# Viral hepatitis, non-alcoholic fatty liver disease and alcohol as risk factors for hepatocellular carcinoma

## Maya Gambarin-Gelwan

Memorial Sloan-Kettering Cancer Center, Gastroenterology and Nutrition Service, New York, NY 10065, USA
*Corresponding to:* Maya Gambarin-Gelwan, MD. Memorial Sloan-Kettering Cancer Center, Gastroenterology and Nutrition Service, 1275 York Ave, Box 481, New York, NY 10065, USA. Email: gambarim@mskcc.org.

**Abstract:** Hepatocellular carcinoma (HCC) is a common cancer worldwide, with significant increase in the incidence observed in the past two decades in the United States. Majority of cases of HCC are due to chronic viral hepatitis B and C infections; however non-alcoholic fatty liver disease, associated with obesity and diabetes emerges as an important risk factor for HCC, in particular in the developed countries. Here we will review viral characteristics associated with increased risk for development of HCC and role of antiviral therapy in decreasing risk of HCC in those with viral hepatitis and cirrhosis. Association of alcoholic cirrhosis and non-alcoholic fatty liver disease with liver cancer will be reviewed as well as possible measures to decrease the risk of HCC in these highly prevalent populations.

**Keywords:** Hepatocellular carcinoma (HCC); hepatitis B; hepatitis C; non-alcoholic fatty liver disease; alcoholic cirrhosis; cancer surveillance

## Liver cancer and viral hepatitis

Worldwide, liver cancer is the fifth most commonly diagnosed cancer (1), with over half a million new cases diagnosed annually (2). The number of deaths per year, attributed to the liver cancer is almost identical to its incidence (1), making it the second leading cause of cancer-related mortality in the world, and the ninth leading cause of cancer death in the United States (3-5). Hepatocellular carcinoma (HCC) accounts for 70-85% of the total liver cancer burden (6), thus representing the major histological subtype of primary liver malignancies.

Almost 80% of cases of HCC are due to underlying chronic hepatitis B and C infection (7,8), not surprising, considering that 1 in 12 individuals worldwide lives either with hepatitis B or C infection. The relative risk of HCC in patients with chronic hepatitis B or chronic hepatitis C infection is about 25-30 times that of those without the infection. The disease burden is the highest in the hepatitis B-endemic areas (hepatitis B surface antigen prevalence ≥8%),

with over 80% of all cases of HCC occurring in sub-Saharan Africa and Eastern Asia, and over 40% in the People's Republic of China (8,9).

Significant increase in the incidence of HCC that has been observed over the past two decades in the United States has been mainly attributed to the large reservoir of long-standing chronic hepatitis C (10,11). As was demonstrated by El-Serag, the rate actually began to accelerate in the mid-1980s, most likely due to the increased incidence of cirrhosis due to chronic hepatitis C infection and non-alcoholic fatty liver disease (NAFLD), combined with large influx of immigrants from hepatitis B-endemic areas, including East Asia (12). As a consequence of high hepatitis C virus (HCV) infection rates in the United States between 1960 and 1980, and the average lag time between HCV acquisition and the development of cirrhosis and HCC of 20-30 years, the incidence of HCC is expected to continue to rise.

While HCC is more common in men, the age distribution of HCC cases depends on the dominant viral hepatitis and age at which it was acquired. In the regions with

high HCC incidence (where hepatitis B virus transmitted at birth is the most common cause), HCC is usually diagnosed a decade earlier compared to North America and Europe, where most HCC is related to HCV acquired later in life (2). In majority of cases (80-90%) HCC occurs in the setting of cirrhosis (13).

## Hepatitis B and HCC

Chronic hepatitis B is the most common cause of viral liver disease worldwide, with over 350 million infected individuals (or 5% of the world population). HCC is one of the major consequences of chronic hepatitis B, and variety of viral and host factors contribute to its development. In hepatitis B virus (HBV)-related cirrhosis, the 5-year cumulative risk of HCC is 15% in high endemic areas and 10% in the West (14). In the recent study from the United States, the death rate from HCC was twice that of decompensated cirrhosis in individuals with chronic hepatitis B infection; with HCC death representing 70% of all cancer-related death in males and 37% in females (15). While only 16% of cases of HCC in the United States are attributed to HBV, worldwide HBV accounts for 54% of all cases of HCC, which is not surprising considering that almost half of the world's population leaves in the areas with high HBV prevalence. It is important to keep in mind, that while 70-90% individuals who develop HCC in the setting of HBV infection will have cirrhosis (16,17), HCC can also develop in the absence of cirrhosis, including inactive HBV carriers (18).

Men with chronic hepatitis B, appear to be at higher risk for HCC compared to women (19-21), with cumulative lifetime incidence of HCC of 27% *vs.* 8%. Family history of HCC, older age, male sex, Asian or African ancestry, alcohol consumption, cigarette smoking, elevated serum alanine aminotrasferase (ALT) levels, and the presence of core and pre-core mutations, also appears to increase the risk of HCC in chronic hepatitis B (17,20,22-27).

### Viral factors of hepatocarcinogenesis in HBV infection

Although cirrhosis is the major risk factor for HCC in the setting of chronic hepatitis B, over the years several other risk factors have been identified, including the viral load, the presence of hepatitis B e antigen (HBeAg), and hepatitis B surface antigen (HBsAg).

The landmark REVEAL study (28), a large community-based study in Taiwan that included 3,653 HBsAg-positive and HCV-negative patients enrolled between 1991 and 1992, demonstrated that the risk of HCC was much greater in individuals with high serum levels of HBV DNA compared to those with low levels (defined as HBV DNA <10,000 copies/mL). In this relatively young cohort (median age 45 years), at enrollment, 85% were HBeAg-positive, 94% had normal ALT levels, and only 2% had cirrhosis. During a mean follow-up of 11 years, HCC developed in 164 patients (4.5%), with higher incidence of HCC associated with a higher HBV DNA at the study entry. Cumulative incidence of HCC of 14.9% was noted among those with HBV DNA >1 million copies/mL, while it was much lower at 1.3% among those with an HBV DNA level <300 copies/mL, at baseline. The HBV DNA level remained an independent predictor for HCC even after adjusting for sex, age, cigarette smoking, alcohol consumption, HBeAg status, serum ALT level, and the presence of cirrhosis at the baseline, i.e., all the other known risk factors for development for HCC. It is important to keep in mind, however, that most of the individuals in this study, likely acquired HBV perinatally; it is not clear if these data can be applied to those who acquired HBV as adults.

Yang *et al.*, in the one of the largest prospective studies that tested for HBsAg and HBeAg, detected 111 cases of HCC after following 11,893 Taiwanese men for approximately 10 years (29). The prevalence of HBeAg was 39% among the men who were positive for HBsAg. The cumulative incidence of HCC was much higher among men who were positive for both HBsAg and HBeAg, than among those who were only positive for HBsAg and even higher than among those who were negative for both (P<0.001 for both comparisons). After adjusting for other risk factors, the relative risk (RR) of HCC was 9.6 for men who were positive for HBsAg alone and 60.2 for those who were positive for both HBsAg and HBeAg, as compared to men who were negative for both.

Increased risk of HCC in inactive carriers of HBV (HBV DNA <10,000 copies/mL), was demonstrated in another population-based study from Taiwan, that included 20,069 individuals with HBV; 1,932 of them were HBsAg-positive (HCV-negative), HBeAg-negative, had normal ALT and serum HBV DNA <10,000 copies/mL. During an average follow-up of 13 years, the annual incidence of HCC was higher in HBsAg-positive patients than in controls (0.06% *vs.* 0.02%) (18).

Moreover, as has been shown in the study that followed 1,271 Alaskan Natives with chronic hepatitis B for an average of 20 years (30), the incidence of HCC, although

lower among those who cleared HBV infection (i.e., became HBsAg negative) compared to those who remained HBsAg-positive (37 *vs.* 196 per 100,000 person-years), was still higher than among the general population. Not surprising however, it appears that the risk of developing HCC in those who cleared HBsAg, at least among Asian patients, is related to the age at which the infection was cleared, with the likelihood of developing HCC higher in those who cleared HBsAg after 50 years of age (31).

Hepatitis B genotype also appears to have an impact on the risk of HCC. As has been shown by studies from Taiwan, Japan and China (32-34), where genotypes B and C are the predominant strains, genotype C is associated with more severe liver disease including cirrhosis and HCC (32, 35); this is not surprising since patients with genotype C tend to have higher frequency of HBeAg-positivity, higher serum HBV DNA, delayed HBeAg-seroconversion, and basal core promoter mutations (all factors associated with higher risk of HCC). It appears, though, that genotype B is actually associated with the development of HCC in young non-cirrhotic population (35,36). In Western Europe and North America, where genotypes A and D prevail, genotype D appears to be associated with a higher incidence of HCC and development of HCC in young carriers without cirrhosis (2).

As has been demonstrated by several studies from Asia and Europe, co-infection with HCV (particularly in those who are HBeAg-positive), hepatitis D virus (HDV) and human immunodeficiency virus (HIV), also appears to increase the risk of HCC (14,24,37-39).

### Prevention of HCC in chronic hepatitis B: anti-viral therapy

Prevention is the best treatment for any condition and HCC is not an exception to the rule, especially in view of the high mortality. Development of HBV vaccine has been a major success in reducing the incidence of HBV and subsequent development of HCC. Benefits of vaccination have been demonstrated by the countries like Taiwan, where 25 years after the adoption of the universal hepatitis B vaccination program, HBV carrier rate among children has decreased to 1.2% and incidence of HCC among vaccinated children decreased by 70% (40). Vaccine is recommended for all newborns, pregnant women at their first neonatal visit and high-risk individuals. Neonates of HBV-infected mothers should get a dose of hepatitis B immunoglobulin (HBIG) in addition to vaccination. It is estimated that >90% of countries routinely vaccinate newborns against HBV, and approximately 70% are now delivering 3 immunization doses (8).

What about those individuals that have chronic hepatitis B infection? First real prove of benefit of an antiviral therapy in reducing the risk of HCC came from a multicenter, randomized, placebo-controlled, parallel group study of lamivudine in patients with advanced liver disease by Liaw *et al.* (41). After a median of 32.4 months of therapy, HCC occurred in 3.9% of those on lamivudine (100 mg daily) and 7.4% of those in the placebo group (hazard ratio, 0.49; P=0.047). Since then, several systematic reviews also suggested that the relative risk of HCC is reduced by approximately 60% following treatment with interferon or nucleos(t)ides (42-44), although benefit seems to be restricted to those with advanced fibrosis or cirrhosis, and is not seen in those who developed nucleos(t)ide resistance. While most of the data on the benefits of oral antiviral therapy comes from the studies on lamivudine and adefovir, a recent retrospective cohort study from Japan demonstrated reduction in the incidence of HCC with long-term use of entecavir, with cumulative 5-year rates of 3.6% *vs.* 12.3% in those on no anti-viral therapy (45).

Analyzing the Taiwan National Health Research database, Wu *et al.* demonstrated that nucleoside analogues reduce the risk of recurrent HBV-related HCC following liver resection (46). Authors demonstrated a 6-year HCC recurrence rate of 45.6% compared to 54.6% in untreated individuals, as well as a 6-year reduction in overall mortality (29% *vs.* 42.4%), with number needed to treat (NNT) 12 to prevent one HCC over 6 years, and 6 to prevent 1 death over that same period of time.

As demonstrated by the above data (41-45), the risk of HCC is reduced, but is not completely eliminated by anti-viral therapy. In the recent meta-analysis, lamivudine treatment significantly reduced the incidence of HCC compared to no treatment, however HCC still developed at a rate of 1.3 per 100 patient years in chronic hepatitis B patients receiving lamivudine (47). This finding highlights the need for continued surveillance for HCC, especially in those without adequate suppression, older age and cirrhosis. While, it is not yet clear whether treatment of non-cirrhotic patients with chronic hepatitis B, if instituted early enough could eliminate the risk of HCC altogether, and as pointed in the recent editorial by Sherman (48), performing such a study will be difficult (and might never be done), anti-viral therapy should be provided to the individuals with active HBV.

## Hepatitis C and HCC

Approximately 2% of world population has evidence of HCV infection (approximately 180 million people) (8). Cohort studies indicate that HCC remains the major cause of liver-related death in patients with compensated cirrhosis, and HCV infection is associated with the highest HCC incidence in persons with cirrhosis, occurring twice as commonly in Japan than in the West (5-year cumulative incidence, 30% and 17%, respectively) (14). Japan has had one of the highest incidence rates of HCC associated with chronic hepatitis C infection; incidence appears to be decreasing in the recent years (49). In the United States, HCV is the leading cause of HCC, where it accounts for 50-60% of cases. HCV infection acquired 2-4 decades ago explains at least half of the observed increase in HCC in the United States, including the fastest increase in white men 45-54 years of age, and HCV-related HCC is expected to continue to increase for another 10-13 years (10,12).

### Viral and host factors in HCV-related HCC

HCV appears to increase the risk of HCC by inducing hepatic inflammation and importantly fibrosis, as well as promoting malignant transformation (50). Although the risk for HCC is highest in those with cirrhosis, occurring at the rate of 1-4% per year (51), it is important to keep in mind that HCC has been reported in chronic hepatitis C in the absence of cirrhosis. In the HALT-C trial, HCC developed in 8% of individuals without cirrhosis but with advanced fibrosis (52).

Not unlike the case with chronic hepatitis B, men and older individuals have an increased risk of HCC. Other risk factors for HCC in the setting of chronic hepatitis C are co-infection with HIV or HBV, diabetes and obesity (see below), as well as chronic alcohol consumption.

The level of viremia in HCV does not appear to impact the risk of HCC (at least based on the European and US data), although any HCV viremia does increase the risk. Interestingly, HCV genotype 1b infection appears to almost double the risk of development of HCC compared to all other genotypes, based on a meta-analysis of 21 studies (53). This might be a contributing factor to the high rate of HCV-related HCC in Japan, where 73% of individuals carry genotype 1b HCV infection.

Vitamin D deficiency is common among individuals with chronic hepatitis C, including those with minimal fibrosis, and severe vitamin D deficiency occurs in about 25% of those with chronic hepatitis C (54). While vitamin D deficiency has been associated with increased risk of colon, breast and prostate cancer (55-59), it remains unclear as to whether vitamin D deficiency is associated with an increased risk of HCC (60). In fact, we were unable to demonstrate an association between vitamin D deficiency and HCC in a case-control study of 51 individuals with HCC and cirrhosis (mainly due to chronic hepatitis C) and age- and liver disease-matched controls without HCC (Samoy, *et al.* 2013; unpublished data). Further studies looking into this association are needed, since they might lead to the preventative and possibly therapeutic strategies.

### Antiviral therapy for chronic hepatitis C and the risk of HCC

Randomized and non-randomized studies, including a recent meta-analysis on the role of antiviral therapy in HCV-related HCC, have shown a 57-75% reduction in the risk of development of HCC with achievement of sustained virologic response, both in those with and without cirrhosis (61-67), and possibly even in those with decompensated cirrhosis (68). It is important to remember however, that individuals with advanced fibrosis who clear HCV viremia with anti-viral therapy (aka achieve sustained virologic response) have a reduced but not eliminated risk of HCC and should continue to undergo surveillance (2,65). This was again recently demonstrated by a study from Sweden (69), showing significantly decreased risk of HCC, liver decompensation and death in patients with HCV-related cirrhosis after sustained virologic response, however long-term risk of development of HCC remained up to 8 years of follow up.

Interestingly, low pre-operative HCV viral load predicted better long-term surgical outcomes in patients undergoing resection for HCC independent of serologic eradication of HCC (70). Both 5-year recurrence-free (36.1% *vs.* 12.4%) and 5-year overall survival rates (76.6% *vs.* 57.7%), were significantly higher in the lower viral group compared to the high viral load group, with reported tumor recurrence hazard ratio of 1.87 in the high viral load group. Moreover, recently published analysis of the 2,237 anti-viral naïve HCV patients with curatively resected HCC from the Taiwan National Health Insurance Research Database, suggested that postoperative peg-interferon plus ribavirin (for at least 16 weeks after surgery) reduced recurrence of HCC (71). After 5 years of follow-up, the recurrence rate of HCC was significantly lower in the treated than matched

untreated cohort: 52.1% *vs.* 63.9%, with NNT 8 to prevent one HCC recurrence at 5 years. Interestingly, the greater risk reduction of recurrent HCC was observed among younger patients (<60 years), and those without cirrhosis or diabetes.

While antiviral treatment for chronic hepatitis C is very efficacious and will become even more so with the approval of novel direct acting anti-virals in the next few years, their effectiveness in the community practice, including endemic regions, is quite low due to barriers in access, diagnosis and cost of medications. It was estimated that approximately 45-85% of the individuals with chronic hepatitis C in the United States are unaware that they are infected and thus do not receive needed care and treatment (72). In the effort to improve detection of HCV, US Centers for Disease Control and Prevention, now recommends routine screening for HCV in all individuals born between 1945 and 1965, who represent approximately 76% of those individuals infected with HCV, and 70% of all HCV-associated deaths. This recommendation was recently supported by the US Preventive Service Task Force (USPSTF), that now recommends screening for HCV infection in persons at high risk for infection, including offering 1-time screening for HCV infection to adults born between 1945-1965 (B recommendation) (73). When accompanied by appropriate care and treatment, as suggested by Ward, HCV testing can reduce risk of HCC by 70% (72).

## Non-alcoholic fatty liver disease and HCC

While worrisome trend of the rising incidence of HCC in the United States has been primarily attributed to the high prevalence of chronic hepatitis C in this population, and is expected to plateau by 2020, epidemiological studies indicate that up to 50% of all cases of HCC do not have a clear etiology (74,75). HCC has been linked to NAFLD, which has become the most common liver disorder in the United States and other industrialized countries. NAFLD is present in 30% of the general adult population, 90% of morbidly obese adults (BMI ≥40 kg/m$^2$), and close to 74% of those with diabetes (76-78).

The exact prevalence of HCC in cirrhotic NAFLD remains unknown; however the risk of HCC due to NAFLD appears to be less than that of chronic hepatitis C. A recent United States study, reported a 2.6% yearly cumulative incidence of HCC in NAFLD and 4.0% in HCV cirrhosis (over a median follow up 3.2 years) (79), while a prospective 5-year study from Japan reported a rate of HCC of 11.3% among patients with NAFLD-cirrhosis compared to 30.5% among those with HCV-associated cirrhosis (80).

Keeping in mind prevalence of NAFLD and its natural history, however, NAFLD may actually become the primary source of HCC in the United States and other developed countries, thereby offsetting the impact of successful measures on reducing HCV-related HCC (81). This concern might be further demonstrated by a recent study from Germany, identifying non-alcoholic steatohepatitis (NASH) as the most common etiology of HCC (24%), surpassing chronic hepatitis C (23.3%), chronic hepatitis B (19.3%) and alcoholic liver disease (12.7%) (82). While it is estimated that 30-40% of all HCC in industrialized countries occur in patients with cryptogenic cirrhosis (74), as has been demonstrated by several studies, majority of these cases are associated with either prior NAFLD or other features of metabolic syndrome (81). Diabetes and obesity have been establishes as independent risk factors for HCC, and that association holds true in the setting of NASH (83,84). Of concern, is the growing body of literature suggesting that NAFLD contributes to non-cirrhotic HCC, and that HCC can develop in patients with metabolic syndrome and NAFLD, in the absence of NASH and fibrosis (85); however as demonstrated by a recent systematic review, while there is an epidemiological evidence to support an association between NAFLD or NASH and increased risk of HCC, the risk seems to be limited to individuals with cirrhosis (86).

### Prevention of HCC in NAFLD

Since insulin resistance and lipotoxicity are distinct molecular mechanisms that may promote development of HCC in NAFLD, effective treatment of insulin resistance and hyperinsulinemia may be in fact critical to prevent hepatocarcinogenesis in this population (81). Several reports have suggested that the use of insulin-sensitizing agents in diabetes may reduce the risk of HCC (87,88). Interestingly, metformin in addition to improving insulin resistance has direct antiproliferative effects primarily by inhibiting the mTOR oncogenic pathway (89). In a case control study of diabetic patients with HCC, Hassan *et al.*, demonstrated that treatment with metformin or the insulin-sensitizing peroxisome proliferators activated receptor-γ (PPAR-γ) agonist thiazolidinediones (TZDs), resulted in an adjusted risk ratio of 0.3 for HCC, while the use of insulin-secretagogue sulfonylureas was associated with a 7.1-fold

increase in the risk of HCC (compared to non-users) (88). A recent meta-analysis of observational studies by Singh *et al.* (90), demonstrated a 50% reduction in the incidence of HCC with metformin use (OR 0.50), while a 62% and 161% increase in HCC incidence was observed with sulfonylureas (OR 1.62) or insulin use (OR 2.67), respectively. TZDs did not appear to modify the risk of HCC. While noting that anti-diabetic medications may modify the risk of HCC in patients with diabetes, especially in the Western population, study authors expressed caution in interpreting the effect of an individual agent, due to the "inherent cancer-modifying effect of the comparator group". Finally, another recent study, suggested that insulin-sensitizers might also improve the prognosis of HCC, demonstrating lower mortality in diabetic patients on metformin, who underwent radiofrequency ablation for early HCC (91). As was suggested by Baffy *et al.*, the use of insuling-sensitizing drugs and avoidance of treatments contributing to hyperinsulinemia is likely to enhance prevention and improve disease outcomes in HCC (81).

A recent study by Ascha *et al.* (79), demonstrated that among individuals with NASH cirrhosis, older age and alcohol consumption were independent variables associated with the development of HCC. Compared to non-drinkers, individuals who reported any lifetime alcohol consumption were 3.6 times more likely to develop HCC compared to those who had no exposure to alcohol.

While individuals with NASH-related cirrhosis should be enrolled in the surveillance program, more epidemiologic, clinical and molecular biology data are needed to determine the relative contribution of obesity, diabetes, and NAFLD to HCC and to develop a cancer surveillance program for potentially affected population of non-cirrhotic NAFLD (81). In the meantime, prevention of obesity, diabetes and NAFLD, and avoiding any alcohol use in those with NASH cirrhosis, appears to be the best long-term strategy.

## Alcohol and HCC

Alcohol abuse may lead to cirrhosis and development of HCC in some individuals with heavy alcohol use. The actual incidence of HCC in those with alcoholic cirrhosis is not very clear, however alcoholic cirrhosis is clearly a risk factor for HCC. The annual incidence of HCC was reported at around 2.5% among Child-Pugh class A or B alcoholic cirrhotics in Spain (92), with higher annual incidence in those 55 years of age and older and platelet count less than 125,000/mm$^3$. In the US and Austrian cohorts, alcoholic

liver disease appears to account for 24-35% of cases of HCC (93-95). Based on the recent data by Welzel *et al.* (94), in the US, the risk of HCC is increased in the alcohol-related disease (OR 4.06) and represents the second greatest population-attributable fraction (PAF) of risk factors for HCC (23.5%), overall and among males (27.8%), whites (25.6%), Hispanics (30.1%), and blacks (18.5%).

Prior exposure to HBV (positive HBcAb in the absence of HBsAg or anti-HCV) in the setting of heavy alcohol use appears to significantly increase the risk of HCC in males with alcoholic cirrhosis based on the earlier epidemiological data from Japan. After prospectively following 91 individuals with alcoholic cirrhosis for a median of 5.9 years, Uetake *et al.* reported cumulative occurrence rates of HCC at 6.4%, 18.0% and 28.7% at the end of the 5th, 7th, and 10th years, respectively (96). When classified by HBcAb status (about 30% of individuals were HBcAb-positive), prior exposure to HBV resulted in much higher rates of HCC: 15.6% *vs.* 2.9% at the 5th year, 28.4% and 13.5% at the 7th year, and 40.4% *vs.* 22.1% at the 10th year, respectively (96). Hepatitis C and diabetes are not uncommon in alcoholics and there also appears to be a synergistic interaction between heavy alcohol consumption (≥80 mL ethanol/day) and chronic viral hepatitis (93,97) and diabetes mellitus (93). Interestingly, however, as observed by Serra *et al.* (98), cumulative survival in alcoholic cirrhosis does not seem to be influenced by the presence or absence of markers of HCV infection: the cumulative survival curve in abstinent alcoholics was significantly different from that of "active" alcoholics, and cumulative survival in patients with HCV-related cirrhosis who stopped drinking after the diagnosis was similar to that in HCV-cirrhotic patients who never consumed alcohol. This observation highlights an importance of complete alcohol abstinence in any cirrhotic patient.

## Surveillance for HCC in chronic viral hepatitis, NAFLD and alcoholic cirrhosis

As demonstrated by the HCC incidence and prevalence data, the number of death per year attributed to liver cancer is almost identical to its incidence (1,99). Only 1 randomized trial from China showed a 37% reduction in HCC-related mortality with surveillance for HCC with α-fetoprotein (AFP) and ultrasound every 6 months (compared to no-surveillance arm) (100). However, long-term survival after curative-intent treatment at early stages of the disease may now reach 50-70% over 5 years (101),

highlighting the importance of effective surveillance and early diagnosis of HCC.

At this time, with the exception of chronic hepatitis B, the primary indication for surveillance for HCC is cirrhosis of any etiology (99). Surveillance is also recommended for Asian male hepatitis B carriers over the age of 40 and females over the age of 50, hepatitis B carriers with family history of HCC, and African and North American Blacks with hepatitis B. Surveillance benefit is unclear at this time in male hepatitis B carriers younger than 40 and females younger than 50, those with hepatitis C and stage 3 fibrosis and non-cirrhotic NAFLD.

Although the most recent American Association for Study of Liver Diseases (AALSD) guidelines recommend screening for HCC with ultrasound every 6 months for at risk individuals, some feel that using the combination of AFP and ultrasonography, can increase the yield of screening (2), albeit with the increased cost due to increase in false positive results. Computed tomography (CT) and magnetic resonance imaging (MRI) although are better at imaging the liver when compared to the ultrasound, have not been studies as surveillance tools, and are currently indicated for diagnosis and staging of HCC, rather than surveillance. However, as reported by the HALT-C investigators, while absence of screening and follow-up are common and potentially contribute to late-stage HCC in 30% of cases, the most common reason for finding HCC at the late stage was an absence of detection (70%), strongly suggesting that better surveillance strategies are in-fact needed (102).

Screening for HCC in alcoholic cirrhosis is a difficult task due to poor compliance and early death. Recent data from a Danish nationwide cohort study (103), suggests a low risk of HCC (5-year cumulative risk of 1.0%) in Danish citizens with alcoholic cirrhosis, as well as its little contribution to their high mortality (5-year cumulative mortality of 43.7% with only 1.8% of all death HCC-related). The study authors suggested, based on their data, that surveillance for HCC would be expected to have a minimal effect on mortality and unlikely to be cost-effective (103). The current AASLD guidelines accept alcoholic cirrhosis as a significant risk factor for HCC, probably sufficient to warrant surveillance for HCC (104). In his comment on the Jepsen et el paper, Sherman (105) noted the Danish study reported the incidence of HCC at the lower end of reported rates in alcoholic cirrhosis, with rates higher in other geographic areas (96,106,107), suggesting that the risk has to be assessed locally. He

concluded that while the data from Denmark needs further confirmation before alcoholic cirrhosis is "scratched off" the list of screening candidates, it should be moved from the "definitive" to "possible" category (along with NAFLD, diabetes, autoimmune hepatitis, and treated hepatitis C), which includes "those patients for whom the risk of HCC has not been accurately assessed, and for whom no recommendation for or against screening can be made" (105).

Although HCC in NAFLD may have a distinct pathogenesis, presence of cirrhosis in NAFLD results in much higher risk of HCC, similar to other forms of chronic liver disease (108), and cirrhotic patients with NAFLD should undergoing screening as currently recommended. However, traditional approach to surveillance for HCC in NAFLD poses several problems. If we were to accept that obesity and diabetes (109,110), are the major risk factor for HCC (even in the absence of cirrhosis), then as observed by Baffy et al. (81), in the United States alone it will imply consideration for surveillance for HCC for every $3^{rd}$ adult, or for the 26 million of diabetics (many of whom also have NAFLD). On the other hand, as has been observed by Caldwell et al. (111), since cryptogenic cirrhosis develops insidiously and individuals do not have pre-existing well-recognized risk factors such as viral hepatitis B or C, or alcoholic liver disease, underlying liver disease might go "unrecognized" in the majority of the affected individuals. This was in fact confirmed by a single-center study from US, where only 47% of those with cryptogenic cirrhosis and HCC, had prior histological diagnosis of NASH or clinically suspected NAFLD; not surprisingly then, was the finding, that much less individuals with cryptogenic cirrhosis were enrolled in the HCC surveillance program (23% vs. 61%, P=0.01), or diagnosed with small, early stage disease, impacting on their success of therapy (112).

Obviously, better understanding of the relative contribution of obesity, diabetes mellitus and NAFLD to HCC, as well as molecular pathways that can accelerate hepatocarcinogenesis in these conditions, is needed in order to develop cancer surveillance recommendations and programs in this vast population.

## Conclusions

Chronic viral hepatitis remains a major risk factor for HCC worldwide. Vaccination of infants at birth for hepatitis B is highly effective in decreasing the incidence of HBV and development of HCC. Antiviral therapies demonstrate

possible decreased but not completely eliminated risk of HCC in both hepatitis B and C individuals and surveillance for HCC needs to continue, especially in those with cirrhosis, even after viral eradication. However, as antiviral therapies continue to improve in efficacy and tolerability and will hopefully lead to decrease in HBV- and HCV-related liver cancer, NAFDL is becoming a leading cause of HCC in developed countries, and with the epidemic of obesity and diabetes on the rise, other parts of the world will likely to follow suit. While we need better understanding of which individuals with NAFLD require surveillance for HCC, as well as better screening modalities to improve detection of early HCC, more efforts need to be directed towards prevention of obesity, diabetes and NAFLD, as well as increased awareness of the magnitude of the problem. As was recently demonstrated by Welzel *et al.* (94), among US persons ≥68 years, while the dominant risk factors for HCC differ by sex and race/ethnicity, diabetes and obesity had the greatest population attributable factor of 36.6%, and eliminating diabetes and obesity could reduce the incidence of HCC more than the elimination of any other factors (including HCV, HBV, and alcohol).

## Acknowledgements

## References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol 2013;47 Suppl:S2-6.
3. GLOBOCAN. International Agency for Research on Cancer (IARC). 2002. Available online: http://www-dep.iarc.fr, accessed 2011.
4. World Health Organization. Mortality Database. WHO Statistical Information System. 2008. Available online: http://www.who.int/whosis
5. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485-91.
6. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-27.
7. Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529-38.
8. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264-73.e1.
9. Skolnick AA. Armed with epidemiologic research, China launches programs to prevent liver cancer. JAMA 1996;276:1458-9.
10. El-Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817-23.
11. Davila JA, Morgan RO, Shaib Y, et al. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 2004;127:1372-80.
12. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 2004;127:S27-34.
13. Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325:675-80.
14. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127:S35-50.
15. Szpakowski JL, Tucker LY. Causes of death in patients with hepatitis B: a natural history cohort study in the United States. Hepatology 2013;58:21-30.
16. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 1988;61:1942-56.
17. Yang JD, Kim WR, Coelho R, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:64-70.
18. Chen JD, Yang HI, Iloeje UH, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology 2010;138:1747-54.
19. Wands J. Hepatocellular carcinoma and sex. N Engl J Med 2007;357:1974-6.
20. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. Gastroenterology 2012;142:1140-9.e3; quiz e13-4.
21. Huang YT, Jen CL, Yang HI, et al. Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B and C. J Clin Oncol 2011;29:3643-50.
22. Chen CF, Lee WC, Yang HI, et al. Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. Gastroenterology

2011;141:1240-8, 1248.e1-2.

23. Chen CJ, Liang KY, Chang AS, et al. Effects of hepatitis B virus, alcohol drinking, cigarette smoking and familial tendency on hepatocellular carcinoma. Hepatology 1991;13:398-406.

24. Yu MW, You SL, Chang AS, et al. Association between hepatitis C virus antibodies and hepatocellular carcinoma in Taiwan. Cancer Res 1991;51:5621-5.

25. Tong MJ, Blatt LM, Kao JH, et al. Basal core promoter T1762/A1764 and precore A1896 gene mutations in hepatitis B surface antigen-positive hepatocellular carcinoma: a comparison with chronic carriers. Liver Int 2007;27:1356-63.

26. Liu S, Zhang H, Gu C, et al. Associations between hepatitis B virus mutations and the risk of hepatocellular carcinoma: a meta-analysis. J Natl Cancer Inst 2009;101:1066-82.

27. Lin CW, Lin CC, Mo LR, et al. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 2013;58:730-5.

28. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.

29. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168-74.

30. Simonetti J, Bulkow L, McMahon BJ, et al. Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus. Hepatology 2010;51:1531-7.

31. Yuen MF, Wong DK, Fung J, et al. HBsAg Seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. Gastroenterology 2008;135:1192-9.

32. Kao JH. Hepatitis B virus genotypes and hepatocellular carcinoma in Taiwan. Intervirology 2003;46:400-7.

33. Ding X, Mizokami M, Yao G, et al. Hepatitis B virus genotype distribution among chronic hepatitis B virus carriers in Shanghai, China. Intervirology 2001;44:43-7.

34. Orito E, Ichida T, Sakugawa H, et al. Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. Hepatology 2001;34:590-4.

35. Kao JH, Chen PJ, Lai MY, et al. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology 2000;118:554-9.

36. Ni YH, Chang MH, Wang KJ, et al. Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. Gastroenterology 2004;127:1733-8.

37. Huang YT, Yang HI, Jen CL, et al. Suppression of hepatitis B virus replication by hepatitis C virus: combined effects on risk of hepatocellular carcinoma (abstract). Hepatology 2005;42:230A.

38. Benvegnù L, Fattovich G, Noventa F, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. Cancer 1994;74:2442-8.

39. Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). Gut 2000;46:420-6.

40. Zanetti AR, Van Damme P, Shouval D. The global impact of vaccination against hepatitis B: a historical overview. Vaccine 2008;26:6266-73.

41. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-31.

42. Sung JJ, Tsoi KK, Wong VW, et al. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2008;28:1067-77.

43. Papatheodoridis GV, Lampertico P, Manolakopoulos S, et al. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol 2010;53:348-56.

44. Shen YC, Hsu C, Cheng CC, et al. A critical evaluation of the preventive effect of antiviral therapy on the development of hepatocellular carcinoma in patients with chronic hepatitis C or B: a novel approach by using meta-regression. Oncology 2012;82:275-89.

45. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013;58:98-107.

46. Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus–related hepatocellular carcinoma recurrence following liver resection. JAMA 2012;308:1906-14.

47. Singal AK, Salameh H, Kuo YF, et al. Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. Aliment Pharmacol Ther 2013;38:98-106.

48. Sherman M. Does hepatitis B treatment reduce the incidence of hepatocellular carcinoma? Hepatology

2013;58:18-20.

49. Tanaka H, Imai Y, Hiramatsu N, et al. Declining incidence of hepatocellular carcinoma in Osaka, Japan, from 1990 to 2003. Ann Intern Med 2008;148:820-6.

50. Lemon SM, McGivern DR. Is hepatitis C virus carcinogenic? Gastroenterology 2012;142:1274-8.

51. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-72.

52. Lok AS, Everhart JE, Wright EC, et al. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology 2011;140:840-9; quiz e12.

53. Raimondi S, Bruno S, Mondelli MU, et al. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. J Hepatol 2009;50:1142-54.

54. Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. J Hepatol 2012;57:897-909.

55. Yin L, Grandi N, Raum E, et al. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Aliment Pharmacol Ther 2009;30:113-25.

56. Yin L, Grandi N, Raum E, et al. Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer 2010;46:2196-205.

57. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. Am J Public Health 2006;96:252-61.

58. Ahonen MH, Tenkanen L, Teppo L, et al. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control 2000;11:847-52.

59. Ahn J, Albanes D, Berndt SI, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. Carcinogenesis 2009;30:769-76.

60. Chiang KC, Yeh CN, Chen MF, et al. Hepatocellular carcinoma and vitamin D: a review. J Gastroenterol Hepatol 2011;26:1597-603.

61. Ogawa E, Furusyo N, Kajiwara E, et al. Efficacy of pegylated interferon alpha-2b and ribavirin treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis C: a prospective, multicenter study. J Hepatol 2013;58:495-501.

62. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med 2005;142:105-14.

63. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833-44.

64. Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013;158:329-37.

65. Koh C, Heller T, Haynes-Williams V, et al. Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. Aliment Pharmacol Ther 2013;37:887-94.

66. Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-8, 288.e1.

67. Singal AK, Singh A, Jaganmohan S, et al. Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. Clin Gastroenterol Hepatol 2010;8:192-9.

68. Ji F, Zhang S, Deng H, et al. Efficacy of interferon-based antiviral therapy on the risk of hepatocellular carcinoma of patients with chronic hepatitis C: further evidence in decompensation cirrhosis. J Hepatol 2013;58:1262-4.

69. Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis 2013;57:230-6.

70. Shindoh J, Hasegawa K, Matsuyama Y, et al. Low hepatitis C viral load predicts better long-term outcomes in patients undergoing resection of hepatocellular carcinoma irrespective of serologic eradication of hepatitis C virus. J Clin Oncol 2013;31:766-73.

71. Hsu YC, Ho HJ, Wu MS, et al. Postoperative peg-interferon plus ribavirin is associated with reduced recurrence of hepatitis C virus-related hepatocellular carcinoma. Hepatology 2013;58:150-7.

72. Ward JW. The epidemiology of chronic hepatitis C and one-time hepatitis C virus testing of persons born during 1945 to 1965 in the United States. Clin Liver Dis 2013;17:1-11.

73. Moyer VA, U.S. Preventive Services Task Force. Screening for Hepatitis C Virus Infection in Adults: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2013;159:349-57.

74. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-76.

75. Charlton M. Cirrhosis and liver failure in nonalcoholic

fatty liver disease: Molehill or mountain? Hepatology 2008;47:1431-3.

76. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40:1387-95.

77. Lazo M, Clark JM. The epidemiology of nonalcoholic fatty liver disease: a global perspective. Semin Liver Dis 2008;28:339-50.

78. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011;140:124-31.

79. Ascha MS, Hanouneh IA, Lopez R, et al. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972-8.

80. Yatsuji S, Hashimoto E, Tobari M, et al. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. J Gastroenterol Hepatol 2009;24:248-54.

81. Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J Hepatol 2012;56:1384-91.

82. Ertle J, Dechêne A, Sowa JP, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer 2011;128:2436-43.

83. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 2010;51:1820-32.

84. Regimbeau JM, Colombat M, Mognol P, et al. Obesity and diabetes as a risk factor for hepatocellular carcinoma. Liver Transpl 2004;10:S69-73.

85. Guzman G, Brunt EM, Petrovic LM, et al. Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis? Arch Pathol Lab Med 2008;132:1761-6.

86. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol 2012;10:1342-1359.e2.

87. Lai SW, Chen PC, Liao KF, et al. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. Am J Gastroenterol 2012;107:46-52.

88. Hassan MM, Curley SA, Li D, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer 2010;116:1938-46.

89. Aljada A, Mousa SA. Metformin and neoplasia: implications and indications. Pharmacol Ther 2012;133:108-15.

90. Singh S, Singh PP, Singh AG, et al. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. Am J Gastroenterol 2013;108:881-91; quiz 892.

91. Chen TM, Lin CC, Huang PT, et al. Metformin associated with lower mortality in diabetic patients with early stage hepatocellular carcinoma after radiofrequency ablation. J Gastroenterol Hepatol 2011;26:858-65.

92. Mancebo A, González-Diéguez ML, Cadahía V, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. Clin Gastroenterol Hepatol 2013;11:95-101.

93. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206-13.

94. Welzel TM, Graubard BI, Quraishi S, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol 2013;108:1314-21.

95. Schöniger-Hekele M, Müller C, Kutilek M, et al. Hepatocellular carcinoma in Austria: aetiological and clinical characteristics at presentation. Eur J Gastroenterol Hepatol 2000;12:941-8.

96. Uetake S, Yamauchi M, Itoh S, et al. Analysis of risk factors for hepatocellular carcinoma in patients with HBs antigen- and anti-HCV antibody-negative alcoholic cirrhosis: clinical significance of prior hepatitis B virus infection. Alcohol Clin Exp Res 2003;27:47S-51S.

97. Donato F, Tagger A, Gelatti U, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002;155:323-31.

98. Serra MA, Escudero A, Rodríguez F, et al. Effect of hepatitis C virus infection and abstinence from alcohol on survival in patients with alcoholic cirrhosis. J Clin Gastroenterol 2003;36:170-4.

99. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.

100. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-22.

101. Forner A, Reig ME, de Lope CR, et al. Current strategy

for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61-74.

102. Singal AG, Nehra M, Adams-Huet B, et al. Detection of hepatocellular carcinoma at advanced stages among patients in the HALT-C trial: where did surveillance fail? Am J Gastroenterol 2013;108:425-32.

103. Jepsen P, Ott P, Andersen PK, et al. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. Ann Intern Med 2012;156:841-7, W295.

104. AASLD Practice Guideline, Management of Hepatocellular Carcinoma: An Update. Bruix J, Sherman M. Available online: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf (Accessed on June 20, 2013).

105. Sherman M. Whither hepatocellular carcinoma screening? Hepatology 2012;56:2412-4.

106. Alvarez MA, Cirera I, Solà R, et al. Long-term clinical course of decompensated alcoholic cirrhosis: a prospective study of 165 patients. J Clin Gastroenterol 2011;45:906-11.

107. Ioannou GN, Splan MF, Weiss NS, et al. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2007;5:938-45, 945.e1-4.

108. Hashimoto E, Yatsuji S, Tobari M, et al. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. J Gastroenterol 2009;44 Suppl 19:89-95.

109. La Vecchia C, Negri E, Decarli A, et al. Diabetes mellitus and the risk of primary liver cancer. Int J Cancer 1997;73:204-7.

110. Braga C, La Vecchia C, Negri E, et al. Attributable risks for hepatocellular carcinoma in northern Italy. Eur J Cancer 1997;33:629-34.

111. Caldwell SH, Oelsner DH, Iezzoni JC, et al. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 1999;29:664-9.

112. Marrero JA, Fontana RJ, Su GL, et al. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology 2002;36:1349-54.