

## Individualized hepatocellular carcinoma risk: The challenges for designing successful chemoprevention strategies

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### Abstract

Hepatocellular carcinoma (HCC) develops in the context of environmental risk factors like chronic viral hepatitis, diabetes and alcohol exposure, often associated to an increased risk of cirrhosis. Antiviral treatments that are effective to counteract hepatitis B and C may also attenuate the risk of tumor development. However, since hepatitis B-related carcinogenesis is promoted independently of the onset of cirrhosis, such antiviral treatments as nucleo(t)side analogs can promote regression of cirrhosis, prevent clinical decompensation and variceal bleeding but not HCC. This means that in successfully treated patients with cirrhosis, HCC is often the consequence of their extended survival. In hepatitis C patients, a sustained virological response to interferon-based therapies can reduce the rate of HCC development, even in patients with cirrhosis who experience histological regression of their liver disease. Future therapies aimed at this endpoint in at risk populations should take into consideration pretreatment patient stratification for host, viral and environmental risk factors. In this context the recent discovery of single nucleotide polymorphisms involved in the immune

system function and tumorigenesis, might permit enrollment of populations of patients enriched with HCC risk factors for targeted chemopreventive therapies. This could finally pave the way to personalized algorithms, as already seen in the diagnosis and treatment schemes for chemoprevention.

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**Key words:** Hepatocellular carcinoma; Hepatitis C virus; Peginterferon; Hepatitis B virus; Human immunodeficiency virus; Nucleoside analogues; Sustained virological response; Single nucleotide polymorphisms

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and seventh in women, accounting for 7% of all cancers, and the third most common cause of cancer related death, worldwide<sup>[1]</sup>. HCC is characterized by peculiar biological and clinical features that may be relevant to primary and secondary prevention strategies. Indeed, up to 95% of all HCCs occur in the context of known and preventable risk factors, such as chronic viral hepatitis, alcohol abuse and cirrhosis (Table 1). Secondly HCC is one of the few cancers that can be diagnosed by radiological techniques, hence avoiding invasive diagnostic methods. Lastly, HCC is the only cancer that does not contraindicate patients to organ transplantation but actually benefits from liver transplantation in accurately selected patients. These rather unique features of HCC, in theory, could be used to implement therapeutic

and diagnostic measures to reduce or prevent the rate of HCC development in patients at risk, enforce surveillance programs in at risk patients aimed at early diagnosis and individualize treatment options based upon patient and tumor characteristics once the tumor has developed. Some of these points have been thoroughly investigated by clinical research studies and have led to significant advances in clinical practice that include the development of specific guidelines on surveillance protocols and on individualized treatment algorithms for HCC. Less successful have been attempts to design primary prophylaxis studies in at risk populations, such as those with hepatitis B virus (HBV) or hepatitis C virus (HCV), a fact that is especially worrisome as HCC arising in these patients still represents the core of the HCC epidemic in most countries. Indeed, chronic HBV and HCV infection affect roughly 400 and 200 million people, respectively, worldwide, and are the current leading causes of liver-related death and the main indication for liver transplantation in developed countries<sup>[2]</sup>.

## HCC RISK FACTORS

### Hepatic disease status

HCC almost invariably occurs in a histologically abnormal liver, the mere existence of chronic liver disease representing a potential risk for the development of this tumor. Indeed, on the top of specific virus mechanisms that may be directly carcinogenetic to the liver, chronic necro-inflammation and accumulation of reactive oxygen species contribute to carcinogenesis through chromosomal injury<sup>[3]</sup>. Cirrhosis, the end stage consequence of hepatic inflammation resulting in nodular transformation of the liver, is considered a premalignant condition, independently of etiology. Whether the association of cirrhosis with HCC reflects a long lasting exposure to carcinogenetic agents capable of causing liver cell inflammation or a carcinogenetic effect of disrupted lobular organization, is a matter of debate<sup>[4]</sup>.

The prevalence of cirrhosis in persons with HCC is about 80%-90% in autopsied series worldwide, whereas approximately only 10%-20% of HCCs may be encountered in non-cirrhotic patients<sup>[5]</sup>. However, only a few non-cirrhotic patients with HCC have absolutely normal liver histology, as the majority show fibrosis stages that range from no fibrosis (F0) to septal (F2) and bridging fibrosis (F3) with necroinflammation, steatosis, and liver cell dysplasia<sup>[6-8]</sup>.

In a detailed study from Japan involving 490 untreated patients with chronic hepatitis C, the HCC incidence per 100 person years increased with the stage of fibrosis at diagnosis, from 0.4 among patients with stage F0 or F1 to 1.5, 5.1 and 6.9 among those with fibrosis stages F2, F3 and F4, respectively<sup>[9]</sup>. The presence of large cell change<sup>[10]</sup>, irregular regeneration of hepatocytes and macroregenerative nodules have been evaluated as morphologic predictors of HCC in cirrhosis independently of baseline disease<sup>[10-14]</sup>.

**Table 1 Risk factors for hepatocellular carcinoma**

Viral	Environmental	Host related
HIV	Alcohol exposure	Age
HBV	Metabolic syndrome	Male sex
HCV		Genetics

HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Cirrhosis is not only driven by viral hepatitis but can also be the consequence of other conditions like hemochromatosis, Wilson's disease, antitrypsin deficiency, primary biliary cirrhosis, and autoimmune hepatitis<sup>[5]</sup>. Patients with cirrhosis stemming from genetic hemochromatosis have a 20-fold relative risk of developing HCC, compared to the general population, with an annual incidence of about 3%-4%<sup>[15]</sup>. In general, the risk of HCC in patients with cirrhosis increases in parallel to ageing, male gender, disease activity, degree of liver cell proliferation, presence of hepatobiliary phenotype on liver cells and serum level of alfa-fetoprotein. Patients with more advanced Child-Pugh scores are at higher risk of liver cancer, Child-Pugh class B/C patients having a 3-fold increased risk compared to Child Pugh A patients<sup>[16,17]</sup>.

### Viral factors

**HBV:** The annual incidence of HCC in patients with chronic hepatitis B, ranges from 2% to 5%, in strict correlation with the histological stage of the underlying liver disease, serologic status and geographic area<sup>[18]</sup>. Chronic HBV infection is commonly considered a primary risk factor for the development of HCC, exerting its pro-oncogenic properties through both indirect and direct mechanisms<sup>[19-23]</sup>. The indirect mechanisms are related to its propensity to induce continuous or recurrent phases of liver necroinflammation and to promote the progression of chronic hepatitis to cirrhosis, often preceding the development of HCC<sup>[24]</sup>. Most cases of HBV-related HCC (70%-90%) occur in patients with cirrhosis secondary to chronic necroinflammation, but HBV itself can cause HCC in the absence of cirrhosis through direct carcinogenic mechanisms that have been related to the capacity of HBV to integrate into the host's genome and to produce proteins (X protein and truncated pre-S protein) with potential transforming properties<sup>[25]</sup>.

In Europe, HBV-related HCC is associated with cirrhosis in the majority of patients<sup>[26,27]</sup>, whereas this is not true in Asia and Africa where the tumor is common also among carriers with mild hepatic fibrosis, likely as a consequence of long standing infection that is often acquired perinatally<sup>[28-30]</sup>.

HCC risk may be modulated by viral load<sup>[31-35]</sup>, even when this predictor is measured years before tumor diagnosis, and can be modified also by serum hepatitis B e antigen (HBeAg) persistence and hepatitis B surface antigen (HBsAg) status<sup>[31,36-38]</sup>.

Recently, it has been demonstrated that HCC may

also develop in Asian carriers with inactive hepatitis (*i.e.*, persistently normal alanine transaminase and serum HBV DNA < 2000 IU/mL)<sup>[26,27,31,39]</sup> and HCC was also found to develop in a significant number of patients from 1 year to more than 10 years following spontaneous clearance of serum HBsAg, with a higher risk among patients who had HBsAg seroclearance after 50 years of age<sup>[40]</sup>. Other studies with sensitive amplification assays have shown that HBV DNA persists in serum or liver as an occult HBV infection, even following spontaneous serologic recovery from transient HBV infection (HBsAg-negative status)<sup>[41]</sup>.

The estimated incidence rates of HCC in subjects with chronic HBV infection in East Asian countries is 0.2 per 100 person-years in inactive carriers, 0.6 per 100 person-years for those with chronic HBV infection without cirrhosis, and 3.7 per 100 person-years for those with compensated cirrhosis; while in Europe/North America the HCC incidence rate was 0.02 per 100 person-years in inactive carriers, 0.3 per 100 person-years in subjects with chronic HBV without cirrhosis, and 2.2 per 100 person-years in subjects with compensated cirrhosis<sup>[42]</sup>.

Male sex, positive family history and African origins are added risk factors for HCC development in HBV positive patients<sup>[28-30]</sup>. Genotype B of the HBV seems to be associated with lower rates of HCC development compared to genotype C of HBV<sup>[43-48]</sup>, since it is characterized by anticipated HBeAg seroconversion, higher rates of sustained remission after HBeAg seroconversion, less active hepatic necroinflammation and slower progression to cirrhosis. Genotype A infections have a generally more favorable outcome than genotype D infections which predominate in the Mediterranean basin<sup>[49,50]</sup>.

**HCV:** Chronic infection with HCV affects more than 170 million individuals, representing a major cause of morbidity and anticipated liver-related death in western countries and Japan. HCC is the dominant, first to appear complication of patients with long standing infection complicated by cirrhosis, which in fact is considered the main risk factor for HCC in patients with HCV infection, as only a minority of HCC cases develop in patients with mild-to-moderate HCV disease. Malignant transformation of hepatocytes occurs through a pathway of increased liver cell turnover, induced by chronic liver injury and regeneration in a context of inflammation and oxidative DNA damage<sup>[51]</sup> which facilitates the occurrence of genetic and epigenetic alterations that over decades can lead to the development of HCC. Still there are lines of evidence that support a direct role for HCV in cancer promotion<sup>[52]</sup>. Clinically this is supported by the incidence of HCC in HCV-related cirrhosis being higher than that reported in cirrhosis resulting from other liver diseases such as autoimmune hepatitis or metabolic syndrome<sup>[53]</sup>. Whether HCV genotype 1b produces a higher risk of HCC development compared to other HCV genotypes, is debatable, yet *de facto* reinforces the concept that HCV itself may promote HCC<sup>[54]</sup>.

The HCV genome consists of a single stranded positive sense RNA of approximately 9.6 kb in length, that encodes a 327 kDa polyprotein that is processed into 10 mature structural and non structural viral proteins<sup>[55]</sup>. HCV proteins have been shown to impact on cell signaling, transcriptional modulation, transformation, apoptosis, membrane rearrangements, vesicular trafficking and translational regulation<sup>[52]</sup>. Four of the HCV gene products (core, NS3, NS4B and NS5A) show transformation potential in cell culture systems. Transgenic mouse models support HCV induced carcinogenesis, with transgenic lineages with high level liver specific expression of the core protein and transgenic mice for the two envelop proteins E1 and E2 developing HCC even in the absence of hepatic inflammation<sup>[56,57]</sup>. HCV can also induce endoplasmic reticulum (ER) stress, a homeostatic mechanism that regulates cellular metabolism and protein synthesis in response to perturbations in protein folding and biosynthesis<sup>[58]</sup>. Persistent ER stress may result in intra- and extra-cellular accumulation of DNA-damaging factors known to predispose cells to mutagenesis.

**Human immunodeficiency virus:** Human immunodeficiency virus (HIV) infection significantly increases the risk of liver-related morbidity and mortality, primarily because during the highly active antiretroviral therapy (HAART) era an important reduction in HIV-related complications has occurred, leading to the emergence of co-infection with HBV (6%-14%) and HCV (25%-30%) as hepatotoxic factors in addition to excessive alcohol consumption, non-alcoholic fatty liver disease and drug-induced liver injury<sup>[59]</sup>.

While the MORTAVIC study in 2001 indicated HCC to be responsible for 25% of all liver deaths in HIV patients, in the HAART era there are studies showing HCC developing in co-infected patients to be more aggressive, to present at an earlier age and to less frequently be curable compared to HCC developing in HCV mono-infected patients. A direct oncogenic effect of the virus has therefore been hypothesized by some<sup>[60,61]</sup>.

### Environmental risk factors

**Alcohol:** Chronic consumption of more than 80 g of ethanol per day for more than 10 years increases the risk of HCC by approximately 5-fold; in women even smaller quantities of alcohol consumption (10 g/d) are associated with a significant (24%) increase of HCC risk<sup>[62]</sup>. Alcohol abuse in patients with chronic hepatitis C doubles the risk for HCC, due to a synergism between alcohol and hepatitis C in anticipating HCC onset or causing more severe histological tumor patterns. In a HCC cohort in Austria, alcoholic liver disease was the likely cause of HCC in 35% of subjects<sup>[63]</sup>, whereas in the United States, the hospitalization rate for HCC related to alcoholic cirrhosis is (8-9)/100 000 people per year compared to about 7/100 000 people per year for hepatitis C<sup>[64]</sup>. Heavy alcohol consumption can lead to liver damage by direct liver cell injury and generation of toxic metabolites, thereby

transforming the liver in a mitogenic and mutagenic environment. This not only causes development of liver fibrosis and cirrhosis<sup>[65,66]</sup>, but also increases conversion of pro-carcinogens to carcinogens through oxidation and metabolism of ethanol in the liver<sup>[67]</sup>. Acetaldehyde and oxygen free radicals deriving from ethanol metabolism may also directly induce cell damage by initiating peroxidation of membrane lipids, through oxidative stress<sup>[68]</sup>.

**Metabolic syndrome:** Diabetes is an independent risk factor for HCC; a recent surveillance epidemiology and end results based re-analysis has shown a 2-3-fold increase in the risk of HCC, regardless of the presence of other major risk factors<sup>[69]</sup>. Further evidence that obesity and diabetes are either jointly or independently associated with an increased risk of HCC is provided by an Italian case control study and by several large-scale epidemiological studies, that have associated the overweight and obesity pandemic in the general population with an increase in HCC risk<sup>[70]</sup>.

In a cohort of 900 000 American adults, the risk of dying from liver cancer was 4.5 times higher in men with a body mass index of 35 kg/m<sup>2</sup> or above compared to men with a normal body mass index (18.5-24.9 kg/m<sup>2</sup>)<sup>[71]</sup>. A meta-analysis of case control and cohort studies concluded that the relative risk of liver cancer was 1.17 for overweight subjects and 1.89 for obese patients<sup>[72]</sup>. These and other studies contribute to the increased recognition of non-alcoholic steatohepatitis (NASH) as a cause of cirrhosis and HCC, with many patients progressing to liver cancer without histological evidence of advanced fibrosis or cirrhosis<sup>[73,74]</sup>.

A yearly cumulative incidence of HCC in 2.6% of patients with NASH compared to 4.0% of those with HCV over a median follow-up time of 3.2 years was also demonstrated in patients referred for liver transplant evaluation at Cleveland Clinic in Ohio<sup>[75]</sup>. Interestingly, in this cohort of patients, older age at diagnosis of cirrhosis and any alcohol consumption were independently associated with the development of HCC in a NASH-cirrhosis population, suggesting that alcohol intake, even in socially accepted amounts, may potentially increase the risk of HCC development both in NASH- and HCV-cirrhotic patients.

The precise mechanisms through which metabolic factors drive HCC development are complex and beyond the scope of this article; however, major systemic and liver specific molecular mechanisms like insulin resistance, hyperinsulinemia, increased expression of tumor necrosis factor signaling pathways and direct lipotoxicity are major players in the development of HCC.

### Host-related risk factors

**Age and sex:** Among host factors, older age and male sex have consistently been found in longitudinal studies to be associated with an increased risk of HCC among persons with cirrhosis of different etiologies, with the caveat, however, that age might reflect longer duration of

hepatic disease<sup>[76-79]</sup>.

In patients with cirrhosis, there is a striking gender imbalance in HCC incidence, with a predominance for males independently from geographic area, etiologic factors and ethnicity with a male to female ratio between 2:1 to > 4:1 being reported across studies<sup>[80]</sup>. While male preponderance could just reflect the greater incidence of viral hepatitis and alcohol-related disease in males, it could also be related to hormonal diversity. High serum levels of testosterone have been associated with increased HCC risk in nested case-control studies of HBV carriers in Taiwan and Shanghai<sup>[81]</sup>, while a cross-sectional study in male veterans with chronic HCV in the United States associated higher total serum levels of testosterone with risk of advanced hepatic fibrosis and inflammatory activity, without examining the association with HCC<sup>[82]</sup>.

Among the complex molecular mechanisms behind gender disparities in HCC, estrogens may play a role in increasing interleukin-6 (IL-6) production and modulation of gene expression through FOXA transcription factors that have been shown to prevent HCC development in experimental models. However, more data are still needed to define the implication of sexual hormones in the molecular pathogenesis of HCC<sup>[83]</sup>.

### Single nucleotide polymorphisms associated with HCC

Genetic host factors play an important role in HCC development. The most common form of genetic variation between individuals is single nucleotide polymorphisms (SNPs) which are a variation in a DNA base at a particular nucleotide locus. A common SNP is defined by having a minor allele frequency of at least 5%. In studies designed with a “candidate gene approach”, a limited number of biologically plausible SNPs were tested. The starting hypothesis is that a given variant in a specific gene involved in a pathway that influences HCC development can sufficiently alter either protein function or expression, and result in the modulation of cancer risk. Another approach to study genetic factors is through “genome wide association studies” (GWAS). These studies are by definition “hypothesis free”, and compare allele/genotype frequency of common variants between cases and unaffected controls and test 100 000 of tag SNPs reflecting common genetic variations across the entire human genome. To reach GWAS significance ( $P$  value = 0.05/number of SNPs tested) a  $P$  value in the order of  $< 10^{-8}$  is typically required<sup>[84]</sup>.

To identify susceptible genetic variants for HCV- and HBV-related HCC many genetic association studies have been conducted; unfortunately most publications suffer from major methodological drawbacks because of their case-control, retrospective and single center design, mainly involving selected Asian populations. This minimizes the potential importance of ethnic diversity, calling for external validation in populations of different ancestry before effectively translating results to clinical practice. Prospective cohort studies conducted in large homogeneous populations with sufficient number of events



**Table 2** Genetic associations with hepatocellular carcinoma at genome wide association studies level

Study	Patients	n	SNP locus	Strength	Comment
Kumar <i>et al</i> <sup>[85]</sup>	CHC	1730	MICA	OR 1.3	This study considers HCV-negative individuals as the controls, hence it isn't useful in distinguishing HCC high risk population among HCV-related cirrhotic patients
	HCV neg	8376			
	CHC-HCC	2115			
Miki <i>et al</i> <sup>[86]</sup>	CHC	2390	DEPDC5	OR 2.2	Given the relatively small number of cases in the GWAS phase, the statistical power to detect an effect caused by this SNP was only 50%, compared to the 80% recommended to detect an association of the expected effect size
	CHC-HCC	922			
Zhang <i>et al</i> <sup>[88]</sup>	CHB	1790	KIF1b	0.6	Confounding non-genetic HCC risk factors cannot be ruled out in multivariate analysis
	CHB-HCC	2317			
Chan <i>et al</i> <sup>[89]</sup>	CHB	825	DLC1	1.3	Factors of selection bias cannot be excluded because 11.6% of the "genotyping cohort" had > 60 g alcohol consumption per day, secondly because 16.5% of the controls received antiviral treatment before enrolment
	CHB-HCC	595			
Clifford <i>et al</i> <sup>[123]</sup>	HCC <sup>1</sup>	386	MHC II	$p1 \times 10^{-13}$	The viral infection status of controls was not ascertained with the consequence that there might be hypothetical cases with chronic liver disease
	Cirrhosis <sup>2</sup>	86			
	Controls <sup>3</sup>	787			

<sup>1</sup>89% HBV or HCV viral infection; <sup>2</sup>76% HBV or HCV viral infection; <sup>3</sup>Not known viral status. CHC: Chronic hepatitis C; CHB: Chronic hepatitis B; GWAS: Genome-wide association study; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; SNP: Single nucleotide polymorphism.

during follow-up require a long time to be conducted and therefore are still scarce.

The genetic regions found to have a significant statistical association with HCC at a GWAS level in chronic hepatitis C patients are the 5' flanking region of *MICA* (the MHC class I polypeptide-related sequence A gene, on chromosome 6p21.33) which is essential for direct immune system functions<sup>[85]</sup> and isoform1 of the *DEPDC5* locus on chromosome, where deletion of the region containing DEPDC has been reported in malignant brain glioblastomas<sup>[86]</sup>. Also the MHC class II locus presenting antigen to CD4 p (helper) T cells contains three variants strongly associated with HCC, probably related to altered MHC class II proteins that result in an ineffective T-cell response<sup>[87]</sup>. *KIF1B* was identified as a new susceptibility locus for HCC in chronic HBV carriers; the loss of heterozygosity on this locus is a common genetic lesion in a broad range of human cancers<sup>[88]</sup>. Variations at chromosome 8p12 may also promote HCC in patients with HBV and risk-associated 8p12 SNPs or haplotypes might have an interacting effect on the *DLC1* locus (Deleted in Liver Cancer 1), which becomes more susceptible to deletion or chromosomal loss<sup>[89]</sup> (Table 2).

In the HALT-C study cohort a significant association between a polymorphism on epidermal growth factor gene and HCC was detected in a retrospective case-control study, by the use of a candidate gene approach<sup>[90]</sup>. With this same approach in HBV patients many other genes involved in immune and tumorigenesis processes were found to be significantly associated with HCC development, among these cytotoxic T-lymphocyte antigen 4 gene<sup>[91]</sup>, the promoter region of *MCM7* gene and the enhancer II (Enh II)<sup>[92]</sup>, basal core promoter, and precore regions of HBV<sup>[93]</sup>.

Still the SNPs identified so far only partly explain the overall variability in HCC susceptibility as they carry a rather low risk ratio for HCC development, have been mostly assessed in well selected patients where HCC tissue was obtained following surgical resection and

therefore at this moment do not permit prediction at the individual and population level. Whole genome sequencing analysis of HCCs nodules are promising approaches; recently Fujimoto *et al*<sup>[94]</sup> have identified etiological diverse specific mutation patterns and several mutation of chromatin regulators in 27 HCCs.

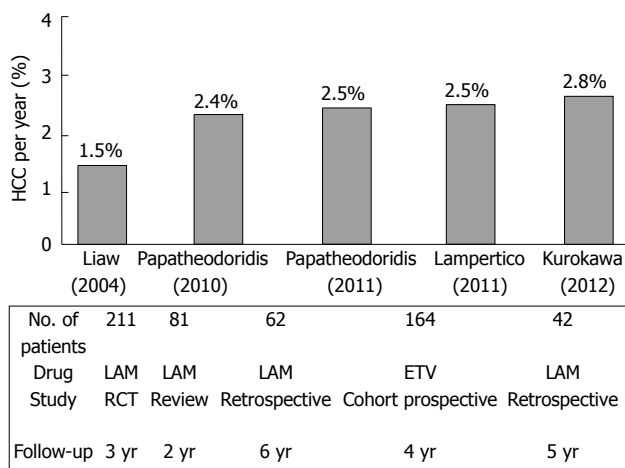
In 2008 the International Cancer Genome Consortium was launched with the purpose to coordinate large-scale cancer genome studies in tumors from 50 cancer types and/or subtypes that are of main importance across the globe, including HCC. Systematic studies of more than 25 000 cancer genomes at the genomic, epigenomic and transcriptomic levels are needed to reveal the repertoire of oncogenic mutations, uncover traces of the mutagenic influences, define clinically relevant subtypes for prognosis and therapeutic management, and enable the development of new cancer therapies. Hopefully in the not so distant future, partial or full cancer genomes will routinely be sequenced as part of the clinical evaluation of cancer patients and as part of their on-going clinical management<sup>[95]</sup>.

## CHEMOPREVENTION

Although all host related HCC risk factors are unmodifiable and at this moment do not call for any preventive measures, environmental and viral factors can either be prevented, suppressed or in some cases cured by effective treatments<sup>[96]</sup>. For viral hepatitis B and C and for HIV infection the question is whether the effective antiviral treatments that have been developed in the last decade to treat patients with virus induced liver disease can be considered chemopreventive approaches for HCC in parallel.

## HBV

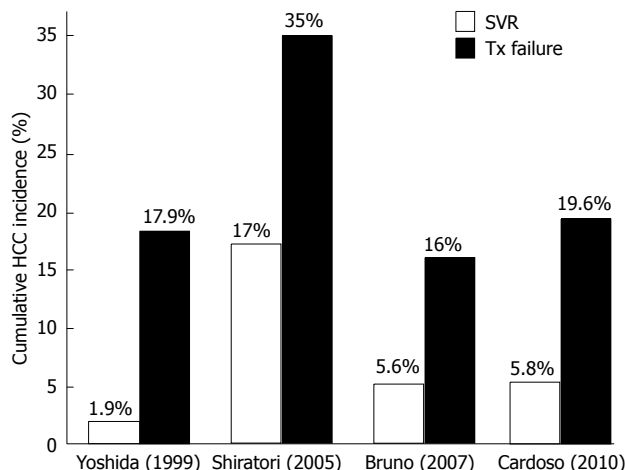
Prevention of HCC in patients with a sustained suppression of HBV following interferon or NUC therapy is far from being convincingly demonstrated, especially since this dramatic and life threatening complication in most



**Figure 1 Hepatocellular carcinoma rates in nucleos(t)ide analogs-naive cirrhotic patients with long-term response.** Several studies have shown that hepatitis B virus patients who achieve a virological response to lamivudine in some cases still develop hepatocellular carcinoma (HCC) as the only complication. LAM: Lamivudine; ETV: Entecavir; RCT: Randomized controlled trial.

patients occurs many decades after viral infection and many years after diagnosis of hepatitis.

The benefits of a virological suppression in patients with cirrhosis are easier to evaluate as these patients are the closest to developing hepatitis-related complications. Several studies have shown that HBV patients who achieve a virological response to lamivudine are protected against HCC during the precirrhotic phase of infection, in fact this is the only complication arising in virological responders with preexisting cirrhosis<sup>[97-101]</sup> (Figure 1). In a systematic review of studies of nucleos(t)ide analog treatment of patients with HBV it was clearly shown that HCC was prevented in patients with chronic hepatitis but not in those with cirrhosis, and in general in patients that could not achieve complete virological suppression<sup>[98]</sup>. This was confirmed by a recent cohort study from Greece where long-term cirrhotic patients responding to lamivudine remained at risk of developing liver cancer<sup>[99]</sup>. All these studies enrolled patients treated with lamivudine or rescued with adefovir, *i.e.*, regimens characterized by limited potency and low to moderate genetic barrier, which are not recommended any more by International guidelines for treatment of patients with chronic hepatitis B in general, and especially in patients with compensated cirrhosis. This raised the hope that more potent anti-HBV drugs, like entecavir and tenofovir, might confer an advantage in terms of HCC prevention in responders with cirrhosis, however with disappointing results. A multicenter study in Italy conducted in patients with compensated cirrhosis who achieved persistently undetectable serum HBV DNA during 4 years of entecavir monotherapy, showed an annual rate of neoplastic transformation of the liver of approximately 2.5%, that mimics the HCC rates in untreated HBeAg negative patients in Europe<sup>[100]</sup>. The reasons for these negative results may be many fold: it should be recalled that development of HCC in successfully treated patients with cirrhosis is often the conse-



**Figure 2 Cumulative incidence of hepatocellular carcinoma in patients with cirrhosis stratified by sustained virological response.** Studies in Caucasian patients as well as in patients from Asia have repeatedly shown that a sustained virological response (SVR) following interferon-based therapies can reduce the rate of hepatocellular carcinoma development in hepatitis C virus related cirrhosis. HCC: Hepatocellular carcinoma.

quence of an extended survival provided by nucleot(s)ide analogues (NUCs) preventing clinical decompensation, as it was the case in the Italian multicenter study. Another explanation is that HBV related liver carcinogenesis is likely to be promoted by cellular events that are established early during chronic infection with HBV, independently on the onset of cirrhosis. This would explain why NUCs can determine regression of cirrhosis, protection from clinical decompensation and variceal bleeding but not from HCC development<sup>[102-104]</sup>.

**HCV**

With regards to HCV there is conclusive evidence that an sustained virological response (SVR) following interferon (IFN) based therapies can reduce the rate of HCC development, independently of fibrosis stage<sup>[9,105-108]</sup>. This has been repeatedly shown both by studies in Caucasian patients as well as in patients from Asia (Figure 2). Interestingly an SVR does not completely negate the risk of HCC, as a small group of patients will still develop HCC in the long term follow-up period, although the annual rate is extremely low and reduced compared to non responders or untreated patients. In an Italian study on 920 patients with compensated cirrhosis who received IFN monotherapy and who were followed-up for a median period of 96 mo after treatment completion, Bruno *et al*<sup>[109]</sup> found that SVR patients had significantly lower rates of HCC (0.66 *vs* 2.10 per 100 person-years) and liver-related death (0.19 *vs* 1.44 per 100 person-years, *P* < 0.001) compared to those with treatment failure. Similar findings were also reported by Cardoso *et al*<sup>[110]</sup> in a study that analyzed 307 patients with bridging fibrosis or cirrhosis followed-up for 3.5 years after the end of treatment. The authors found significantly lower incidence rates per 100 person-years of liver-related complications, liver-related deaths, and HCC in SVR than in non-SVR patients (0.62

*vs* 4.16, 0.61 *vs* 3.76 and 1.24 *vs* 5.85, respectively;  $P < 0.001$  for all comparisons). A study from France analyzing a cohort of HCV cirrhotics subjected to repeated liver biopsies following an SVR, has linked the protective effect of an SVR on HCC development on regression of cirrhosis<sup>[111]</sup>. Indeed the 44% of patients who showed cirrhosis regression had 0% occurrence of HCC during a 118 mo follow-up period, while in the 22 patients without cirrhosis regression 3 patients developed HCC.

Unfortunately the clinical significance of the protective effect of an SVR on HCC development in HCV patients with cirrhosis is limited as the vast majority of HCV cirrhotics fail to achieve a SVR to IFN plus ribavirin therapy. In fact cirrhosis is one of the main factors associated with treatment failure to any regimen based on IFN, hence most of HCV cirrhotics even if treated remain at high risk of HCC. In this context it is important to understand the role played by other clinical and demographic factors in determining treatment outcome to PegIFN plus ribavirin and their interplay with the presence of cirrhosis<sup>[112,113]</sup>. Not all cirrhotics show reduced rates of SVR, since the presence of a treatment favorable HCV genotype, HCV-2 and in part HCV-3, or a protective SNP in the IL-28B coding region in HCV-1 and HCV-4 patients can lead to SVR rates in the 70% range<sup>[114-116]</sup>. IL-28B has been shown by several studies to be the strongest baseline predictor of treatment outcome; however its clinical utility in terms of individualized chemoprevention strategies is limited by its relatively low negative predictive power that should never lead to treatment deferral, especially considering the significant advantages obtained by an SVR in patients with advanced fibrosis/cirrhosis<sup>[117]</sup>.

Given that IFN also exerts several important indirect effects in the virus-infected liver that might result in tumor prevention, including immunostimulation and expression of HLA class 1 MC, and inhibition of mutagenic factor beta-UGF, three randomized controlled studies were designed to assess if a long term course of low dose PegIFN therapy could reduce the rate of liver related complications in patients with advanced fibrosis/cirrhosis who did not achieve an SVR to a full course of PegIFN plus ribavirin therapy<sup>[116-120]</sup>. Although the three studies are hardly comparable due to differences in the patients characteristics and in the assigned treatment regimens, still they unanimously failed to demonstrate any positive impact of PegIFN maintenance therapy on HCC incidence rates<sup>[121]</sup>. A recent extended analysis of the original HALT-C study, performed by Lok *et al.*<sup>[122]</sup> and focused on the development of HCC, has partially contradicted these findings as long-term PegIFN maintenance therapy was associated with reduced HCC rates in patients with pre-treatment cirrhosis. The cumulative incidence of HCC at 3, 5 and 7 years was 2.6%, 5.1% and 7.8% in the PegIFN group and 4.0%, 11.1% and 24.2% in the untreated group (log-rank test,  $P = 0.009$ ).

These results are hard to interpret and require caution before suggesting PegIFN maintenance therapy as an ef-

fective chemoprevention strategy in HCV cirrhotics; still they provide important clues and directions for future studies. Indeed, it shows patients enrolled in chemoprevention studies need to be stratified for risk factors at baseline; in this particular case enrolling patients with different disease severity stage might have precluded observation of a protective effect of low dose PegIFN on HCC development. Secondly it suggests that conducting studies on high risk rather than medium risk patients might provide more clinically meaningful data.

## HIV

Although a detailed discussion about the effect of antiviral therapy in HIV positive patients on HCC development is beyond the purpose of this study, convincing evidence has been provided that HCC incidence is rising amongst the HIV positive population receiving HAART, almost exclusively in patients with concomitant HCV or HBV infection. The main explanation behind these findings is probably the increased longevity obtained by effective antiviral treatment in this population of patients. An investigation of the Swiss HIV cohort assessed that latest CD4 $\beta$  cell count and CD4 $\beta$  cell count percentage were significantly associated with HCC, but no association between HAART use and HCC risk was detected<sup>[123]</sup>. Similarly, Sulkowski *et al.*<sup>[124]</sup> reported that HCC occurred in many patients despite the use of effective HAART for a median of more than 7 years.

Thus, antiretroviral therapy is unlikely to modify the risk of HCC in HCV-infected patients in whom the risk of cancer is driven by HCV-related cirrhosis and where antiretroviral therapy is also known to have some direct hepatotoxic effects which are worsened by co-infection with HBV or HCV, raising the possibility that HAART *per se* might hasten the progression to cirrhosis and hence HCC<sup>[125]</sup>. However the role of HAART on HCC development is controversial because its ability to preserve immune system functions could in theory provide a putatively more active anti-tumor response, since once HCC has developed, chronically low CD4+ and CD8+ lymphocyte counts may result in more rapid growth and spread of disease.

## CONCLUSION

HCC develops in the context of readily identifiable environmental risk factors, first of all HBV and HCV, a fact that in theory should enable for successful primary prophylaxis. There are solid treatment endpoints that allow hepatologists to determine the efficacy of an antiviral regimen and its ability to positively modify both the natural course of the disease as well as to reduce the risk of HCC development.

Unfortunately in patients with chronic HBV and HCV infection tumor prevention is an end point quite difficult to assess in patients with early, mild hepatitis whereas it can only partially be achieved in patients with established cirrhosis given they are at higher risk of liver cancer.

In these patients there is increasing need to improve diagnosis rate, ensure equal access to antiviral therapies and develop well tolerated therapies that will finally allow most, if not all, patients with viral hepatitis to benefit from effective antiviral treatment. In fact it is estimated that as few as 35% of patients with chronic HBV and only 25% of HCV patients are aware of their disease in developed countries, with this number obviously shrinking even more in developing countries<sup>[126]</sup>. Moreover in Europe and the United States, even if patients are diagnosed correctly only 1%-16% of HBV and HCV patients are estimated to receive treatment<sup>[127-129]</sup>.

This highlights that one of the key issues for therapies aimed at HCC chemoprevention is to broaden access to therapies by containing costs and increasing disease awareness, or eventually concentrate treatment in those more at risk of HCC development. Performing prospective studies where patients are stratified according to complex models of “genomic risk prediction” that incorporate various panels of specific SNPs, is undoubtedly a bold and possibly unreachable goal, but still it could lead to individualized chemoprevention strategies in the future, while reducing the number of patients needed to be enrolled into chemoprevention studies to assess efficacy of a treatment regimen. Until this is reached, secondary prevention through surveillance of risk populations aiming at early diagnosis is the only approach to improve treatment and survival of patients with HCC.

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