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EDITORIAL

Hepatocellular carcinoma prevention: A worldwide emergence between the opulence of developed countries and the economic constraints of developing nations

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm, the major cause of death in patients with liver cirrhosis, and the third most common cause of cancer-related death in the world. The geographic distribution of HCC varies significantly and 80% of cases occur in developing countries (Far East and South Asia) where the prevalence of viral hepatitis is higher. The treatment of HCC is difficult because most patients are diagnosed when the tumour is in an advanced stage and is not amenable to potential curative therapy, thus prevention is the key to reducing HCC and its related morbidity and mortality. HCC is unique among cancers, occurring mostly in patients with a known risk factor. Ninety percent of HCCs develop in the context of chronic liver diseases and mainly in patients with cirrhosis. Viral hepatitis is the most common cause of HCC worldwide, followed by alcoholic liver disease (ALD) and other causes such as non-alcoholic fatty liver disease (NAFLD), genetic haemocromatosis (GH) and primary biliary cirrhosis in an advanced stage (Ⅲ-Ⅴ). In certain areas of the People's Republic of China, exposure to aflatoxin and HBV infection are thought to be responsible for the extraordinary high risk of HCC. Substantial progresses in the prevention of virusl-related hepatitis (screening of blood units, use of disposable sanitary tools, HBV vaccination) have been achieved in developed countries, but in the same areas, alcohol- and dysmetabolism-related HCCs are emerging problems which require specific interventions in terms of public health measures. In developing countries, economic constraints limit the development of any program for the prevention of viral hepatitis transmission (including health education campaigns, healthcare politics, primary prevention and the improvement of hygienic and sanitary conditions). When viral liver disease is established, only a minority of patients are treated worldwide and benefit a possible preventive effect of medical treatment on HCC development. Thus the real contribution of medical treatment to HCC prevention in patients with chronic viral hepatitis is small. Great efforts are needed to identify more effective medical measures for primary and secondary prevention of HCC.

Key words: Hepatocellular carcinoma; Viral hepatitis; Cirrhosis; Treatment; Prevention programs

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm, the major cause of death in patients with liver cirrhosis, and the third most common cause of cancer-related death in the world[1,2]. Every year, 560000 people in the world develop HCC and about the same number die of liver cancer. It is reported to be the leading cause of death in patients with cirrhosis in Europe[3] and Asia[4]. In Italy, its incidence varies from 2% to 4% each year in patients with cirrhosis[5-7].

The geographic distribution of HCC varies significantly and 80% of cases occur in developing countries (Far East and South Asia) where the prevalence of viral hepatitis is higher[8]. Epidemiological data show that its incidence is changing around the world according to the etiology since it is increasing in many developed countries, whereas HCC is declining in developing countries[9]. Studies on the epidemiology and natural history of chronic hepatitis C virus (HCV) infection suggest that HCC frequency has been increasing over the past 20-30 years in USA[10,11] and Europe[12]. HCC is one of the few types of cancer increasing in frequency and mortality in USA[11]. In Japan there has been a three-fold increase in HCC incidence since 1970[13]. Moreover, it has been shown that 80% of newly diagnosed HCCs in Japan are HCV-positive patients[14]. It has been hypothesized that HCC incidence and mortality will indeed increase over the next 10-20 years because

of the increased incidence of HCV-related cirrhosis[10]. With regard to the decline of hepatocellular cancer in developing countries, the introduction of mass hepatitis B virus (HBV) vaccination programs seems to play an important role. In Taiwan the carrier rate of HBsAg in children and adolescents has been significantly reduced[15], as has the incidence of childhood HCC[16]. Nevertheless, the decrease in the incidence of HCC among adults is still a long way off and is not expected for another 3 or 4 decades later[17]. Thus, the role of HBV vaccination in the current decline of HCC incidence, at least in Taiwan, is still to be clarified. In addition, other factors may have a role in changing the epidemiology of HCC incidence around the world: the migration of people from endemic areas and better detection of HCC in Western countries.

The treatment of HCC is difficult because most patients are diagnosed when the tumour is in an advanced stage and is not amenable to potential curative therapy[18], thus prevention is the key to reducing HCC and its related morbidity and mortality.

Notably, HCC is unique among cancers, occurring mostly in patients with a known risk factor. Ninety percent of HCCs develop in the context of chronic liver diseases and mainly in patients with cirrhosis[19,20]. Viral hepatitis is the most common cause of HCC worldwide, accounting for more than 80% of cases, followed by alcoholic liver disease (ALD) and other causes such as non-alcoholic fatty liver disease (NAFLD), genetic haemocromatosis (GH) and primary biliary cirrhosis in an advanced stage (Ⅲ-Ⅳ)[20-23]. In certain areas of the People's Republic of China where HCC is the leading cause of cancer death, exposure to aflatoxin, a potent hepatocarcinogen produced by food contaminant, and HBV infection are thought to be responsible for the extraordinary high risk of HCC[24].

Therefore, a prevention strategy should be addressed to each single risk factor ranging from food conservation to alcohol abuse, metabolic disease (NAFLD) and viral infection. Then, HCC prevention can focus on different levels: prevention of the underlying disease (primary prevention), prevention of liver disease progression to cirrhosis and cancer (secondary prevention), prevention of cancer relapse in successfully treated HCC (tertiary prevention).

HCC RELATED TO VIRUSES AND OTHER FACTORS

HBV

HBV-related chronic hepatitis is the most common cause of HCC in the world[25]. The incidence and ways of transmission of this virus vary substantially in different endemic areas throughout the world. HBV is usually acquired in adulthood and its incidence is low in Western countries, while its incidence is high in Asia and in most African countries and its transmission is vertical from mother to child[26].

The relationship between HBV and HCC development is not completely understood. Nevertheless, it seems that two main mechanisms play a role in the induction of liver cancer: one involves repeated liver damage causing necroinflammation and consequent regeneration of hepatocytes, the other is the direct oncogenic property of HBV which integrates itself into the hepatocyte DNA, producing cis- or transactivation of the cellular oncogenes[27,28]. It is important to note that HBV and HCV have been classified among human carcinogens by the International Agency for Research on Cancer[1].

There is a relationship between viral replication (defined as the presence of detectable HBV-DNA by non-PCR assay or HBeAg positivity) and HCC development. A recent study showed that the cumulative risk of HCC development is higher (87%) in patients at the age of 30-70 years persistently positive for HBsAg and HBeAg than in those (12%) who are positive for HBsAg only and in those (1%) who are HBsAg-negative[29]. HBeAg prevalence, a marker of infectivity and viral proliferation, decreases with increasing age. HBeAg seroconversion (both spontaneous and IFN-induced) usually confers a favourable outcome. However, the selection of the e minus mutant (HBV-DNA positive) leads to the development of cirrhosis (not only in the Mediterranean area but also worldwide) which is the prerequisite for HCC development[30].

Therefore, two strategies can be used to prevent HBV-related HCC: one is the prevention of HBV infection, the other which is more questionable is the treatment of HBV-related liver disease and cirrhosis. Only a minority of patients treated with interferon-α (IFN-α) achieve HBs clearance while the majority of HBsAg-positive and HBeAg-negative patients have a persistent viral replication. These patients are still at risk of developing cancer. About 35% of patients[31] who respond to IFN-α treatment achieve HBs clearance and therefore can be considered cured. In the remaining HBsAg-positive patients who can clear HBeAg, a persistent viral replication is still detectable[31]. These patients, especially those with liver cirrhosis remain at risk of developing cancer. On the other hand, the occult HBV infection (HBsAg-negative patients) is related to an increasing or a persistant risk of HCC development in both anti-HCV-related and unrelated cirrhosis[32].

Therefore, occult HBV infection should be investigated specially in patients with chronic HCV infection and considered as an additional factor related to HCC development.

HCV

HCV-related carcinogenesis is still not clearly understood. Hepatitis C virus infection increases the risk of developing HCC and its prevalence among patients with liver cancer varies between different geographic areas from 20% to 90%[10,33]. HCC occurs mostly in patients with end stage liver disease and advanced fibrosis[34]. In this population, the risk of developing liver cancer is 2%-8% per year[35-37] based on clinical studies. The only prospective study evaluating HCC risk in HCV-positive patients, has attributed a 20-fold increased risk to viral infection, but the presence of cirrhosis in the study population was not evaluated[38]. Other studies have not evaluated the presence of co-factors, such as alcohol intake or HBV co-infection and the eventual role of antiviral therapy. Therefore, a bias may exist in the literature, which may explain the variation in the incidence estimates of HCC among patients with HCV infection[11].

HCV itself probably has a direct role in the induction of HCC. Some studies showed that the HCV replicon and both non-structural and core viral proteins are capable of inducing a complex series of intracellular events leading to apoptosis suppression and cellular growth through the down-regulation of PKR and the up-regulation of transcription factors including NF-κB, STAT-3 and ATF-6[39-41].

Other causes of HCC

Alcohol consumption is a risk factor for the development of HCC[42,43]. HCC develops mostly in patients with cirrhosis although a direct carcinogenetic role of alcohol has been documented and is a known risk factor also for cancers other than HCC[44]. Ethanol is mainly metabolized in the liver, producing acetaldehyde and free radicals which produce liver injury and DNA damage through the increase of oxidant stress[45]. Moreover, alcohol abuse produces an accumulation of iron which in turn, contributes to oxidative stress[46] with an additive and possibly synergistic mechanism causing hepatocellular damage.

Hereditary hemochromatosis is a common genetic defect in the Caucasian population causing iron accumulation in different organs as well as in the liver[47]. As has already been stated, iron itself may have a direct role in the development of HCC. The risk of developing HCC in these patients is reported to be 20-200 times greater than that in healthy controls[48-51]. Male sex, older age, cirrhosis and the presence of co-factors such as alcohol, viral hepatitis and tobacco smoking are known risk factors[52,53].

Non-alcoholic fatty liver disease (NAFLD) has recently been described in cohorts of patients as a cause of HCC[54-56], but larger prospective studies are needed to define the real incidence and risk factors for HCC development in this setting of patients

Aflatoxins are hepatocarcinogens produced by *Aspergillus Flavus* and contaminate the food supply in South-east Asia and Africa[57,58], increasing the risk of HCC development, especially in patients with HBV infection, by causing a mutation of the p53 gene[59]. This kind of contamination occurs mostly in developing countries with a hot-humid climate where a variety of oilseeds and cereal crops are produced[60].

PUBLIC HEALTH MEASURES FOR PRIMARY PREVENTION OF LIVER DISEASE

As already mentioned, HCC occurs in the context of known risk factors and its treatment is disappointing. Therefore the best way to prevent its development is preventing the onset of acquired liver diseases and applying surveillance programs for patients with estabilished liver diseases.

In developed countries, viral hepatitis infection has decreased since the mid-1980s when blood donor screening for viral hepatitis became available. Moreover, the use of medical disposables has contributed to this phenomenon[61] and nowadays, the risk of HBV infection is limited to sexual risk relations, intravenous drug users and in a few cases of patients undergoing dental therapy, acupuncture, piercing and tattooing[62-64]. In developing countries, this field is still a matter of public health because almost half of the blood units are not screened for viral hepatitis[65], sanitary conditions are poor and disposable sanitary tools are often not available.

Table 1 Recommended doses and schedules for HBV vaccine

Vaccine	Patients	Dose (mcg)	Volume (mL)	Schedule (mo)
Engerix-B	< 11 yr	10	0.5	0, 1, 6
(GlaxoSmithKline, Research Triangle Park, NC)	11-19 yr	10	0.5	0, 1, 6
	> 20 yr	20	1.0	0, 1, 6
	Dialysis	40	2.0	0, 1, 2, 6
Recombivax HB (Merk & Co. Inc., Whitehouse Station, NJ)	< 11 yr	5	0.5	0, 1, 6
	11-19 yr	5	0.5	0, 1, 6
	> 20 yr	10	1.0	0, 1, 6
	Predialysis/ dialysis	40	1.0	0, 1, 6

With regard to HBV, the development of a specific vaccine has dramatically changed the virus epidemiology. This is very important in developing countries where HBV transmission is mostly vertical. HBV vaccination has been shown to be able to prevent cancer[16]. Effective vaccines have been available since 1982 and the World Health Organization has recommended the implementation of mass immunization programs since 1991. This has led to a significant decrease in HCC incidence among children and adolescents in Taiwan and it is expected to occur in the next few decades, also in those countries where the vaccination program was started later[16,66-68]. Different HBV vaccines are available, with recombinant HBs antigen (Table 1). HBV vaccination is one of the fundamental and effective forms of public health prevention measures. Unfortunately, immunization programs have a cost and a large proportion of children do not receive basic vaccines because of economic problems in many developing countries[65]. A plant-derived HBV vaccination could be a cheaper approach, this vaccine is under study with the aim of incorporating the vaccine into the alimentary chain[69].

Especially in developing countries where HBV transmission is mainly vertical with a high prevalence of infection, the screening for HBV is advisable at least in late pregnancy. Mothers positive for HBV-DNA should be given lamivudine or continue lamivudine treatment in order to reduce the viral load and the risk of vertical transmission[70]. Passive immune prophylaxis and immediate vaccination of newborns are required immediately within the perinatal period[70].

Unfortunately, an effective vaccine against HCV is still unavailable. The lack of a small animal model, genomic HCV diversity and the difficulties in establishing an *in vitro* culture of large quantities of HCV are some of the problems encountered by researchers in this field[71]. Therefore, the uncertainty of obtaining an effective vaccine imposes the call for the hygienic strategies already applied in the Western countries in order to reduce the incidence of new cases from about 50×10^5[72,73] to $< 1 \times 10^5$ inhabitants[74].

The first step in the prevention of alcohol and

NAFLD-related HCC is the fight against chronic abuse and the education for a healthier lifestyle in the general population. Similarly, warnings against alcohol abuse or unsuitable diets and a campaign for the control of body weight through moderate physical activity could play a major role. These concepts are also good for the primary prevention of colon, breast and pancreatic cancer which recognizes a risky lifestyle as their primum movements.

Iron depletion is reported to have a protective effect[75] against the development of hepatocellular carcinoma in genetic hemochromatosis, therefore phlebotomy should be performed when indicated in patients with iron accumulation.

With regard to aflatoxin, the best preventive approach would be pre-harvesting crop management, avoiding infection of the crop with *Aspergillus*[60]. Irrigation and use of fungicides or pesticides may be helpful, but this approach is expensive, especially in poor countries. Post-harvesting technologies are available to limit fungus growth and crop contamination. There are drugs capable of modulating the aflatoxin metabolism once ingested. Oltipraz, an antischistosomal drug, has been shown to be effective in detoxifying patients with serum aflatoxin-albumin adducts[76]. Chlorophyllin is a cheaper drug which has been tested in a perspective, randomised study in China with good results[77].

PATIENTS WITH ESTABLISHED LIVER DISEASE

HBV

Although it varies according to different geographic areas, HCC incidence among subjects chronically infected with HBV is higher in cirrhotics than in patients with chronic viral hepatitis[6,7,18,30,78-100] (Table 2, adapted from[101]), suggesting that other factors play a relevant role in cancerogenesis. In general, endemic East Asian countries as compared to Western countries where HBV prevalence is low or intermediate have a higher incidence of HCC among all groups considered: asymptomatic carriers, inactive carriers, chronic hepatitis and cirrhosis. It was reported that the five-year cumulative incidence in cirrhotic patients is 15% in East Asian studies and 10% in European studies with a 3-fold higher risk of developing liver cancer in endemic areas than in those with a lower prevalence[101].

This phenomenon is due to several factors associated with an increased risk of HCC development such as patient's age at onset of infection, core promoter variants, the presence of HBe antigen, and probably HBV genotypes. However, the role of HBe antigen and HBV DNA replication in the development of HCC is still being debated. A large study from Taiwan on 11 893 men with chronic hepatitis B, found that the risk of developing HCC is 10-fold higher in patients with HBsAg alone at diagnosis and 60-fold higher in those with both HBs and HBeAg than in HBsAg negative patients[102]. The EUROHEP cohort, with a smaller sample size and a low incidence of HCC showed different results, suggesting that probably in different geographical areas, the same co-factors may produce different results[78]. However, two additional European cohort studies showed that cirrhotic patients, who cleared HBeAg and HBV-DNA (and eventually HBsAg), and achieved ALT normalization, are at low risk of developing HCC[3,103]. Therefore, suppressing HBV replication which represents "per se" a major risk factor may prevent HCC development. Only one randomised controlled trial has reported a decreased incidence of HCC in 67 Taiwanese men treated with interferon as compared to 34 untreated men followed up for 1-12 years. HCC occurred in 1.5% of patients in the treated group as compared to 12% in the untreated group ($P = 0.04$). It is important to note that the only patient who developed HCC in the treated group initially cleared HBeAg, but relapsed later, again becoming HBeAg-positive with elevated transaminases[96]. A meta-analysis of 7 studies comparing treated patients *versus* untreated controls with HBV-related compensated cirrhosis has shown a very weak protective effect of interferon with a 6.4% difference in risk (95% CI: 2.8% to 10%)[104].

In conclusion, interferon treatment may have a beneficial effect on the development of HCC in HBV-infected patients, particularly when a virological response is achieved.

Nowadays, different nucleotide and nucleoside analogues are available for the treatment of HBV. The oldest in this family is lamivudine, a cytidine analogue, which is able to inhibit HBV replication, improve liver enzymes and inflammatory score and arrest progression to fibrosis[105]. A retrospective study evaluated the efficacy of lamivudine in terms of HCC prevention in 377 Japanese patients, compared to the same number of untreated HBV infected controls. HCC occurred in 1.1% of patients with an annual incidence of 0.4% (patient/year) in the treated group and in 13.3% of patients with an annual incidence of 2.5% (patient/year) in the untreated group ($P < 0.001$)[106]. Only one prospective randomized controlled

Table 2 HCC incidence rates according to clinical setting and geographic areas

Clinical setting	Geographic area	Studies (*n*)	Patients (*n*)	Mean follow-up (yr)	HCC incidence	95% CI
Asymptomatic carrier	North America	2	1804	16	0.1	0.07-0.14
	Taiwan and China	4	18869	8	0.7	0.61-0.70
	Japan	1	513	7.3	0.2	0.08-0.39
Inactive carrier	Europe	3	410	16	0.02	0-0.04
	Taiwan	1	189	8	0.2	0-0.42
Chronic hepatitis	Europe	6	471	5.9	0.1	0-0.27
	Taiwan	2	461	4.0	1.0	0.36-1.56
	Japan	2	737	5.1	0.8	0.46-1.06
Compensated cirrhosis	Europe	6	401	5.8	2.2	1.62-2.80
	Taiwan/ Singapore	3	278	4.3	3.2	1.94-4.55
	Japan	2	306	5.8	4.3	3.40-5.25

Adapted from ref. 101 with permission from American Gastroenterological Association.

study has been conducted using HCC development as an endpoint. In this study 651 patients with HBV-related cirrhosis or advanced fibrosis were randomly assigned with a 2:1 ratio, to receive lamivudine or a placebo. The study was stopped after a median duration of treatment of 32.4 mo based on the recommendations of an independent data and safety monitoring board because of a significant difference between the treated groups in the number of endpoints reached. HCC occurred in 3.9% in the lamivudine group and 7.4% in the placebo group (hazard ratio, 0.49; $P = 0.047$)[25]. This study showed that lamivudine plays a role in preventing HCC but a longer follow-up is needed to confirm this result in consideration of the high rate of lamivudine resistance which could reactivate HBV DNA replication.

A large Italian retrospective analysis of 656 patients with chronic HBV infection, with or without cirrhosis, showed that the likelihood of developing HCC is significantly less in cirrhotic patients having a virological response than in those having a virological breakthrough[84]. Further studies are also needed to evaluate the effect of the newest antiviral drugs (adefovir, entecavir, tenofovir, emtricitabine, *etc*) in terms of HCC prevention.

In conclusion, different factors contribute to the risk of HCC development in patients with HBV infection: HBV replication, HBV direct oncogenetic effect through the integration in host genoma and cirrhosis itself. Until now, the only mechanism we could control pharmacologically is viral replication and consequently liver disease evolution to cirrhosis. Therefore, a strict imaging follow-up is recommended in all patients even those responding to therapy.

HCV

HCC incidence is higher in patients with cirrhosis due to chronic hepatitis C infection with a variable incidence in cirrhotics of 2%-8% per year[35-37,107]. As for HBV its incidence varies between geographic areas. Studies from Japan [79,108-112] have documented a summary HCC incidence of 1.8 per 100 subjects per year in patients with chronic hepatitis as compared to 7.1 in patients with cirrhosis. Therefore there is a 4-fold risk of developing HCC when cirrhosis is present[101]. In Europe and the United States[5-7,23,36,37,78,80,113-117], the summary incidence is 3.7 in cirrhotic patients whereas it is impossible to calculate it in non-cirrhotic patients due to the lack of HCC in the only study available[36]. Analyzing these data showed that the 5-year cumulative risk of HCC development in cirrhotics is 17% in Europe and 30% in Japan[101]. Thus the best way of preventing HCC development in HCV-infected patients is preventing cirrhosis itself. This is a challenging issue but difficult to carry out, as a large proportion of patients are unaware of their status and the disease is mostly asymptomatic. Therapy is offered to a small proportion of patients worldwide, and moreover, the infection can be eradicated in only about half of the treatable patients[118-120].

IFN may prevent HCC by preventing liver damage evolution by the eradication of viral hepatitis, this is generally the case of sustained responders[121]. Eradicating HCV infection may prevent HCC development, at least in patients without cirrhosis. With regard to cirrhosis, a different incidence of HCC between treated and untreated cirrhotics (Table 3) and a decline in HCC incidence in patients achieving a sustained virological response have been reported[104,108]. The residual risk is related to the cirrhosis itself. Moreover, if some dysplastic or neoplastic cells are present, IFN alone is not capable of eradicating them. As a consequence, we should follow up patients by ultrasonography even after eradication of the infection. In fact, the cirrhotic background probably persists and HCC may develop years after clearance of the virus[122]. A study recently published by our group has shown the best results in terms of HCC prevention in cirrhotic patients treated with IFN plus ribavirin as compared to those treated with IFN alone, and the reduction in HCC incidence after re-treatment of non-responders[122]. The tight relationship between a high Ag-NOR proliferative index [silver stained (Ag)-nucleolar organizing region (NOR)] and HCC development in this study confirms that clinical utility of cellular proliferation markers can predict HCC development as reported in previous studies[5,122]. Since IFN is an anti-proliferative cytokine, it may have a beneficial role in preventing HCC development in cirrhotic paptiens through the reduction of hepatocyte proliferation,

Table 3 Effect of IFN on HCC incidence among HCV cirrhotic patients

Author, year	*n*	Follow-up month (range)	HCC rate	
			Treated (*n*/*n*)	Controls (*n*/*n*)
Nishiguchi 1995[150]	90	54 (24-86)	2/45	17/45
Mazzella 1996[7]	284	32 (12-71)	5/193	9/91
Bruno 1997[5]	163	68 (60-84)	6/82	14/81
Fattovich 1997[35]	329	60 (1-153)	7/193	16/136
IIHCSG 1998[151]	491	n.r.	21/232	48/259
Imai 1998[111]	52	48 (3-65)	8/32	7/20
Gramenzi 1998[115]	144	72 (n.r.)	6/72	19/72
Serfaty 1998[116]	103	40 (6-42)	2/59	9/44
Sofia 1998[152]	162	43 (n.r.)	11/103	4/59
Benvegnù 1999[6]	152	72 (n.r.)	4/75	20/77
Mura 1999[153]	57	76 (n.r.)	0/28	5/29
Shioda 1999[154]	646	55 (n.r.)	22/588	18/58
Yoshida 1999[108]	337	52 (n.r.)	33/230	29/107
Valla 1999[117]	99	37 (37-53)	5/47	9/52
Overall	3109		132/1979	224/1130

Adapted from ref. 104 with permission from EASL. Meta-analysis of the three randomised controlled trials and 11 non randomised trials. Risk difference: -12.8; 95% CI: -8.3-17.2; $P \leqslant 0.0001$ (chi square test for heterogeneity).

even when a virological response is not achieved[122]. Moreover, a recent retrospective study has shown a lower incidence of HCC in patients with HCV chronic hepatitis who were non-responders to long-term IFN treatment as compared to those treated for less than 24 mo[123].

Data on non-cirrhotic patients derive from retrospective analysis. The largest from Japan, included 2890 patients, 490 of whom were untreated. HCC incidence was higher in the untreated group (3.1% per year) than in the treated group (1.1% per year), but the difference reached a statistical significance only among patients with stage 2 or 3 fibrosis. Patients were also stratified according to virological response showing the greater benefit in responder patients with fibrosis F2-F3[108]. These data have been confirmed by a recent update of the study[124].

This study has also confirmed that HCC development seems related to the transaminase level, which is basically the rationale of treatment, the aim of which is to reduce liver inflammation. The long term use of glycyrrhizin, an aqueous extract from licorice root capable of reducing transaminases when administered for a short period of time, can significantly reduce HCC incidence in HCV patients[125]. Long-term glycyrrhizin injections have recently been shown to reduce the incidence of HCC in patients with HCV-related chronic hepatitis C with or without cirrhosis and in non-responders to IFN-based treatment[126]. Similarly, ursodeoxycholic acid (UDCA) administration has been shown to reduce transaminases in patients with HCV-related chronic hepatitis although the data are insufficient to support this effect on viral markers, mortality, incidence of cirrhosis, or liver histology[127,128]. The mechanisms involved in ALT normalisation are unknown. However, the reduction of HLA antigen expression and cholestasis, changes in membrane plasticity and bile acid pool hydrophobicity may reduce liver inflammation[129]. All these mechanisms are probably involved in the ability of UDCA to lower the incidence of HCC both in rats and in humans[130,131]. Vitamin K_2 may also have a protective effect against HCC development in women with cirrhosis[132].

The preventive role of these drugs needs to be further investigated and their use in the treatment of HCV is not recommended as the only effective drug is interferon.

Finally, epidemiological studies have shown that coffee consumption lowers the incidence of HCC in patients with HCV-, HBV- or alcohol-related cirrhosis[133-136], and that the preventive effect is cup-dependent (3 cups decrease the risk of HCC by 75%).

HCC RECURRENCE PREVENTION (TERTIARY PREVENTION)

HCC recurrence is about 80% after 5 years of curative treatment[137,138] with a local tumour progression of 10% after 5 years of radiofrequency ablation[138]. Recurrence may originate in intrahepatic metastasis from the treated tumour or from multicentric occurrence.

Several approaches to the prevention of HCC recurrence have been attempted. The most convincing seems to be polyprenoic acid administration. Polyprenoic acid is an acyclic derivate of retinoic acid which has been shown to have chemopreventive activity[139-142] by interfering with cellular regulation and differentiation. It was reported that oral administration of polyprenoic acid could significantly reduce the incidence of new HCCs after a median follow-up of 38 mo[143,144]. Its effect does not seem to be mediated by the reduction of liver inflammation (the transaminase level did not differ between the treatment and control groups)[145], but is related to the clearance of dysplastic/HCC clones by apoptotic mechanisms. The mechanism of polyprenoic acid seems to be different from that of interferon which seems to be related to multiple mechanisms such as increased immune-surveillance, S0 arrest of the cell cycle and restoration of apoptosis. A randomised controlled study on patients with HCV-related HCC showed that administration of IFN-α for 48 wk after the effective ethanol injection treatment of HCC, could improve the prognosis by reduction of the second and third recurrence with an improvement of survival in treated patients[146]. Thus, IFN seems to play a more significant role in cirrhosis as a pre-cancer condition than in liver cancer itself. IFN-α lymphoblastoids also seem to be capable of reducing HCC recurrence and improving survival in HBsAg-positive patients with their HCC resected[147]. Another small randomised controlled study showed that the recurrence rate is lower in patients treated with IFN-β after surgery or curative alcohol injection than in untreated patients[148]. The problem in these studies is that they included a small number of patients who were treated with different kinds of IFN and different treatment schedules.

Another approach is irradiation of the liver using intra-arterial iodine^{131}-labeled lipiodol after HCC resection with the aim of eradicating neoplastic foci. This strategy has been used in a small randomised controlled trial, showing a reduction in the recurrence rate and an increase in disease-free survival when compared to controls[149].

There is evidence that IFN and polyprenoic acid have a modest effects at least in small studies. In practice, when HCC develops in a cirrhotic liver, medical treatment has a very limited efficacy on the prevention of recurrence.

CONCLUSION

HCC prevention is a public health challenge. Since HCC mostly develops in a sick liver and the secondary prevention is of little effect, the best strategy is to prevent the onset of liver diseases.

Substantial progresses have been achieved in developed countries in the prevention of virusl-related hepatitis (screening of blood units, use of disposable sanitary tools, HBV vaccination) , but alcohol- and dysmetabolism-related HCCs are emerging problems in the same areas, which require specific interventions in terms of public health measures.

In developing countries, there is still a long way to go. In fact, economic constraints limit the development of any program for the prevention of viral hepatitis transmission (including health education campaigns, healthcare politicies, primary prevention and improvement of hygienic and sanitary conditions). In this setting, the

first step should be a political approach aimed to increase people awareness, extensive vaccination programs, blood units screening, sanitary conditions and use of disposables in poor countries. It is obvious that pharmacological approach should follow. In Western countries our efforts should be directed towards educational approach and counceling activities in order to reduce alcohol abuse and obesity.

As a rule, when the diagnosis of viral liver disease is established, only a minority of patients are treated worldwide and benefit from a possible preventive effect of medical treatment for HCC. Once again economic support in developed countries should be given to treat those patients who could benefit from antiviral treatment.

With regard to HCC recurrence, the real contribution of medical treatment to prevention of chronic viral hepatitis is small. However, more effective medical measures against secondary and tertiary prevention of HCC should be taken.

Finally, the role of co-factors in the development of HCC is still unknown and should be further investigated. Co-factors may also clarify the large differences in the geographic incidence of HCC and give further targets of intervention.

REFERENCES

1 **Parkin DM**, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001; **94**: 153-156
2 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917
3 **Fattovich G**, Giustina G, Realdi G, Corrocher R, Schalm SW. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology* 1997; **26**: 1338-1342
4 **Kao JH**, Chen DS. Changing disease burden of hepatocellular carcinoma in the Far East and Southeast Asia. *Liver Int* 2005; **25**: 696-703
5 **Bruno S**, Silini E, Crosignani A, Borzio F, Leandro G, Bono F, Asti M, Rossi S, Larghi A, Cerino A, Podda M, Mondelli MU. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. *Hepatology* 1997; **25**: 754-758
6 **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
7 **Mazzella G**, Accogli E, Sottili S, Festi D, Orsini M, Salzetta A, Novelli V, Cipolla A, Fabbri C, Pezzoli A, Roda E. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. *J Hepatol* 1996; **24**: 141-147
8 **Parkin DM**, Stjernswärd J, Muir CS. Estimates of the worldwide frequency of twelve major cancers. *Bull World Health Organ* 1984; **62**: 163-182
9 **McGlynn KA**, Tsao L, Hsing AW, Devesa SS, Fraumeni JF Jr. International trends and patterns of primary liver cancer. *Int J Cancer* 2001; **94**: 290-296
10 **el-Serag HB**. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2001; **5**: 87-107, vi
11 **Goodgame B**, Shaheen NJ, Galanko J, El-Serag HB. The risk of end stage liver disease and hepatocellular carcinoma among persons infected with hepatitis C virus: publication bias? *Am J Gastroenterol* 2003; **98**: 2535-2542
12 **Deuffic S**, Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. *Lancet* 1998; **351**: 214-215
13 **Okuda K**, Fujimoto I, Hanai A, Urano Y. Changing incidence of hepatocellular carcinoma in Japan. *Cancer Res* 1987; **47**: 4967-4972
14 **Okuda K**. Liver Cancer. London: Churvhill Livingstone, 1993
15 **Ni YH**, Chang MH, Huang LM, Chen HL, Hsu HY, Chiu TY, Tsai KS, Chen DS. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. *Ann Intern Med* 2001; **135**: 796-800
16 **Chang MH**, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997; **336**: 1855-1859
17 **Kao JH**, Chen DS. Global control of hepatitis B virus infection. *Lancet Infect Dis* 2002; **2**: 395-403
18 **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
19 **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
20 **Bosch FX**, Ribes J, Borràs J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999; **19**: 271-285
21 **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
22 **Tsukuma H**, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, Nakanishi K, Fujimoto I, Inoue A, Yamazaki H. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993; **328**: 1797-1801
23 **Velázquez RF,** Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorríos NG, Martínez I, Rodrigo L. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003; **37**: 520-527
24 **Chen JG**, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC, Zhu YR. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. *J Med Screen* 2003; **10**: 204-209
25 **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
26 **Lavanchy D**. Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention. *J Clin Virol* 2005; **34** Suppl 1: S1-S3
27 **Chisari FV**, Klopchin K, Moriyama T, Pasquinelli C, Dunsford HA, Sell S, Pinkert CA, Brinster RL, Palmiter RD. Molecular pathogenesis of hepatocellular carcinoma in hepatitis B virus transgenic mice. *Cell* 1989; **59**: 1145-1156
28 **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
29 **You SL**, Yang HI, Chen CJ. Seropositivity of hepatitis B e antigen and hepatocellular carcinoma. *Ann Med* 2004; **36**: 215-224
30 **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
31 **Mazzella G**, Saracco G, Festi D, Rosina F, Marchetto S, Jaboli F, Sostegni R, Pezzoli A, Azzaroli F, Cancellieri C, Montagnani M, Roda E, Rizzetto M. Long-term results with interferon therapy in chronic type B hepatitis: a prospective randomized trial. *Am J Gastroenterol* 1999; **94**: 2246-2250
32 **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

33 **Donato F**, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer* 1998; **75**: 347-354

34 **Di Bisceglie AM**. Hepatitis C and hepatocellular carcinoma. *Hepatology* 1997; **26**: 34S-38S

35 **Fattovich G**, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW, Realdi G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; **112**: 463-472

36 **Niederau C**, Lange S, Heintges T, Erhardt A, Buschkamp M, Hürter D, Nawrocki M, Kruska L, Hensel F, Petry W, Häussinger D. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. *Hepatology* 1998; **28**: 1687-1695

37 **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

38 **Sun CA**, Wu DM, Lin CC, Lu SN, You SL, Wang LY, Wu MH, Chen CJ. Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. *Am J Epidemiol* 2003; **157**: 674-682

39 **Waris G**, Tardif KD, Siddiqui A. Endoplasmic reticulum (ER) stress: hepatitis C virus induces an ER-nucleus signal transduction pathway and activates NF-kappaB and STAT-3. *Biochem Pharmacol* 2002; **64**: 1425-1430

40 **Gale M Jr**, Blakely CM, Kwieciszewski B, Tan SL, Dossett M, Tang NM, Korth MJ, Polyak SJ, Gretch DR, Katze MG. Control of PKR protein kinase by hepatitis C virus nonstructural 5A protein: molecular mechanisms of kinase regulation. *Mol Cell Biol* 1998; **18**: 5208-5218

41 **Pflugheber J**, Fredericksen B, Sumpter R Jr, Wang C, Ware F, Sodora DL, Gale M Jr. Regulation of PKR and IRF-1 during hepatitis C virus RNA replication. *Proc Natl Acad Sci USA* 2002; **99**: 4650-4655

42 **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

43 **Longnecker MP**. Alcohol consumption and risk of cancer in humans: an overview. *Alcohol* 1995; **12**: 87-96

44 **Voigt MD**. Alcohol in hepatocellular cancer. *Clin Liver Dis* 2005; **9**: 151-169

45 **McKillop IH**, Schrum LW. Alcohol and liver cancer. *Alcohol* 2005; **35**: 195-203

46 **Petersen DR**. Alcohol, iron-associated oxidative stress, and cancer. *Alcohol* 2005; **35**: 243-249

47 **Limdi JK**, Crampton JR. Hereditary haemochromatosis. *QJM* 2004; **97**: 315-324

48 **Bradbear RA**, Bain C, Siskind V, Schofield FD, Webb S, Axelsen EM, Halliday JW, Bassett ML, Powell LW. Cohort study of internal malignancy in genetic hemochromatosis and other chronic nonalcoholic liver diseases. *J Natl Cancer Inst* 1985; **75**: 81-84

49 **Niederau C**, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985; **313**: 1256-1262

50 **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

51 **Fracanzani AL**, Conte D, Fraquelli M, Taioli E, Mattioli M, Losco A, Fargion S. Increased cancer risk in a cohort of 230 patients with hereditary hemochromatosis in comparison to matched control patients with non-iron-related chronic liver disease. *Hepatology* 2001; **33**: 647-651

52 **Deugnier YM**, Guyader D, Crantock L, Lopez JM, Turlin B, Yaouanq J, Jouanolle H, Campion JP, Launois B, Halliday JW. Primary liver cancer in genetic hemochromatosis: a clinical, pathological, and pathogenetic study of 54 cases. *Gastroenterology* 1993; **104**: 228-234

53 **Fargion S**, Fracanzani AL, Piperno A, Braga M, D'Alba R, Ronchi G, Fiorelli G. Prognostic factors for hepatocellular carcinoma in genetic hemochromatosis. *Hepatology* 1994; **20**: 1426-1431

54 **Cuadrado A**, Orive A, Garcia-Suarez C, Dominguez A, Fernandez-Escalante JC, Crespo J, Pons-Romero F. Non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma. *Obes Surg* 2005; **15**: 442-446

55 **Bugianesi E**, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, Musso A, De Paolis P, Capussotti L, Salizzoni M, Rizzetto M. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002; **123**: 134-140

56 **Shimada M**, Hashimoto E, Taniai M, Hasegawa K, Okuda H, Hayashi N, Takasaki K, Ludwig J. Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *J Hepatol* 2002; **37**: 154-160

57 **Kensler TW**, Egner PA, Wang JB, Zhu YR, Zhang BC, Lu PX, Chen JG, Qian GS, Kuang SY, Jackson PE, Gange SJ, Jacobson LP, Muñoz A, Groopman JD. Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas. *Gastroenterology* 2004; **127**: S310-S318

58 **Turner PC**, Sylla A, Diallo MS, Castegnaro JJ, Hall AJ, Wild CP. The role of aflatoxins and hepatitis viruses in the etiopathogenesis of hepatocellular carcinoma: A basis for primary prevention in Guinea-Conakry, West Africa. *J Gastroenterol Hepatol* 2002; **17** Suppl: S441-S448

59 **Wogan GN**. Aflatoxin as a human carcinogen. *Hepatology* 1999; **30**: 573-575

60 **Wild CP**, Hall AJ. Primary prevention of hepatocellular carcinoma in developing countries. *Mutat Res* 2000; **462**: 381-393

61 **Colombo M**, Donato MF. Prevention of hepatocellular carcinoma. *Semin Liver Dis* 2005; **25**: 155-161

62 **Mele A**, Spada E, Sagliocca L, Ragni P, Tosti ME, Gallo G, Moiraghi A, Balocchini E, Sangalli M, Lopalco PL, Stroffoli T. Risk of parenterally transmitted hepatitis following exposure to surgery or other invasive procedures: results from the hepatitis surveillance system in Italy. *J Hepatol* 2001; **35**: 284-289

63 **Schreiber GB**, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med* 1996; **334**: 1685-1690

64 **Armstrong GL**, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**: 705-714

65 **Global Alliance for Vaccines and Immunization (GAVI)**: Report of the Second Board Meeting. Davos, Switzerland, 2000

66 **WHO**: Hepatitis B Fact Sheet No. 204 (Revised October 2000). In WHO Website. 2000

67 **Chang MH**, Shau WY, Chen CJ, Wu TC, Kong MS, Liang DC, Hsu HM, Chen HL, Hsu HY, Chen DS. Hepatitis B vaccination and hepatocellular carcinoma rates in boys and girls. *JAMA* 2000; **284**: 3040-3042

68 **Montesano R**. Hepatitis B immunization and hepatocellular carcinoma: The Gambia Hepatitis Intervention Study. *J Med Virol* 2002; **67**: 444-446

69 **Kapusta J**, Modelska A, Figlerowicz M, Pniewski T, Letellier M, Lisowa O, Yusibov V, Koprowski H, Plucienniczak A, Legocki AB. A plant-derived edible vaccine against hepatitis B virus. *FASEB J* 1999; **13**: 1796-1799

70 **Wright TL**. Introduction to chronic hepatitis B infection. *Am J Gastroenterol* 2006; **101** Suppl 1: S1-S6

71 **Koff RS**. Hepatitis vaccines: recent advances. *Int J Parasitol* 2003; **33**: 517-523

72 **Mazzeo C**, Azzaroli F, Giovanelli S, Dormi A, Festi D, Colecchia A, Miracolo A, Natale P, Nigro G, Alberti A, Roda E, Mazzella G. Ten year incidence of HCV infection in northern Italy and frequency of spontaneous viral clearance. *Gut* 2003; **52**: 1030-1034

73 **Osella AR**, Misciagna G, Leone A, Di Leo A, Fiore G. Epidemiology of hepatitis C virus infection in an area of Southern Italy. *J Hepatol* 1997; **27**: 30-35

74 **D'Amelio R**, Mele A, Mariano A, Romanò L, Biselli R, Lista F, Zanetti A, Stroffolini T. Stable low levels of hepatitis C virus infection among Italian young males over the past decade. *Dig Liver Dis* 2006; **38**: 64-65

75 **Goh J**, Callagy G, McEntee G, O'Keane JC, Bomford A, Crowe J. Hepatocellular carcinoma arising in the absence of cirrhosis in genetic haemochromatosis: three case reports and review of literature. *Eur J Gastroenterol Hepatol* 1999; **11**: 915-919

76 **Wang JS**, Shen X, He X, Zhu YR, Zhang BC, Wang JB, Qian GS, Kuang SY, Zarba A, Egner PA, Jacobson LP, Muñoz A, Helzlsouer KJ, Groopman JD, Kensler TW. Protective alterations in phase 1 and 2 metabolism of aflatoxin B1 by oltipraz in residents of Qidong, People's Republic of China. *J Natl Cancer Inst* 1999; **91**: 347-354

77 **Egner PA**, Wang JB, Zhu YR, Zhang BC, Wu Y, Zhang QN, Qian GS, Kuang SY, Gange SJ, Jacobson LP, Helzlsouer KJ, Bailey GS, Groopman JD, Kensler TW. Chlorophyllin intervention reduces aflatoxin-DNA adducts in individuals at high risk for liver cancer. *Proc Natl Acad Sci USA* 2001; **98**: 14601-14606

78 **Fattovich G**, Pantalena M, Zagni I, Realdi G, Schalm SW, Christensen E. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. *Am J Gastroenterol* 2002; **97**: 2886-2895

79 **Takano S**, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995; **21**: 650-655

80 **Chiaramonte M**, Stroffolini T, Vian A, Stazi MA, Floreani A, Lorenzoni U, Lobello S, Farinati F, Naccarato R. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999; **85**: 2132-2137

81 **Kato Y**, Nakata K, Omagari K, Furukawa R, Kusumoto Y, Mori I, Tajima H, Tanioka H, Yano M, Nagataki S. Risk of hepatocellular carcinoma in patients with cirrhosis in Japan. Analysis of infectious hepatitis viruses. *Cancer* 1994; **74**: 2234-2238

82 **Evans AA**, Chen G, Ross EA, Shen FM, Lin WY, London WT. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 369-376

83 **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

84 **Di Marco V**, Marzano A, Lampertico P, Andreone P, Santantonio T, Almasio PL, Rizzetto M, Craxì A. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. *Hepatology* 2004; **40**: 883-891

85 **McMahon BJ**, Bulkow L, Harpster A, Snowball M, Lanier A, Sacco F, Dunaway E, Williams J. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. *Hepatology* 2000; **32**: 842-846

86 **Beasley RP**. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988; **61**: 1942-1956

87 **Yu MW**, Hsu FC, Sheen IS, Chu CM, Lin DY, Chen CJ, Liaw YF. Prospective study of hepatocellular carcinoma and liver cirrhosis in asymptomatic chronic hepatitis B virus carriers. *Am J Epidemiol* 1997; **145**: 1039-1047

88 **Sakuma K**, Saitoh N, Kasai M, Jitsukawa H, Yoshino I, Yamaguchi M, Nobutomo K, Yamumi M, Tsuda F, Komazawa T. Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study. *Hepatology* 1988; **8**: 1642-1646

89 **Bellentani S**, Dal Molin G, Miglioli L, Crocè lS, Masutti F, Castiglione A, Campello C, Tribelli C. Natural history of HBV infection: a 9 years follow-up of the Dyonisos cohort. *J Hepatol* 2002; **36**: S228

90 **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

91 **Di Marco V**, Lo Iacono O, Cammà C, Vaccaro A, Giunta M, Martorana G, Fuschi P, Almasio PL, Craxì A. The long-term course of chronic hepatitis B. *Hepatology* 1999; **30**: 257-264

92 **Brunetto MR**, Oliveri F, Coco B, Leandro G, Colombatto P, Gorin JM, Bonino F. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: a long term cohort study. *J Hepatol* 2002; **36**: 263-270

93 **Esteban JI**, Gómez J, Martell M, Cabot B, Quer J, Camps J, González A, Otero T, Moya A, Esteban R. Transmission of hepatitis C virus by a cardiac surgeon. *N Engl J Med* 1996; **334**: 555-560

94 **Papatheodoridis GV**, Manesis E, Hadziyannis SJ. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. *J Hepatol* 2001; **34**: 306-313

95 **Liaw YF**, Tai DI, Chu CM, Lin DY, Sheen IS, Chen TJ, Pao CC. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study. *Gastroenterology* 1986; **90**: 263-267

96 **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

97 **Ikeda K**, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I, Arase Y, Fukuda M, Chayama K, Murashima N, Kumada H. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol* 1998; **28**: 930-938

98 **Liaw YF**, Lin DY, Chen TJ, Chu CM. Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Liver* 1989; **9**: 235-241

99 **Ikeda K**, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Fukuda M, Koida I, Arase Y, Chayama K, Murashima N, Kumada H. Interferon decreases hepatocellular carcinogenesis in patients with cirrhosis caused by the hepatitis B virus: a pilot study. *Cancer* 1998; **82**: 827-835

100 **Oon CJ**. Long-term survival following treatment of hepatocellular carcinoma in Singapore: evaluation of Wellferon in the prophylaxis of high-risk pre-cancerous conditions. *Cancer Chemother Pharmacol* 1992; **31** Suppl: S137-S142

101 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50

102 **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

103 **Fattovich G**, Giustina G, Sanchez-Tapias J, Quero C, Mas A, Olivotto PG, Solinas A, Almasio P, Hadziyannis S, Degos F, de Moura MC, Krogsgaard K, Pantalena M, Realdi G, Corrocher R, Schalm SW. Delayed clearance of serum HBsAg in compensated cirrhosis B: relation to interferon alpha therapy and disease prognosis. European Concerted Action on Viral Hepatitis (EUROHEP). *Am J Gastroenterol* 1998; **93**: 896-900

104 **Cammà C,** Giunta M, Andreone P, Craxì A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. *J Hepatol* 2001; **34**: 593-602

105 **Karayiannis P**. Hepatitis B virus: old, new and future approaches to antiviral treatment. *J Antimicrob Chemother* 2003; **51**: 761-785

106 **Matsumoto A**, Tanaka E, Rokuhara A, Kiyosawa K, Kumada H, Omata M, Okita K, Hayashi N, Okanoue T, Iino S, Tanikawa K. Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: A multicenter retrospective study of 2795 patients. *Hepatol Res* 2005; **32**: 173-184

107 **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

108 **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

109 **Kobayashi M**, Tanaka E, Sodeyama T, Urushihara A, Matsumoto A, Kiyosawa K. The natural course of chronic hepatitis C: a comparison between patients with genotypes 1 and 2 hepatitis C viruses. *Hepatology* 1996; **23**: 695-699

110 **Chiba T**, Matsuzaki Y, Abei M, Shoda J, Tanaka N, Osuga T, Aikawa T. The role of previous hepatitis B virus infection and heavy smoking in hepatitis C virus-related hepatocellular carcinoma. *Am J Gastroenterol* 1996; **91**: 1195-1203

111 **Imai Y**, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, Maeda Y, Shirai Y, Fukuzaki T, Kaji I, Ishikawa H, Matsuda Y, Nishikawa M, Seki K, Matsuzawa Y. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. *Ann Intern Med* 1998; **129**: 94-99

112 **Ikeda K**, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, Tsubota A, Nakamura I, Murashima N, Kumada H, Kawanishi M. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: A long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* 1999; **29**: 1124-1130

113 **Gordon SC**, Bayati N, Silverman AL. Clinical outcome of hepatitis C as a function of mode of transmission. *Hepatology* 1998; **28**: 562-567

114 **Mazziotti G**, Sorvillo F, Morisco F, Carbone A, Rotondi M, Stornaiuolo G, Precone DF, Cioffi M, Gaeta GB, Caporaso N, Carella C. Serum insulin-like growth factor I evaluation as a useful tool for predicting the risk of developing hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a prospective study. *Cancer* 2002; **95**: 2539-2545

115 **Gramenzi A**, Andreone P, Fiorino S, Cammà C, Giunta M, Magalotti D, Cursaro C, Calabrese C, Arienti V, Rossi C, Di Febo G, Zoli M, Craxì A, Gasbarrini G, Bernardi M. Impact of interferon therapy on the natural history of hepatitis C virus related cirrhosis. *Gut* 2001; **48**: 843-848

116 **Serfaty L**, Aumaître H, Chazouillères O, Bonnand AM, Rosmorduc O, Poupon RE, Poupon R. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; **27**: 1435-1440

117 **Valla DC**, Chevallier M, Marcellin P, Payen JL, Trepo C, Fonck M, Bourliere M, Boucher E, Miguet JP, Parlier D, Lemonnier C, Opolon P. Treatment of hepatitis C virus-related cirrhosis: a randomized, controlled trial of interferon alfa-2b versus no treatment. *Hepatology* 1999; **29**: 1870-1875

118 **Heathcote EJ**. Prevention of hepatitis C virus-related hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S294-S302

119 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965

120 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982

121 **Di Bisceglie AM**, Hoofnagle JH. Optimal therapy of hepatitis C. *Hepatology* 2002; **36**: S121-S127

122 **Azzaroli F**, Accogli E, Nigro G, Trere D, Giovanelli S, Miracolo A, Lodato F, Montagnani M, Tamé M, Colecchia A, Mwangemi C, Festi D, Roda E, Derenzini M, Mazzella G. Interferon plus ribavirin and interferon alone in preventing hepatocellular carcinoma: a prospective study on patients with HCV related cirrhosis. *World J Gastroenterol* 2004; **10**: 3099-3102

123 **Saito Y**, Saito H, Tada S, Nakamoto N, Horikawa H, Kurita S, Kitamura K, Ebinuma H, Ishii H, Hibi T. Effect of long-term interferon therapy for refractory chronic hepatitis c: preventive effect on hepatocarcinogenesis. *Hepatogastroenterology* 2005; **52**: 1491-1496

124 **Yoshida H**, Tateishi R, Arakawa Y, Sata M, Fujiyama S, Nishiguchi S, Ishibashi H, Yamada G, Yokosuka O, Shiratori Y, Omata M. Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. *Gut* 2004; **53**: 425-430

125 **Arase Y**, Ikeda K, Murashima N, Chayama K, Tsubota A, Koida I, Suzuki Y, Saitoh S, Kobayashi M, Kumada H. The long term efficacy of glycyrrhizin in chronic hepatitis C patients. *Cancer* 1997; **79**: 1494-1500

126 **Ikeda K**, Arase Y, Kobayashi M, Saitoh S, Someya T, Hosaka T, Sezaki H, Akuta N, Suzuki Y, Suzuki F, Kumada H. A long-term glycyrrhizin injection therapy reduces hepatocellular carcinogenesis rate in patients with interferon-resistant active chronic hepatitis C: a cohort study of 1249 patients. *Dig Dis Sci* 2006; **51**: 603-609

127 **Leuschner U**, Leuschner M, Sieratzki J, Kurtz W, Hübner K. Gallstone dissolution with ursodeoxycholic acid in patients with chronic active hepatitis and two years follow-up. A pilot study. *Dig Dis Sci* 1985; **30**: 642-649

128 **Chen W**, Liu J, Gluud C. Bile acids for viral hepatitis. *Cochrane Database Syst Rev* 2003; CD003181

129 **Lazaridis KN**, Gores GJ, Lindor KD. Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disorders'. *J Hepatol* 2001; **35**: 134-146

130 **Tarao K**, Fujiyama S, Ohkawa S, Miyakawa K, Tamai S, Hirokawa S, Masaki T, Tanaka K. Ursodiol use is possibly associated with lower incidence of hepatocellular carcinoma in hepatitis C virus-associated liver cirrhosis. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 164-169

131 **Oyama K**, Shiota G, Ito H, Murawaki Y, Kawasaki H. Reduction of hepatocarcinogenesis by ursodeoxycholic acid in rats. *Carcinogenesis* 2002; **23**: 885-892

132 **Habu D**, Shiomi S, Tamori A, Takeda T, Tanaka T, Kubo S, Nishiguchi S. Role of vitamin K2 in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004; **292**: 358-361

133 **Asahina Y**, Izumi N, Enomoto N, Uchihara M, Kurosaki M, Onuki Y, Nishimura Y, Ueda K, Tsuchiya K, Nakanishi H, Kitamura T, Miyake S. Mutagenic effects of ribavirin and response to interferon/ribavirin combination therapy in chronic hepatitis C. *J Hepatol* 2005; **43**: 623-629

134 **Gelatti U**, Covolo L, Franceschini M, Pirali F, Tagger A, Ribero ML, Trevisi P, Martelli C, Nardi G, Donato F. Coffee consumption reduces the risk of hepatocellular carcinoma independently of its aetiology: a case-control study. *J Hepatol* 2005; **42**: 528-534

135 **La Vecchia C**. Coffee, liver enzymes, cirrhosis and liver cancer. *J Hepatol* 2005; **42**: 444-446

136 **Gallus S**, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, Lagiou P, Trichopoulos D. Does coffee protect against hepatocellular carcinoma? *Br J Cancer* 2002; **87**: 956-959

137 **Kumada T**, Nakano S, Takeda I, Sugiyama K, Osada T, Kiriyama S, Sone Y, Toyoda H, Shimada S, Takahashi M, Sassa T. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. *Hepatology* 1997; **25**: 87-92

138 **Lencioni R**, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, Bartolozzi C. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology* 2005; **234**: 961-967

139 **Sporn MB**. Carcinogenesis and cancer: different perspectives on the same disease. *Cancer Res* 1991; **51**: 6215-6218

140 **Boone CW**, Kelloff GJ, Malone WE. Identification of candidate cancer chemopreventive agents and their evaluation in animal models and human clinical trials: a review. *Cancer Res* 1990; **50**: 2-9

141 **Okuno M**, Kojima S, Matsushima-Nishiwaki R, Tsurumi H, Muto Y, Friedman SL, Moriwaki H. Retinoids in cancer chemoprevention. *Curr Cancer Drug Targets* 2004; **4**: 285-298

142 **Kojima S**, Okuno M, Matsushima-Nishiwaki R, Friedman SL, Moriwaki H. Acyclic retinoid in the chemoprevention of

hepatocellular carcinoma (review). *Int J Oncol* 2004; **24**: 797-805
143 **Muto Y**, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, Tanaka T, Tsurumi K, Okuno M, Tomita E, Nakamura T, Kojima T. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med* 1996; **334**: 1561-1567
144 **Muto Y**, Moriwaki H, Saito A. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *N Engl J Med* 1999; **340**: 1046-1047
145 **Takai K**, Okuno M, Yasuda I, Matsushima-Nishiwaki R, Uematsu T, Tsurumi H, Shiratori Y, Muto Y, Moriwaki H. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. Updated analysis of the long-term follow-up data. *Intervirology* 2005; **48**: 39-45
146 **Shiratori Y**, Shiina S, Teratani T, Imamura M, Obi S, Sato S, Koike Y, Yoshida H, Omata M. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med* 2003; **138**: 299-306
147 **Oon CJ**, Chen WN. Lymphoblastoid alpha-interferon in the prevention of hepatocellular carcinoma (HCC) in high-risk HbsAg-positive resected cirrhotic HCC cases: a 14-year follow-up. *Cancer Invest* 2003; **21**: 394-399
148 **Ikeda K**, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, Tsubota A, Chayama K, Murashima N, Kumada H. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000; **32**: 228-232
149 **Lau WY**, Leung TW, Ho SK, Chan M, Machin D, Lau J, Chan AT, Yeo W, Mok TS, Yu SC, Leung NW, Johnson PJ. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999; **353**: 797-801
150 **Nishiguchi S**, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, Shiomi S, Seki S, Kobayashi K, Otani S. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; **346**: 1051-1055
151 **Effect of interferon-alpha on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study**. International Interferon-alpha Hepatocellular Carcinoma Study Group. *Lancet* 1998; **351**: 1535-1539
152 **Sofia S**, Casali A, Buscarini E, Castagnetti E, Rapaccini GL, Levantesi L. Effect of lymphoblastoid IFN in the treatment of liver cirrhosis and prevention of HCC. *Ital Jf Gastroenterol Hepatol* 1998; **30**: A31
153 **Mura D**, Deliperi R, Fastame L, Carlini A, Cussu PA, Pisanu G. Five years follo-up after Interferon therapy in HCV-positive compensated cirrhosis. *Ital Jf Gastroenterol Hepatol* 1998; **30**: A114
154 **Shioda A**, Moriyama M, Kaneko M, Shimizu T, Gotou I, Tanaka N. Long-term prognosis of hepatocellular carcinoma developing after treatment of interferon in patients with chronic hepatitis C and liver cirrhosis. *Hepatology* 1999; **30**: 268A

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