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Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention

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Abstract

One quarter of the global population is estimated to have nonalcoholic fatty liver disease (NAFLD). The incidence of nonalcoholic steatohepatitis (NASH) is projected to increase by up to 56% in the next 10 years. NAFLD is already the fastest growing cause of hepatocellular carcinoma (HCC) in the USA, France and the UK. Globally, the prevalence of NAFLD-related HCC is likely to increase concomitantly with the growing obesity epidemic. The estimated annual incidence of HCC ranges from 0.5% to 2.6% among patients with NASH cirrhosis. The incidence of HCC

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Competing interests

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among patients with non-cirrhotic NAFLD is lower, approximately 0.1 to 1.3 per 1,000 patient-years. Although the incidence of NAFLD-related HCC is lower than that of HCC of other aetiologies such as hepatitis C, more people have NAFLD than other liver diseases. Urgent measures that increase global awareness and tackle the metabolic risk factors are necessary to reduce the impending burden of NAFLD-related HCC. Emerging evidence indicates that reduced immune surveillance, increased gut inflammation and gut dysbiosis are potential key steps in tumorigenesis. In this Review, we discuss the global epidemiology, projections and risk factors for NAFLD-related HCC, and propose preventive strategies to tackle this growing problem.

The incidence and prevalence of nonalcoholic fatty liver disease (NAFLD) are rapidly rising worldwide[1–4]. The global prevalence of NAFLD is approximately 25%[1], ranging from 13% in Africa[1] to 42% in southeast Asia[4]. NAFLD encompasses a spectrum of diseases including nonalcoholic fatty liver (NAFL) or simple steatosis, which has a more benign course, and nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma (HCC)[5,6]. NASH prevalence is projected to increase by up to 56% between 2016 and 2030 in China, France, Germany, Italy, Japan, Spain, UK and USA[7]. NAFLD is driven by metabolic syndrome and is associated with obesity, insulin resistance and hyperlipidaemia[2]. Obesity and insulin resistance lead to chronic inflammation, altered lipid metabolism and a pro-carcinogenic state that promotes HCC development[8,9]. Some experts in the field have proposed changing the nomenclature from NAFLD to metabolic associated fatty liver disease (MAFLD)[10]. Others, however, have highlighted that the molecular basis of the disease entity is still unclear and a switch in terminology at this stage might create confusion[11].

HCC is the fourth-leading cause of cancer death worldwide[12,13]. It is the second-leading cause of years of life lost worldwide to cancer, which highlights the high disease burden of liver cancer[14]. In the USA, the incidence of liver cancer is increasing at the highest rate of cancers of all sites[15]. Owing to a combination of ageing, population growth and an increase in metabolic syndrome, there was a 75% increase in incident cases of HCC between 1990 and 2015, with the highest burden of liver cancer incidence, death and years of life lost in east Asia[12].

NAFLD-related HCC tends to occur in older individuals (mean age 73 years in patients with NAFLD-related HCC versus 66 years in patients with hepatitis C virus (HCV) infection and 70 years in patients with hepatitis B virus (HBV) infection)[16], tends to be diagnosed at a later stage and is associated with poorer survival than viral hepatitis-related HCC[16]. NAFLD-related HCC is also well known to develop in the absence of liver cirrhosis, unlike liver diseases of other aetiologies such as alcohol-related and autoimmune liver disease[17,18]. The absence of HCC screening protocols in patients with NAFLD but without cirrhosis contributes to the late diagnosis and management. It is likely that the rates of NAFLD-related HCC will increase in parallel with the obesity epidemic. In 2012, 35% of the US population had obesity[19]. By 2030, 48.9% of the total US population is projected to have obesity[19,20]. NAFLD is now the fastest growing cause of HCC in liver transplant recipients and transplantation candidates on the waiting list in the USA[21]. Similarly, studies from Europe, South Korea and southeast Asia have demonstrated a rapid increase in the

proportion of patients with HCC attributed to NAFLD over the past two decades[22–25]. In this Review, we discuss the global epidemiology, trends and projections for NAFLD-related HCC. We highlight data regarding HCC development in patients with non-cirrhotic NAFLD and propose surveillance strategies in patients without cirrhosis. In addition, we review the risk factors for NAFLD-related HCC and discuss preventive measures.

Global NAFLD-related HCC epidemiology

HCC in NASH cirrhosis

Studies of HCC incidence in patients with NASH cirrhosis from the USA and Europe.—The annual incidence of HCC in cohorts of patients with NASH in the USA and Europe ranges from 0.7% to 2.6%[26,27] (TABLE 1). In our opinion, the wide variation is explained in part by the differences in age, metabolic profile and presence or severity of hepatic decompensation in the patients included in these studies. The data are largely from either clinic-based or hospital-based cohort studies and transplant registry databases. However, high-quality, population-based cohort studies are generally lacking. In a cohort of 195 patients with NASH cirrhosis referred for transplantation evaluation between 2003 and 2007 at the Cleveland Clinic in Ohio, USA, Ascha and colleagues found that the annual incidence of HCC development was 2.6% in patients with NASH cirrhosis and 4.0% in patients with HCV-related cirrhosis[26]. Sanyal and colleagues conducted a study of patients between 1992 and 2004 at Virginia Commonwealth University in Virginia, USA, and found a lower HCC incidence in 152 patients with biopsy-proven NASH cirrhosis than in patients with HCV-related cirrhosis (10 of 149 versus 25 of 147 patients at risk over 10 years)[27]. The higher rate of HCC incidence found in the study by Ascha et al. was possibly because they included a higher proportion of patients with diabetes and patients with a past history of high alcohol use, unlike the study by Sanyal et al.[27]. A multinational study in 247 patients with biopsy-proven NASH (118 with F3 fibrosis and 129 with F4 fibrosis) from the USA, UK, Italy and Australia between 1984 and 2006 found an annual incidence of HCC development of 0.05%, which was probably related to the fact that approximately half of the cohort had cirrhosis[28]. HCC incidence in patients with NASH cirrhosis is higher in older patients, in men, and in patients with diabetes and higher alcohol intake[26,29,30].

Studies of HCC incidence in patients with NASH cirrhosis from Japan and India.—In a prospective cohort of 68 patients with biopsy-proven NASH cirrhosis diagnosed between 1990 and 2006 from Japan, the 5-year HCC incidence was 11.3% compared with 30.5% in a retrospective cohort of 69 patients with HCV-related cirrhosis matched for age and sex[31] (TABLE 1). The NASH cirrhosis cohort in this study was older (63 years versus 55 years) and had a higher prevalence of diabetes (68% versus 59%) than the patients in the study by Sanyal et al.[27], which possibly accounts for the higher HCC incidence. In the Japanese study, patients who developed HCC had a higher prevalence of diabetes than those who did not develop HCC[31]. Furthermore, the global estimated prevalence of NAFLD far exceeds that of HCV infection (25% versus 2.8%)[1,32]. In a prospective study conducted in Mumbai, India, Amarapurkar and colleagues found an HCC incidence of 0.5% annually in a cohort of 41 patients with NASH cirrhosis[33]. This study was limited by a small sample size. However, there are consistent data, such as from the Japan

study[31] as well as the Cleveland Clinic study[26], indicating that the HCC incidence was substantially lower in patients with NASH cirrhosis than in those with HCV-related cirrhosis. Overall, the data from Japan and India are consistent with the data from the USA and Europe.

HCC in patients with non-cirrhotic NASH

A growing body of evidence has shown that HCC develops in patients with NASH even in the absence of cirrhosis. A systematic review with a meta-analysis of 19 studies and 168,571 individuals with NASH showed that the prevalence of NAFLD-related HCC in patients with NASH but without cirrhosis is approximately 38%, compared with 14% in patients with liver diseases of other aetiologies (that is, liver disease related to alcohol consumption, or HBV or HCV infection) without cirrhosis ($P < 0.001$)[17]. This study found a remarkably high prevalence of HCC among patients with NASH. However, a large number of studies were excluded from the meta-analysis due to missing data, potentially skewing the results. In addition, the researchers were unable to provide data comparing stages of fibrosis. In a cross-sectional study including 120 patients with NAFLD-related HCC diagnosed from 2005 to 2010 in Veterans Health Administration hospitals, only 58.3% had cirrhosis[34]. Sanyal et al.[35] found that only 46% of patients with NAFLD-related HCC had cirrhosis, based on data from a health-care claims-based database. In a cohort of 1,500 patients with HCC from the US Veterans Health Administration, NAFLD was the leading cause of HCC among patients without cirrhosis[36]. Similarly, in a multicentre Japanese cohort comprising 596 patients with NAFLD-related HCC diagnosed between 1991 and 2010, 36.6% of the patients did not have cirrhosis[37]. Consistent with these findings, in a multicentre Italian cohort comprising 145 patients with NAFLD-related HCC enrolled between 2010 and 2012, 50% of the patients did not have cirrhosis[38]. In this Italian study, the patients without cirrhosis with histology available mainly had NASH with advanced fibrosis rather than simple steatosis without fibrosis, suggesting that the stage of fibrosis might be relevant in the future risk of HCC in the absence of cirrhosis. Similarly, in a multicentre Japanese cohort of 87 patients with histologically proven NAFLD-related HCC diagnosed between 1993 and 2010, 72% had advanced fibrosis (F3 and F4), whereas 65% had at least moderate-to-severe necroinflammatory activity[39]. The Italian and Japanese studies suggest that in the majority of patients, HCC develops in the setting of NASH with advanced fibrosis. Current practice guidelines do not recommend routine HCC screening in patients with non-cirrhotic NAFLD or NASH[40–42].

Studies of HCC incidence in patients with non-cirrhotic NAFLD–NASH from the USA and Europe.—HCC incidence in patients with non-cirrhotic NAFLD or NASH ranges from 0.1 to 1.3 per 1,000 patient-years, with the higher estimates found in cohorts with a higher degree of NASH or stage of fibrosis[30,43] (TABLE 2). A population-based study by Alexander et al.[43] included 136,703 individuals identified from European primary care databases who were coded for either NAFLD or NASH. Within the Spanish and UK databases, NAFLD and NASH were separately coded; therefore, the incidence could be distinguished between the two subgroups. The study found an HCC incidence of 0.2 and 0.6 per 1,000 patient-years among patients with NAFLD in Spain and the UK, respectively. Among patients with NASH, the study found a higher HCC incidence of 1.1 and 1.3 per

1,000 patient-years in Spain and the UK, respectively. HCC incidence for NAFL–NASH in Netherlands and Italy was 0.4 and 0.3 per 1,000 patient-years, respectively. Owing to coding limitations, the differences in HCC incidence between NAFLD and NASH could not be ascertained from data from Netherlands and Italy.

Kanwal and colleagues performed a large retrospective cohort study including 296,707 Veterans Health Administration patients with NAFLD diagnosed between 2004 and 2008 (REF.[30]). In this study, NAFLD was diagnosed based on elevated alanine aminotransferase (ALT) levels in the absence of HBV or HCV infection and International Classification of Diseases (ICD) 9 codes for liver diseases. The study found an HCC incidence of 0.21 per 1,000 patient-years. Only 0.4% of the cohort had cirrhosis. In a subgroup analysis, the HCC incidence was lower in patients without cirrhosis (0.08 per 1,000 patient-years) than in patients with cirrhosis (10.6 per 1,000 patient-years). Although the incidence of HCC among patients with NAFLD is substantially lower in those without cirrhosis than in those with cirrhosis, the prevalence of HCC among those without cirrhosis is sizeable owing to the high frequency of patients who have NAFLD with fibrosis.

Studies of HCC incidence in patients with non-cirrhotic NAFLD–NASH from Asia.—Studies from Asia in patients with NAFLD found annual HCC incidences ranging from 0.04% to 0.6%[44,45] (TABLE 2). The presence of NASH, diabetes and advanced fibrosis were associated with a higher HCC incidence in patients with NAFLD.

Among the studies from Japan, Kawamura et al.[44] found an annual HCC incidence of 0.043% based on a cohort of 6,508 patients with NAFLD diagnosed by ultrasonography. The prevalence of significant fibrosis in this cohort was low (aspartate aminotransferase to platelet ratio index >1.5 in only 2.8% of patients). Therefore, this cohort is more representative of patients with uncomplicated NAFLD due to its low rates of significant fibrosis, and notably has a similar incidence to the NAFLD subgroups in the study by Alexander et al.[43]. By contrast, Seko et al.[46] found a higher annual HCC incidence of 0.4% in a cohort of 238 patients with biopsy-proven NAFLD–NASH, with 18% of the patients having advanced fibrosis. The proportion of patients with diabetes was higher, which probably contributed to the higher HCC incidence in patients with NAFLD compared with the incidence found in other studies in patients with NAFLD. Similarly, Ito et al.[45] found a relatively high 10-year HCC incidence of 6.04% in a cohort of patients with biopsy-proven NAFLD. This cohort included a substantially higher proportion of patients with advanced fibrosis (20.4%) and diabetes (45.1%), resulting in a higher HCC incidence.

A South Korean study including 8,721 patients with NAFLD diagnosed using ultrasonography, of whom 25% had intermediate or high NAFLD fibrosis scores, found an HCC incidence of 23 per 100,000 patient-years, lower than the incidence found in the Japanese studies[47]. It is difficult to compare such a study with other studies in which histology was used to evaluate fibrosis. Notably, the rate of diabetes found in this study was lower (16.2%) than in the studies by Seko et al.[46] (45.0%) and Ito et al.[45] (45.1%). In a Taiwanese cohort, Lee et al.[48] found a 10-year HCC incidence of 2.73%, which was similar to that seen in the South Korean study. The cohort of 31,571 patients with NAFLD without cirrhosis identified by ICD-9 codes was derived from Taiwan’s National Health Insurance

Research Database, which had a lower median age and prevalence of diabetes than the patients in the studies by Ito et al. and Seko et al. The stage of fibrosis in the Taiwanese cohort could not be accurately determined. Overall, the data from Japan, South Korea, and Taiwan are consistent with the data from the USA and Europe.

Proportion of HCC attributable to NAFLD

There is substantial heterogeneity in how NAFLD is defined among studies reporting the proportion of patients with HCC attributable to NAFLD. In the USA, several studies have defined NAFLD using either ICD-9 codes from large national registries or primary diagnoses listed in national transplantation databases. As NAFLD is often under-reported[49], many studies have expanded their study definitions to include patients with cryptogenic cirrhosis[50] (where the underlying aetiology remains unknown after extensive investigations have been performed) and varying components of metabolic syndrome. Some studies have also included patients with cryptogenic cirrhosis without a requirement for the presence of metabolic syndrome. The inclusion of these patients could result in misclassification, but many clinicians would agree that most patients with cryptogenic cirrhosis have NASH cirrhosis[51]. Thuluvath et al. analysed the United Network for Organ Sharing database and compared the clinical characteristics of 7,999 individuals with a listed diagnosis code for cryptogenic cirrhosis against 11,302 individuals with a listed diagnosis code for NASH cirrhosis[52]. They found a higher prevalence of diabetes and obesity in the NASH cirrhosis group and found that the risk factor profile of patients with cryptogenic cirrhosis seemed to be different from that of patients with NASH cirrhosis. They concluded that cryptogenic cirrhosis might be neither equivalent to nor interchangeable with NASH cirrhosis. However, the retrospective nature of the study and the use of the United Network for Organ Sharing database limits validity and generalizability, respectively[51]. Further refinement in the definitions of suspected NASH cirrhosis and cryptogenic cirrhosis would improve the precision around the estimates of HCC risk in patients with cirrhosis of either aetiology as well as the proportion of patients with NAFLD-related HCC without cirrhosis. In Asia, in many studies NAFLD was defined based on imaging or histology, and multiple smaller studies included patients with either cryptogenic cirrhosis alone (that is, without reporting NASH cirrhosis) or both cryptogenic and NASH cirrhosis. There is a lack of high-quality, population-based studies in which the prevalence of NAFLD-related HCC was estimated. In this Review, cryptogenic cirrhosis is included under NASH cirrhosis in estimating the prevalence of NAFLD-related HCC. The studies reporting the proportion of patients with HCC attributable to NAFLD are summarized in TABLES 3,4. The estimated global proportions of patients with HCC attributable to NAFLD range between 1% and 38% in the different countries/regions (FIG. 1). In general, countries with a higher proportion and rising trend of NAFLD-related HCC have a higher prevalence of obesity[53]. In the following section, we highlight several studies that provide insights into NAFLD-related HCC trends in each region.

Regions with a high proportion of patients with HCC attributable to NAFLD.— In the UK, Dyson et al.[24] studied 632 consecutive patients with HCC referred to Newcastle-upon-Tyne Hospitals and found the proportion of patients with NAFLD-related HCC increased from <10% in 2000 to 34.8% in 2010 (TABLE 3). Notably, only patients with

biopsy-proven NAFLD or radiological evidence of steatosis were recorded as having NAFLD. Of the 20.4% of patients with HCC who were recorded as having ‘no known chronic liver disease’, 48.4% had at least one metabolic risk factor. This observation suggests that the true proportion of patients with NAFLD-related HCC in this cohort might have been substantially higher than 34.8%. The absence of true population-based studies of HCC and systematic ascertainment of NAFLD precludes more definitive statements. Estes et al.[7], using a Markov model, forecast that the incidence of NAFLD-related HCC in the UK would increase by 88% between 2016 and 2030, from 850 to 1,600 cases. These studies support the possibility that NAFLD might already be the leading cause of HCC in the UK.

In Germany, a comparative analysis of a historical cohort from 1988 to 1999 and 484 consecutive patients with HCC admitted to a tertiary German hospital from 1999 to 2013 showed an increase in the proportion of patients with NASH-related and aetiology-unknown HCC from 7% to 23.9%, respectively[54] (TABLE 3). In that study, Ganslmayer et al. defined NASH on the basis of histology and an absence of significant alcohol consumption. It is possible that a large proportion of the patients with an unknown aetiology had NAFLD-related HCC. Among European countries/regions, Germany is projected to have the highest prevalence of NAFLD-related HCC (4,090 cases) in 2030, due to its high projected prevalence of NASH (4.7 million by 2030)[7].

In Saudi Arabia, Aljumah et al.[55] found that, of 253 patients with HCC who presented to a hospital from 2009 to 2011, 21.7% had cryptogenic and possible NAFLD-related HCC (TABLE 4). The aetiology of HCC among various countries/regions in the Middle East was also explored in a review by Yapali et al.[56]. After exclusion of HCV and HBV infection and alcohol consumption, 10–20% of the patients had HCC with ‘other causes’ in most of the Middle East, except in Afghanistan, Iran, Pakistan and Saudi Arabia, where the prevalence was >20%. In a substantial proportion of the patients with HCC with other causes, the cause was likely to have been NAFLD due to the high prevalence of obesity in the region[53].

The Africa Liver Cancer Consortium studied 2,566 patients with HCC from nine countries/regions from 2006 to 2016 (REF.[57]) (TABLE 3). The most common cause of HCC in Egypt was HCV infection (84%). In all other African countries/regions included, such as Nigeria and Ghana, HBV infection was the most common aetiological factor (55%). In patients with HCC not attributed to HCV or HBV infection or alcohol consumption, the HCC was classified as cause ‘other or unknown’, and these patients comprised 12% and 22% of the Egyptian and non-Egyptian cohorts, respectively. The other or unknown causes were not elaborated upon, but it can be assumed that in a substantial proportion of these patients the HCC was NAFLD-related.

In a study of 324 patients with HCC presenting to a tertiary centre in India between 1990 and 2005, 21.6% of the patients were considered to have cryptogenic HCC[58] (TABLE 4). In a study from India in 144 patients with HCC who underwent surgical resection[59] between 2009 and 2017, an extremely high proportion (38%) of the patients had NAFLD-related HCC, which was second only to the proportion with HBV infection (40%). A selection bias might have been present in this resection cohort towards patients with NAFLD given that

NAFLD-related HCC can occur in patients without cirrhosis who have relatively preserved liver function.

The prevalence of cryptogenic HCC in southeast Asia ranges from 12.6% in Singapore to 24.9% in the Philippines[23,60–63] (TABLE 4). In Singapore, Liew et al. found a major increase in the proportion of patients with cryptogenic cirrhosis-related HCC from 1980–2005 to 2006–2015 (12.9% to 20.4%, respectively)[23]. With the exception of the study from Singapore, none of these studies specified the diagnostic criteria for NAFLD.

Regions with a moderate proportion of patients with HCC attributable to NAFLD.—Data from the USA show that the prevalence of NAFLD-related HCC is rapidly increasing. In a population-based study that used the Surveillance, Epidemiology and End Results (SEER) registries to identify patients with HCC in the USA from 2004 to 2009, Younossi et al.[16] estimated that 14.1% of patients had NAFLD-related HCC (TABLE 3). The average annual increase in NAFLD-related HCC from 2004 to 2009 was 9%, which is lower than the 13% annual increase in HCV-related HCC. However, the researchers used non-validated ICD-9 codes to define NAFLD and included cases coded as cryptogenic cirrhosis, and therefore might have overestimated the number of patients with NAFLD-related HCC.

Among patients with HCC requiring liver transplantation in the USA, patients with NAFLD are the fastest growing group. In an analysis of trends in HCC aetiology from 2002 to 2012 using the United Network for Organ Sharing Registry, Wong et al.[64] found an increase in the prevalence of NASH HCC from 8.3% in 2002 to 13.5% in 2012. After HCV infection, patients with NASH are the second largest group among patients with HCC requiring liver transplantation. Using the Scientific Registry of Transplant Recipients from 2002 to 2016, Younossi et al.[21] analysed 26,121 patients with HCC who were either listed for or underwent transplantation in the USA. This analysis considered the presence of cryptogenic cirrhosis to indicate NASH. The proportion of patients with HCC secondary to NASH increased 7.7-fold from 2.1% to 16.2% (trend $P < 0.0001$) among all study participants, and 8.5-fold (2.2% to 17.9%; trend $P < 0.0001$) between 2002 and 2017 among candidates on the waiting list. By contrast, the proportions of patients with HCC secondary to HCV infection (47.9% to 60.3%; trend $P = 0.89$) and to alcohol consumption (8.3% to 14.2%; trend $P = 0.39$) remained stable.

Although HCV infection remains the leading cause of HCC in the USA and confers a higher HCC risk compared with NAFLD[26], the high efficacy of direct-acting antiviral treatments and improvements in access to care will eventually reduce the incidence of HCV-related HCC[65]. By contrast, NASH and NAFLD-related HCC rates in the USA are projected to increase considerably. Using a Markov model to predict NAFLD incidence in the USA on the basis of historical and projected changes in rates of diabetes and obesity, Estes et al.[66] forecast that the prevalence of NASH and NAFLD-related HCC would increase by 63% and 146%, respectively, from 2015 to 2030. By 2030 in the USA, the yearly incidence of NAFLD-related HCC is projected to increase by 137%, from 5,160 to 12,240 cases. Between 2015 and 2030, NAFLD-related HCC is projected to cause 110,900 deaths in the

USA. It is unclear how much of the rapid rise in NAFLD-related HCC diagnoses is due to better awareness of this disease or to a true increase in incidence.

A population-based study conducted in Manitoba, Canada, in 320 patients diagnosed with HCC between 2011 and 2015 found that in 39% of the patients the aetiology was unknown[67]. The authors of this study speculated that NASH cirrhosis would have been the cause of the liver disease in most of these patients with an unknown aetiology. The authors reported, however, that data regarding aetiology were not reliably captured. A modelling study estimated that the number of new NAFLD-related HCC cases per year would increase by 80% from 660 cases in 2019 to 1,200 by 2030 (REF.[68]).

In South America, a multicentre study involving 1,336 patients with HCC from six countries between 2005 and 2015 found that in 9% of the cohort the HCC was secondary to NAFLD and in 3% was attributable to cryptogenic cirrhosis[69] (TABLE 3). Notably, the median age at diagnosis in patients with NAFLD-related HCC in this study was significantly higher than that in patients with HBV-related HCC (67 years versus 58 years; $P < 0.001$), reinforcing the findings of previous studies demonstrating a more advanced age at diagnosis in patients with NAFLD-related HCC[16]. In comparison, an earlier prospective study from nine countries in South America recruited 240 patients with HCC between 2006 and 2008 and found that the proportion of patients with HCC attributable to biopsy-proven NAFLD was only 5%. However, in 15% of the patients, the HCC was attributable to cryptogenic cirrhosis, and many of these patients might have had underlying NAFLD[70].

In a study in 323 patients with HCC who underwent liver resection at two tertiary centres in France between 1995 and 2014 (REF.[25]), Pais et al. found that the prevalence of NAFLD-related HCC increased from 2.6% (1995–1999) to 19.5% (2010–2014). NAFLD was defined by the presence of metabolic risk factors in the absence of other causes of chronic liver disease. By contrast, the prevalence of HCV-related HCC declined from 43.6% to 19.5% over the same time period (TABLE 3). However, given that NAFLD-related HCC can occur in patients without cirrhosis who have relatively preserved liver function, it should be noted that a selection bias might have been present in the resection cohort towards patients with NAFLD rather than those with HCC of other aetiologies. In a modelling study, Estes et al.[7] estimated that the incidence of NAFLD-related HCC in France will have increased by 117%, from 560 to 1,200 cases annually, by 2030.

Regions with a low proportion of patients with HCC attributable to NAFLD.— The BRIDGE study was an international consortium consisting of 42 sites in 14 countries/regions that contributed data from 18,031 patients with HCC diagnosed between 2005 and 2011 (REF.[71]). Of the 8,683 patients from China in this study, in only 1% was the HCC attributable to NAFLD. In the vast majority of patients the HCC was secondary to HBV infection. However, it should be noted that the current population with NAFLD in China is estimated to be 243.7 million, compared with 85.3 million in the USA[7]. An obesity epidemic combined with an ageing population is projected to fuel an 86% rise in the prevalence of NAFLD-related HCC in China, from 14,090 cases in 2016 to 26,240 cases by 2030 (REFs[3,7]).

The proportion of patients with NAFLD-related HCC in Japan is generally lower than in the USA and Europe. In a retrospective multicentre study using data from 53 hospitals in Japan, Tateishi and colleagues found that of 33,782 patients with HCC treated between 1991 and 2010, 1.8% had NAFLD-related HCC and 8.5% had 'unclassified' HCC[37] (TABLE 4). In a substantial proportion of patients, the unclassified HCC might have been secondary to burnt-out NASH, which is the loss of hepatic fat often observed in association with advanced liver fibrosis[72]. In a nationwide survey of patients with HCC conducted by sending questionnaires to hospitals throughout Japan, Tokushige and colleagues found that of 14,530 patients with HCC diagnosed between 1996 and 2009, 2.0% had NAFLD-related HCC and 5.1% had cryptogenic HCC[73]. In both studies, the criteria for NAFLD were based on imaging and histological evidence without the presence of other causes of liver disease. Similarly a low proportion of patients with NAFLD-related HCC in Japan (2%) was also found in the BRIDGE study, although the investigators did not specify how NAFLD was diagnosed[71]. The projection of a modelling study indicated that Japan would experience a 47% increase in NAFLD-related HCC from 2,200 cases in 2016 to 3,240 cases by 2030. This increase in NAFLD-related HCC is smaller than that projected for China or the USA (86% and 130%, respectively)[7], with viral hepatitis likely to remain the leading cause of HCC.

Risk factors for NAFLD-related HCC

Risk factors for NAFLD-related HCC include older age, male sex, Latino/Latina ethnicity and presence of cirrhosis. In a large cohort study involving 296,707 patients with NAFLD, Kanwal and colleagues found that 290 patients developed HCC[30]. In this study, an age of ≥65 years was an independent risk factor for HCC development (HR 1.83, 95% CI 1.53–2.18; $P < 0.0001$). HCC developed more often in men than in women (0.22 versus 0.04 per 1,000 patient-years, respectively). The incidence of HCC was higher in Hispanic individuals (0.29 per 1,000 patient-years) than in white individuals (0.21 per 1,000 patient-years) and African American individuals (0.12 per 1,000 patient-years). In patients with cirrhosis, HCC incidence jumped to 10.6 per 1,000 patient-years compared with 0.08 per 1,000 patient-years in individuals without cirrhosis. Diabetes and obesity are also major risk factors among patients with NAFLD, and can act independently or jointly with NAFLD to increase the risk of HCC. The prevalence of NAFLD and advanced fibrosis among individuals with diabetes has been estimated at 56% and 17%, respectively[74]. Emerging data also implicate gut dysbiosis and inflammation as additional key risk factors for HCC development in patients with NAFLD. In studies in mouse models, Ma et al.[75] and Shalapour et al.[76] demonstrated that NASH causes suppression of $CD4^+$ and $CD8^+$ T cells, and thereby reduces immune surveillance and promotes hepatocarcinogenesis. Factors influencing NAFLD-related HCC pathogenesis and development are summarized in FIG. 2.

Diabetes mellitus

The relationship between diabetes and NAFLD-related HCC has been investigated in several studies around the world. In a Mayo Clinic study, 354 patients with NASH cirrhosis were followed for 47 months. In this cohort, 30 patients developed HCC[29]. The presence of diabetes increased the risk of HCC in patients with NASH cirrhosis by fourfold (HR 4.2, 95% CI 1.2–14.2; $P = 0.02$). The authors validated these findings using liver transplant

registrants identified within the United Network for Organ Sharing. Among patients with NASH cirrhosis within the network, diabetes was an independent risk factor for HCC development. Diabetes was also found to be the strongest independent risk factor for the development of HCC in a large European population-based study that included 136,703 individuals with NAFLD, with only 4.7% having a high fibrosis score (Fib-4)[43]. Notably, the effect of diabetes on HCC risk is not unique to NAFLD. Multiple studies from the USA, Europe and Asia have also shown an increased risk of HCC in patients with diabetes, regardless of the aetiology of the liver disease[77,78].

Kanwal and colleagues evaluated the independent and combined effects of the components of metabolic syndrome on the risk of HCC in patients with NAFLD without cirrhosis[79]. They evaluated 271,906 individuals in the USA, 253 of whom developed HCC during follow-up. The analyses showed that additional metabolic traits led to a stepwise increase in risk, with diabetes being associated with the highest risk of HCC development. The collective findings suggest that both patients with cirrhotic NAFLD and patients with non-cirrhotic NAFLD should be screened regularly for diabetes or pre-diabetes.

Obesity

Obesity has been shown to mediate inflammation and hepatocarcinogenesis via production of the tumour-promoting cytokines IL-6 and TNF[8]. Lipid accumulation results in chronic low-grade inflammation, triggering increased levels of IL-6 and TNF. IL-6 leads to activation of signal transducer and activator of transcription 3 (STAT3), which stimulates hepatocyte proliferation and malignant transformation[80]. Notably, oestrogen has been found to inhibit IL-6 production in vivo, which could explain the lower incidence of HCC in women[80]. A meta-analysis of 26 prospective studies showed that obesity increases the risk of primary liver cancer by 83%, and overweight increases the risk by 48%[81]. However, NAFLD status was not examined in these studies. An older systematic review by Saunders and colleagues, published in 2010, identified ten cohort studies (including a total of >7 million individuals) that examined the association between obesity and HCC[82]. Seven of the ten cohort studies found a positive association, with the relative risks ranging from 1.4 to 4.1. Hassan and colleagues performed a case–control study comparing 622 patients with newly diagnosed HCC and 660 healthy controls, matched for age and sex[83]. The researchers found that obesity in early adulthood was associated with HCC development (OR 2.6, 95% CI 1.4–4.4). However, obesity did not affect prognosis after a diagnosis of NAFLD-related HCC.

In the previously mentioned study by Kanwal and colleagues[79], patients without cirrhosis with obesity had a 1.3-fold increased risk of developing HCC, although this finding did not reach statistical significance (HR 1.31, 95% CI 0.98–1.74). Obesity in the presence of diabetes, hypertension and hyperlipidaemia further increased the risk of developing HCC to 2.6 (HR 2.57, 95% CI 2.3–2.9). A study performed using the United Network for Organ Sharing database found that obesity was an independent risk factor for HCC in patients with cryptogenic cirrhosis and alcoholic cirrhosis but not in patients with liver diseases of other aetiologies[84]. Thus, obesity is a risk factor for HCC development in both patients with non-cirrhotic NAFLD and patients with cirrhotic NAFLD.

Smoking

Smoking has been associated with an increased risk of HCC in general[85]. In a meta-analysis of 81 studies, the pooled odds ratio for HCC development was 1.55 (95% CI 1.46–1.65) in current smokers and 1.39 (95% CI 1.26–1.52) in former smokers[86]. However, no studies have specifically examined the association between smoking and NAFLD-related HCC[26,29,43]. In our opinion, individuals with NAFLD should still be advised to stop smoking.

The gut microbiota and bile acid metabolism

NAFLD is associated with disruption of intestinal enterocyte intercellular tight junctions, increasing gut permeability and translocation of gut bacteria and lipopolysaccharides; this leads to hepatic inflammation and fibrosis[87–91]. The gut microbiota regulates the bile acid pool and consequently the farnesoid X receptor (FXR), a bile acid sensor[92]. In mouse models, FXR helps to prevent hepatocarcinogenesis by protecting against bile acid-related liver injury and modulating fibrosis[93–95]. In a study evaluating the gut microbiota profile of patients with NAFLD-related HCC, faecal calprotectin was increased and *Akkermansia* and *Bifidobacterium* species were decreased in patients with NAFLD-related HCC ($n = 21$) compared with patients with NASH cirrhosis ($n = 20$)[96]. *Akkermansia* and *Bifidobacterium* species have been shown in mouse and rat models, respectively, to reinforce the gut barrier and reduce liver inflammation[97,98]. The researchers of the study[96] concluded that reduced abundance of these protective bacteria could have led to increased intestinal and liver inflammation, promoting HCC development[97,98]. More data are needed to clarify the mechanisms and role of the microbiota in hepatocarcinogenesis.

PNPLA3 single-nucleotide polymorphism

The patatin-like phospholipase domain-containing 3 (PNPLA3) c.444 C>G single nucleotide polymorphism, which encodes the I148M variant, has been strongly linked to an increased risk of HCC in humans[99]. Hassan and colleagues compared 257 patients with histologically confirmed HCC (60.7% cirrhotic) and 494 controls with non-liver cancers[100]. Individuals with the homozygous GG genotype had an increased risk of HCC (OR 3.2, 95% CI 1.7–6.4) compared with those with CC or CG genotypes. To evaluate the association between the PNPLA3 rs738409 single-nucleotide polymorphism and HCC, Singal et al. performed a systematic review involving 24 studies and 9,915 patients with liver disease[101]. The polymorphism was associated with a higher risk of HCC in patients with cirrhosis (OR 1.40, 95% CI 1.12–1.75). A subgroup analysis showed an increased risk of HCC among patients with NASH-related or alcohol-related cirrhosis (OR 1.67, 95% CI 1.27–2.21), but not among patients with cirrhosis of other aetiologies.

In a case–control study comparing 100 patients with NAFLD-related HCC (67% cirrhotic) and 275 patients with biopsy-proven NAFLD, possession of the PNPLA3 rs738409 C>G polymorphism was shown to be an independent risk factor for HCC development (OR 5.05 in GG homozygotes, 95% CI 1.47–17.29; $P = 0.01$)[102]. This significant association persisted following adjustment for diabetes, BMI and the presence of cirrhosis. When GG homozygotes were compared with the general population of the UK (CC homozygotes), the effect was even more marked (OR 12.19, 95% CI 6.89–21.58; $P < 0.0001$)[99,102]. Further

studies are needed to clarify the mechanisms by which the PNPLA3 I148M mutation contributes to hepatocarcinogenesis. By contrast, the TM6SF2 rs58542926 gene polymorphism was not significantly associated with an increased risk of HCC in a European cohort, but this might have been related to the small cohort size ($n = 99$)[103]. The MBOAT7 rs641738 variant was strongly associated with HCC in a cohort of 765 Italian patients with NAFLD, especially in those without advanced fibrosis, but was not associated with HCC in a validation cohort of 358 patients with NAFLD without cirrhosis in the UK[104].

Surveillance

Currently, there is no direct high-level evidence to support or refute the value, method or frequency of HCC surveillance of the NAFLD or NASH cirrhosis population. However, on the basis of cost effectiveness modelling, the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend considering HCC surveillance in patients with cirrhosis when the expected HCC incidence is 1.5% per year or higher[42,105]. Therefore, patients with compensated cirrhosis as well as patients with decompensated cirrhosis awaiting liver transplantation should undergo HCC screening[40,105]. In addition, as up to 30% of patients with NAFLD-related HCC[17] do not have a cirrhosis diagnosis, HCC surveillance might also be considered in patients with advanced fibrosis on a case-by-case basis. The American Gastroenterology Association (AGA) Clinical Practice Update recommends that HCC screening be considered in patients with non-invasive markers that indicate the presence of advanced fibrosis (F3) or cirrhosis[106]. To minimize the likelihood of misclassification, the AGA recommends combining two or more non-invasive fibrosis tests of separate categories (that is, blood-based and imaging-based). If the results of the tests are concordant for either advanced fibrosis or cirrhosis, the update supports consideration of HCC surveillance (FIG. 3). The EASL guidelines recommend that patients with liver disease (of any aetiology, not limited to NAFLD) with advanced fibrosis (F3) might be considered for HCC surveillance on the basis of an individual risk assessment[42], while the Asian Pacific Association for the Study of Liver Diseases (APASL) clinical practice guidelines do not provide a specific recommendation for surveillance in patients with NAFLD without cirrhosis[41,107]. In patients without advanced fibrosis, the risk of HCC is too low to recommend routine screening[30].

Ultrasonography with or without concomitant α-fetoprotein level measurements, is the recommended modality for HCC surveillance in the AASLD, APASL and EASL practice guidelines[41,42,105]. In a study of 941 patients with cirrhosis who underwent ultrasonography, Simmons et al. found that 20% of the scans were of inadequate quality to exclude liver lesions[108]. NASH cirrhosis and elevated BMI were two independent fators associated with an inadequate scan quality. In our opinion, the ultrasound liver visualization score should be documented, and if found to be inadequate, MRI or CT should be considered instead[105,106,109] (FIG. 3).

Prevention

Weight loss

In patients diagnosed with NAFLD, the AASLD, EASL and Asia-Pacific Working Party on NAFLD practice guidelines recommend a combination of a hypocaloric diet and moderate intensity exercise to sustain weight loss, but do not recommend specific weight loss programmes[40,110,111]. A target weight loss of 10% or more showed efficacy in the resolution of NASH and regression of fibrosis in up to 90% and 45% of patients, respectively, in a Cuban study of 293 patients with NASH[112]. However, most patients with NAFLD are unable to sufficiently modify their lifestyles to lose weight, despite intensive dietary counselling and encouragement to perform physical exercise[113].

To evaluate the association between weight loss interventions and biomarkers of liver disease, Koutoukidis et al. performed a systematic review and meta-analysis of 22 randomized clinical trials that had enrolled a total of 2,588 individuals with NAFLD[114]. Of these studies, 15 evaluated behavioural weight loss programmes, six evaluated pharmacotherapy and one evaluated gastric balloons. Although no statistically significant change in histological liver fibrosis was noted in these studies, these weight loss interventions were associated with improvements in ALT levels, steatosis, NASH and histological NAFLD activity score.

A separate meta-analysis of 32 studies comprising 3,093 biopsy samples evaluating the effects of bariatric surgery in patients with NAFLD and obesity found complete resolution of steatosis and fibrosis in 66% and 40% of patients, respectively[115]. It should be noted, however, that features of NAFLD, including fibrosis, steatosis and inflammation, worsened in 12% of these patients.

Currently, there is no direct evidence indicating that weight loss leads to a reduction in NAFLD-related HCC. However, patients with NAFLD should still be encouraged to lose weight, and formal weight loss programmes might be considered in patients at high risk of NAFLD-related HCC. Bariatric surgery, in our opinion, cannot yet be recommended for NAFLD-related HCC prevention.

Statins

Statins have anti-inflammatory, anti-angiogenic and anti-proliferative effects and have been suggested to be effective against inflammation-driven cancers[116]. In a systematic review and meta-analysis of ten studies including 4,298 patients with HCC within a total population of 1,459,417 patients, statin use was associated with a significantly reduced HCC risk, especially in Asian populations[117]. In a separate analysis of 15,422 patients with HCC from the Veterans Affairs Central Cancer Registry, use of statins (both high and low doses) after HCC diagnosis was associated with lower rates of cancer-specific and all-cause mortality[118]. Contrary to these findings, a post hoc analysis of 22 randomized trials failed to show any benefit of statins with regard to HCC risk[119]. It should be noted, however, that none of the randomized trials in this study was designed or adequately powered to detect differences in HCC incidence. None of these observational or interventional studies were conducted in exclusively defined NAFLD or NASH populations. Therefore, at this point in time, statins

cannot be routinely recommended for chemoprevention of HCC. However, in our opinion, statins should certainly be considered to treat dyslipidaemia in patients with NAFLD to reduce cardiovascular risk.

Metformin

Metformin is an anti-diabetic agent that potentially reduces hepatocarcinogenesis through its activation of AMP-activated protein kinase, which downregulates c-MYC as demonstrated in a mouse model[120]. In several meta-analyses, metformin use was associated with an approximately 50% reduction in HCC risk, regardless of liver disease aetiology[121–123]. However, the reported benefits seen with metformin in these studies could possibly have been inflated by immortal time bias, time-window bias and time-lag bias[124].

In a retrospective cohort study, Tseng used propensity score matching analysis to compare HCC risk in 21,900 metformin users versus 21,900 individuals who had never used the drug. This study showed an overall hazard ratio of 0.5 (95% CI 0.45–0.54)[125]. None of these studies was conducted in well-defined NAFLD or NAFLD-related HCC populations. On the basis of these findings, metformin cannot be routinely recommended for HCC prevention. However, it should remain as the first-line treatment for diabetes in the presence of NAFLD–NASH. Further studies are underway regarding the role of glucagon-like-peptide-1 (GLP-1) analogues in the treatment of NASH, and their results are eagerly awaited.

Aspirin

Aspirin has been shown to reduce T cell-mediated inflammation, slow the development of hepatic fibrosis and potentially reduce HCC tumour formation in mouse models[126]. Sahasrabuddhe and colleagues analysed prospective data from 300,504 participants in the National Institutes of Health American Association of Retired Persons Diet and Health Study and found a significantly lower risk of HCC among self-reported users of aspirin compared with non-users (RR 0.59, 95% CI 0.45–0.77)[127]. This study, however, did not establish a dose–response relationship or take into account the effect of concomitant statin use[128]. In a pooled analysis of two prospective cohort studies in the USA involving 133,371 health-care professionals who reported data on aspirin use, Simon et al. showed that regular use of at least 650 mg aspirin a week was associated with a 50% reduction in HCC risk (HR 0.51, 95% CI 0.34–0.77)[129]. The benefit of aspirin in reducing HCC risk exhibited a dose–response relationship and was unaffected by statin use, based on a sensitivity analysis. Given the observational nature of these studies and their limited number, more research is required to confirm these findings and identify which subgroups of patients with NAFLD would benefit most from prophylactic aspirin use.

Conclusions

The prevalence of NAFLD-related HCC is high in several regions worldwide. In particular, the incidence of NAFLD-related HCC is increasing in the USA and China, with an increased number of cases expected by 2030. Patients with NAFLD and cirrhosis are at highest risk of HCC; additional risk factors include old age, possibly male sex and PNPLA3 variants. Diabetes and obesity are the main risk factors for HCC development. In our opinion,

individuals with NAFLD should undergo intensive lifestyle modifications to reduce the risk of diabetes, obesity and subsequent HCC. HCC screening should be considered in patients with advanced fibrosis and cirrhosis. On the basis of current evidence, chemoprevention cannot be routinely recommended for primary prophylaxis in HCC at this point but metformin, statins and possibly aspirin might have a role.

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References

1. Younossi ZM. et al.. Global epidemiology of nonalcoholic fatty liver disease–meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64, 73–84 (2016). [PubMed: 26707365] This meta-analysis of studies from 1989 to 2015 reported that the global prevalence of NAFLD is 25%.
2. Loomba R. & Sanyal AJ The global NAFLD epidemic. Nat. Rev. Gastroenterol. Hepatol 10, 686–690 (2013). [PubMed: 24042449]
3. Zhou F. et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018: a systematic review and meta-analysis. Hepatology 70, 1119–1133 (2019). [PubMed: 31070259]
4. Li J. et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. Lancet Gastroenterol. Hepatol 4, 389–398 (2019). [PubMed: 30902670]
5. Adams LA et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 129, 113–121 (2005). [PubMed: 16012941]
6. White DL, Kanwal F. & El-Serag HB Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin. Gastroenterol. Hepatol 10, 1342–1359.e2 (2012). [PubMed: 23041539]
7. Estes C. et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J. Hepatol 69, 896–904 (2018). [PubMed: 29886156] This modelling study projected a rapid increase in incidence and prevalence of NAFLD-related HCC in the USA, Europe and China by 2030.
8. Park EJ et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 140, 197–208 (2010). [PubMed: 20141834]
9. Baffy G, Brunt EM & Caldwell SH Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J. Hepatol 56, 1384–1391 (2012). [PubMed: 22326465]
10. Eslam M, Sanyal AJ & George J, & International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 158, 1999–2014.e1 (2020). [PubMed: 32044314]
11. Younossi ZM et al. From NAFLD to MAFLD: implications of a premature change in terminology. Hepatology 10.1002/hep.31420 (2020).
12. Global Burden of Disease Liver Cancer Collaboration et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol. 3, 1683–1691 (2017). [PubMed: 28983565]
13. Yang JD et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat. Rev. Gastroenterol. Hepatol 16, 589–604 (2019). [PubMed: 31439937]

14. Global Burden of Disease Cancer Collaboration et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol. 5, 1749–1768 (2019). [PubMed: 31560378]
15. Henley SJ et al. Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer 126, 2225–2249 (2020). [PubMed: 32162336]
16. Younossi ZM et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 62, 1723–1730 (2015). [PubMed: 26274335] This article reported a 9% yearly increase in NAFLD-related HCC prevalence in the USA from 2004 to 2009.
17. Stine JG et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment. Pharmacol. Ther 48, 696–703 (2018). [PubMed: 30136293] This meta-analysis of 19 studies and 168,571 individuals with NASH reported that the prevalence of NAFLD-related HCC in patients with NASH but without cirrhosis is approximately 38% compared with 14% for other liver diseases.
18. Desai A, Sandhu S, Lai J-P & Sandhu DS Hepatocellular carcinoma in non-cirrhotic liver: a comprehensive review. World J. Hepatol 11, 1–18 (2019). [PubMed: 30705715]
19. Ward ZJ et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. N. Engl. J. Med 381, 2440–2450 (2019). [PubMed: 31851800]
20. Ogden CL, Carroll MD, Kit BK & Flegal KM Prevalence of obesity among adults: United States, 2011–2012. NCHS Data Brief. 131, 1–8 (2013).
21. Younossi Z. et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin. Gastroenterol. Hepatol 17, 748–755.e3 (2019). [PubMed: 29908364]
22. Cho EJ et al. Relative etiological role of prior hepatitis B virus infection and nonalcoholic fatty liver disease in the development of non-B non-C hepatocellular carcinoma in a hepatitis B-endemic area. Digestion 84, 17–22 (2011). [PubMed: 22156481]
23. Liew Z-H, Goh GB-B, Hao Y, Chang P-E & Tan C-K Comparison of hepatocellular carcinoma in patients with cryptogenic versus hepatitis B etiology: a study of 1079 cases over 3 decades. Dig. Dis. Sci 64, 585–590 (2019). [PubMed: 30327962]
24. Dyson J. et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J. Hepatol 60, 110–117 (2014). [PubMed: 23978719] This study from the UK showed a substantial increase in the proportion of NAFLD-related HCC from <10% in 2000 to 34.8% in 2010.
25. Pais R. et al. Temporal trends, clinical patterns and outcomes of NAFLD-related HCC in patients undergoing liver resection over a 20-year period. Aliment. Pharmacol. Ther 46, 856–863 (2017). [PubMed: 28857208]
26. Ascha MS et al. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 51, 1972–1978 (2010). [PubMed: 20209604]
27. Sanyal AJ et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology 43, 682–689 (2006). [PubMed: 16502396]
28. Bhala N. et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology 54, 1208–1216 (2011). [PubMed: 21688282]
29. Yang JD et al. Diabetes is associated with increased risk of hepatocellular carcinoma in patients with cirrhosis from nonalcoholic fatty liver disease. Hepatology 71, 907–916 (2020). [PubMed: 31309602]
30. Kanwal F. et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterology 155, 1828–1837.e2 (2018). [PubMed: 30144434]
31. Yatsuji S. et al. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. J. Gastroenterol. Hepatol 24, 248–254 (2009). [PubMed: 19032450]
32. Thrift AP, El-Serag HB & Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. Nat. Rev. Gastroenterol. Hepatol 14, 122–132 (2017). [PubMed: 27924080]

33. Amarapurkar DN, Dharod M, Gautam S. & Patel N. Risk of development of hepatocellular carcinoma in patients with NASH-related cirrhosis. Trop. Gastroenterol 34, 159–163 (2013). [PubMed: 24851525]
34. Mittal S. et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. Clin. Gastroenterol. Hepatol 13, 594–601.e1 (2015). [PubMed: 25148760]
35. Sanyal A, Poklepovic A, Moyneur E. & Barghout V. Population-based risk factors and resource utilization for HCC: US perspective. Curr. Med. Res. Opin 26, 2183–2191 (2010). [PubMed: 20666689]
36. Mittal S. et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin. Gastroenterol. Hepatol 14, 124–131.e1 (2016). [PubMed: 26196445]
37. Tateishi R. et al. Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. J. Gastroenterol 50, 350–360 (2015). [PubMed: 24929638]
38. Piscaglia F. et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. Hepatology 63, 827–838 (2016). [PubMed: 26599351]
39. Yasui K. et al. Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. Clin. Gastroenterol. Hepatol 9, 428–433 (2011). [PubMed: 21320639]
40. Chalasani N. et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 67, 328–357 (2018). [PubMed: 28714183]
41. Omata M. et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol. Int 11, 317–370 (2017). [PubMed: 28620797]
42. EASL clinical practice guidelines: management of hepatocellular carcinoma. J. Hepatol 69, 182–236 (2018). [PubMed: 29628281]
43. Alexander M. et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. BMC Med. 17, 95 (2019). [PubMed: 31104631]
44. Kawamura Y. et al. Large-scale long-term follow-up study of Japanese patients with non-alcoholic fatty liver disease for the onset of hepatocellular carcinoma. Am. J. Gastroenterol 107, 253–261 (2012). [PubMed: 22008893]
45. Ito T. et al. Utility and limitations of noninvasive fibrosis markers for predicting prognosis in biopsy-proven Japanese non-alcoholic fatty liver disease patients. J. Gastroenterol. Hepatol 34, 207–214 (2019). [PubMed: 30144360]
46. Seko Y. et al. Development of hepatocellular carcinoma in Japanese patients with biopsy-proven non-alcoholic fatty liver disease: association between PNPLA3 genotype and hepatocarcinogenesis/fibrosis progression. Hepatol. Res 47, 1083–1092 (2017). [PubMed: 27862719]
47. Kim G-A et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J. Hepatol 68, 140–146 (2018).
48. Lee T-Y et al. The occurrence of hepatocellular carcinoma in different risk stratifications of clinically noncirrhotic nonalcoholic fatty liver disease. Int. J. Cancer 141, 1307–1314 (2017). [PubMed: 28509327]
49. Alexander M. et al. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. BMC Med. 16, 130 (2018). [PubMed: 30099968]
50. Mercado-Irizarry A. & Torres EA Cryptogenic cirrhosis: current knowledge and future directions. Clin. Liver Dis 7, 69–72 (2016).
51. Caldwell S. & Marchesini G. Cryptogenic vs. NASH-cirrhosis: the rose exists well before its name... J. Hepatol 68, 391–392 (2018). [PubMed: 29247726]
52. Thuluvath PJ, Kantsevoy S, Thuluvath AJ & Savva Y. Is cryptogenic cirrhosis different from NASH cirrhosis? J. Hepatol 68, 519–525 (2018). [PubMed: 29162389]
53. Blüher M. Obesity: global epidemiology and pathogenesis. Nat. Rev. Endocrinol 15, 288–298 (2019). [PubMed: 30814686]

54. Ganslmayer M. et al. A large cohort of patients with hepatocellular carcinoma in a single European centre: aetiology and prognosis now and in a historical cohort. Swiss Med. Wkly 144, w13900 (2014).
55. Aljumah AA et al. Clinical presentation, risk factors, and treatment modalities of hepatocellular carcinoma: a single tertiary care center experience. Gastroenterol. Res. Pract 2016, 1989045 (2016).
56. Yapali S. & Tozun N. Epidemiology and viral risk factors for hepatocellular carcinoma in the Eastern Mediterranean countries. Hepatoma Res. 4, 24 (2018).
57. Yang JD et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. Lancet Gastroenterol. Hepatol 2, 103–111 (2017). [PubMed: 28403980]
58. Paul SB et al. Clinical profile, etiology and therapeutic outcome in 324 hepatocellular carcinoma patients at a tertiary care center in India. Oncology 77, 162–171 (2009). [PubMed: 19641335]
59. Patkar S, Parray A, Mahendra B, Kurunkar S. & Goel M. Performance of Hong Kong liver cancer staging system in patients of hepatocellular carcinoma treated with surgical resection: an Indian validation study. J. Surg. Oncol 120, 1119–1125 (2019). [PubMed: 31549392]
60. Yuen M-F, Hou J-L & Chutaputti A, Asia Pacific Working Party on Prevention of Hepatocellular Carcinoma. Hepatocellular carcinoma in the Asia Pacific region. J. Gastroenterol. Hepatol 24, 346–353 (2009). [PubMed: 19220670]
61. Goh K-L et al. Liver cancer in Malaysia: epidemiology and clinical presentation in a multiracial Asian population. J. Dig. Dis 16, 152–158 (2015). [PubMed: 25512092]
62. Jasirwan COM et al. Risk factors of mortality in the patients with hepatocellular carcinoma: a multicenter study in Indonesia. Curr. Probl. Cancer 44, 100480 (2019).
63. Somboon K, Siramolpiwat S. & Vilaichone R-K Epidemiology and survival of hepatocellular carcinoma in the central region of Thailand. Asian Pac. J. Cancer Prev 15, 3567–3570 (2014). [PubMed: 24870758]
64. Wong RJ, Cheung R. & Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the US. Hepatology 59, 2188–2195 (2014). [PubMed: 24375711]
65. Heffernan A, Cooke GS, Nayagam S, Thursz M. & Hallett TB Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. Lancet 393, 1319–1329 (2019). [PubMed: 30704789]
66. Estes C, Razavi H, Loomba R, Younossi Z. & Sanyal AJ Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 67, 123–133 (2018). [PubMed: 28802062]
67. Hanumanthappa N. et al. Epidemiology, clinical treatment patterns, and survival of hepatocellular carcinoma in Manitoba. Can. Liv. J 3, 194–202 (2020).
68. Swain MG et al. Burden of nonalcoholic fatty liver disease in Canada, 2019–2030: a modelling study. CMAJ Open 8, E429–E436 (2020).
69. Debes JD et al. Hepatocellular carcinoma in South America: evaluation of risk factors, demographics and therapy. Liver Int. 38, 136–143 (2018). [PubMed: 28640517]
70. Fassio E. et al. Etiology of hepatocellular carcinoma in Latin America: a prospective, multicenter, international study. Ann. Hepatol 9, 63–69 (2010). [PubMed: 20332549]
71. Park J-W et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE study. Liver Int. 35, 2155–2166 (2015). [PubMed: 25752327]
72. van der Poorten D. et al. Hepatic fat loss in advanced nonalcoholic steatohepatitis: are alterations in serum adiponectin the cause? Hepatology 57, 2180–2188 (2013). [PubMed: 22996622]
73. Tokushige K, Hashimoto E, Horie Y, Taniai M. & Higuchi S. Hepatocellular carcinoma in Japanese patients with nonalcoholic fatty liver disease, alcoholic liver disease, and chronic liver disease of unknown etiology: report of the nationwide survey. J. Gastroenterol 46, 1230–1237 (2011). [PubMed: 21748549]
74. Younossi ZM et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J. Hepatol 71, 793–801 (2019). [PubMed: 31279902]

75. Ma C. et al. NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. Nature 531, 253–257 (2016). [PubMed: 26934227]
76. Shalapour S. et al. Inflammation-induced IgA^{+} cells dismantle anti-liver cancer immunity. Nature 551, 340–345 (2017). [PubMed: 29144460] This study demonstrated in a mouse model that IgA cells accumulated in patients with NASH and suppressed CD8+ T cells, which reduced immune surveillance and promoted hepatocarcinogenesis.
77. Davila JA, Morgan RO, Shaib Y, McGlynn KA & El-Serag HB Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut 54, 533–539 (2005). [PubMed: 15753540]
78. El-Serag HB, Hampel H. & Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin. Gastroenterol. Hepatol 4, 369–380 (2006). [PubMed: 16527702]
79. Kanwal F. et al. Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in nonalcoholic fatty liver disease. Hepatology 71, 808–819 (2020). [PubMed: 31675427] In this study of 271,906 patients with NAFLD diagnosed between 2004 and 2008, diabetes had the strongest association with HCC development (adjusted HR 2.77, 95% CI 2.03–3.77) among the metabolic risk factors.
80. Naugler WE et al. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. Science 317, 121–124 (2007). [PubMed: 17615358]
81. Chen Y, Wang X, Wang J, Yan Z. & Luo J. Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies. Eur. J. Cancer 48, 2137–2145 (2012). [PubMed: 22446023]
82. Saunders D, Seidel D, Allison M. & Lyratzopoulos G. Systematic review: the association between obesity and hepatocellular carcinoma – epidemiological evidence. Aliment. Pharmacol. Ther 31, 1051–1063 (2010). [PubMed: 20175765]
83. Hassan MM et al. Obesity early in adulthood increases risk but does not affect outcomes of hepatocellular carcinoma. Gastroenterology 149, 119–129 (2015). [PubMed: 25836985]
84. Nair S, Mason A, Eason J, Loss G. & Perrillo RP Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? Hepatology 36, 150–155 (2002). [PubMed: 12085359]
85. Petrick JL et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the Liver Cancer Pooling Project. Br. J. Cancer 118, 1005–1012 (2018). [PubMed: 29520041]
86. Abdel-Rahman O. et al. Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: an updated systematic review of 81 epidemiological studies. J. Evid. Based Med 10, 245–254 (2017). [PubMed: 28891275]
87. Miele L. et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 49, 1877–1887 (2009). [PubMed: 19291785]
88. Zhang H-L et al. Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats. J. Hepatol 57, 803–812 (2012). [PubMed: 22727732]
89. Sharpton SR, Ajmera V. & Loomba R. Emerging role of the gut microbiome in nonalcoholic fatty liver disease: from composition to function. Clin. Gastroenterol. Hepatol 17, 296–306 (2019). [PubMed: 30196156]
90. Luther J. et al. Hepatic injury in nonalcoholic steatohepatitis contributes to altered intestinal permeability. Cell. Mol. Gastroenterol. Hepatol 1, 222–232 (2015). [PubMed: 26405687]
91. Gäbele E. et al. DSS induced colitis increases portal LPS levels and enhances hepatic inflammation and fibrogenesis in experimental NASH. J. Hepatol 55, 1391–1399 (2011). [PubMed: 21703208]
92. Makishima M. et al. Identification of a nuclear receptor for bile acids. Science 284, 1362–1365 (1999). [PubMed: 10334992]
93. Meng Z. et al. FXR regulates liver repair after CCl4-induced toxic injury. Mol. Endocrinol 24, 886–897 (2010). [PubMed: 20211986]
94. Yang F. et al. Spontaneous development of liver tumors in the absence of the bile acid receptor farnesoid X receptor. Cancer Res. 67, 863–867 (2007). [PubMed: 17283114]

95. Fickert P. et al. Farnesoid X receptor critically determines the fibrotic response in mice but is expressed to a low extent in human hepatic stellate cells and periductal myofibroblasts. Am. J. Pathol 175, 2392–2405 (2009). [PubMed: 19910507]
96. Ponziani FR et al. Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. Hepatology 69, 107–120 (2019). [PubMed: 29665135] This study from Italy demonstrated that Akkermansia and Bifidobacterium species are decreased in patients with NAFLD-related HCC compared with patients with NASH cirrhosis, highlighting that dysregulation of the gut microbiome might influence NAFLD-related hepatocarcinogenesis.
97. Wu W. et al. Protective effect of Akkermansia muciniphila against immune-mediated liver injury in a mouse model. Front. Microbiol 8, 1804 (2017). [PubMed: 29033903]
98. Fang D. et al. Bifidobacterium pseudocatenulatum LI09 and Bifidobacterium catenulatum LI10 attenuate D-galactosamine-induced liver injury by modifying the gut microbiota. Sci. Rep 7, 8770 (2017). [PubMed: 28821814]
99. Stender S. & Loomba R. PNPLA3 genotype and risk of liver and all-cause mortality. Hepatology 71, 777–779 (2020). [PubMed: 31954067]
100. Hassan MM et al. Genetic variation in the PNPLA3 gene and hepatocellular carcinoma in USA: risk and prognosis prediction. Mol. Carcinog 52, E139–E147 (2013). [PubMed: 23776098]
101. Singal AG et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. Am. J. Gastroenterol 109, 325–334 (2014). [PubMed: 24445574]
102. Liu Y-L et al. Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J. Hepatol 61, 75–81 (2014). [PubMed: 24607626]
103. Liu Y-L et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nat. Commun 5, 4309 (2014). [PubMed: 24978903]
104. Donati B. et al. MBOAT7 rs641738 variant and hepatocellular carcinoma in non-cirrhotic individuals. Sci. Rep 7, 4492 (2017). [PubMed: 28674415]
105. Marrero JA et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 68, 723–750 (2018). [PubMed: 29624699]
106. Loomba R, Lim JK, Patton H. & El-Serag HB AGA clinical practice update on screening and surveillance for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: expert review. Gastroenterology 158, 1822–1830 (2020). [PubMed: 32006545]
107. Eslam M. et al.. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol. Int 10.1007/s12072-020-10094-2 (2020).
108. Simmons O. et al. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. Aliment. Pharmacol. Ther 45, 169–177 (2017). [PubMed: 27862091]
109. Morgan TA et al. US LI-RADS: ultrasound liver imaging reporting and data system for screening and surveillance of hepatocellular carcinoma. Abdom. Radiol 43, 41–55 (2018).
110. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) & European Association for the Study of Obesity (EASO). EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J. Hepatol 64, 1388–1402 (2016). [PubMed: 27062661]
111. Chitturi S. et al. The Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017–Part 2: management and special groups. J. Gastroenterol. Hepatol 33, 86–98 (2018). [PubMed: 28692197]
112. Vilar-Gomez E. et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 149, 367–378.e5 (2015). [PubMed: 25865049]
113. Promrat K. et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 51, 121–129 (2010). [PubMed: 19827166]

114. Koutoukidis DA et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. JAMA Intern. Med 179, 1262–1271 (2019).
115. Lee Y. et al. Complete resolution of non-alcoholic fatty liver disease after bariatric surgery: a systematic review and meta-analysis. Clin. Gastroenterol. Hepatol 17, 1040–1060.e11 (2019). [PubMed: 30326299]
116. Demierre M-F, Higgins PDR, Gruber SB, Hawk E. & Lippman SM Statins and cancer prevention. Nat. Rev. Cancer 5, 930–942 (2005). [PubMed: 16341084]
117. Singh S, Singh PP, Singh AG, Murad MH & Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. Gastroenterology 144, 323–332 (2013). [PubMed: 23063971]
118. Thrift AP, Natarajan Y, Liu Y. & El-Serag HB Statin use after diagnosis of hepatocellular carcinoma is associated with decreased mortality. Clin. Gastroenterol. Hepatol 17, 2117–2125.e3 (2019). [PubMed: 30625400]
119. Cholesterol Treatment Trialists' (CTT) Collaboration et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS ONE 7, e29849 (2012).
120. Blandino G. et al. Metformin elicits anticancer effects through the sequential modulation of DICER and c-MYC. Nat. Commun 3, 865 (2012). [PubMed: 22643892]
121. Singh S, Singh PP, Singh AG, Murad MH & Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. Am. J. Gastroenterol 108, 881–891 (2013). [PubMed: 23381014]
122. Ma S, Zheng Y, Xiao Y, Zhou P. & Tan H. Meta-analysis of studies using metformin as a reducer for liver cancer risk in diabetic patients. Medicine 96, e6888 (2017).
123. Zhou Y-Y et al. Systematic review with network meta-analysis: antidiabetic medication and risk of hepatocellular carcinoma. Sci. Rep 6, 33743 (2016). [PubMed: 27642100]
124. Suissa S. & Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 35, 2665–2673 (2012). [PubMed: 23173135]
125. Tseng C-H Metformin and risk of hepatocellular carcinoma in patients with type 2 diabetes. Liver Int. 38, 2018–2027 (2018). [PubMed: 29956875]
126. Sitia G. et al. Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. Proc. Natl Acad. Sci. USA 109, E2165–E2172 (2012). [PubMed: 22753481]
127. Sahasrabuddhe VV et al. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma. J. Natl Cancer Inst 104, 1808–1814 (2012). [PubMed: 23197492]
128. Singh P. & Singh S. Re: nonsteroidal antiinflammatory drug use, chronic liver disease, and hepatocellular carcinoma. J. Natl Cancer Inst 105, 666–667 (2013). [PubMed: 23591463]
129. Simon TG et al. Association between aspirin use and risk of hepatocellular carcinoma. JAMA Oncol. 4, 1683–1690 (2018). [PubMed: 30286235]
130. Ioannou GN, Green P, Lowy E, Mun EJ & Berry K. Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. PLoS ONE 13, e0204412 (2018).
131. Paranaguá-Vezozzo DC et al. Epidemiology of HCC in Brazil: incidence and risk factors in a ten-year cohort. Ann. Hepatol 13, 386–393 (2014). [PubMed: 24927609]
132. Hsiang JC et al. Epidemiology, disease burden and outcomes of cirrhosis in a large secondary care hospital in South Auckland, New Zealand. Intern. Med. J 45, 160–169 (2015).
133. Kimura T. et al. Mild drinking habit is a risk factor for hepatocarcinogenesis in non-alcoholic fatty liver disease with advanced fibrosis. World J. Gastroenterol 24, 1440–1450 (2018). [PubMed: 29632425]
134. Wong VW-S et al. Long-term clinical outcomes after fatty liver screening in patients undergoing coronary angiogram: a prospective cohort study. Hepatology 63, 754–763 (2016). [PubMed: 26406278]
135. Lopes F. et al. Influence of hepatocellular carcinoma etiology in the survival after resection. Arq. Bras. Cir. Dig 29, 105–108 (2016). [PubMed: 27438037]

136. Raptis I, Koskinas J, Emmanouil T. & Hadziyannis S. Changing relative roles of hepatitis B and C viruses in the aetiology of hepatocellular carcinoma in Greece. Epidemiological and clinical observations. J. Viral Hepat 10, 450–454 (2003). [PubMed: 14633179]

137. Liu P-H et al. Hong Kong liver cancer staging system is associated with better performance for hepatocellular carcinoma: special emphasis on viral etiology. Medicine 94, e1772 (2015). [PubMed: 26469917]

138. Hong TP et al. Novel population-based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed. Hepatology 63, 1205–1212 (2016). [PubMed: 26435297]

Key points

- Nonalcoholic fatty liver disease (NAFLD) includes simple steatosis and nonalcoholic steatohepatitis (NASH); NASH can be progressive and predisposes individuals to the development of fibrosis and cancer.
- NAFLD-related hepatocellular carcinoma (HCC) can develop in the absence of cirrhosis.
- NAFLD is the fastest growing cause of HCC in many parts of the world, including the USA and parts of Europe.
- The incidence of NAFLD-related HCC is projected to increase dramatically by 2030, with increases of 82%, 117% and 122% from 2016 in China, France and the USA, respectively.
- Diabetes is the most important risk factor for HCC development in patients with NAFLD; thus, screening and early treatment are essential.
- Dysregulation of the gut microbiota and reduced immune surveillance are two new mechanisms that have been implicated in NAFLD hepatocarcinogenesis, and further research is warranted

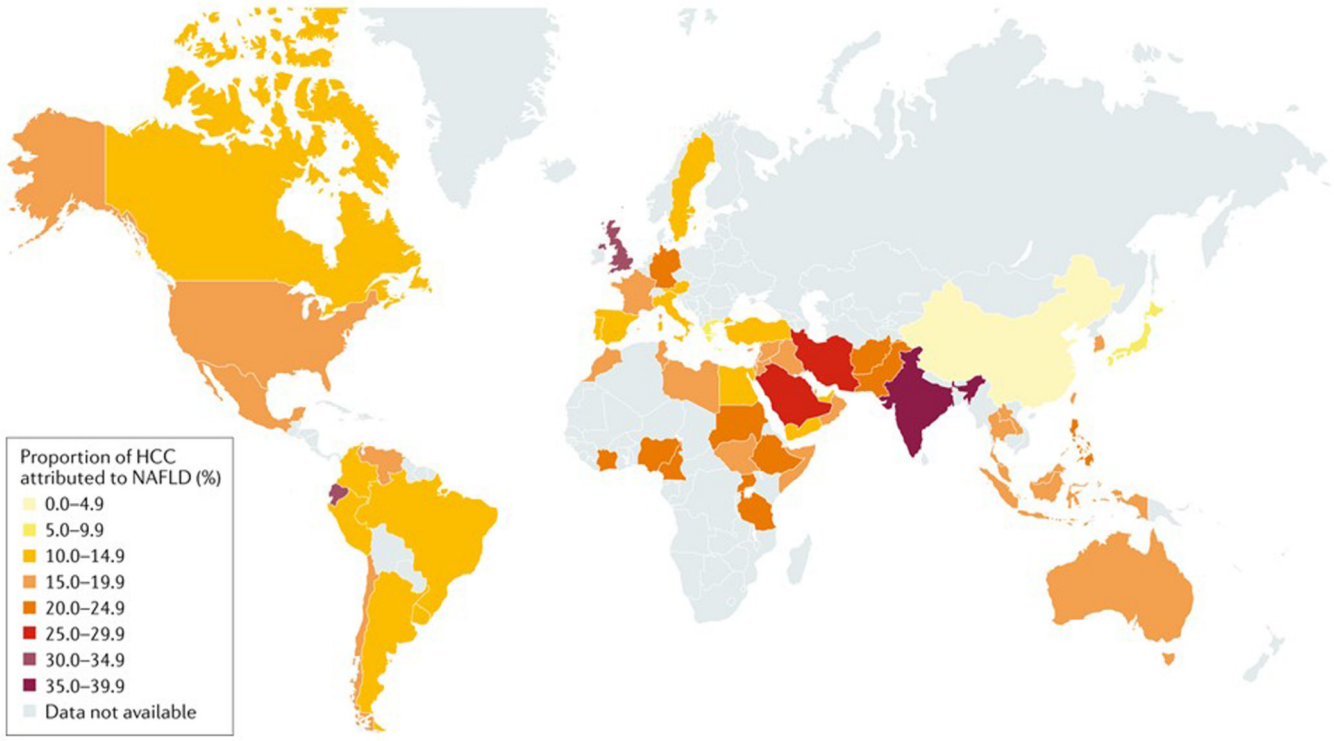

Fig. 1 |. The estimated proportion of HCC attributed to NAFLD.

The proportion of hepatocellular carcinoma (HCC) attributable to nonalcoholic fatty liver disease (NAFLD) is high in the UK, India, Germany and the Middle East[16,21–25,37,55–58,60–65,70–72,74,137,138].

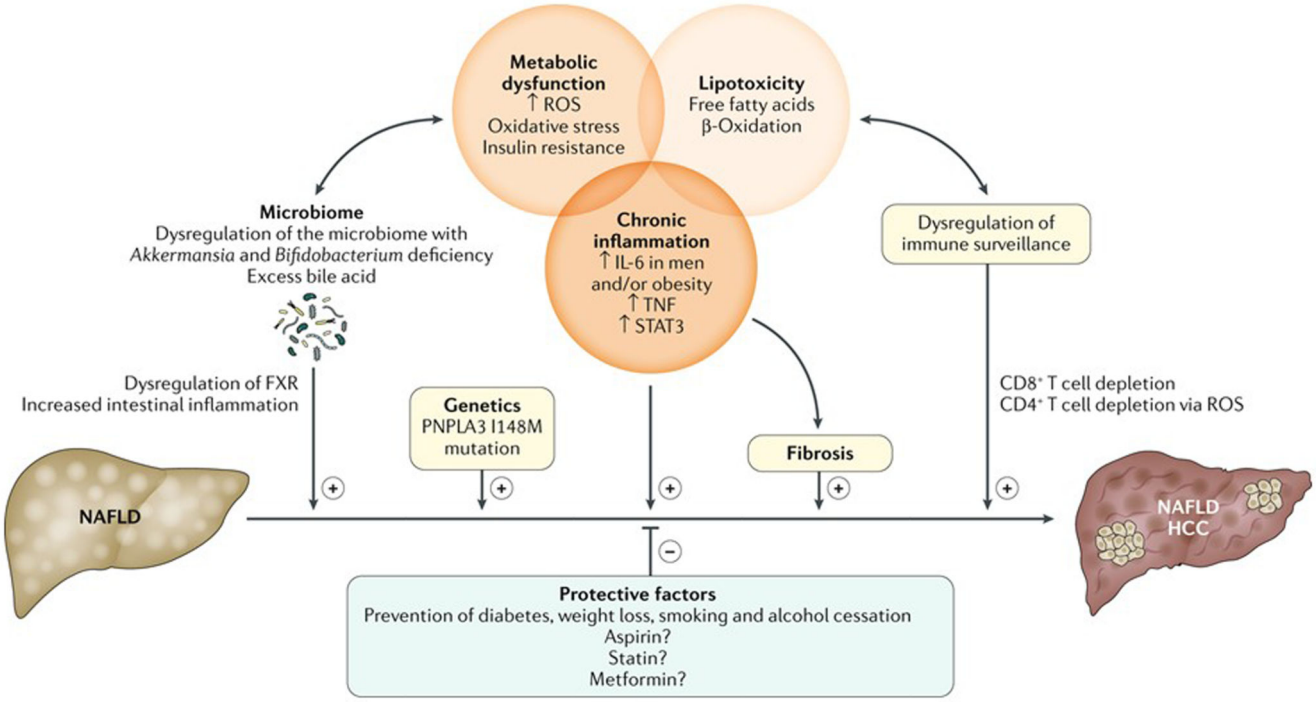

Fig. 2 |. Pathogenesis and prevention of NAFLD-related HCC.

Insulin resistance and metabolic dysfunction promote the release of free fatty acids. β-Oxidation of free fatty acids induces the generation of reactive oxygen species (ROS) and the release of pro-inflammatory cytokines. Obesity further induces elevation of IL-6 and tumour necrosis factor (TNF), which promotes the development of chronic inflammation and activates STAT3, an oncogenic transcription factor that promotes tumour formation. The free fatty acid linoleic acid disrupts mitochondrial function and mediates selective ROS-mediated death of $CD4^+$ T lymphocytes, reducing immune surveillance. IgA^+ cells accumulate in nonalcoholic steatohepatitis (NASH), suppressing $CD8^+$ T cells and accelerating hepatocarcinogenesis. Loss of protective gut bacteria and dysregulated farnesoid X receptor (FXR) signalling in nonalcoholic fatty liver disease (NAFLD) increases intestinal permeability and hepatic inflammation, hastening hepatocarcinogenesis. HCC, hepatocellular carcinoma.

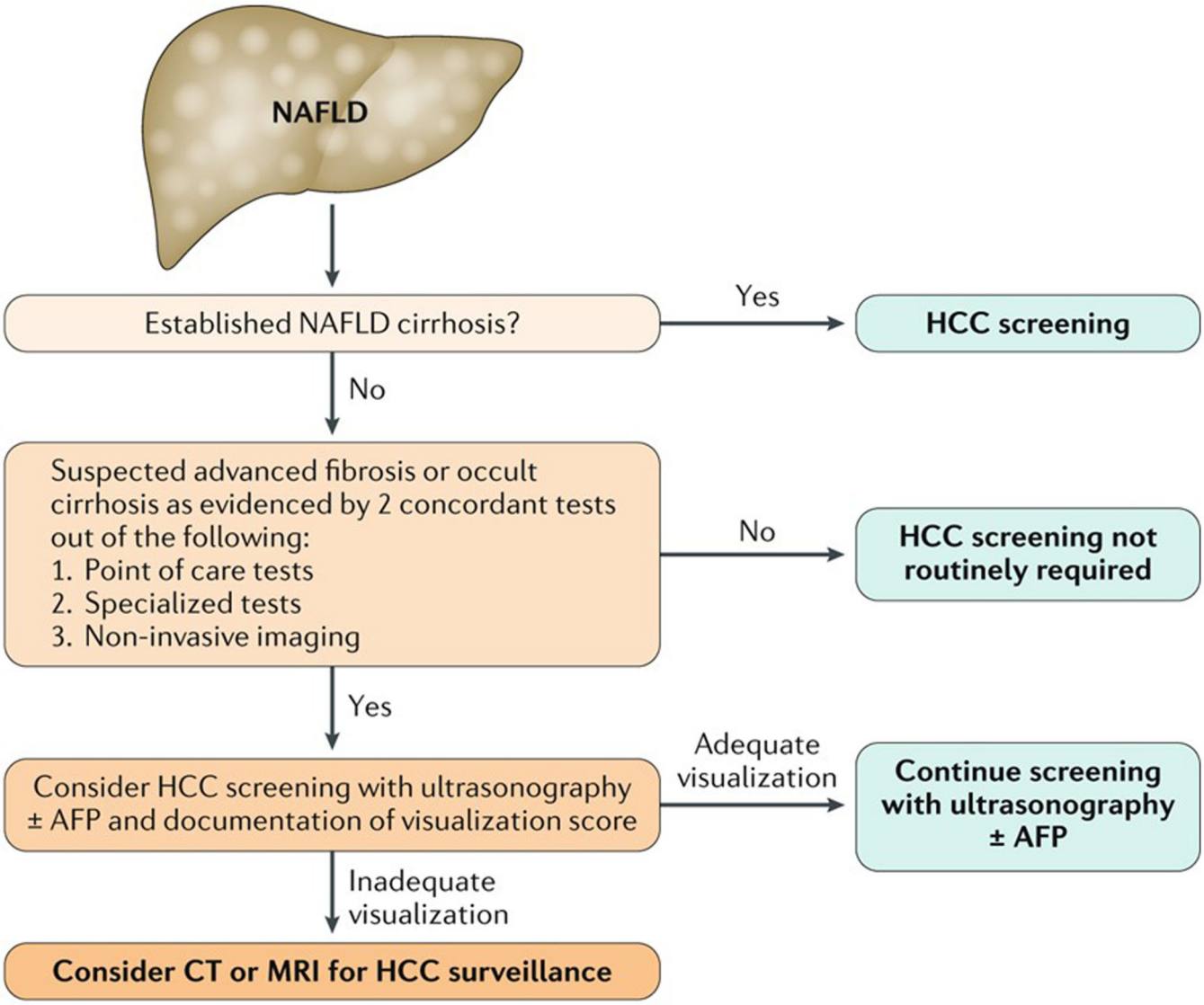

Fig. 3 |. Proposed algorithm for HCC screening in NAFLD.

Hepatocellular carcinoma (HCC) screening might be considered in patients with nonalcoholic fatty liver disease (NAFLD) without cirrhosis when the results of at least two non-invasive tests are concordant and indicate the presence of advanced fibrosis. The adequacy of liver ultrasonography should be documented, and alternative imaging modalities should be considered when the ultrasound image quality is inadequate. AFP, α-fetoprotein.

Table 1 |

Selected studies reporting the incidence of HCC among patients with NASH cirrhosis

Study	Study period	Country/ region	Study population	Diagnostic criteria for NAFLD–NASH–NASH cirrhosis	Presence of diabetes (%)	Follow-up (years)	HCC incidence
Ascha et al.[26]	2003–2007	USA	195 patients with NASH cirrhosis referred for transplant evaluation; median age 56.6 years, 44.1% men; 25 with incident HCC	Histology, or cryptogenic cirrhosis with significant alcohol intake	73.1	2.7	2.6% yearly cumulative incidence
Sanyal et al.[27]	1992–2004	USA	152 patients with biopsy-proven NASH cirrhosis; mean age 55.3 years, 48.7% men; 10 with incident HCC	Histology	58.6	10	10/149 patients at risk over 10 years
Ioannou et al.[130]	2001–2014	USA	17,354 patients with NASH cirrhosis from the Veterans Health Administration system; mean age 66.3 years, 96% men; 608 with incident HCC	Derived from ICD-9 codes	74	4.3	0.9 per 100 patient-years
Bhala et al.[28]	1984–2006	USA, UK, Australia, Italy	247 patients with NAFLD; 118 patients with NASH F3 fibrosis; 129 patients with NASH F4 fibrosis; mean age 54.7 years, 39.7% men; 6 with incident HCC	Histology	50.6	7.1	0.05% annual incidence
Paranaguá-Vezozzo et al.[131]	1998–2008	Brazil	27 patients with compensated NASH cirrhosis; 1 with incident HCC	Histology or presence of metabolic syndrome	NA	≥5	4% over 5 years
Amarapurkar et al.[33]	2010–2011	India	Prospective cohort of 41 patients with NASH cirrhosis; mean age 62.2 years, 49.4% men; 6 with incident HCC	Histology and presence of at least two of the following: diabetes, obesity, dyslipidaemia	NA	6.8	0.5% annual incidence
Yatsuji et al.[31]	1990–2006	Japan	Prospective cohort of 68 patients with NASH cirrhosis; mean age 62.7 years, 43% men; 7 with incident HCC	Histology	68	3.4	11.3% in 5 years
Hsiang et al.[132]	2000–2011	New Zealand	122 patients with NASH cirrhosis diagnosed in secondary public hospitals in Auckland; mean age 63 years, 50.8% men	Histology, radiology, or transient elastography, in the presence of metabolic risk factors	NA	3.9	4.5 per 100 patient-years

Selected studies to highlight the variation in reported NAFLD-related HCC incidence from different countries/regions. HCC, hepatocellular carcinoma; NA, not available; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Table 2 |

Selected studies reporting incidence of HCC among patients with non-cirrhotic NAFLD–NAsH

Study	Study period	Country/ region	Study population	Diagnostic criteria for NAFLD–NASH–NASH cirrhosis	Presence of diabetes (%)	Follow-up (years)	HCC incidence
Alexander et al.[43]	Prior to 2016	UK, Spain, Netherlands, Italy	European primary care database study; 20,424 patients with NAFLD (UK), 896 with NASH (UK), 73,045 with NAFLD (Spain), 1,816 with NASH (Spain), 22,424 with NAFLD/NASH (Italy), 18,432 with NAFLD/ NASH (Netherlands); mean age 55.8, 52.7% male; 4.7% high Fib-4 (>2.67)	Derived from Read/ ICD-10/IPCI/ICD-9 codes	19.8	3.3	0.57 per 1,000 patient-years (UK NAFLD) 1.32 per 1,000 patient-years (UK NASH) 0.22 per 1,000 patient-years (Spain NAFLD) 1.11 per 1,000 patient-years (Spain NASH) 0.37 per 1,000 patient-years (Netherlands NAFLD/NASH) 0.29 per 1,000 patient-years (Italy NAFLD/NASH)
Kanwal et al.[30]	2004–2015	USA	296,707 patients with NAFLD from the Veterans Health Administration system; mean age 55.4 years; 94.4% men; 0.4% cirrhosis; 290 with incident HCC	Persistently raised ALT values in the absence of HBV, HCV and ICD-9 codes for other liver diseases	29.9	9.0	0.21 per 1,000 patient-years (overall) 0.08 per 1,000 patient-years (subgroup without cirrhosis) 10.6 per 1,000 patient-years (subgroup with cirrhosis)
Adams et al.[5]	1980–2000	USA	Population based study of 420 patients with NAFLD (2% cirrhotic at baseline); mean age 49 years, 49% men; 2 with incident HCC (of which 1 HCC developed in an individual with cirrhosis)	Steatosis on imaging, histology, cryptogenic cirrhosis with metabolic syndrome	26	7.6	0.6 per 1,000 patient-years[a]
Kawamura et al.[44]	1997–2010	Japan	6,508 patients with NAFLD; median age 49 years, 87.7% men; 2.8% significant fibrosis (APRI >1.5); 16 with incident HCC	Ultrasonography, in the absence of substantial liver disease	8.2	5.6	0.043% annual incidence
Seko et al.[46]	1999–2014	Japan	238 patients with NAFLD; 47.9% men, median age 60 years; 82.4% F0–F2, 11.3% F3, 6.3% F4; 10 with incident HCC	Histology	45.0	6.1	0.4% annual incidence
Ito et al.[45]	1999–2014	Japan	90 patients with NAFLD, 156 with NASH; median age 55 years, 52% men; 79.6% F0–F2, 20.4% F3–F4; 9 with incident HCC	Histology	45.1	7.0	10-year cumulative incidence 6.04%
Kimura et al.[133]	2003–2016	Japan	301 patients with NAFLD; median age 56 years, 45% men; 56% NASH; 26% F3–F4; 9 with incident HCC	Histology	35.6	6	10-year cumulative incidence 6.0%
Wong et al.[134]	2007–2008	Hong Kong	356 patients with NAFLD who required coronary angiography; mean age 63 years, 74.2% men; fibrosis grading not available; 2 with incident HCC	Ultrasonography	41.3	6.2	0.9 per 1,000 patient-years[a]
Lee et al.[48]	1998–2012	Taiwan	18,080 patients with NAFLD from a health insurance database; median age 52.7 years, 52.6% men; fibrosis grading not available; 41 with incident HCC	ICD-9 codes	37.0	6.3	10-year cumulative incidence 2.73%

Study	Study period	Country/ region	Study population	Diagnostic criteria for NAFLD–NASH–NASH cirrhosis	Presence of diabetes (%)	Follow-up (years)	HCC incidence
Kim et al.[47]	2004–2005	South Korea	8,721 patients with NAFLD identified from a health check-up; mean age 50.1 years, 71.1% men; 24.8% intermediate and high NFS; 13 with incident HCC	Ultrasonography	16.2	16.2	23.1 per 100,000 patient-years

Selected studies to highlight the variation in reported NAFLD-related HCC incidence from different countries/regions. ALT, alanine aminotransferase; APRI, aspartate amino transferase to platelet ratio index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score.

[a]HCC incidence derived by the following formula: (number of incident HCC)/(total number of individuals at risk × mean follow up) × 1,000.

Table 3 |

Selected studies from America, Europe and Africa reporting the proportion of patients with HCC secondary to NAFLD

Study	Study period	Country/ region	Study population	Diagnostic criteria for NAFLD	NAFLD-related HCC prevalence
Sanyal et al.[35]	2002–2008	USA	4,406 patients with HCC identified within a health-care claims database, 2,578 patients with NAFLD-related HCC identified	ICD-9 codes for NAFLD	58.5%
Younossi et al.[16]	2004–2009	USA	4,929 patients with HCC identified within the Surveillance, Epidemiology and End Results registry; 701 patients with NAFLD-related HCC	ICD-9 codes for NAFLD, cryptogenic liver disease with diabetes or obesity, liver cirrhosis without mention of alcohol or other liver diseases	14.1% (9% yearly increase in NAFLD-related HCC prevalence from 2004 to 2009)
Wong et al.[64]	2002–2012	USA	10,061 liver transplant recipients who underwent liver transplantation for HCC identified within United Network for Organ Sharing registry	Recipients with NASH, plus patients with obesity with a primary or secondary diagnosis of cryptogenic cirrhosis and unknown	2002: 8.3% 2007: 10.3% 2012: 13.5%
Mittal et al.[34]	2005–2010	USA	1,500 patients with HCC identified within Veterans Health Administration hospitals	Histopathology or presence of metabolic syndrome in the absence of other liver diseases	7.5 to 12.0% between 2005 and 2010
Younossi et al.[21]	2002–2017	USA	26,121 liver transplant recipients and candidates transplanted or on the waiting list for HCC identified within the Scientific Registry of Transplant Recipients	Listing diagnosis of NASH and cryptogenic cirrhosis	2002: 2.1% 2016: 16.2%
Debes et al.[69]	2005–2015	South America	1,336 patients with HCC within a multi-country/region retrospective cohort: Brazil $n = 540$, Argentina $n = 251$, Colombia $n = 239$, Peru $n = 220$, Ecuador $n = 65$, Uruguay $n = 21$	Not specified	NAFLD: 9% Cryptogenic: 3.3%
Fassio et al.[70]	2006–2008	South America	240 patients with HCC in a prospective multi-country/region cohort: Argentina $n = 90$, Brazil $n = 44$, Venezuela $n = 43$, Colombia $n = 43$, Chile $n = 10$, Uruguay $n = 8$, Mexico $n = 6$, Antigua and Barbuda $n = 4$, Ecuador $n = 3$	Not specified	NASH: 4.6% Cryptogenic: 14.6%
Lopes et al.[135]	2000–2014	Brazil	Resection cohort of 101 patients with HCC	Not specified	7.9%
Dyson et al.[24]	2000–2010	UK	632 consecutive patients with HCC referred to a central multidisciplinary meeting serving North East England, Cumbria and North Yorkshire	Histology or imaging, with an otherwise negative liver screen and no significant alcohol consumption	2000: <10% 2010: 34.8%
Pais et al.[25]	1995–2014	France	Resection cohort of 323 patients with HCC	Present or past exposure to metabolic risk factors in the absence of any other cause of chronic liver disease	1995–2014: 12% 1995–1999: 2.6% 2010–2014: 19.5%
Ganslmayer et al.[54]	1999–2013	Germany	484 consecutive patients with HCC admitted to a tertiary hospital	Histology and an absence of significant alcohol consumption	1988–1999: 7% aetiology unknown 1999–2013: 3.9% NASH, 20% aetiology unknown
Raptis et al.[136]	1996–2000	Greece	306 patients with HCC referred to a university hospital	Not specified	Cryptogenic: 9%

Study	Study period	Country/ region	Study population	Diagnostic criteria for NAFLD	NAFLD-related HCC prevalence
Park et al.[71]	2005–2011	Multiple	18,031 patients with HCC diagnosed during study period, from 42 sites in 14 countries/regions: North America *n* = 2,326, Europe *n* = 3673, China *n* = 8,683, Taiwan *n* = 1,587, South Korea *n* = 1,227, Japan *n* = 534	Not specified	North America: 12% Europe: 10% China: 1% Taiwan: 5% South Korea: 6% Japan: 2%
Yang et al.57	2006–2016	Africa	2,566 patients with HCC gathered from a multi-country/region observational cohort: Egypt *n* = 1251, Ghana *n* = 491, Nigeria *n* = 363, Cote d'Ivoire *n* = 277, Cameroon *n* = 59, Sudan *n* = 51, Ethiopia *n* = 33, Tanzania *n* = 21, Uganda *n* = 20	Not specified	12%[a] (Egypt) 22%[a] (other countries/ regions)

Selected studies to highlight the variation in reported proportion of patients with HCC attributable to NAFLD from different countries/regions. HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

[a]Classified as 'other' or 'unknown' aetiology after exclusion of hepatitis B and hepatitis C infection and alcohol consumption.

Table 4 |

Selected studies from Asia and the Middle East reporting the proportion of patients with HCC secondary to NAFLD

Study	Study period	Country/ region	Study population	Diagnostic criteria for NAFLD	NAFLD-related HCC prevalence
Tateishi et al.[37]	1991–2010	Japan	33,782 patients with HCC diagnosed at 53 participating hospitals	NAFLD defined as either a history of fatty liver or found to have NAFLD on imaging or histology, with alcohol consumption ≤20 g/day; cryptogenic liver disease was categorized as unclassified	NAFLD: 1.8% Unclassified: 8.5%
Tokushige et al.[73]	2006–2009	Japan	14,530 patients with HCC, information gathered by nationwide survey via questionnaires sent to hospitals throughout Japan	Hepatic steatosis on imaging or histology, without significant alcohol consumption or other causes of liver disease	NAFLD: 2.0% Unknown aetiology: 5.1%
Cho et al.[22]	2001–2010	South Korea	6,015 consecutive patients with HCC diagnosed at a single centre	NAFLD diagnosed on ultrasonography in the absence of significant alcohol consumption and no evidence of other causes of liver disease	Overall NAFLD: 8.2% 2001–2005: 3.8% 2006–2010: 12.2%
Park et al.[71]	2005–2011	Multiple	18,031 patients with HCC diagnosed during study period, from 42 sites in 14 countries/regions: North America *n* = 2,326, Europe *n* = 3673, China *n* = 8,683, Taiwan *n* = 1,587, South Korea *n* = 1,227, Japan *n* = 534	Not specified	North America: 12% Europe: 10% China: 1% Taiwan: 5% South Korea: 6% Japan: 2%
Liu et al.[137]	2002–2013	Taiwan	3,182 patients with newly diagnosed HCC admitted to a hospital	Not specified	Cryptogenic: 15%
Hong et al.[138]	2012–2013	Australia	Population-based study conducted in Melbourne in 272 patients with HCC	Not specified	NAFLD: 14% Unknown/other aetiology: 6%
Aljumah et al.[55]	2009–2011	Saudi Arabia	253 patients with HCC presenting to a hospital	Not specified	Cryptogenic: 21.7%
Paul et al.[58]	1990–2005	India	324 patients with HCC presenting to a tertiary centre	Not specified	Cryptogenic: 21.6%
Patkar et al.[59]	2009–2017	India	Resection cohort of 144 patients with HCC	Not specified	NASH: 38%
Somboon et al.[63]	2007–2012	Thailand	308 patients with HCC diagnosed at a hospital	Not specified	NASH: 1.6% Cryptogenic: 16%
Yuen et al.[60]	2008	Philippines	Statistics from the University of Santo Tomas	Not specified	Cryptogenic: 24.9%
Jasirwan et al.[62]	2015–2017	Indonesia	282 patients with HCC recruited by two hospitals in Jakarta	Not specified	Non-B non-C: 16.3%
Goh et al.[61]	2006–2009	Malaysia	348 consecutive patients with HCC	Not specified	Cryptogenic: 16.4%
Liew et al.[23]	1980–2015	Singapore	1,292 patients with HCC presenting to a tertiary centre	Cryptogenic, defined as fatty infiltration on imaging, with the exclusion of other liver disease	1980–2015: 12.6% cryptogenic 1980–2005: 12.9%[a] cryptogenic 2006–2015: 20.4%[a] cryptogenic

Selected studies to highlight the variation in reported proportion of patients with HCC attributable to NAFLD from different countries/regions. HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

[a] As a proportion of patients with cryptogenic HCC and hepatitis B HCC combined.