World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i9.1359

World J Gastroenterol 2013 March 7; 19(9): 1359-1371
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

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

Cristina Della Corte, Alessio Aghemo, Massimo Colombo

Cristina Della Corte, Alessio Aghemo, Massimo Colombo, AM Migliavacca Center for Liver Diseases, First Division of Gastroenterology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, 20122 Milan, Italy
Author contributions: Della Corte C, Aghemo A and Colombo M jointly contributed to this paper.
Correspondence to: Massimo Colombo, MD, AM Migliavacca Center for Liver Diseases, First Division of Gastroenterology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via F. Sforza 35, 20122 Milan, Italy. massimo.colombo@unimi.it
Telephone: +39-25-5035432 Fax: +39-25-0320410
Received: November 24, 2012 Revised: January 28, 2013
Accepted: February 5, 2013
Published online: March 7, 2013

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.

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

Della Corte C, Aghemo A, Colombo M. Individualized hepatocellular carcinoma risk: The challenges for designing successful chemoprevention strategies. *World J Gastroenterol* 2013; 19(9): 1359-1371 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i9/1359.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i9.1359

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[1]. 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[2].

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[3]. 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[4].

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[5]. 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[6-8].

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[9]. The presence of large cell change[10], irregular regeneration of hepatocytes and macroregenerative nodules have been evaluated as morphologic predictors of HCC in cirrhosis independently of baseline disease[10-14].

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[5]. 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%[15]. 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[16,17].

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[18]. 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[19-23]. 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[24]. 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 preS-S protein) with potential transforming properties[25].

In Europe, HBV-related HCC is associated with cirrhosis in the majority of patients[26,27], 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[28-30].

HCC risk may be modulated by viral load[31-35], 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[31,36-38].

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)[26,27,31,39] 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[40]. 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)[41].

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[42].

Male sex, positive family history and African origins are added risk factors for HCC development in HBV positive patients[28-30]. Genotype B of the HBV seems to be associated with lower rates of HCC development compared to genotype C of HBV[43-48], 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[49,50].

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[51] 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[52]. 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[53]. 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[54].

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[55]. HCV proteins have been shown to impact on cell signalling, transcriptional modulation, transformation, apoptosis, membrane rearrangements, vesicular trafficking and translational regulation[52]. 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[56,57]. 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[58]. 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[59].

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[60,61].

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[62]. 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[63], 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[64]. 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[65,66], but also increases conversion of pro-carcinogens to carcinogens through oxidation and metabolism of ethanol in the liver[67]. Acetaldehyde and oxygen free radicals deriving from ethanol metabolism may also directly induce cell damage by initiating peroxidation of membrane lipids, through oxidative stress[68].

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[69]. 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[70].

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^2 or above compared to men with a normal body mass index (18.5-24.9 kg/m^2)[71]. 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[72]. 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[73,74].

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[75]. 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[76-79].

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[80]. 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[81], 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[82].

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[83].

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[84].

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 *et al*[85]	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 *et al*[86]	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 *et al*[88]	CHB	1790	KIF1b	0.6	Confounding non-genetic HCC risk factors cannot be ruled out in multivariate analysis
	CHB-HCC	2317			
Chan *et al*[89]	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 *et al*[123]	HCC[1]	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[2]	86			
	Controls[3]	787			

[1]89% HBV or HCV viral infection; [2]76% HBV or HCV viral infection; [3]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[85] and isoform1 of the *DEPDC5* locus on chromosome, where deletion of the region containing DEPDC has been reported in malignant brain glioblastomas[86]. Also the MHC class Ⅱ locus presenting antigen to CD4 þ (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[87]. *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[88]. 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[89] (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[90]. 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[91], the promoter region of *MCM7* gene and the enhancer Ⅱ (Enh Ⅱ)[92], basal core promoter, and precore regions of HBV[93].

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*[94] 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[95].

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[96]. 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

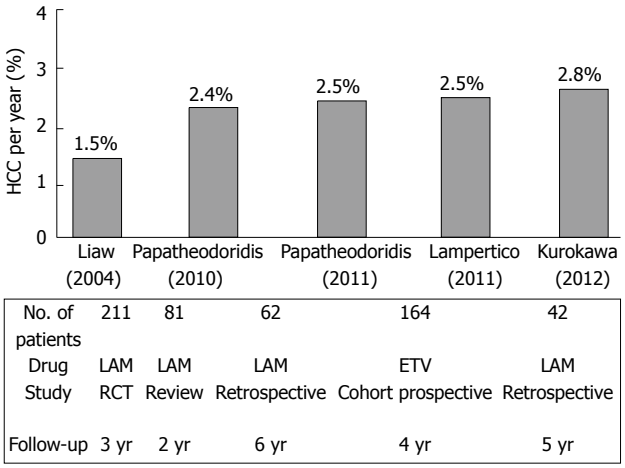

Figure 1 Hepatocellular carcinoma rates in nucleos(t)ide analogs-naive cirrhotic patients with long-term response. Several studies have shown that hepatitis B virus patients who achieve a virological response to lamivudine in some cases still develop hepatocellular carcinoma (HCC) as the only complication.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

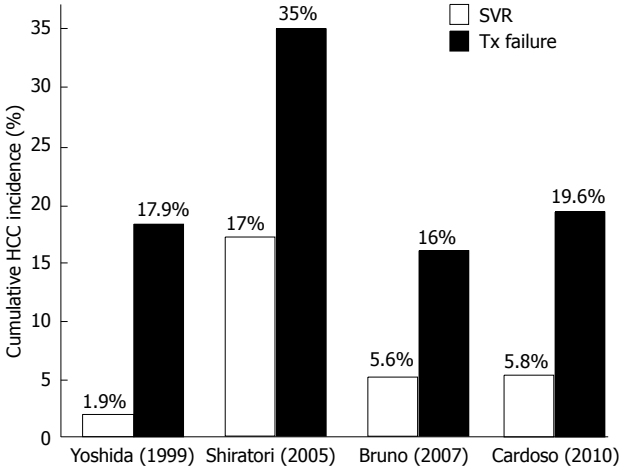

Figure 2 Cumulative incidence of hepatocellular carcinoma in patients with cirrhosis stratified by sustained virological response. Studies in Caucasian patients as well as in patients from Asia have repeatedly shown that a sustained virological response (SVR) following interferon-based therapies can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

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[97-101] (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[98]. 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[99]. 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[100]. 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 consequence 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[102-104].

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[9,105-108]. 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*[109] 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*[110] 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[111]. 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[112,113]. 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[114-116]. 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[117].

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[116-120]. 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[121]. A recent extended analysis of the original HALT-C study, performed by Lok *et al*[122] 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 effective 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 CD4þ cell count and CD4þ cell count percentage were significantly associated with HCC, but no association between HAART use and HCC risk was detected[123]. Similarly, Sulkowski *et al*[124] 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[125]. 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[126]. 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[127-129].

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.

ACKNOWLEDGMENTS

Financial disclosure: Alessio Aghemo, MD; Grant and research support: Roche, Gilead Sciences; Speaking and Teaching: Roche and Janssen; Travel support: BMS, Glaxo Smith-Kline, Bayer, Janssen and Roche; Financial disclosure: Massimo Colombo, MD; Grant and research support: Merck, Roche, BMS and Gilead Science; Advisory committees: Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex and Achillion; Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science and Vertex; Cristina della Corte, MD: nothing to disclose.

REFERENCES

1 IARC. Available from: URL: http: //www.dep.iarc.fr. Accessed November 1, 2011
2 **EASL-EORTC.** Clinical Practice Guidelines: Management of hepatocellular carcinoma European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. *J Hepatol* 2012; **56**: 908-943
3 **Fattovich G**, Stroffolini T, Zagni I and Donato F. Cirrhosis and hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S35-S50 [DOI: 10.1053/j.gast.2004.09.014]
4 **Friedman SL**. Liver fibrosis -- from bench to bedside. *J Hepatol* 2003; **38** Suppl 1: S38-S53 [PMID: 12591185]
5 **Simonetti RG**, Cammà C, Fiorello F, Politi F, D'Amico G, Pagliaro L. Hepatocellular carcinoma. A worldwide problem and the major risk factors. *Dig Dis Sci* 1991; **36**: 962-972 [PMID: 1649041]
6 **Bralet MP**, Régimbeau JM, Pineau P, Dubois S, Loas G, Degos F, Valla D, Belghiti J, Degott C, Terris B. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. *Hepatology* 2000; **32**: 200-204 [PMID: 10915724]
7 **Chiesa R**, Donato F, Tagger A, Favret M, Ribero ML, Nardi G, Gelatti U, Bucella E, Tomasi E, Portolani N, Bonetti M, Bettini L, Pelizzari G, Salmi A, Savio A, Garatti M, Callea F. Etiology of hepatocellular carcinoma in Italian patients with and without cirrhosis. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 213-216 [PMID: 10698484]
8 **Grando-Lemaire V**, Guettier C, Chevret S, Beaugrand M, Trinchet JC. Hepatocellular carcinoma without cirrhosis in the West: epidemiological factors and histopathology of the non-tumorous liver. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. *J Hepatol* 1999; **31**: 508-513 [PMID: 10488711]
9 **Yoshida H**, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999; **131**: 174-181 [PMID: 10428733 DOI: 10.1186/1471-230X-12-139]
10 **Degos F**, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M, Chevret S. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. *Gut* 2000; **47**: 131-136 [PMID: 10861275]
11 **Borzio M**, Bruno S, Roncalli M, Mels GC, Ramella G, Borzio F, Leandro G, Servida E, Podda M. Liver cell dysplasia is a major risk factor for hepatocellular carcinoma in cirrhosis: a prospective study. *Gastroenterology* 1995; **108**: 812-817 [PMID: 7875483]
12 **Ganne-Carrié N**, Chastang C, Chapel F, Munz C, Pateron D, Sibony M, Dény P, Trinchet JC, Callard P, Guettier C, Beaugrand M. Predictive score for the development of hepatocellular carcinoma and additional value of liver large cell dysplasia in Western patients with cirrhosis. *Hepatology* 1996; **23**: 1112-1118 [PMID: 8621142]
13 **Shibata M**, Morizane T, Uchida T, Yamagami T, Onozuka Y, Nakano M, Mitamura K, Ueno Y. Irregular regeneration of hepatocytes and risk of hepatocellular carcinoma in chronic hepatitis and cirrhosis with hepatitis-C-virus infection. *Lancet* 1998; **351**: 1773-1777 [PMID: 9635950]
14 **Borzio M**, Fargion S, Borzio F, Fracanzani AL, Croce AM, Stroffolini T, Oldani S, Cotichini R, Roncalli M. Impact of large regenerative, low grade and high grade dysplastic nodules in hepatocellular carcinoma development. *J Hepatol* 2003; **39**: 208-214 [PMID: 12873817]
15 **Elmberg M**, Hultcrantz R, Ekbom A, Brandt L, Olsson S, Olsson R, Lindgren S, Lööf L, Stål P, Wallerstedt S, Almer S, Sandberg-Gertzén H, Askling J. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* 2003; **125**: 1733-1741 [PMID: 14724826]
16 **Bolondi L**, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, Gramantieri L, Zanetti M, Sherman M. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 2001; **48**: 251-259 [PMID: 11156649]
17 **Tsai JF**, Jeng JE, Ho MS, Chang WY, Hsieh MY, Lin ZY, Tsai JH. Effect of hepatitis C and B virus infection on risk of hepatocellular carcinoma: a prospective study. *Br J Cancer* 1997; **76**: 968-974 [PMID: 9328161]
18 **Fattovich G**, Brollo L, Giustina G, Noventa F, Pontisso P, Alberti A, Realdi G, Ruol A. Natural history and prognostic factors for chronic hepatitis type B. *Gut* 1991; **32**: 294-298 [PMID: 2013423]
19 **Pollicino T**, Squadrito G, Cerenzia G, Cacciola I, Raffa G,

Craxi A, Farinati F, Missale G, Smedile A, Tiribelli C, Villa E, Raimondo G. Hepatitis B virus maintains its pro-oncogenic properties in the case of occult HBV infection. *Gastroenterology* 2004; **126**: 102-110 [PMID: 14699492]
20 **Hilleman MR**. Overview of the pathogenesis, prophylaxis and therapeusis of viral hepatitis B, with focus on reduction to practical applications. *Vaccine* 2001; **19**: 1837-1848 [PMID: 11228353]
21 **Chisari FV**. Rous-Whipple Award Lecture. Viruses, immunity, and cancer: lessons from hepatitis B. *Am J Pathol* 2000; **156**: 1117-1132 [PMID: 10751335]
22 **Chen PJ**, Chen DS. Hepatitis B virus infection and hepatocellular carcinoma: molecular genetics and clinical perspectives. *Semin Liver Dis* 1999; **19**: 253-262 [PMID: 10518305]
23 **Buendia MA**, Pineau P. The complex role of hepatitis B virus in human hepatocarcinogenesis. In: Barbanti-Brodano G, editor. DNA tumor viruses: oncogenic mechanisms. New York: Plenum, 1995: 171-193
24 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430 [PMID: 11592607]
25 **Bréchot C**, Gozuacik D, Murakami Y, Paterlini-Bréchot P. Molecular bases for the development of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). *Semin Cancer Biol* 2000; **10**: 211-231 [PMID: 10936070]
26 **Manno M**, Cammà C, Schepis F, Bassi F, Gelmini R, Giannini F, Miselli F, Grottola A, Ferretti I, Vecchi C, De Palma M, Villa E. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. *Gastroenterology* 2004; **127**: 756-763 [PMID: 15362032]
27 **Hsu YS**, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002; **35**: 1522-1527 [PMID: 12029639]
28 **Yu MW**, Chang HC, Liaw YF, Lin SM, Lee SD, Liu CJ, Chen PJ, Hsiao TJ, Lee PH, Chen CJ. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. *J Natl Cancer Inst* 2000; **92**: 1159-1164 [PMID: 10904089]
29 **Kew MC**, Marcus R, Geddes EW. Some characteristics of Mozambican Shangaans with primary hepatocellular cancer. *S Afr Med J* 1977; **51**: 306-309 [PMID: 66757]
30 **Kew MC**, Macerollo P. Effect of age on the etiologic role of the hepatitis B virus in hepatocellular carcinoma in blacks. *Gastroenterology* 1988; **94**: 439-442 [PMID: 2446950]
31 **Bellentani S**, Miglioli L, Croce L, Masutti F, Castiglione A. Natural history of HBV infection: a nine years follow-up of the Dionysius cohort. *J Hepatol* 2002; **36**: 228S [DOI: 10.1016/S0168-8278(02)80819-4]
32 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73 [PMID: 16391218]
33 **Yuen MF**, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: The effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. *Hepatology* 2001; **34**: 139-145 [PMID: 11431745]
34 **Yang HI**, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS, Chen CJ. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002; **347**: 168-174 [PMID: 12124405]
35 **Chen G**, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006; **101**: 1797-1803 [PMID: 16817842]
36 **Huo TI**, Wu JC, Lee PC, Chau GY, Lui WY, Tsay SH, Ting LT, Chang FY, Lee SD. Sero-clearance of hepatitis B surface antigen in chronic carriers does not necessarily imply a good prognosis. *Hepatology* 1998; **28**: 231-236 [PMID: 9657117]
37 **Lin SM**, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* 1999; **29**: 971-975 [PMID: 10051505]
38 **Niederau C**, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Häussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996; **334**: 1422-1427 [PMID: 8618580]
39 **de Franchis R**, Meucci G, Vecchi M, Tatarella M, Colombo M, Del Ninno E, Rumi MG, Donato MF, Ronchi G. The natural history of asymptomatic hepatitis B surface antigen carriers. *Ann Intern Med* 1993; **118**: 191-194 [PMID: 8417636]
40 **Yuen MF**, Wong DK, Fung J, Ip P, But D, Hung I, Lau K, Yuen JC, Lai CL. HBsAg Seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. *Gastroenterology* 2008; **135**: 1192-1199 [PMID: 18722377]
41 **EASL**. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; **57**: 167-185 [PMID: 22436845]
42 **Fattovich G**, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; **48**: 335-352 [PMID: 18096267]
43 **Chan HL**, Hui AY, Wong ML, Tse AM, Hung LC, Wong VW, Sung JJ. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. *Gut* 2004; **53**: 1494-1498 [PMID: 15361502]
44 **Chu CJ**, Hussain M, Lok AS. Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus genotype C. *Gastroenterology* 2002; **122**: 1756-1762 [PMID: 12055581]
45 **Kao JH**, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. *Gastroenterology* 2000; **118**: 554-559 [PMID: 10702206]
46 **Chu CM**, Liaw YF. Genotype C hepatitis B virus infection is associated with a higher risk of reactivation of hepatitis B and progression to cirrhosis than genotype B: a longitudinal study of hepatitis B e antigen-positive patients with normal aminotransferase levels at baseline. *J Hepatol* 2005; **43**: 411-417 [PMID: 16006001]
47 **Sumi H**, Yokosuka O, Seki N, Arai M, Imazeki F, Kurihara T, Kanda T, Fukai K, Kato M, Saisho H. Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. *Hepatology* 2003; **37**: 19-26 [PMID: 12500184]
48 **Yu MW**, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005; **97**: 265-272 [PMID: 15713961]
49 **Sánchez-Tapias JM**, Costa J, Mas A, Bruguera M, Rodés J. Influence of hepatitis B virus genotype on the long-term outcome of chronic hepatitis B in western patients. *Gastroenterology* 2002; **123**: 1848-1856 [PMID: 12454842]
50 **Erhardt A**, Blondin D, Hauck K, Sagir A, Kohnle T, Heintges T, Häussinger D. Response to interferon alfa is hepatitis B virus genotype dependent: genotype A is more sensitive to interferon than genotype D. *Gut* 2005; **54**: 1009-1013 [PMID: 15951551]
51 **Levrero M**. Viral hepatitis and liver cancer: the case of hepatitis C. *Oncogene* 2006; **25**: 3834-3847 [PMID: 16799625]
52 **McGivern DR**, Lemon SM. Virus-specific mechanisms of carcinogenesis in hepatitis C virus associated liver cancer. *Oncogene* 2011; **30**: 1969-1983 [PMID: 21258404]

53 **Teufel A**, Weinmann A, Centner C, Piendl A, Lohse AW, Galle PR, Kanzler S. Hepatocellular carcinoma in patients with autoimmune hepatitis. *World J Gastroenterol* 2009; **15**: 578-582 [PMID: 19195059]

54 **Raimondi S**, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142-1154 [PMID: 19395111]

55 **Houghton M**. The long and winding road leading to the identification of the hepatitis C virus. *J Hepatol* 2009; **51**: 939-948 [PMID: 19781804]

56 **Moriya K**, Fujie H, Shintani Y, Yotsuyanagi H, Tsutsumi T, Ishibashi K, Matsuura Y, Kimura S, Miyamura T, Koike K. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nat Med* 1998; **4**: 1065-1067 [PMID: 9734402]

57 **Naas T**, Ghorbani M, Alvarez-Maya I, Lapner M, Kothary R, De Repentigny Y, Gomes S, Babiuk L, Giulivi A, Soare C, Azizi A, Diaz-Mitoma F. Characterization of liver histopathology in a transgenic mouse model expressing genotype 1a hepatitis C virus core and envelope proteins 1 and 2. *J Gen Virol* 2005; **86**: 2185-2196 [PMID: 16033966]

58 **Tardif KD**, Mori K, Siddiqui A. Hepatitis C virus subgenomic replicons induce endoplasmic reticulum stress activating an intracellular signaling pathway. *J Virol* 2002; **76**: 7453-7459 [PMID: 12097557]

59 **Salmon-Ceron D**, Rosenthal E, Lewden C, Bouteloup V, May T, Burty C, Bonnet F, Costagliola D, Jougla E, Semaille C, Morlat P, Cacoub P, Chêne G. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalité 2005 study. *J Hepatol* 2009; **50**: 736-745 [PMID: 19231018]

60 **Puoti M**, Bruno R, Soriano V, Donato F, Gaeta GB, Quinzan GP, Precone D, Gelatti U, Asensi V, Vaccher E. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS* 2004; **18**: 2285-2293 [PMID: 15577541]

61 **Rosenthal E**, Poirée M, Pradier C, Perronne C, Salmon-Ceron D, Geffray L, Myers RP, Morlat P, Pialoux G, Pol S, Cacoub P. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS* 2003; **17**: 1803-1809 [PMID: 12891066]

62 **Allen NE**, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, Green J. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst* 2009; **101**: 296-305 [PMID: 19244173]

63 **Schöniger-Hekele M**, Müller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Austria: aetiological and clinical characteristics at presentation. *Eur J Gastroenterol Hepatol* 2000; **12**: 941-948 [PMID: 10958223]

64 **El-Serag HB**, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. *Arch Intern Med* 2000; **160**: 3227-3230 [PMID: 11088082]

65 **Hassan MM**, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002; **36**: 1206-1213 [PMID: 12395331]

66 **Batey RG**, Burns T, Benson RJ, Byth K. Alcohol consumption and the risk of cirrhosis. *Med J Aust* 1992; **156**: 413-416

67 **Lieber CS**, Seitz HK, Garro AJ, Worner TM. Alcohol-related diseases and carcinogenesis. *Cancer Res* 1979; **39**: 2863-2886 [PMID: 221110]

68 **Lieber CS**. Mechanism of ethanol induced hepatic injury. *Pharmacol Ther* 1990; **46**: 1-41 [PMID: 2181486]

69 **Davila JA**, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005; **54**: 533-539 [PMID: 15753540]

70 **Polesel J**, Zucchetto A, Montella M, Dal Maso L, Crispo A, La Vecchia C, Serraino D, Franceschi S, Talamini R. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. *Ann Oncol* 2009; **20**: 353-357 [PMID: 18723550]

71 **Calle EE**, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; **348**: 1625-1638 [PMID: 12711737]

72 **Larsson SC**, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. *Br J Cancer* 2007; **97**: 1005-1008 [PMID: 17700568]

73 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152]

74 **Caldwell SH**, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999; **29**: 664-669 [PMID: 10051466]

75 **Ascha MS**, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604]

76 **Sangiovanni A**, Del Ninno E, Fasani P, De Fazio C, Ronchi G, Romeo R, Morabito A, De Franchis R, Colombo M. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology* 2004; **126**: 1005-1014 [PMID: 15057740]

77 **Benvegnù L**, Chemello L, Noventa F, Fattovich G, Pontisso P, Alberti A. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. *Cancer* 1998; **83**: 901-909 [PMID: 9731893]

78 **Zaman SN**, Melia WM, Johnson RD, Portmann BC, Johnson PJ, Williams R. Risk factors in development of hepatocellular carcinoma in cirrhosis: prospective study of 613 patients. *Lancet* 1985; **1**: 1357-1360 [PMID: 2861313]

79 **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**: 1485-1491 [PMID: 19224838]

80 **El-Serag HB**, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132**: 2557-2576 [PMID: 17570226]

81 **Yuan JM**, Ross RK, Stanczyk FZ, Govindarajan S, Gao YT, Henderson BE, Yu MC. A cohort study of serum testosterone and hepatocellular carcinoma in Shanghai, China. *Int J Cancer* 1995; **63**: 491-493 [PMID: 7591255]

82 **White DL**, Tavakoli-Tabasi S, Kuzniarek J, Pascua R, Ramsey DJ, El-Serag HB. Higher serum testosterone is associated with increased risk of advanced hepatitis C-related liver disease in males. *Hepatology* 2012; **55**: 759-768 [PMID: 21858849]

83 **Keng VW**, Largaespada DA, Villanueva A. Why men are at higher risk for hepatocellular carcinoma? *J Hepatol* 2012; **57**: 453-454 [PMID: 22425699]

84 **Pearson TA**, Manolio TA. How to interpret a genome-wide association study. *JAMA* 2008; **299**: 1335-1344 [PMID: 18349094]

85 **Kumar V**, Kato N, Urabe Y, Takahashi A, Muroyama R, Hosono N, Otsuka M, Tateishi R, Omata M, Nakagawa H, Koike K, Kamatani N, Kubo M, Nakamura Y, Matsuda K. Genome-wide association study identifies a susceptibility locus for HCV-induced hepatocellular carcinoma. *Nat Genet* 2011; **43**: 455-458 [PMID: 21499248 DOI: 10.1038/ng.809]

86 **Miki D**, Ochi H, Hayes CN, Abe H, Yoshima T, Aikata H, Ikeda K, Kumada H, Toyota J, Morizono T, Tsunoda T, Kubo M, Nakamura Y, Kamatani N, Chayama K. Variation in the DEPDC5 locus is associated with progression to hepatocellular carcinoma in chronic hepatitis C virus carriers. *Nat Genet* 2011; **43**: 797-800 [PMID: 21725309]

87 **Clifford RJ**, Zhang J, Meerzaman DM, Lyu MS, Hu Y, Cultraro CM, Finney RP, Kelley JM, Efroni S, Greenblum SI,

Nguyen CV, Rowe WL, Sharma S, Wu G, Yan C, Zhang H, Chung YH, Kim JA, Park NH, Song IH, Buetow KH. Genetic variations at loci involved in the immune response are risk factors for hepatocellular carcinoma. *Hepatology* 2010; **52**: 2034-2043 [PMID: 21105107]

88 **Zhang H**, Zhai Y, Hu Z, Wu C, Qian J, Jia W, Ma F, Huang W, Yu L, Yue W, Wang Z, Li P, Zhang Y, Liang R, Wei Z, Cui Y, Xie W, Cai M, Yu X, Yuan Y, Xia X, Zhang X, Yang H, Qiu W, Yang J, Gong F, Chen M, Shen H, Lin D, Zeng YX, He F, Zhou G. Genome-wide association study identifies 1p36.22 as a new susceptibility locus for hepatocellular carcinoma in chronic hepatitis B virus carriers. *Nat Genet* 2010; **42**: 755-758 [PMID: 20676096 DOI: 10.1038/ng.638]

89 **Chan KY**, Wong CM, Kwan JS, Lee JM, Cheung KW, Yuen MF, Lai CL, Poon RT, Sham PC, Ng IO. Genome-wide association study of hepatocellular carcinoma in Southern Chinese patients with chronic hepatitis B virus infection. *PLoS One* 2011; **6**: e28798 [PMID: 22174901]

90 **Abu Dayyeh BK**, Yang M, Fuchs BC, Karl DL, Yamada S, Sninsky JJ, O'Brien TR, Dienstag JL, Tanabe KK, Chung RT. A functional polymorphism in the epidermal growth factor gene is associated with risk for hepatocellular carcinoma. *Gastroenterology* 2011; **141**: 141-149 [PMID: 21440548]

91 **Gu X**, Qi P, Zhou F, Ji Q, Wang H, Dou T, Zhao Y, Gao C. +49G & gt; A polymorphism in the cytotoxic T-lymphocyte antigen-4 gene increases susceptibility to hepatitis B-related hepatocellular carcinoma in a male Chinese population. *Hum Immunol* 2010; **71**: 83-87 [PMID: 19778566 DOI: 10.1016/j.humimm.2009.09.353]

92 **Liu Y**, Zhang Y, Wen J, Liu L, Zhai X, Liu J, Pan S, Chen J, Shen H, Hu Z. A genetic variant in the promoter region of miR-106b-25 cluster and risk of HBV infection and hepatocellular carcinoma. *PLoS One* 2012; **7**: e32230 [PMID: 22393390]

93 **Chou YC**, Yu MW, Wu CF, Yang SY, Lin CL, Liu CJ, Shih WL, Chen PJ, Liaw YF, Chen CJ. Temporal relationship between hepatitis B virus enhancer II/basal core promoter sequence variation and risk of hepatocellular carcinoma. *Gut* 2008; **57**: 91-97 [PMID: 17502344]

94 **Fujimoto A**, Totoki Y, Abe T, Boroevich KA, Hosoda F, Nguyen HH, Aoki M, Hosono N, Kubo M, Miya F, Arai Y, Takahashi H, Shirakihara T, Nagasaki M, Shibuya T, Nakano K, Watanabe-Makino K, Tanaka H, Nakamura H, Kusuda J, Ojima H, Shimada K, Okusaka T, Ueno M, Shigekawa Y, Kawakami Y, Arihiro K, Ohdan H, Gotoh K, Ishikawa O, Ariizumi S, Yamamoto M, Yamada T, Chayama K, Kosuge T, Yamaue H, Kamatani N, Miyano S, Nakagama H, Nakamura Y, Tsunoda T, Shibata T, Nakagawa H. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. *Nat Genet* 2012; **44**: 760-764 [PMID: 22634756]

95 **Hudson TJ**, Anderson W, Artez A, Barker AD, Bell C, Bernabé RR, Bhan MK, Calvo F, Eerola I, Gerhard DS, Guttmacher A, Guyer M, Hemsley FM, Jennings JL, Kerr D, Klatt P, Kolar P, Kusada J, Lane DP, Laplace F, Youyong L, Nettekoven G, Ozenberger B, Peterson J, Rao TS, Remacle J, Schafer AJ, Shibata T, Stratton MR, Vockley JG, Watanabe K, Yang H, Yuen MM, Knoppers BM, Bobrow M, Cambon-Thomsen A, Dressler LG, Dyke SO, Joly Y, Kato K, Kennedy KL, Nicolás P, Parker MJ, Rial-Sebbag E, Romeo-Casabona CM, Shaw KM, Wallace S, Wiesner GL, Zeps N, Lichter P, Biankin AV, Chabannon C, Chin L, Clément B, de Alava E, Degos F, Ferguson ML, Geary P, Hayes DN, Hudson TJ, Johns AL, Kasprzyk A, Nakagawa H, Penny R, Piris MA, Sarin R, Scarpa A, Shibata T, van de Vijver M, Futreal PA, Aburatani H, Bayés M, Botwell DD, Campbell PJ, Estivill X, Gerhard DS, Grimmond SM, Gut I, Hirst M, López-Otín C, Majumder P, Marra M, McPherson JD, Nakagawa H, Ning Z, Puente XS, Ruan Y, Shibata T, Stratton MR, Stunnenberg HG, Swerdlow H, Velculescu VE, Wilson RK, Xue HH, Yang L, Spellman PT, Bader GD, Boutros PC, Campbell PJ, Flicek P, Getz G, Guigó R, Guo G, Haussler D, Heath S, Hubbard TJ, Jiang T, Jones SM, Li Q, López-Bigas N, Luo R, Muthuswamy L, Ouellette BF, Pearson JV, Puente XS, Quesada V, Raphael BJ, Sander C, Shibata T, Speed TP, Stein LD, Stuart JM, Teague JW, Totoki Y, Tsunoda T, Valencia A, Wheeler DA, Wu H, Zhao S, Zhou G, Stein LD, Guigó R, Hubbard TJ, Joly Y, Jones SM, Kasprzyk A, Lathrop M, López-Bigas N, Ouellette BF, Spellman PT, Teague JW, Thomas G, Valencia A, Yoshida T, Kennedy KL, Axton M, Dyke SO, Futreal PA, Gerhard DS, Gunter C, Guyer M, Hudson TJ, McPherson JD, Miller LJ, Ozenberger B, Shaw KM, Kasprzyk A, Stein LD, Zhang J, Haider SA, Wang J, Yung CK, Cros A, Liang Y, Gnaneshan S, Guberman J, Hsu J, Bobrow M, Chalmers DR, Hasel KW, Joly Y, Kaan TS, Kennedy KL, Knoppers BM, Lowrance WW, Masui T, Nicolás P, Rial-Sebbag E, Rodriguez LL, Vergely C, Yoshida T, Grimmond SM, Biankin AV, Bowtell DD, Cloonan N, deFazio A, Eshleman JR, Etemadmoghadam D, Gardiner BB, Kench JG, Scarpa A, Sutherland RL, Tempero MA, Waddell NJ, Wilson PJ, McPherson JD, Gallinger S, Tsao MS, Shaw PA, Petersen GM, Mukhopadhyay D, Chin L, DePinho RA, Thayer S, Muthuswamy L, Shazand K, Beck T, Sam M, Timms L, Ballin V, Lu Y, Ji J, Zhang X, Chen F, Hu X, Zhou G, Yang Q, Tian G, Zhang L, Xing X, Li X, Zhu Z, Yu Y, Yu J, Yang H, Lathrop M, Tost J, Brennan P, Holcatova I, Zaridze D, Brazma A, Egevard L, Prokhortchouk E, Banks RE, Uhlén M, Cambon-Thomsen A, Viksna J, Ponten F, Skryabin K, Stratton MR, Futreal PA, Birney E, Borg A, Børresen-Dale AL, Caldas C, Foekens JA, Martin S, Reis-Filho JS, Richardson AL, Sotiriou C, Stunnenberg HG, Thoms G, van de Vijver M, van't Veer L, Calvo F, Birnbaum D, Blanche H, Boucher P, Boyault S, Chabannon C, Gut I, Masson-Jacquemier JD, Lathrop M, Pauporté I, Pivot X, Vincent-Salomon A, Tabone E, Theillet C, Thomas G, Tost J, Treilleux I, Calvo F, Bioulac-Sage P, Clément B, Decaens T, Degos F, Franco D, Gut I, Gut M, Heath S, Lathrop M, Samuel D, Thomas G, Zucman-Rossi J, Lichter P, Eils R, Brors B, Korbel JO, Korshunov A, Landgraf P, Lehrach H, Pfister S, Radlwimmer B, Reifenberger G, Taylor MD, von Kalle C, Majumder PP, Sarin R, Rao TS, Bhan MK, Scarpa A, Pederzoli P, Lawlor RA, Delledonne M, Bardelli A, Biankin AV, Grimmond SM, Gress T, Klimstra D, Zamboni G, Shibata T, Nakamura Y, Nakagawa H, Kusada J, Tsunoda T, Miyano S, Aburatani H, Kato K, Fujimoto A, Yoshida T, Campo E, López-Otín C, Estivill X, Guigó R, de Sanjosé S, Piris MA, Montserrat E, González-Díaz M, Puente XS, Jares P, Valencia A, Himmelbauer H, Quesada V, Bea S, Stratton MR, Futreal PA, Campbell PJ, Vincent-Salomon A, Richardson AL, Reis-Filho JS, van de Vijver M, Thomas G, Masson-Jacquemier JD, Aparicio S, Borg A, Børresen-Dale AL, Caldas C, Foekens JA, Stunnenberg HG, van't Veer L, Easton DF, Spellman PT, Martin S, Barker AD, Chin L, Collins FS, Compton CC, Ferguson ML, Gerhard DS, Getz G, Gunter C, Guttmacher A, Guyer M, Hayes DN, Lander ES, Ozenberger B, Penny R, Peterson J, Sander C, Shaw KM, Speed TP, Spellman PT, Vockley JG, Wheeler DA, Wilson RK, Hudson TJ, Chin L, Knoppers BM, Lander ES, Lichter P, Stein LD, Stratton MR, Anderson W, Barker AD, Bell C, Bobrow M, Burke W, Collins FS, Compton CC, DePinho RA, Easton DF, Futreal PA, Gerhard DS, Green AR, Guyer M, Hamilton SR, Hubbard TJ, Kallioniemi OP, Kennedy KL, Ley TJ, Liu ET, Lu Y, Majumder P, Marra M, Ozenberger B, Peterson J, Schafer AJ, Spellman PT, Stunnenberg HG, Wainwright BJ, Wilson RK, Yang H. International network of cancer genome projects. *Nature* 2010; **464**: 993-998 [PMID: 20393554]

96 **Aghemo A**, Lampertico P, Colombo M. Assessing long-term treatment efficacy in chronic hepatitis B and C: between evidence and common sense. *J Hepatol* 2012; **57**: 1326-1335 [PMID: 22750749]

97 **Liaw YF**, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351**: 1521-1531 [PMID: 15470215]

98 **Papatheodoridis GV**, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol* 2010; **53**: 348-356 [PMID: 20483498]

99 **Papatheodoridis GV**, Manolakopoulos S, Touloumi G, Vourli G, Raptopoulou-Gigi M, Vafiadis-Zoumbouli I, Vasiliadis T, Mimidis K, Gogos C, Ketikoglou I, Manesis EK. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut* 2011; **60**: 1109-1116 [PMID: 21270118 DOI: 10.1136/gut.2010.221846]

100 **Lampertico P**, Viganò M, Soffredini R, Facchetti F, Minola E, Fracassetti O, Suter F, Zaltron S, Vavassori A, Carosi G, Angeli E, Gubertini GA, Magni CF, Testa A, Antonucci G, Vinci M, Pinzello G, Fatta E, Fargion S, Del Poggio P, Coco B, Brunetto MR, Andreoletti M, Colli A, Fasano M, Santantonio T, Colloredo G, Pasulo L, Fagiuoli S, Colombo AE, Bellati GA, Fumagalli Maldini F, Milanese M, Pozzi M, Terreni NM, Spinzi G, Quagliuolo M, Lunghi G, Colombo M. Entecavir monotherapy for nuc-naive chronic hepatitis B patients from field practice: high efficacy and favorable safety profile over 3 years. *Hepatology* 2011; **54** Suppl 1: 1043A. Abstract 1436

101 **Kurokawa M**, Hiramatsu N, Oze T, Yakushijin T, Miyazaki M, Hosui A, Miyagi T, Yoshida Y, Ishida H, Tatsumi T, Kiso S, Kanto T, Kasahara A, Iio S, Doi Y, Yamada A, Oshita M, Kaneko A, Mochizuki K, Hagiwara H, Mita E, Ito T, Inui Y, Katayama K, Yoshihara H, Imai Y, Hayashi E, Hayashi N, Takehara T. Long-term effect of lamivudine treatment on the incidence of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Gastroenterol* 2012; **47**: 577-585 [PMID: 22231575]

102 **Koga H**, Ide T, Oho K, Kuwahara R, Hino T, Ogata K, Hisamochi A, Tanaka K, Kumashiro R, Toyonaga A, Sata M. Lamivudine treatment-related morphological changes of esophageal varices in patients with liver cirrhosis. *Hepatol Res* 2007; **37**: 503-509 [PMID: 17539992]

103 **Iavarone M**, Lampertico P, Vigano M, Primignani M, de Franchis R, Colombo M. Six years of on demand LAM ADV combination therapy significantly reduces the development and progression of esophageal varices in patients with HBeAg-negative cirrhosis. *J Hepatol* 2007; **39**: A20

104 **Manolakopoulos S**, Triantos C, Theodoropoulos J, Vlachogiannakos J, Kougioumtzan A, Papatheodoridis G, Tzourmakliotis D, Karamanolis D, Burroughs AK, Archimandritis A, Raptis S, Avgerinos A. Antiviral therapy reduces portal pressure in patients with cirrhosis due to HBeAg-negative chronic hepatitis B and significant portal hypertension. *J Hepatol* 2009; **51**: 468-474 [PMID: 19616339]

105 **Yoshida H**, Arakawa Y, Sata M, Nishiguchi S, Yano M, Fujiyama S, Yamada G, Yokosuka O, Shiratori Y, Omata M. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. *Gastroenterology* 2002; **123**: 483-491 [PMID: 12145802]

106 **Fattovich G**, Giustina G, Degos F, Diodati G, Tremolada F, Nevens F, Almasio P, Solinas A, Brouwer JT, Thomas H, Realdi G, Corrocher R, Schalm SW. Effectiveness of interferon alfa on incidence of hepatocellular carcinoma and decompensation in cirrhosis type C. European Concerted Action on Viral Hepatitis (EUROHEP). *J Hepatol* 1997; **27**: 201-205 [PMID: 9252096 DOI: 10.1016/S0168-8278(97)80302-9]

107 **Yu ML**, Lin SM, Chuang WL, Dai CY, Wang JH, Lu SN, Sheen IS, Chang WY, Lee CM, Liaw YF. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. *Antivir Ther* 2006; **11**: 985-994 [PMID: 17302368]

108 **Shiratori Y**, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, Arakawa Y, Hashimoto E, Hirota K, Yoshida H, Ohashi Y, Omata M. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med* 2005; **142**: 105-114 [PMID: 15657158]

109 **Bruno S**, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, Ascione A, Santantonio T, Piccinino F, Andreone P, Mangia A, Gaeta GB, Persico M, Fagiuoli S, Almasio PL. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007; **45**: 579-587 [PMID: 17326216]

110 **Cardoso AC**, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, Boyer N, Asselah T, Martinot-Peignoux M, Maylin S, Carvalho-Filho RJ, Valla D, Bedossa P, Marcellin P. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol* 2010; **52**: 652-657 [PMID: 20346533]

111 **Mallet V**, Gilgenkrantz H, Serpaggi J, Verkarre V, Vallet-Pichard A, Fontaine H, Pol S. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. *Ann Intern Med* 2008; **149**: 399-403 [PMID: 18794559]

112 **Kau A**, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol* 2008; **49**: 634-651 [PMID: 18715665]

113 **Aghemo A**, Rumi MG, Monico S, Prati GM, D'Ambrosio R, Donato MF, Colombo M. The pattern of pegylated interferon-alpha2b and ribavirin treatment failure in cirrhotic patients depends on hepatitis C virus genotype. *Antivir Ther* 2009; **14**: 577-584 [PMID: 19578243]

114 **Tanaka Y**, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; **41**: 1105-1109 [PMID: 19749757]

115 **Thompson AJ**, Fellay J, Patel K, Tillmann HL, Naggie S, Ge D, Urban TJ, Shianna KV, Muir AJ, Fried MW, Afdhal NH, Goldstein DB, McHutchison JG. Variants in the ITPA gene protect against ribavirin-induced hemolytic anemia and decrease the need for ribavirin dose reduction. *Gastroenterology* 2010; **139**: 1181-1189 [PMID: 20547162]

116 **De Nicola S**, Aghemo A, Rumi MG, Galmozzi E, Valenti L, Soffredini R, De Francesco R, Prati GM, D'Ambrosio R, Cheroni C, Donato MF, Colombo M. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. *Hepatology* 2012; **55**: 336-342 [PMID: 21932415]

117 **Thompson AJ**, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, Urban T, Afdhal NH, Jacobson IM, Esteban R, Poordad F, Lawitz EJ, McCone J, Shiffman ML, Galler GW, Lee WM, Reindollar R, King JW, Kwo PY, Ghalib RH, Freilich B, Nyberg LM, Zeuzem S, Poynard T, Vock DM, Pieper KS, Patel K, Tillmann HL, Noviello S, Koury K, Pedicone LD, Brass CA, Albrecht JK, Goldstein DB, McHutchison JG. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 2010; **139**: 120-129.e18 [PMID: 20399780]

118 **Di Bisceglie AM**, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, Lee WM, Lok AS, Bonkovsky HL, Morgan TR, Ghany MG, Morishima C, Snow KK, Dienstag

JL. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008; **359**: 2429-2441 [PMID: 19052125 DOI: 10.1056/NEJMoa0707615]

119 **Bruix J**, Poynard T, Colombo M, Schiff E, Burak K, Heathcote EJ, Berg T, Poo JL, Mello CB, Guenther R, Niederau C, Terg R, Bedossa P, Boparai N, Griffel LH, Burroughs M, Brass CA, Albrecht JK. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. *Gastroenterology* 2011; **140**: 1990-1999 [PMID: 21419770]

120 **Afdhal N**, Levine R, Brown R. Colchicine versus peginterferon alfa 2b long-term therapy: results of the 4 year COPILOT trial (oral presentation). Proceedings of 43rd Annual Meeting of the European Association for the Study of the Liver; 2008 Apr 23-27; Milan, Italy

121 **Aghemo A**, Colombo M. Peginterferon maintenance therapy in patients with advanced hepatitis C to prevent hepatocellular carcinoma: the plot thickens. *J Hepatol* 2012; **56**: 276-278 [PMID: 21782763 DOI: 10.1016/j.jhep.2011.05.034]

122 **Lok AS**, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, Everson GT, Lindsay KL, Lee WM, Bonkovsky HL, Dienstag JL, Ghany MG, Morishima C, Morgan TR. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology* 2011; **140**: 840-849; quiz e12 [PMID: 21129375]

123 **Clifford GM**, Rickenbach M, Polesel J, Dal Maso L, Steffen I, Ledergerber B, Rauch A, Probst-Hensch NM, Bouchardy C, Levi F, Franceschi S. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *AIDS* 2008; **22**: 2135-2141 [PMID: 18832877]

124 **Sulkowski M**. Hepatocellular carcinoma in HIV-infected patients comes of age: The convergence of epidemiology and treatment effectiveness. *J Hepatol* 2009; **50**: 655-658 [PMID: 19243854 DOI: 10.1016/j.jhep.2009.01.009]

125 **MacDonald DC**, Nelson M, Bower M, Powles T. Hepatocellular carcinoma, human immunodeficiency virus and viral hepatitis in the HAART era. *World J Gastroenterol* 2008; **14**: 1657-1663 [PMID: 18350596 DOI: 10.3748/wjg.14.1657]

126 **Ward JW**, Lok AS, Thomas DL, El-Serag HB, Kim WR. Report on a single-topic conference on "Chronic viral hepatitis--strategies to improve effectiveness of screening and treatment". *Hepatology* 2012; **55**: 307-315 [PMID: 22105599]

127 **Volk ML**, Tocco R, Saini S, Lok AS. Public health impact of antiviral therapy for hepatitis C in the United States. *Hepatology* 2009; **50**: 1750-1755 [PMID: 19824079]

128 **Cohen C**, Holmberg SD, McMahon BJ, Block JM, Brosgart CL, Gish RG, London WT, Block TM. Is chronic hepatitis B being undertreated in the United States? *J Viral Hepat* 2011; **18**: 377-383 [PMID: 21143343]

129 **Lettmeier B**, Mühlberger N, Schwarzer R, Sroczynski G, Wright D, Zeuzem S, Siebert U. Market uptake of new antiviral drugs for the treatment of hepatitis C. *J Hepatol* 2008; **49**: 528-536 [PMID: 18682313]

P- Reviewer Yamaue H **S- Editor** Song XX
L- Editor O'Neill M **E- Editor** Li JY