] that enrolled 782 patients with primary liver cancer and evaluated their habitual dietary intake found that an urban prudent dietary pattern (consisting of higher intake of eggs, mushrooms, dairy products, soy foods and nuts, and lower intake of refined grains) and a traditional Cantonese dietary pattern (characterized by a high intake of fruit and vegetables, Cantonese soup, fish, and Chinese herb tea) have been associated with a lower risk of primary liver cancer (OR: 0.25 and 0.61, respectively), while a diet rich in meat and preserved foods

increased the risk (OR: 1.98). Moreover, a prospective study that enrolled 887 patients with newly diagnosed HCC suggested that a higher adherence to the 2016 Chinese Dietary Guidelines was associated with a lower risk of HCC-specific mortality (HR: 0.74) and all-cause mortality (HR: 0.75)[90].

Inflammation is a key pathogenetic mechanism that influences NASH progression and hepatocarcinogenesis. Two studies have evaluated the correlation between dietary inflammatory score/index (that reflect the overall inflammatory potential of a diet) and the risk of HCC/primary liver cancer mortality. The first one showed that higher dietary inflammatory index values (indicating a proinflammatory diet) were associated with an increased risk of liver cancer (HR: 2.05) and liver cancer-associated mortality (HR: 1.97)[91]. The second study reported that higher adherence to empirical dietary inflammatory pattern score (indicating a proinflammatory potential of the diet) was associated with an increased risk of HCC (HR: 2.03; $P_{\text{trend}} = 0.001$)[92]. The same study reported that several other scores (empirical dietary index/lifestyle pattern score for hyperinsulinemia and insulin resistance) indicating a higher insulin resistance potential of a diet were also correlated with a higher risk of HCC[92].

Thus, a healthy dietary pattern (generally characterized by an increased intake of vegetables, fruits, nuts, and whole grains and a decreased intake of red and processed meats) appears to be protective against HCC and HCC-related mortality. However, more specific evaluations are needed to confirm the data and assess the strength of these associations in patients with NAFLD/NASH.

There is little evidence with respect to the impact of dietary macro- and micronutrients upon liver histology in patients with NAFLD/NASH (*e.g.*, reversal of fibrosis) and the risk of progression to HCC.

Data coming from observational studies are heterogenous. Some studies showed that increased carbohydrate intake was associated with higher aminotransferases levels, liver fat, and NASH, while others indicated the opposite or were neutral[81,93-97]. A meta-analysis of ten RCTs concluded that low-carb diets significantly reduced the intrahepatic lipid content but did not change the serum liver enzyme concentrations in patients with NAFLD[98]. There is also sparse and inconsistent evidence regarding the association between food glycemic index and load with HCC[35]. Data from the European Prospective Investigation into Cancer and Nutrition cohort (EPIC) study (477206 subjects) did not find significant associations between dietary glycemic index or glycemic load or total carbohydrate intake with risk of liver cancer[99]. However, the risk of HCC in correlation with types of carbohydrates appeared to be divergent: 43% higher risk per 50 g total sugar intake/d and 30% lower per 50 g starch/d[99]. The analysis of the Shanghai Women's Health Study and the Shanghai Men's Health Study data also indicated no consistent association between dietary carbohydrates, glycemic index, and glycemic load and risk of liver cancer[100].

On the other hand, higher intake of dietary fructose/sugar-sweetened beverages (surrogate for free sugars) has been associated with NAFLD, independent of other risk factors in several studies, as well as with higher intrahepatic lipid content, mainly when consumed in the context of excessive caloric intake [81,101-105]. The meta-analysis by Li *et al*[106] (71 observational studies) reported that higher sugar-sweetened beverages intake was associated with higher overall cancer risk [relative risk (RR): 1.12; $P = 0.000$] and mortality risk (RR: 1.07; $P = 0.029$) as well as higher risk of HCC (RR: 2.00; $P = 0.001$) (but HCC results were based only on two studies). Interestingly, the EPIC study data suggested that consumption of > 6 servings of combined soft drinks per week was associated with higher HCC risk (HR: 1.83; $P_{\text{trend}} = 0.01$) but artificially-sweetened rather than sugar-sweetened soft drinks intake appeared to be deleterious[107]. A significant positive association between carbonated beverages consumption and HCC risk was also seen in a case-control study of 582 cirrhotic patients (181 with HCC) (OR: 2.44; $P_{\text{trend}} = 0.021$)[108].

The same study showed an inverse correlation of HCC risk with fiber intake (OR: 0.49; $P_{\text{trend}} = 0.012$), which is in accordance with the EPIC study results indicating a 30% HCC risk reduction per 10 g/d of total dietary fiber intake, even in viral hepatitis-free individuals[99,108]. However, the analysis of data from two United States cohort studies (125455 participants) did not find a significant association of HCC risk with cereal, fruit, or vegetable fiber intake[109]. On the other hand, lower daily (mainly soluble) fiber intake was observed in patients with NAFLD/NASH in several observational studies[94,96,110].

There is inconsistent evidence with regards to the role of dietary proteins (types, amount) in the progression of NAFLD/NASH and occurrence of HCC. The Rotterdam Study which included 3882 individuals (1337 with NAFLD) showed that animal protein intake was significantly associated with overweight NAFLD after adjustment for metabolic covariates (OR: 1.36)[111]. Indirect evidence, in line with these results, was provided by another cross-sectional study that showed that total and animal protein consumption was positively associated with estimates of liver steatosis (OR: 1.25 and 1.27, respectively), while vegetable proteins had an inverse association with these (OR: 0.81)[112]. On the other hand, a recent RCT that evaluated the effect of a low-carbohydrate high-protein diet on liver fat in 72 T2DM patients demonstrated that it reduced the liver fat content to a slightly greater extent compared to a conventional diet (64% vs 51%, $P = 0.051$) beyond the effects of (similar) weight loss[73]. Similarly, a small prospective study in NAFLD patients with T2DM showed that high protein diets (30% of total caloric daily intake), either animal or plant-based, significantly reduced liver fat independent of change in body weight, and decreased the serum levels of fibroblast growth factor 21[113]. The animal protein diet determined a greater increase in postprandial levels of methionine and branched chain amino acids but this was not accompanied by beneficial or deleterious effects[113]. Some experimental data suggested potential benefits of branched chain amino acids in terms of hepatocarcinogenesis

inhibition (changes in growth factors gene expression, inhibition of proliferation), increased apoptosis in liver cancer cell lines, and improvement of fibrosis[82,114,115]. In addition, few Japanese clinical studies suggested that branched chain amino acid supplementation in patients with HCC may reduce cancer recurrence after hepatic resection (mainly in patients with higher insulin resistance), but others showed no effect[116-119]. Certainly, additional good-quality evidence is needed regarding the role of dietary proteins/amino acids in the progression of NAFLD/NASH and associated HCC.

Most studies concerning dietary fats in NAFLD/NASH and HCC evaluated the role of type rather than amount of fats[120]. Observational studies seem to indicate that total dietary fat intake is not correlated with HCC risk[121-123]. Some but not all results suggested that vegetable fats might be associated with reduced HCC risk[121,123]. Higher consumption of saturated fatty acids however was shown to be associated with hepatic steatosis/NAFLD and NASH[81,95,124]. A large Chinese prospective cohort study also indicated that dietary saturated fats were associated with higher liver cancer risk [adjusted HR (aHR): 1.14; $P = 0.005$], but results from the EPIC study and a hospital-based case-control study from the United States did not support a direct association of saturated fats intake with HCC[125-127]. However, a meta-analysis of 14 studies by Zhao *et al*[128] demonstrated that higher dietary intake of saturated fats was associated with an increased risk of liver cancer (RR: 1.34 for highest *vs* lowest intake) in a dose-dependent manner.

On the other hand, the same United States case-control study showed that monounsaturated fatty acids (MUFA) but not total PUFA intake was inversely correlated with the risk of HCC (OR: 0.49 and 1.82)[122]. This was in contrast with the study by Yang *et al*[123] that showed that PUFA was inversely associated with HCC risk (aHR: 0.83; $P = 0.03$) (with MUFA being neutral). The study by Li *et al*[125] indicated that MUFA had a neutral effect (aHR: 1.26, 95%CI: 0.96-1.65; $P = 0.034$), while PUFA intake was associated with higher HCC risk (aHR: 1.41, 95%CI: 1.07-1.86 for highest *vs* lowest quartile; $P = 0.005$). Thus, data on MUFA and total PUFA seems quite heterogenous (maybe explained in part by dietary source, type of study, and study population).

In a NASH animal model, dietary intake of docosahexaenoic acid appeared to be superior to that of eicosapentaenoic acid in attenuating Western-diet induced liver injury, oxidative stress and fibrosis, and potentially in reducing the risk of HCC, thus suggesting differential effects of the two dietary omega-3 PUFAs[129]. Evidence is more convergent regarding the effect of omega-3 PUFA supplementation on liver fat content. Two meta-analyses actually showed that it decreased liver fat, and this was confirmed by a small histologic study in non-cirrhotic NASH patients that received 3000 mg/d omega-3 PUFA for 1 year[130-132]. However, the study did not reach the primary end-point (*i.e.* NAS reduction of ≥ 2 points without fibrosis progression)[132].

In addition, the evidence regarding the effect of omega-3 PUFA on HCC risk is not unequivocal. The case-control study by Moussa *et al*[127] demonstrated an inverse association between dietary omega-3 intake and HCC risk (OR: 0.50), but other epidemiological data seemed to indicate a neutral effect (HR: 0.63; $P_{\text{trend}} = 0.14$ and aHR: 0.89, 95%CI: 0.75-1.04; $P = 0.14$, respectively)[122,123,125]. Some observational studies showed a positive relationship between dietary intake of omega-6 PUFA and HCC risk (adjusted OR: 2.29 for highest *vs* lowest tertile, and OR: 4.36), indicating a potentially negative effect, although other data showed an inverse association (HR: 0.54; $P_{\text{trend}} = 0.02$)[123,127,133]. Linoleic acid intake might be inversely associated with HCC risk (OR: 0.35, $P < 0.01$)[122].

Even if the role of micronutrients in preventing the progression of NASH to HCC might be hypothetically explained from a pathogenetic perspective (*i.e.* antioxidant, anti-inflammatory, anti-fibrotic effects), and the experimental data is quite consistent. There is insufficient good quality clinical research regarding their dietary intake or supplementation effect in NAFLD patients[134].

Two United States prospective studies have shown an inverse relationship between (dietary and supplemental) magnesium intake and risk of liver cancer (HR: 0.65 and HR: 0.44; $P_{\text{trend}} = 0.0065$, respectively)[135,136]. Results from two large cohort studies in China demonstrated an inverse association between dietary manganese intake and liver cancer risk long-term (HR: 0.51; $P_{\text{trend}} = 0.001$), even after adjustment for HBV infection[137]. The case-control study by Rizk *et al*[108] also found that manganese intake was significantly lower in HCC patients *vs* controls (OR: 0.56; $P_{\text{trend}} = 0.038$) as well as potassium intake (OR: 0.44; $P_{\text{trend}} = 0.004$). On the other hand, the sodium intake was significantly higher [104]. Nevertheless, more studies are needed to clarify the role of minerals in NASH and HCC.

The same above-mentioned case-control study also indicated lower intake of vitamins E and B9 in HCC patients[108]. In the same sense, a report from two Chinese cohort studies showed that dietary vitamin E intake and supplement use were inversely associated with the risk of liver cancer (HR: 0.52) [138]. The effect of therapeutic intervention with vitamin E will be discussed below. An inverse association between HCC risk and (β) carotenes/vitamin A was noted in several studies (with OR: 0.48 for β carotene, 0.34 for vitamin A, and 0.35 for carotenes)[122,139].

Food items/groups have been evaluated with regards to their association with HCC risk. We will only briefly mention the main findings here. Several systematic reviews and meta-analyses have evaluated data regarding the association between meat consumption and risk of HCC. Even if not totally in agreement, they seem to indicate that red meat consumption is associated with increased HCC risk (RR: 1.22) or is neutral (RR: 1.04 and 1.10), and there is an increased HCC risk associated with processed meat consumption (RR: 1.20, and 1.01)[140-142]. Total meat intake had no significant effect [140-142]. On the contrary, white meat and fish intake were found to be inversely associated with the

risk of HCC (RR: 0.69, 0.76 for white meat and RR: 0.78, 0.91 for fish)[141,142]. Some epidemiological data suggested that increased dairy product intake (mainly milk and high-fat dairy) was associated with a higher risk of HCC, although not all studies agreed (yogurt seemed to be associated with a decreased risk or had a neutral effect)[121,143-145]. Two meta-analyses indicated that increased vegetable consumption was associated with a lower risk of HCC[146,147]. For other food items, there is insufficiently consistent evidence so far.

There have been suggestions for the use of many herbal and dietary natural compounds, such as prebiotics/polyphenols, resveratrol, and curcumin in NAFLD/NASH therapy, including for HCC prevention, with some small studies suggesting anti-inflammatory effects of prebiotics, but until now there is very limited data from clinical trials, and no clear conclusion can be drawn[134,148-150]. Preclinical data demonstrated the anti-inflammatory effects of the catechin-rich green tea extract that may attenuate NASH-associated liver injury through a decrease of hepatic nuclear factor kappa-B activation but also indirectly through prebiotic and antimicrobial effects on gut microbiota, resulting in decreased translocation of the gut-derived endotoxins[151]. Green tea contains several bioactive compounds that may exert anticarcinogenic properties (*e.g.*, flavonoids, caffeine, polyphenols, *etc.*) through modulation of different signaling transduction and metabolic pathways (reduction of chronic inflammation, oxidative stress, insulin resistance, liver steatosis, *etc.*)[80,152]. The EPIC study data showed an inverse association between tea consumption and HCC risk (HR: 0.41, 95%CI: 0.22-0.78; $P_{\text{trend}} = 0.003$), while a meta-analysis of 15 RCTs demonstrated that green tea reduced the liver enzymes values in NAFLD patients[153,154].

The use of probiotics in NAFLD/NASH, cirrhosis, and HCC has been reported in several studies and indicated that they can improve aminotransferases and insulin resistance and have anti-inflammatory effects, but there is no evidence so far with regards to HCC prevention[150,155]. A meta-analysis of 21 RCTs (1252 participants) suggested that the use of probiotics/synbiotics was associated with a decrease of inflammation markers, liver stiffness, and steatosis in subjects with NAFLD[156]. However, well-designed RCTs are further needed to fully understand their protective effect in patients with NASH.

Coffee: Eight meta-analyses of prospective cohort and case-control studies provided consistent evidence regarding an inverse relationship between coffee drinking and risk of HCC (RR ranging between 0.54 and 0.78), with only one meta-analysis indicating a neutral effect (RR: 0.93)[157-164]. Caffeinated rather than decaffeinated coffee seemed to have a more consistent effect on HCC[158,161]. Also, the association appeared to be related to the amount of daily coffee intake. The beneficial effects generally started at two cups/d. An extra cup of coffee/d reduced the cancer risk by about 15%-25% (RRs between 0.75 and 0.85), and two extra cups/d by about 14%-44% (RRs between 0.56 and 0.86)[157-164].

Alcohol: Alcohol is a major risk factor for HCC, and it has synergistic effects with the metabolic risk factors (T2DM, obesity) in inducing carcinogenic mechanisms[80,165]. Evidence suggests that a modest alcohol intake is protective against fatty liver, NASH, and fibrosis, but it was not firmly established if it is also protective against HCC[82,166]. A meta-analysis of 19 cohorts (4445 incident cases of liver cancer) showed neutral effects of moderate drinking (< 3 drinks/d) on liver cancer risk (RR: 0.91, 95%CI: 0.81-1.02) compared to no drinking, while heavy drinking (defined as ≥ 3 drinks/d) significantly increased the risk (RR: 1.16, 95%CI: 1.01-1.34)[167]. In line with these results, a prospective evaluation of 8345 subjects with hepatic steatosis (mean follow-up duration of 11.1 years) demonstrated a dose-response relationship for advanced liver outcomes/liver cancer that became significant at ≥ 10 g of alcohol intake/d (for liver outcomes) and ≥ 30 g/d (for liver cancer) after multivariate adjustments[168]. The decrease in risk of HCC after alcohol drinking cessation is uncertain, but a meta-analysis of four studies suggested a decline of HCC risk with 6%-7%/year, although caution was advised in data interpretation [169].

Physical activity: The benefits of physical activity in reducing insulin resistance and hepatic liver content in NAFLD patients are well known[170,171]. The meta-analysis by Golabi *et al*[170] (eight studies with 8 to 48 wk duration) reported that aerobic and resistance exercises determined a liver fat reduction of 30.2%.

Physical exercise intervenes at multiple levels in the pathogenic pathways of NAFLD by reducing the free fatty acid (FFA) flux to the liver, FFA hepatic synthesis, the mitochondrial and cellular damage, oxidative stress, damage-associated molecular patterns release, and hepatic stellate cell activation and by increasing the FFA oxidation and activating the AMP-activated protein kinase-regulated pathways, *etc.*[172]. Physical exercise also improved mitochondrial function (*i.e.* autophagy, biogenesis) and modulated the carcinogenic signaling pathways[80,173,174]. Taken together, these might explain the potential protective effects of exercise in NAFLD/NASH and HCC. Indeed, a meta-analysis of 14 prospective studies indicated that physical activity was inversely correlated with the risk of liver cancer (HR for high *vs* low physical activity: 0.75, 95%CI: 0.63-0.89)[175]. These results were in accordance with the EPIC study that reported an aHR of 0.55, 95%CI: 0.38-0.80 for HCC in active *vs* inactive individuals [176]. The associations seemed to be at least in part mediated by obesity[176]. However, no prospective study evaluated the effect of physical exercise on HCC risk, as this might be rather difficult to perform [172].

Smoking cessation: Data from the Liver Cancer Pooling Project, a consortium of 14 prospective cohort studies comprising 1518741 individuals indicated that cigarette smoking significantly increased the risk of HCC (HR: 1.86, 95%CI: 1.57–2.20)[177]. It also demonstrated that in individuals who quit smoking for > 30 years, the risk of HCC decreased to values almost similar to non-smokers (HR: 1.09, 95%CI: 0.74–1.61)[177]. In addition, quitters seemed to have a lower risk of HCC-related mortality (HR, 0.62, 95%CI: 0.39–0.97), but this was seen in subjects without diabetes[178].

Pharmacological interventions

Several drugs have been suggested to bring benefits for NAFLD/NASH and to potentially reduce the risk of associated HCC, although there is limited evidence for HCC chemoprevention. It is assumed however that by improving histological features associated with NASH and the primary drivers of fibrogenesis ultimately leading to cirrhosis (and HCC), the disease progression will be attenuated, and HCC occurrence eventually prevented[179].

Metformin: Metformin does not seem to improve NASH/fibrosis, but several meta-analyses suggested that it might reduce the risk of HCC in patients with T2DM[180–182]. A recent meta-analysis of 24 studies including 1.4 million individuals reported that metformin was associated with a 41% lower risk of HCC in DM patients treated with metformin ($P < 0.001$) and a significant reduction of all-cause mortality (HR: 0.74, 95%CI: 0.66–0.83; $P = 0.037$)[180]. Moreover, a network meta-analysis that compared several antidiabetic medications has shown that in comparison with sulphonylureas and insulin, metformin significantly decreased the risk of HCC (RR: 0.45, 95%CI: 0.27–0.74 and RR: 0.28, 95%CI: 0.17–0.47)[181]. Postulated mechanisms of chemoprotective effects of metformin are the activation of AMP-activated protein kinase and inhibition of the mammalian target of rapamycin pathway, the inhibition of angiogenesis and induction of apoptosis[183]. It was also suggested that metformin may inhibit the progression of high fat diet-induced HCC by modulating the innate immune-mediated inflammation and restoring tumor surveillance[184]. However, these data should be interpreted with caution, and there is still need for further substantiation.

Thiazolidinediones: The meta-analysis by Musso *et al*[185] has delineated the effects of the two thiazolidinediones (TZDs), indicating that only pioglitazone (30/45 mg/d, for 6 to 24 mo) was associated with improvement in fibrosis (even advanced fibrosis) and NASH resolution in patients with or without diabetes. In addition to increasing adiponectin levels and decreasing excessive lipolysis and FFA flux into the liver, pioglitazone attenuated oxidative stress and inflammation and, the activation and proliferation of hepatic stellate cells, extracellular matrix deposition, fibrosis, *etc*[12,186–188]. The possible role of the TZDs in hepatic chemoprevention is further suggested by *in vitro* data, showing that they may inhibit hepatocarcinogenesis by the regulation of nucleophosmin, a ubiquitously expressed cellular phosphoprotein involved in both proliferation and growth-suppression pathways[189,190]. Animal data also showed that pioglitazone reduced the HCC development, possibly through the upregulation of the AMP-activated protein kinase pathway and the reduction of the mitogen-activated protein kinase activation[191]. However, data in humans are scarce, and no definite conclusions can be drawn yet. The results of the network meta-analysis by Zhou *et al*[181] suggested possible beneficial effects of TZDs in reducing HCC incidence, but these were seen only in comparison with sulphonylureas (RR: 0.47, 95%CI: 0.22–0.97) and with insulin (RR: 0.30, 95%CI: 0.14–0.61), but not *vs* observation alone.

GLP-1 receptor agonists: Two histological studies with GLP-1 receptor agonists (GLP-1 RAs) (liraglutide and semaglutide) in patients with or without T2DM have proven NASH resolution, but results regarding fibrosis were inconclusive[192,193]. Preclinical studies have suggested potential chemoprotective effects of the GLP-1 RAs through various mechanisms like enhancing natural killer cell-mediated cytotoxicity and, inducing autophagy and senescence of the HCC cells by the increase of transforming growth factor β 1, promoting their apoptosis through activation of the JNK signaling pathway, *etc*[194–196]. There is very limited information regarding the long-term effect of GLP-1 RAs on HCC incidence in humans so far.

Statins: Two recent meta-analyses of observational and interventional studies have confirmed liver safety for statin use in patients with NAFLD and even a reduction of transaminases levels[197,198]. Moreover, the meta-analysis by Fatima *et al*[198], which also analyzed the liver histology outcomes, reported a significant reduction of steatosis grade, necro-inflammatory stage, and of significant fibrosis but not the fibrosis stage. Several meta-analyses (mostly of observational studies) have consistently reported reduced risk of HCC in statin users (RRs/ORs/HR between 0.52–0.75 for all statins), with some indication of differences between them[199–208]. In particular, it seemed that the lipophilic statins exert preventive effects (OR: 0.51, 95%CI: 0.46–0.57 and HR:0.49, 95%CI: 0.39–0.62) rather than the hydrophilic statins (OR: 0.77, 95%CI: 0.58–1.02 and HR: 0.73, 95%CI: 0.40–1.34)[205,208]. Higher doses appeared to be associated with better protective effects (HR: 0.38 *vs* 0.55)[195]. Moreover, a meta-analysis of nine retrospective cohort studies also reported a lower risk of HCC-related mortality (RR: 0.78, $P = 0.001$) and reduced HCC recurrence (RR: 0.55, $P < 0.001$) with statin use[208]. However, another meta-analysis

indicated that statin usage decreased the risk of all-cause mortality (HR: 0.80, 95%CI: 0.68-0.94; $P < 0.0001$) but not of HCC-specific mortality (HR: 0.80, 95%CI: 0.62-1.03; $P = 0.002$)[200].

Apart from exerting lipid-lowering effects, statins have anti-inflammatory, antioxidant, anti-proliferative, and anti-angiogenic properties[12,209,210]. Their potential anti-tumor effects might be mediated through the downregulation of the RAF/mitogen-activated protein kinase 1/extracellular signal regulated kinase and nuclear factor kappa-B pathways, limitation of the cyclin-dependent kinase inhibitors (p21 and p27) degradation, prevention of the c-Myc activation, reduction of proinflammatory cytokines, *etc.*, which determine apoptotic responses, tumor-suppressor effects, cell survival reduction, and cell growth inhibition[183,211]. Nevertheless, data from well-designed RCTs (that limit the effect of confounding factors) in support of the HCC chemopreventive effects of statins in NAFLD/NASH population is scant.

For the other anti-hyperglycemic and lipid-lowering drug classes there is no consistent evidence so far regarding potential HCC protective effects.

Resmetirom is a thyroid hormone receptor β -selective agonist, which was shown to significantly reduce the liver fat after 12 and 36 wk of treatment[212]. It is currently under evaluation for safety and efficacy in improving NASH and preventing progression to cirrhosis and/or advanced liver disease in a phase 3 RCT (MAESTRO-NASH; NCT03900429)[213].

Aspirin: Growing evidence coming from preclinical and clinical observational studies suggest that aspirin might play a role in HCC prevention[80,165]. The mechanisms are related to inhibition of selective cyclooxygenase-2 as well as of platelet-derived growth factor, P4HA2, nuclear factor kappa-B activation, and protein kinase 3 signaling, *etc.*, which may prevent proliferation of liver cancer cells and angiogenesis and promote fibrosis resolution[80,165]. Several meta-analyses have explored the potential HCC protective effect of aspirin and have shown that it is associated with reduced incidence/risk of HCC (RRs/HRs/ORs between 0.74 and 0.51)[214-219]. The meta-analysis by Memel *et al*[214] implied stronger association after adjustment for metformin/statin use and accounting for cirrhosis. Also, an inverse relationship seems to exist between aspirin dose/duration of use and HCC risk, but this should be further confirmed[215,219]. There was no evidence of higher risk of bleeding with aspirin use, including in patients with HCC in most meta-analyses except one[216-220]. Moreover, the systematic review and meta-analysis by Tan *et al*[216] showed that aspirin use was associated with improved liver-related mortality (OR: 0.32, 95%CI: 0.15-0.70) and reduced risk of HCC recurrence (HR: 0.80, 95%CI: 0.75-0.86). The same was observed in the meta-analysis by Li *et al*[220], which demonstrated a reduced risk of HCC recurrence (RR: 0.74, 95%CI: 0.59-0.93; $P = 0.01$) and all-cause mortality (RR: 0.59, 95%CI: 0.47-0.73; $P < 0.001$). Although the evidence points toward a potential benefit of aspirin use in prevention of HCC, further prospective data is still necessary in the NAFLD/NASH population.

Vitamin E has anti-oxidative properties, and it might modulate fibrogenesis through inhibition of transforming growth factor β 1[12,221]. A recent meta-analysis of eight RCTs reported that vitamin E supplementation (400-800 IU/d, between 8-96 wk) was associated with reduction of fibrosis score (MD *vs* placebo: -0.26, 95%CI: -0.47 to -0.04; $P = 0.02$) as well as a decrease in steatosis, lobular inflammation, and hepatocellular ballooning compared with placebo[222]. However, only one study included patients with T2DM. In fact, the study by Bril *et al*[223] that randomized 105 T2DM patients with biopsy-proven NASH to vitamin E 400 IU b.i.d., vitamin E 400 IU b.i.d. plus pioglitazone 45 mg/d, or placebo did not reach the primary outcome (two-point reduction of NAS from two different parameters, without worsening of fibrosis) in patients receiving vitamin E *vs* placebo but resulted in improvement of steatosis. Thus, it is not clear if the benefit of vitamin E supplementation is restricted to individuals without diabetes, and more data is needed in the T2DM population.

Experimental studies have suggested that antifibrotic therapies may serve as HCC preventive interventions by addressing the underlying cause of carcinogenesis onset[224,225]. Unfortunately, no anti-fibrotic drug has been approved so far by the European Medicines Agency or by the United States Food and Drug Administration for NASH treatment.

Obeticholic acid (OCA) is a farnesoid X receptor agonist shown to improve fibrosis without worsening NASH in an interim analysis of a phase 3 RCT (REGENERATE; NCT02548351)[226,227]. In this analysis, a significantly higher proportion of patients treated with OCA 25 mg daily presented improvement in fibrosis by ≥ 1 stage with no worsening of NASH (23% *vs* 12% in placebo group, $P = 0.0002$)[227]. In the analysis that included patients receiving at least 15 mo of therapy, three times more patients in the OCA 25 mg/d group obtained ≥ 1 stage improvement in fibrosis (38%) *vs* progression of fibrosis (13%) compared with the placebo group, in which similar proportions of patients presented improvement (23%) *vs* worsening (21%) of fibrosis[227]. The FLINT (Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment) trial had previously shown that treatment with OCA 25 mg/d for 72 wk improved liver histology (RR: 1.9, 95%CI: 1.3-2.8; $P = 0.0002$) in patients with biopsy-proven NASH[228]. However, in both trials, a higher proportion of patients treated with OCA presented pruritus (23% in FLINT study and 51% in REGENERATE study) in a dose-dependent manner[227,228]. In addition, OCA therapy was associated with increased low-density lipoprotein cholesterol levels, but this could be attenuated by concomitant statin therapy[80,229]. HCC animal model data suggested that the OCA might attenuate the development and progression of NASH-associated HCC by upregulating

sirtuin-1 and modulating the SOCS3/Jak2/STAT3 pathway[230].

Pentoxifylline: Although few small histological studies have suggested liver-related benefits with pentoxifylline 400 mg t.i.d. treatment [*i.e.* improvement of steatosis, lobular inflammation, and liver fibrosis score (mean change: -0.2 *vs* +0.4 on placebo, $P = 0.038$)] and regression of fibrosis when combined with vitamin E ($P = 0.003$), data is still scarce and not consistent[231,232]. Four meta-analyses have reported conflicting results with regards to the effect of pentoxifylline on liver fibrosis, with only two of them suggesting benefits[233-236]. Therefore, additional data is required.

Two other initially promising anti-fibrotic medications have failed to prove a significant impact on hepatic fibrosis in phase 3 clinical trials. Elafibranor, an agonist of PPAR- α/δ , reduced steatohepatitis without worsening fibrosis in a phase 2 trial in NASH patients, but the primary end-point was not met [237]. The phase 3 RCT (RESOLVE-IT-NCT02704403) was prematurely discontinued due to limited efficacy at the time of the interim analysis[238]. Cenicriviroc, a dual inhibitor of C-C motif chemokine receptor 2/5, reduced liver fibrosis in NASH patients but did not reach the primary outcome in a phase 2b study[239]. This was followed by a phase 3 trial (AURORA-NCT03028740), which was also terminated early due to lack of efficacy resulting from the planned interim analysis[240]. Several other drugs with potential anti-fibrotic effects are currently in development/evaluation, and the results are expected with interest[241].

CONCLUSION

Regardless of the risk status, all NAFLD/NASH patients should consider adopting lifestyle changes (healthy diet and physical exercise) and controlling their body weight, as these are the cornerstone interventions for NAFLD/NASH management and possibly through altering the natural course of the disease for HCC prevention.

Data suggest a possible role of comprehensive lifestyle changes in reducing the risk of HCC, but specific evidence in NAFLD/NASH patients is rather limited at this point and not sufficient to clearly indicate preventive effects on NAFLD/NASH-associated HCC. Moreover, there is no consensus regarding the composition of a protective diet but decreasing the intake of deleterious nutrients/foods and beverages (*i.e.* saturated fats, sugar-sweetened beverages, alcohol), increasing the beneficial nutrients/foods/beverages (vegetables, coffee, dietary fiber, omega-3 PUFA), and adherence to a healthy dietary pattern (such as the Mediterranean diet or traditional Cantonese dietary pattern) are reasonable and safe approaches. However, their role in HCC prevention still needs to be confirmed by further well-designed prospective studies and experimental research.

Several drug classes (metformin, statins, and aspirin and possibly TZDs, GLP-1 RA, vitamin E, and obeticholic acid) might exert chemopreventive effects by addressing the underlying mechanisms of the disease, but direct evidence regarding their role in NAFLD/NASH-associated HCC prevention is insufficient at the moment.

A timing combination of therapies/non-pharmacological interventions and perhaps adapting them to the stage of disease and/or patient particularities will be necessary to obtain disease resolution and prevention of cirrhosis/NASH-associated HCC.

FOOTNOTES

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