World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i6.311

World J Hepatol 2013 June 27; 5(6): 311-322
ISSN 1948-5182 (online)

REVIEW

Non-viral factors contributing to hepatocellular carcinoma

Manal A Hamed, Sanaa A Ali

Manal A Hamed, Sanaa A Ali, Therapeutic Chemistry Department, Pharmaceutical and Drug Industries Division, National Research Centre, Dokki, Giza 12622, Egypt
Author contributions: Hamed MA and Ali SA designed the study, wrote the review and were also involved in editing the review in addition to providing financial support for this work.
Correspondence to: Sanaa A Ali, Professor of Biochemistry, Therapeutic Chemistry Department, Pharmaceutical and Drug Industries Division, National Research Centre, El-Behooth St., Dokki, Cairo 12622, Egypt. sanaa_ahmedibrahim@yahoo.com
Telephone: +20-2-33371499 Fax: +20-2-33370931
Received: February 21, 2013 Revised: May 10, 2013
Accepted: May 18, 2013
Published online: June 27, 2013

Abstract

Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide, accounting for over half a million deaths per year. The geographic pattern of HCC incidence is parallel to exposure to viral etiologic factors. Its incidence is increasing, ranging between 3% and 9% annually depending on the geographical location, and variability in the incidence rates correspond closely to the prevalence and pattern of the primary etiologic factors. Chronic infections with hepatitis B viruses or hepatitis C viruses have both been recognized as human liver carcinogens with a combined attributable fraction of at least 75% of all HCC cases. Multiple non-viral factors have been implicated in the development of HCC. Increased body mass index and diabetes with subsequent development of non-alcoholic steatohepatitis represent significant risk factors for HCC. Other non-viral causes of HCC include iron overload syndromes, alcohol use, tobacco, oral contraceptive, aflatoxin, pesticides exposure and betel quid chewing, a prevalent habit in the developing world. Wilson disease, α-1 antitrypsin deficiency, Porphyrias, autoimmune hepatitis, *Schistosoma japonicum* associated with positive hepatitis B surface antigen, and thorotrast-ray are also contributing hepatocellualar carcinoma. In addition, primary biliary cirrhosis, congestive liver disease and family history of liver cancer increase the risk of HCC incident. In conclusion, clarification of relevant non-viral causes of HCC will help to focus clinicians on those risk factors that are modifiable. The multilevel preventative approach will hopefully lead to a reduction in incidence of non-viral HCC, and a decrease in the patient morbidity and mortality as well as the societal economic burden associated with HCC.

Key words: Hepatocellular carcinoma; Viral etiologic factors; Non viral factors

Core tip: Hepatocellular carcinoma (HCC) is one of the most common and deadly cancers worldwide, there are multiple non-viral factors have been implicated in the development of HCC, hemochromatosis, obesity, diabetes, alcohol and tobacco have consistently been shown to dramatically increase the rate of HCC. Oral contraceptive, aflatoxin, pesticides exposure and betel quid chewing also increase HCC risk, in addition, Wilson disease, α-1 antitrypsin deficiency, porphyries, autoimmune hepatitis, *Schistosoma japonicum* infection associated with positive hepatitis B surface antigen, and thorotrast-ray are contributing in the prevalence of the disease. Moreover, primary biliary cirrhosis, congestive liver disease and family history of liver cancer play a significant role of disease progression.

Hamed MA, Ali SA. Non-viral factors contributing to hepatocellular carcinoma. *World J Hepatol* 2013; 5(6): 311-322 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i6/311.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i6.311

INTRODUCTION

Hepatocellular carcinoma (HCC) represents an international public health concern as one of the most common and deadly cancers worldwide[1]. It is the fifth most common cancers[2] and the third cancer-related death worldwide[1]. It is rarely to be detected early and usually fatal within a few

months of diagnosis[3]. HCC is represented by 85%-90% of primary liver cancers[4] accounting for 3.5% and 7.5% of all cancers among women and men, respectively[5] and accounts for half a million deaths per year[6].

Although this disease typically affects elderly males, in recent years there has been a shift towards relatively younger age groups[7]. In patients who are not transplant candidates, HCC is particularly lethal, with a 5-year survival of less than 5%[8]. HCC has a high incidence rate in sub-Saharan Africa and Southeast Asia, but a low incidence rate in the United States and Europe[9]. In Middle Eastern countries, liver cancer is a major concern among men, especially in certain countries such as Egypt and Saudi Arabia, and to a lesser extent in other countries of this region[5]. In Egypt, several attempts were made to establish cancer registries[10]. Among these attempts in 1998, the Egyptian Ministry of Health and Population in collaboration with the National Cancer Institute of Cairo University established a population-based Cancer Registry (NCR).

The NCR data confirmed the high incidence of HCC in Egypt and the change in the trends during the last decade. HCC was reported to account for about 4.7% of chronic liver disease patients[11]. It formed 11.75% of the malignancies of all digestive organs and 1.68% of total malignancies. Liver tumors were mostly HCC (70.48%), while hepatoblastoma constituted 10.24%, non-Hodgkin's lymphoma 4.21% of hepatic malignancies and adenocarcinoma unspecified 9.03%[10].

VIRAL FACTORS CONTRIBUTING TO HCC

HCC has been increasing in worldwide with a doubling in the incidence rate in the past 10 years due to several biological and environmental factors[10]. A significant proportion of this increase is accounted by the growing prevalence of hepatitis C and B viruses (HCV and HBV) infection[8,12].

NON-VIRAL FACTORS CONTRIBUTING TO HCC

Other potential causes of HCC are garnering close attention. Increased body mass index and diabetes with subsequent development of non-alcoholic steatohepatitis (NASH) represent significant risk factors for HCC[13-15]. This is especially concerning in light of the growing epidemic of obesity in adults and children over the past 25 years[16,17]. Other no viral causes of HCC include iron overload syndromes, alcohol use, tobacco, oral contraceptive, aflatoxin, pesticides exposure and betel quid chewing, a prevalent habit in the developing world[10,18]. Wilson disease, α-1 antitrypsin deficiency, Porphyries, autoimmune hepatitis, *Schist soma jabonium*, and thorotrastray are also contributing hepatocellualar carcinoma[19-22]. Primary biliary cirrhosis, congestive liver disease and family history of liver cancer increase the risk of HCC incident[9]. These factors are clearly illustrated in Table 1.

Table 1 Non-viral factors associated with hepatocellular carcinoma

Non-viral factors contributing hepatocellular carcinoma	Ref.
Hereditary hemochromatosis	Powell *et al*[23]
Non-alcoholic fatty liver disease	Caldwell *et al*[14]
Obesity	Wolk *et al*[36]
Diabetes	El-Serag *et al*[15]
Diet	Polesel *et al*[44]
N-nitroso compounds	Sauvaget *et al*[47]
Alcohol	Donato *et al*[52]
Smoking	Marrero *et al*[55]
Oral contraceptives	Rosenberg[63]
Betel quid	Tsai *et al*[70]
Aflatoxin	Qian *et al*[77]
Coffee	La Vecchia *et al*[81]
Schistosomiasis	Ezzat *et al*[87]
Pesticides	Anwar *et al*[10]
Thorotrast	Bull *et al*[89]
Alpha-1 antitrypsin deficiency	Van Thiel *et al*[90]
Autoimmune hepatitis	Wong *et al*[92]
Porphyrias	Mogl *et al*[96]
Wilson disease	Reyes[98]
Primary biliary cirrhosis	Liang *et al*[100]
Congestive liver disease	Muguti *et al*[102]
Family history of liver cancer	Turati *et al*[103]

Emerging evidence suggests that the etiology of many cases of HCC is in fact multifactorial, including both viral infections and non-viral environmental and dietary exposures[18].

Hereditary hemochromatosis (iron overload syndromes)

Hereditary hemochromatosis, a condition characterized by excess iron absorption, is caused by mutations in the *HFE* gene and/or other mutations in the iron metabolism machinery. This condition represents one of the most common autosomal recessive genetic disorders, affecting as many as 1 in 200 people of Northern European descent[23]. The *HFE* gene is required for efficient *in vivo* iron metabolism and two mutations within the *HFE* gene product, C282Y and H63D, have been well described in patients with hereditary hemochromatosis[24]. The C282Y mutation, which results in a base pair substitution in which tyrosine is substituted for cysteine at amino acid 282, is found in the homozygous state in up to 83% of patients with hereditary hemochromatosis[24].

The H63D mutation, characterized by substitution of histidine with aspartic acid at codon 63, is present in a minority of cases of hereditary hemochromatosis either in a homozygous state or with one copy of the C282Y mutation, a state referred to as a compound heterozygote[24]. The clinical significance of this latter mutation within the *HFE* gene, however, continues to be controversial. The altered iron metabolism seen in hereditary hemochromatosis leads to excess iron storage in the liver and the subsequent development of liver dysfunction.

Although other organs systems are also susceptible to iron overload, the liver bears the majority of malignant disease, with those patients with hereditary hemochromatosis being 20 times more likely to develop liver cancer

than all other cancers combined[25]. Several population-based and case-control studies have shown that the diagnosis of hereditary hemochromatosis confers a consistent and markedly elevated risk for the development of HCC[25-27].

In addition, the relationship between hereditary hemochromatosis and HCC is modified by diabetes, sex and genetics. Subjects with liver cancer and concomitant diabetes mellitus were 82 times more likely to have a diagnosis of hemochromatosis[26]. Furthermore, a population-based study from Scandinavia found that men with hemochromatosis had a 29-fold increase in risk of liver cancer, whereas women with hemochromatosis had a sevenfold increase in risk[25].

In fact, those patients with excess total body iron secondary to other etiologies have been shown to have a higher risk of HCC in the absence of genetic hemochromatosis[28]. Studies have suggested that conditions such as β thalassemia or iron overload in people of African descent might be associated with an increased risk of HCC[28,29]. Mandishona *et al*[28] found that African iron loaded subjects had a 10-fold increase in the risk of developing HCC after adjusting for viral hepatitis, alcohol use and environmental exposures, such as aflatoxin. Regardless of etiology, iron overload is not a benign condition and when recognized, surveillance for HCC should be undertaken[30].

Non-alcoholic fatty liver disease

Several case reports and subsequent observational studies have proposed that non-alcoholic fatty liver disease (NALFD), and more specifically, NASH, confers an elevated risk of developing HCC[14]. NAFLD is a spectrum of clinical disease that ranges from benign or bland steatosis to NASH. The latter stage of this disease, through a process of chronic inflammation and subsequent hepatic fibrosis, can lead to cirrhosis[31]. The presence of cirrhosis itself is an independent risk factor for the development of HCC[32].

To characterize the natural history of NAFLD, 420 patients identified in Olmstead County, United States with liver disorder were followed for an average of 7 years to determine overall mortality. In this population based study, NAFLD was associated with a 34% increase in mortality and a significant increase in the risk of HCC, with two cases or 0.5% being diagnosed over the period of follow-up[33]. NASH-related cirrhosis, however, the rate of HCC approached 10%[33]. In another study in Japan, among 82 NASH patients treated from 1990 through 2001, six patients with HCC were identified over 11 years of follow-up[34]. All six patients developed HCC in the setting of NASH-related cirrhosis[34]. These data highlight an association between NASH cirrhosis and an increase in the incidence of HCC over that of the general population. Therefore, regular HCC surveillance is imperative in patients with NASH cirrhosis.

In advanced fibrosis, an absence of steatosis may be appreciated, a finding which can obscure identification of the underlying etiology of liver injury in these patients, in this case, patients might be classified as having cryptogenic cirrhosis (cirrhosis due to unidentified causes). In a United States study that examined 105 consecutive patients with HCC, after HCV, cryptogenic cirrhosis was the most common etiology of liver injury[35]. Furthermore, only 23% of patients with cryptogenic cirrhosis were undergoing surveillance for HCC in comparison to 61% of subjects who had a history of HCV-related liver disease[35]. These observations emphasize the importance of HCC surveillance in this group of patients and the failure thus far to appropriately screen for HCC in this disease process[18].

Obesity

The prevalence of obesity has increased to epidemic proportions over the last three decades. Excess body mass is classified as overweight if the body mass index (BMI) is > 25 kg/m^2 and < 30 kg/m^2, or obese if the BMI is $\geqslant 30$ kg/m^2. In addition to the increase in an array of disease processes observed with being overweight or obese, both classifications of excess body mass are associated with a higher risk of developing all cancers, including liver cancer[13].

In one population-based study from Sweden, 28 cases of HCC were diagnosed in 28129 patients from 1965 to 1993, thus conferring an almost threefold higher risk of HCC in obese patients[36]. A recent European case-control study observed a significantly increased risk of HCC among obese or diabetic patients without viral hepatitis. This risk of HCC was even greater if both obesity and diabetes were present in co morbid conditions[37].

A Danish study further confirmed these results, finding a twofold increase in liver cancer incidence in obese subjects compared to non-obese subjects[38]. Generally, it was concluded that patients who were overweight had a 17% increase in risk of developing HCC, whereas obese patients had an 89% increase in risk[39]. Based on the prevalence of HCC, it was estimated that 28% of HCC cases in men and 27% in women were due to being overweight or obese[39].

In addition to an increased risk of developing HCC, overweight or obese patients appear to be at increased risk for HCC-related mortality. In a population-based study of cancer mortality and BMI, men with a BMI of 30-34.9 were found to have a twofold increase in the risk of death from HCC, with a 4.5-fold increase noted in men with BMI > 35[13]. Lastly, *via* the pathway of the metabolic syndrome with resultant NASH cirrhosis, obese patients have been found to be at an increased risk for HCC occurrence.

Many lines of evidence point to the role of cirrhosis as a mediator in these patients. Patients presenting with cryptogenic cirrhosis were found to have a significantly higher prevalence of obesity than patients with cirrhosis from non-alcoholic hepatitis C or autoimmune liver disease, but a similar prevalence of obesity when compared to patients with documented NASH[40]. These data are

supported by a case-control study in which 49 patients with cryptogenic cirrhosis were compared to 98 matched controls with an established cause of cirrhosis. In that study, obesity was significantly more prevalent in the cryptogenic cirrhosis patients[41].

Therefore, being overweight and obesity, secondary to cryptogenic cirrhosis, or more likely undiagnosed NASH cirrhosis, can increase the risk of developing HCC. Clearly, these data suggest that screening is important for diagnosis of asymptomatic HCC and highlight the need for surveillance in this population.

Diabetes

Diabetes has been found to increase the risk of developing chronic liver disease and HCC[15]. The mechanisms are yet to be elucidated but insulin resistance with secondary hyperinsulinemia is the most supported hypothesis since it may have a mitogenic effect by activating insulin-like growth factor-1 receptor[42]. Studies that have compared patients with cryptogenic cirrhosis to patients with a known etiology of their cirrhosis have shown a significantly higher prevalence of diabetes among the latter group[40,41]. As noted with the overweight and obese, a similar prevalence of diabetes has been observed among patients with cryptogenic and NASH cirrhosis[40].

In a recent systematic review of 13 case control studies, 11 supported an association between diabetes and the development of HCC[38]. Among the 13 case-control studies, subjects with diabetes were found to have a two-fold increase in the risk of HCC, an association that was further strengthened by excluding studies with significant heterogeneity[43].

The presence of diabetes remained an independent risk factor for HCC after adjustment for alcohol use or viral hepatitis[43]. However, as dictated by the limitations of the studies available in the literature, further well-defined studies are required to account for dietary factors and obesity[18].

Diet

Several studies have examined whether alterations in diet have an effect on the risk of HCC. A trial from Italy has examined a broad range of dietary habits among 185 patients with HCC and 412 patients without cancer[44]. HCC were more likely to consume a large amount of calories, were five times more likely to be former drinkers, and were 30 times more likely to be infected with either HCV or HBV.

Among dietary compounds, consumption of iron and thiamine were associated with a significant threefold and twofold increase in risk of HCC, respectively. An association between intakes of iron was also evaluated according to the presence or absence of viral hepatitis[44]. When compared to appropriate controls, consumption of iron among patients without viral hepatitis was associated with a significantly increased risk of HCC[44]. This increase in risk was not conferred to those with HCV or HBV, Conversely, β-carotene and linoleic acid consumption was associated with a reduced risk of HCC[44].

In a similar study, those subjects with consumption in the highest quartile for yogurt and milk, white meat and eggs had a significantly lower likelihood of developing HCC[45]. This effect was observed in patients with and without viral hepatitis[45]. Other studies from Japan and Europe have found those who consume a large amount of green vegetables have a significantly lower likelihood of developing HCC[46,47]. Sauvaget *et al*[47] added that eating green vegetables daily had a protective effect against the development of HCC, as compared with consumption fewer times per week.

In summary, there is evidence to suggest that consumption of yogurt and milk as well as vitamin supplements offers a protective effect against HCC. The enthusiasm for these findings however should be tempered by the fact that the majority of these studies were retrospective in nature[18].

Food containing N-nitroso compounds

Nitrites are found in smoked and cured fish, cheeses, bacon, hotdogs and other cured meats[48]. Nitrites are mainly manufactured as a food preservative. Both nitrates and nitrites are used extensively to enhance the color and extend the shelf life of processed meats. Nitrate is a normal component of the human diet, with the average daily intake from all sources estimated at 75 milligrams. Upon ingestion, about 5% of the nitrate taken in by healthy adults is converted (reduced) to nitrite by bacteria in saliva; further nitrate is converted by bacteria inside the alimentary tract[49].

Certain conditions in the stomach can increase the conversion of nitrate to nitrite, specifically when the pH of the gastric fluid is high enough (above 5) to favor the growth of nitrate-reducing bacteria. This process is of major concern for infants, whose gastrointestinal systems normally have a higher pH than those of adults. Nitrites in the stomach can react with food proteins to form N-nitroso compounds; these compounds can also be produced when meat containing nitrites or nitrates is cooked, particularly using high heat[49].

Animals with low or long-term exposure to N-nitroso compounds in food or drinking water recorded liver cancer[50]. However, all animals exposed to N-nitroso compounds suffered internal bleeding, usually followed by death[51]. It is not yet known if these compounds will cause similar effects in humans. However, there is a high probability that breathing or touching N-nitroso compounds causes liver disease and cancer[51].

Alcohol

The mechanism by which alcohol consumption increases the risk of HCC is primarily through the development of cirrhosis. It has been suggested that heavy alcohol consumption of > 80 g/d ethanol for at least 5 years increases the risk of HCC by nearly 5-fold[52]. The risk appears to be proportional to the amount of alcohol consumed. In addition to a daily dose response, persistent alcohol

consumption appears to have a long-term effect on the risk of HCC occurrence. A prospective case-control study from Japan has observed that heavy alcohol drinkers, defined as > 600 L of alcohol during a lifetime, had a five-fold increase in the risk of HCC in comparison to non-drinkers or those who consumed < 600 L of alcohol[53]. However, the risk of HCC among those who consume low or moderate levels of alcohol remains unknown[4].

An association between genetic polymorphisms of the enzymes participating in the metabolic pathway of ethanol and the increased risk of HCC in heavy alcohol drinkers has been also proposed as a mechanism by which HCC develops. The frequency of aldehyde dehydrogenase 2 (*ALDH2*) genotype polymorphisms is significantly associated with increased risk of HCC in heavy alcohol drinkers[53].

Glutathione S-transferases (GST) are a super family of detoxifying enzymes involved in the neutralization of endogenous by-products of oxidative stress and exogenous chemicals of proven carcinogenicity. A study from Italy has observed that, among subjects who consumed > 100 g/d of ethanol and were bearers of the GST M1 (*GSTM1*) null genotype (*i.e.*, partial deletion of the coding sequence causes the total absence of enzymatic function) had twice the risk of HCC compared with bearers of the *GSTM1* non-null genotype[54].

Smoking

Several studies have evaluated the association between smoking and development of primary liver cancer. An effect of tobacco in the development of HCC is biologically plausible, due to the carcinogenic potential of several of the ingredients in tobacco that are metabolized in the liver[55]. A prospective cohort study including 4050 men aged ⩾ 40 years who were followed-up for an average length of 9 years observed that those who smoked had a threefold increased risk of primary liver cancer when compared to never smokers[56]. Additionally, a study from Korea has found a 50% increase in the risk of primary liver cancer for current male smokers compared to never smokers[57]. In contrast however, a recent population-based case-control study from the United States did not observe a significantly increased risk of primary liver cancer among current male smokers[58]. Male ex-smokers, however, had a significant increase in risk of primary liver cancer, which suggests that there is perhaps a dose or duration response underlying this association[56-58]. Although the amount of smoking did not alter the risk of HCC, the duration of smoking significantly increased the risk of HCC for subjects who had smoked for > 20 years when compared to those who had smoked for < 10 years[59].

The association between tobacco and liver cancer and its reliance on host factors such as genetics, sex, and an underlying history of viral hepatitis has also been explored. With respect to the role of genetics, a small study from Japan has evaluated 78 patients with HCC and genetic polymorphisms of tobacco and alcohol-related metabolizing enzymes and 138 hospital controls without cancer. They have demonstrated that cigarette smokers did not have a significantly increased risk of HCC when compared with non-smokers[53]. To analyze the effect of sex, a prospective cohort study that included 83885 patients followed up for 8 years observed a positive association between smoking and HCC in women who smoked > 10 cigarettes per day[60]. However, no significant increase in the risk of HCC was demonstrated among male smokers[60].

In addition to an increase in the risk of developing HCC, it is also suggested in the literature that smoking increases the risk of death in HCC. In the Korean Cancer Prevention cohort study, men who were current smokers had an increased risk of death from HCC[59]. Women who were current smokers did not have the same elevation in risk of HCC-related death as that observed in men[59]. Marrero *et al*[55] showed a synergistic interaction between heavy alcohol consumption, heavy tobacco smoking and obesity on the risk of HCC. However, the biological mechanism for the synergy between tobacco, alcohol and obesity is unknown.

Lastly, to determine the effect of viral hepatitis on the association between HCC and tobacco, a prospective study of 12008 men observed that smoking significantly increased the risk of HCC only in anti-HCV-positive patients but not in those who were anti-HCV-negative when compared to anti-HCV-negative nonsmoking individuals[61].

Oral contraceptives

Prior to the widespread use of oral contraceptives (OCs), benign liver tumors in young women were rarely observed[18]. In current literatures, therapy with oral contraceptives appears to be associated with the development of benign liver tumors such as hepatic hemangioma, hepatocellular adenoma or focal nodular hyperplasia[62]. Although not well researched, it has been proposed that OCs might also be associated with malignant liver tumors including HCC[63].

Rarely, malignant transformation can occur within the context of hepatic adenomas. It is unclear, however, whether the use of OCs influences the likelihood of developing adenoma and that these benign tumors transform into tumor[64]. Within the literature, there have been 14 cases of hepatic adenoma with focal malignant transformation to HCC in women taking OCs[64,65]. The mean age of these patients at the time of diagnosis of malignant transformation was 36 years (range: 23-57 years) and the mean duration of OCs use was 11 years (range: 1 mo-20 years)[66]. The frequency of HCC among hepatic adenomas appears to vary from 5% to 18%[67,68].

To evaluate further the risk of HCC in the setting of OCs use, several observational studies have been conducted. A recent meta-analysis of 12 case-control studies, including 739 cases and 5223 controls, which evaluated the risk of HCC among women using OCs indicated that there was no increase in risk of HCC with short-term use; defined as < 5 years of exposure[69].

An adjusted analysis, which accounted for variables

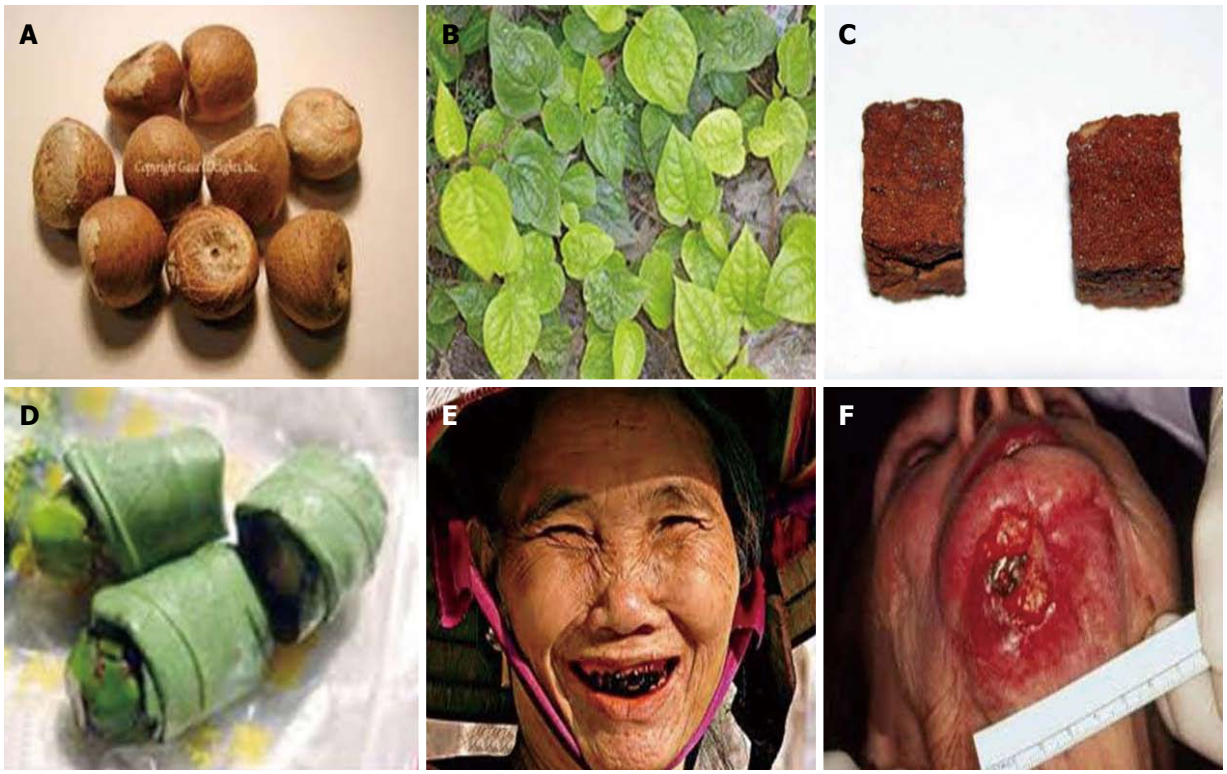

Figure 1 These ingredients have been shown to have genotoxic, mutagenic and tumorigenic properties. A, B: Nuts and leaves of Piper betle; C, D: Different forms of betel quid chew; E, F: Side effects of betel quid chewing. (A: medicalinspection.net; B: iamshaman.com; C: wholesaleshamanicherbs.com; D: gethealthyclarkcounty.org; E: vietnamgrouptour.com; F: medianlinspection.net.)

such as age, race and parity, did not yield significant findings[69]. On the contrary, another study has observed a significantly increased risk of HCC among women taking OCs for > 5 years; an increase in risk of 2-20 fold[69]. However, given the variable periods of duration used in the study, a pooled estimate of risk could not be generated[69]. Based on these results, further studies are required to evaluate the association between OCs and the risk of HCC and how such risk is modified by duration of OCs use. Additionally, it should be noted that an association between new-generation OCs with lower doses of hormones and the risk of HCC has not yet been explored[18].

Betel quid

Betel quid is one of the most addictive substances used in Asia and among migrated communities in Africa, Europe and North America. The chewing of betel quid is woven into the cultural fabric of up to 20% of the world population. Betel quid consists of the nut of the *Areca catechu* palm (areca nut), betel leaf or fruit from *Piper betle* and red slaked paste[70]. These ingredients have been shown to have genotoxic, mutagenic and tumorigenic properties[71] (Figure 1).

A case-control study from Taiwan has shown that betel quid chewing was an independent risk factor for liver cirrhosis[72]. Contrary, a prospective case-control study from Asia has observed a significant association between betel quid chewing and the incidence of HCC. This study included 263 pairs of age- and sex-matched patients with HCC and healthy controls and observed that betel quid chewing was a dependent risk factor for HCC, with a threefold risk noted. The aggregate risk increased with increasing duration and/or quantity of consumption[70]. These data were further supported by a study from Taiwan, including 420 age- and sex-matched patients with HCC and liver cirrhosis, liver cirrhosis only and healthy controls. In this study, a nearly six fold and nearly twofold increased risk of HCC was observed in patients with HCC compared with healthy controls and patients with liver cirrhosis, respectively[73].

Aflatoxin

Aflatoxin B1 (AFB1) is the major metabolite of the molds *Aspergillus fumigatus* and *Aspergillus parasiticus*. These molds grow on a variety of food products that are stored in warm and damp conditions or are cultivated in countries with hot and humid climates[6]. AFB1 induces a single nucleotide substitution in codon 249 in the *p53* tumor suppressor gene, which results in the change of the amino acid arginine to serine[74] which is indigenous to geographic regions with high exposure to AFB1[75]. On the other hand, this mutation is absent in patients with HCC from regions with low exposure to AFB1[75]. Moreover, it has been recently demonstrated that AFB1-albumin adducts in patients with HCC correlate significantly with the presence of plasma DNA hypermethylation and mutations in the *p16* and *p53* tumor suppressor genes[76].

Several studies have evaluated an association between

the risk of HCC and exposure to AFB1. A prospective case-control study from China which included 18244 middle-aged men showed that individuals with the presence of urinary aflatoxin biomarkers had a significantly increased risk of HCC after adjusting for HBV surface antigen seropositivity and cigarette smoking[77]. These data were further supported by a community-based cohort study from Taiwan which found that elevated AFB1 exposure measured by detectable AFB1-albumin adducts was an independent risk factor for HCC after adjustment for important confounders.

In Egypt, Dilber *et al*[78] detected a significant higher percent of aflatoxins in the serum of Egyptian patients with HCC compared to their controls; with a twofold increased risk. Hifnawy *et al*[79] revealed the prevalence of AFB1 contamination in corn, wheat, peanut, lupine, white rice, cowpea, fava bean and brown rice by 64.7%, 53%, 53%, 47%, 47%, 41%, 29.4% and 29.4%, respectively.

It should be stressed that areas with high exposure to AFB1 are also characterized by a high prevalence of HBV infection. AFB1 is independent of the risk conferred by HBV; however concomitant exposure to both HBV and AFB1 markedly increases the risk of HCC. The risk of HCC was 60 times higher in patients with HBV infection and a concomitant elevation of urinary AFB1 markers[80]. Patients with HBV infection and normal urinary AFB1 markers had sevenfold increase in risk of HCC when compared to those without HBV infection[81].

Coffee

In addition to its reported association with reductions in bladder cancer and colorectal cancer, coffee consumption has also been extensively studied and appears to have a potentially favorable effect on the prevention of liver diseases, including HCC[82]. There are several hypotheses that could explain why consuming coffee attenuates the risk of developing HCC. One hypothesis argues that coffee intake lowers serum levels of γ-glutamyl transferase, which is associated with a lower incidence of HCC[83,84]. Coffee consumption has also been linked to a lower incidence of cirrhosis, which is a major risk factor for the development of HCC[84].

An analysis of two large prospective studies of 70000 participants in Japan has shown that those who drank one or more cups of coffee daily had a significantly lower risk of developing HCC[85]. A case-control study of 2746 people has found that those who drank three or more cups of coffee were 40% less likely to develop HCC[84].

In summary, those who drank any coffee compared to non-drinkers had a significantly lower risk of HCC. The greater the coffee consumption, the greater the attenuation in HCC risk. Low coffee consumption was associated with a 30% reduction in risk and high consumption with a 55% reduction in HCC risk[85].

Although these results are impressive and consistent, one must consider that the findings of an inverse relationship between coffee consumption and the risk of HCC might be influenced by bias. Coffee metabolism is impaired in cirrhotic livers as compared to the normal liver. This altered metabolism generates an increase in the untoward side effects of the beverage. Therefore, the presence of liver disease might lead affected patients to consume less coffee. This could result in a falsely negative association. Therefore, the potential bias of this association in the liver disease patient cannot be discounted[18].

Schistosomiasis

Schistosomiasis, caused by infestation with trematode blood flukes, is endemic in tropical areas of Africa, South America, Asia and the Caribbean. Three species of schistosomes, *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi* preferentially infect the liver, however, only *S. japonicum* has been classified as possibly carcinogenic in humans[86]. A recent study has supported the role of *S. japonicum* infection in HCC as a cofactor with HBV and HCV infections rather than as a primary hepatocarcinogen[87].

Pesticides

Occupational exposure to pesticides may have a contributory role in the etiology or progression of HCC[10]. According to McGlynn *et al*[88] no statistically significant associations between HCC and household application of pesticides were observed for urban males or for females. As expected, the strongest risk factors for HCC were HCV and current HBV infection. This study therefore suggested that exposures to organophophorus and carbamate pesticides are additive risk factors to current HCV and HBV infection among rural males. Future investigation should address the possible hepatocarcinogenicity of pesticides using biomarkers of exposure and other techniques to better estimate dose-response relationships[10].

Thorotrast

Persons exposed to Thorotrast, an X-ray contrast medium (thorium dioxide) have found a 120-fold increased risk of primary liver cancer, largely due to risks of angiosarcoma and intrahepatic cholangiocarcinoma[89].

Alpha-1 antitrypsin deficiency

It is an autosomal recessive disorder resulting in the expression of a defective alpha-1 antitrypsin protein as a consequence of the presence of an abnormal allele. Liver disease in alpha-1-antitrypsin deficiency is caused by a gain-of-toxic function mechanism engendered by the accumulation of a mutant glycoprotein in the endoplasmic reticulum[20]. HCC is common in children with alpha-1 antitrypsin deficiency and cirrhosis as well as in adults who are 50-60 years of age. In the adult cases of alpha-1 antitrypsin with cirrhosis, HCC is reported to occur in 31%-67% of cases[90]. The hepatic endoplasmic reticulum and mitochondrion in individuals with alpha-1 antitrypsin deficiency demonstrate morphologic and biochemical abnormalities. As a result, the sum of the many different cellular injuries associated with oxidative stress especially with mitochondrial injury is thought to be the driving force for HCC development in cases of alpha-1 antitryp-

sin deficiency[91].

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a disease of unknown etiology[21]. It is an inflammation of the liver that occurs when immune cells mistake the liver's normal cells for harmful invaders and attack them. It is an anomalous presentation of human leukocyte antigen class Ⅱ on the surface of hepatocytes, possibly due to genetic predisposition or acute liver infection that causes a cell-mediated immune response against the body's own liver. Researchers think a genetic factor may make some people more susceptible to autoimmune diseases. About 70 percent of those with autoimmune hepatitis are female. The disease is usually quite serious and, if not treated, gets worse over time. Autoimmune hepatitis is typically chronic, meaning it can last for years, and can lead to cirrhosis the liver. Eventually, liver failure can result[92].

The risk of HCC among patients with AIH is believed to be low compared with other chronic liver diseases. The risk of HCC among AIH patients with cirrhosis is 1.9% per year. This is comparable to HCC risk among patients with cirrhosis secondary to HBV, HCV, hemochromatosis, or alcohol-related liver disease[93]. Meza-Junco *et al*[21] added that HCC occur in 7% of patients with AIH and cirrhosis of at least 5 year durations, with an incident of 1 per 350 patients-years. When this study excluded HCV infection, they found that one case of HCC with 212 patients with HIA (0.5%) in absence of viral infection.

Porphyries

Hepatic porphyries are a group of inherited diseases caused by partial enzyme defects in haem biosynthesis. They manifest with either neurological complications ("acute") or skin problems ("cutaneous"), or occasionally both. The term derives from the Greek, *porphyira,* meaning "purple pigment". The name is likely to have been a reference to the purple discolouration of feces and urine in patients during an attack[94]. The commonest types are acute intermittent porphyria (AIP) and variegate porphyria. Clinically these porphyrias are characterized by occasional acute attacks consisting of abdominal pain and various neuropsychiatric symptoms. The prognosis of patients with acute hepatic porphyria has improved greatly during recent decades[95].

An association between HCC and AIP was first suggested by Mogl *et al*[96] in Sweden. Kauppinen *et al*[19] recorded that in acute hepatic porphyria, the calculated risk of hepatocellular carcinoma is increased 61-fold. In addition, a significant iron overload, as found in hereditary hemochromatosis, is a risk factor for HCC and may also promote the symptoms of porphyria cutanea tarda.

Wilson disease

Wilson disease (WD), an inborn copper metabolism defect, is traditionally diagnosed on the basis of clinical features, positive family history, biochemical parameters, the presence of Kayser-Fleischer rings on slit lamp eye examination, and neurologic abnormalities[97].

Carcinogenesis in WD is thought to be the result of accumulated copper in the liver and underlying cirrhosis[22]. Although copper deposition in the liver is actually a risk factor for the development of HCC, some researchers have observed that decreased copper in patients following D-penicillamine and other chelator treatments may enhance the risk of developing HCC[98]. Guan *et al*[99] reported the occurrence of HCC in a young woman with Wilson's disease who had never been took oral contraceptives or exposed to hepatitis B virus. Therefore, all newly researches indicated that WD is a risk factor for HCC[22].

Primary biliary cirrhosis

Several studies have indicated that primary biliary cirrhosis (PBC) may be associated with increased risk of some cancers and HCC[100]. PBC primarily affects females and is rarely complicated by HCC. Although HCC incidence in PBC patients is low, several characteristics and risk factors associated with its development have been reported. Males are at risk of developing HCC at any histological stage of PBC. Therefore, male PBC patients in particular should be carefully screened for HCC from the early stages of PBC[101].

Congestive liver disease

Muguti *et al*[102] found that among 17 patients with hepatic focal nodular hyperplasia (FNH), FNH was found in association with hepatocellular carcinoma in three, one of whom also had peliosis and an hepatic adenoma. FNH was also found in association with other conditions which may affect hepatic function, structure or circulation, including chronic obstructive airways disease, congestive cardiomyopathy, chronic active hepatitis, granulomatous hepatitis, coeliac artery stenosis and metastatic malignant melanoma. This observation draws attention to a possible link between FNH, hepatic malignancy and conditions which may disturb the hepatic circulation. Therefore, patients with FNH should be investigated thoroughly and an aggressive management policy should be adopted.

Family history of liver cancer

In a study conducted in the United States, individuals with a first-degree family history of liver cancer (liver cancer in a parent, sibling, or child) were roughly four times more likely to develop liver cancer than individuals without such a family history. This increased risk was observed even in the subset of people without viral hepatitis[9,103]. This study suggests that either genetic factors or shared environmental factors influence the risk of liver cancer.

CONCLUSION

Multiple non-viral factors have been implicated in the development of HCC. Hemochromatosis and iron overload

syndromes have consistently been shown to dramatically increase the rate of HCC. Additionally, factors such as obesity and diabetes, which operate *via* NASH cirrhosis or perhaps independently, have also been demonstrated to increase the risk of HCC. With respect to other exposures, although alcohol and tobacco clearly increase the risk of HCC development and mortality, other exposures such as coffee and high levels of vegetable consumption may be protective against this condition.

Further studies are urgently needed to determine the pathogenesis that underlies the occurrence of HCC in the setting of these exposures, as well as the way in which such risk is modified by environmental and host characteristics such as genetics.

Clarification of relevant non-viral causes of HCC will help to focus clinicians on those risk factors that are modifiable. With more information, future surveillance efforts will be more appropriately targeted toward populations at greatest risk.

This multilevel preventative approach will hopefully lead to a reduction in incidence of non-viral HCC, and a decrease in the patient morbidity and mortality as well as the societal economic burden associated with HCC.

REFERENCES

1 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]

2 **El-Serag HB**. Hepatocellular carcinoma: an epidemiologic view. *J Clin Gastroenterol* 2002; **35**: S72-S78 [PMID: 12394209 DOI: 10.1097/00004836-200211002-00002]

3 **Thomas MB**, Zhu AX. Hepatocellular carcinoma: the need for progress. *J Clin Oncol* 2005; **23**: 2892-2899 [PMID: 15860847 DOI: 10.1200/JCO.2005.03.196]

4 **El-Serag HB**, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132**: 2557-2576 [PMID: 17570226 DOI: 10.1053/j.gastro.2007.04.061]

5 **Poustchi H**, Sepanlou SG, Esmaili1 S, Mehrabi N, Ansarymoghadam A. Hepatocellular carcinoma in the world and the Middle East. *Middle East J Diges Dis* 2010; **2**: 31-41

6 **Kirk GD**, Bah E, Montesano R. Molecular epidemiology of human liver cancer: insights into etiology, pathogenesis and prevention from The Gambia, West Africa. *Carcinogenesis* 2006; **27**: 2070-2082 [PMID: 16679307 DOI: 10.1093/carcin/bgl060]

7 **Addario L**, Tritto G, Cavaglià E, Amodio F, Giannelli E, Di Costanzo GG. Preserved liver function, portal thrombosis and absence of oesophageal varices are risk factors for metastasis of hepatocellular carcinoma. *Dig Liver Dis* 2011; **43**: 319-324 [PMID: 20952262 DOI: 10.1016/j.dld.2010.09.003]

8 **El-Serag HB**, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; **340**: 745-750 [PMID: 10072408 DOI: 10.1056/NEJM199903113401001]

9 **Hassan MM**, Spitz MR, Thomas MB, Curley SA, Patt YZ, Vauthey JN, Glover KY, Kaseb A, Lozano RD, El-Deeb AS, Nguyen NT, Wei SH, Chan W, Abbruzzese JL, Li D. The association of family history of liver cancer with hepatocellular carcinoma: a case-control study in the United States. *J Hepatol* 2009; **50**: 334-341 [PMID: 19070394 DOI: 10.1016/j.jhep.2008.08.016]

10 **Anwar WA**, Khaled HM, Amra HA, El-Nezami H, Loffredo CA. Changing pattern of hepatocellular carcinoma (HCC) and its risk factors in Egypt: possibilities for prevention. *Mutat Res* 2008; **659**: 176-184 [PMID: 18346933 DOI: 10.1016/j.mrrev.2008.01.005]

11 **Rahman El-Zayadi A**, Abaza H, Shawky S, Mohamed MK, Selim OE, Badran HM. Prevalence and epidemiological features of hepatocellular carcinoma in Egypt-a single center experience. *Hepatol Res* 2001; **19**: 170-179 [PMID: 11164741 DOI: 10.1016/S1386-6346(00)00105-4]

12 **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 DOI: 10.1001/archinte.160.21.3227]

13 **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 DOI: 10.1056/NEJMoa021423]

14 **Caldwell SH**, Crespo DM. The spectrum expanded: cryptogenic cirrhosis and the natural history of non-alcoholic fatty liver disease. *J Hepatol* 2004; **40**: 578-584 [PMID: 15030972 DOI: 10.1016/j.jhep.2004.02.013]

15 **El-Serag HB**, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; **126**: 460-468 [PMID: 14762783 DOI: 10.1053/j.gastro.2003.10.065]

16 **Regimbeau JM**, Colombat M, Mognol P, Durand F, Abdalla E, Degott C, Degos F, Farges O, Belghiti J. Obesity and diabetes as a risk factor for hepatocellular carcinoma. *Liver Transpl* 2004; **10** (Suppl 1): S69-73 [PMID: 14762843]

17 **James WP**. The epidemiology of obesity: the size of the problem. *J Intern Med* 2008; **263**: 336-352 [PMID: 18312311 DOI: 10.1111/j.1365-2796.2008.01922.x]

18 **Blonski W**, Kotlyar DS, Forde KA. Non-viral causes of hepatocellular carcinoma. *World J Gastroenterol* 2010; **16**: 3603-3615 [PMID: 20677332 DOI: 10.3748/wjg.v16.i29.3603]

19 **Kauppinen R**, Mustajoki P. Acute hepatic porphyria and hepatocellular carcinoma. *Br J Cancer* 1988; **57**: 117-120 [PMID: 2831925 DOI: 10.1038/bjc.1988.23]

20 **Rudnick DA**, Perlmutter DH. Alpha-1-antitrypsin deficiency: a new paradigm for hepatocellular carcinoma in genetic liver disease. *Hepatology* 2005; **42**: 514-521 [PMID: 16044402 DOI: 10.1002/hep.20815]

21 **Meza-Junco J**, Montaño-Loza AJ, Martínez-Benitez B, Kimura-Hayama E. Hepatocellular carcinoma in patients with autoimmune liver diseases: two case reports and literature review. *Ann Hepatol* 2007; **6**: 122-126 [PMID: 17519838]

22 **Xu R**, Hajdu CH. Wilson Disease and Hepatocellular Carcinoma. *Gastroenterol Hepatol* (N Y) 2008; **4**: 438-439

23 **Powell LW**, Subramaniam VN, Yapp TR. Haemochromatosis in the new millennium. *J Hepatol* 2000; **32** (Suppl 1): 48-62 [PMID: 10728794]

24 **Feder JN**, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R Jr, Ellis MC, Fullan A, Hinton LM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier GA, Moeller N, Moore T, Morikan. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996; **13**: 399-408 [PMID: 8696333]

25 **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 DOI: 10.1053/j.gastro.2003.09.035]

26 **Yang Q**, McDonnell SM, Khoury MJ, Cono J, Parrish RG. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of Multiple-Cause Mortality Data. *Ann Intern Med* 1998; **129**: 946-953 [PMID: 9867747]

27 **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 [PMID: 11230745 DOI: 10.1053/jhep.2001.22506]

28 **Mandishona E**, MacPhail AP, Gordeuk VR, Kedda MA, Paterson AC, Rouault TA, Kew MC. Dietary iron overload as a risk factor for hepatocellular carcinoma in Black Africans. *Hepatology* 1998; **27**: 1563-1566 [PMID: 9620327 DOI: 10.1002/hep.510270614]

29 **Borgna-Pignatti C**, Vergine G, Lombardo T, Cappellini MD, Cianciulli P, Maggio A, Renda D, Lai ME, Mandas A, Forni G, Piga A, Bisconte MG. Hepatocellular carcinoma in the thalassaemia syndromes. *Br J Haematol* 2004; **124**: 114-117 [PMID: 14675416 DOI: 10.1046/j.1365-2141.2003.04732.x]

30 **Moyo VM**, Makunike R, Gangaidzo IT, Gordeuk VR, McLaren CE, Khumalo H, Saungweme T, Rouault T, Kiire CF. African iron overload and hepatocellular carcinoma (HA-7-0-080). *Eur J Haematol* 1998; **60**: 28-34 [PMID: 9451425 DOI: 10.1111/j.1600-0609.1998.tb00993.x]

31 **Powell EE**, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology* 1990; **11**: 74-80 [PMID: 2295475 DOI: 10.1002/hep.1840110114]

32 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]

33 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121 [PMID: 16012941 DOI: 10.1053/j.gastro.2005.04.014]

34 **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 [PMID: 12076877 DOI: 10.1016/S0168-8278(02)00099-5]

35 **Marrero JA**, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 2002; **36**: 1349-1354 [PMID: 12447858]

36 **Wolk A**, Gridley G, Svensson M, Nyrén O, McLaughlin JK, Fraumeni JF, Adam HO. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* 2001; **12**: 13-21 [PMID: 11227921]

37 **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 DOI: 10.1093/annonc/mdn565]

38 **Moller H**, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer* 1994; **30A**: 344-350 [PMID: 8204357 DOI: 10.1016/0959-8049(94)90254-2]

39 **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]

40 **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 DOI: 10.1002/hep.510290347]

41 **Poonawala A**, Nair SP, Thuluvath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. *Hepatology* 2000; **32**: 689-692 [PMID: 11003611 DOI: 10.1053/jhep.2000.17894]

42 **Noto H**, Osame K, Sasazuki T, Noda M. Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. *J Diabetes Complications* 2010; **24**: 345-353 [PMID: 20656522 DOI: 10.1016/j.jdiacomp.2010.06.004]

43 **El-Serag HB**, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; **4**: 369-380 [PMID: 16527702 DOI: 10.1016/j.cgh.2005.12.007]

44 **Polesel J**, Talamini R, Montella M, Maso LD, Crovatto M, Parpinel M, Izzo F, Tommasi LG, Serraino D, La Vecchia C, Franceschi S. Nutrients intake and the risk of hepatocellular carcinoma in Italy. *Eur J Cancer* 2007; **43**: 2381-2387 [PMID: 17719221 DOI: 10.1016/j.ejca.2007.07.012]

45 **Talamini R**, Polesel J, Montella M, Dal Maso L, Crispo A, Tommasi LG, Izzo F, Crovatto M, La Vecchia C, Franceschi S. Food groups and risk of hepatocellular carcinoma: A multicenter case-control study in Italy. *Int J Cancer* 2006; **119**: 2916-2921 [PMID: 16998792 DOI: 10.1002/ijc.22267]

46 **La Vecchia C**, Negri E, Decarli A, D'Avanzo B, Franceschi S. Risk factors for hepatocellular carcinoma in northern Italy. *Int J Cancer* 1988; **42**: 872-876 [PMID: 2847988 DOI: 10.1002/ijc.2910420614]

47 **Sauvaget C**, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. *Br J Cancer* 2003; **88**: 689-694 [PMID: 12618875 DOI: 10.1038/sj.bjc.6600775]

48 **Sarasua S**, Savitz DA. Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States). *Cancer Causes Control* 1994; **5**: 141-148 [PMID: 8167261 DOI: 10.1007/BF01830260]

49 **Lijinsky W**. N-Nitroso compounds in the diet. *Mutat Res* 1999; **443**: 129-138 [PMID: 10415436 DOI: 10.1016/S1383-5742(99)00015-0]

50 **Ramanathan S**, kuppusamy A, Nallasamy VM, Perumal P. Antitumor effects and antioxidant role of Scutia myrtina in N-Nitroso-diethylamine (NDEA) induced hepatocellular carcinoma in rats. *Asian J Pharm Biol Res* 2011; **1**: 71-78

51 **Agency for Toxic Substances and Disease Registry**. Toxicological profile for N nitrosodimethylamine. Atlanta, GA: US Department of Health and Human Services, 1989

52 **Donato F**, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, Decarli A, Trevisi P, Ribero ML, Martelli C, Porru S, Nardi G. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol* 2002; **155**: 323-331 [PMID: 11836196 DOI: 10.1093/aje/155.4.323]

53 **Munaka M**, Kohshi K, Kawamoto T, Takasawa S, Nagata N, Itoh H, Oda S, Katoh T. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and the risk of hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2003; **129**: 355-360 [PMID: 12759747 DOI: 10.1007/s00432-003-0439-5]

54 **Covolo L**, Gelatti U, Talamini R, Garte S, Trevisi P, Franceschi S, Franceschini M, Barbone F, Tagger A, Ribero ML, Parrinello G, Donadon V, Nardi G, Donato F. Alcohol dehydrogenase 3, glutathione S-transferase M1 and T1 polymorphisms, alcohol consumption and hepatocellular carcinoma (Italy). *Cancer Causes Control* 2005; **16**: 831-838 [PMID: 16132793 DOI: 10.1007/s10552-005-2302-2]

55 **Marrero JA**, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. *J Hepatol* 2005; **42**: 218-224 [PMID: 15664247 DOI: 10.1016/j.jhep.2004.10.005]

56 **Mizoue T**, Tokui N, Nishisaka K, Nishisaka S, Ogimoto I, Ikeda M, Yoshimura T. Prospective study on the relation of cigarette smoking with cancer of the liver and stomach in an endemic region. *Int J Epidemiol* 2000; **29**: 232-237 [PMID: 10817118 DOI: 10.1093/ije/29.2.232]

57 **Yun YH**, Jung KW, Bae JM, Lee JS, Shin SA, Min Park S, Yoo T, Yul Huh B. Cigarette smoking and cancer incidence risk in adult men: National Health Insurance Corporation Study. *Cancer Detect Prev* 2005; **29**: 15-24 [PMID: 15734213 DOI:

10.1016/j.cdp.2004.08.006]
58 **Zhu K**, Moriarty C, Caplan LS, Levine RS. Cigarette smoking and primary liver cancer: a population-based case-control study in US men. *Cancer Causes Control* 2007; **18**: 315-321 [PMID: 17294291 DOI: 10.1007/s10552-006-0105-8]
59 **Jee SH**, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *J Natl Cancer Inst* 2004; **96**: 1851-1856 [PMID: 15601641 DOI: 10.1093/jnci/djh334]
60 **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 [PMID: 11927497]
61 **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 [PMID: 12697571 DOI: 10.1093/aje/kwg041]
62 **Tajada M**, Nerín J, Ruiz MM, Sánchez-Dehesa M, Fabre E. Liver adenoma and focal nodular hyperplasia associated with oral contraceptives. *Eur J Contracept Reprod Health Care* 2001; **6**: 227-230 [PMID: 11848652]
63 **Rosenberg L**. The risk of liver neoplasia in relation to combined oral contraceptive use. *Contraception* 1991; **43**: 643-652 [PMID: 1651205 DOI: 10.1016/0010-7824(91)90007-3]
64 **Korula J**, Yellin A, Kanel G, Campofiori G, Nichols P. Hepatocellular carcinoma coexisting with hepatic adenoma. Incidental discovery after long-term oral contraceptive use. *West J Med* 1991; **155**: 416-418 [PMID: 1663298]
65 **Gordon SC**, Reddy KR, Livingstone AS, Jeffers LJ, Schiff ER. Resolution of a contraceptive-steroid-induced hepatic adenoma with subsequent evolution into hepatocellular carcinoma. *Ann Intern Med* 1986; **105**: 547-549 [PMID: 3019201]
66 **Ito M**, Sasaki M, Wen CY, Nakashima M, Ueki T, Ishibashi H, Yano M, Kage M, Kojiro M. Liver cell adenoma with malignant transformation: a case report. *World J Gastroenterol* 2003; **9**: 2379-2381 [PMID: 14562419]
67 **Zucman-Rossi J**, Jeannot E, Nhieu JT, Scoazec JY, Guettier C, Rebouissou S, Bacq Y, Leteurtre E, Paradis V, Michalak S, Wendum D, Chiche L, Fabre M, Mellottee L, Laurent C, Partensky C, Castaing D, Zafrani ES, Laurent-Puig P, Balabaud C, Bioulac-Sage P. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. *Hepatology* 2006; **43**: 515-524 [PMID: 16496320 DOI: 10.1002/hep.21068]
68 **Micchelli ST**, Vivekanandan P, Boitnott JK, Pawlik TM, Choti MA, Torbenson M. Malignant transformation of hepatic adenomas. *Mod Pathol* 2008; **21**: 491-497 [PMID: 18246041 DOI: 10.1038/modpathol.2008.8]
69 **Maheshwari S**, Sarraj A, Kramer J, El-Serag HB. Oral contraception and the risk of hepatocellular carcinoma. *J Hepatol* 2007; **47**: 506-513 [PMID: 17462781 DOI: 10.1016/j.jhep.2007.03.015]
70 **Tsai JF**, Chuang LY, Jeng JE, Ho MS, Hsieh MY, Lin ZY, Wang LY. Betel quid chewing as a risk factor for hepatocellular carcinoma: a case-control study. *Br J Cancer* 2001; **84**: 709-713 [PMID: 11237396 DOI: 10.1054/bjoc.1999.1597]
71 **Jeng JH**, Chang MC, Hahn LJ. Role of areca nut in betel quidassociated chemical carcinogenesis: current awareness and future perspectives. *Oral Oncol* 2001; **37**: 477-492 [PMID: 11435174 DOI: 10.1016/S1368-8375(01)00003-3]
72 **Tsai JF**, Jeng JE, Chuang LY, Ho MS, Ko YC, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML, Dai CY, Ho C. Habitual betel quid chewing as a risk factor for cirrhosis: a case-control study. *Medicine* (Baltimore) 2003; **82**: 365-372 [PMID: 14530785 DOI: 10.1097/01.md.0000090401.56130.59]
73 **Tsai JF**, Jeng JE, Chuang LY, Ho MS, Ko YC, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML, Dai CY. Habitual betel quid chewing and risk for hepatocellular carcinoma complicating cirrhosis. *Medicine* (Baltimore) 2004; **83**: 176-187 [PMID: 15118544 DOI: 10.1097/01.md.0000126971.80227.a4]
74 **Aguilar F**, Hussain SP, Cerutti P. Aflatoxin B1 induces the transversion of G--& gt; T in codon 249 of the p53 tumor suppressor gene in human hepatocytes. *Proc Natl Acad Sci USA* 1993; **90**: 8586-8590 [PMID: 8397412 DOI: 10.1073/pnas.90.18.8586]
75 **Aguilar F**, Harris CC, Sun T, Hollstein M, Cerutti P. Geographic variation of p53 mutational profile in nonmalignant human liver. *Science* 1994; **264**: 1317-1319 [PMID: 8191284 DOI: 10.1126/science.8191284]
76 **Zhang YJ**, Rossner P, Chen Y, Agrawal M, Wang Q, Wang L, Ahsan H, Yu MW, Lee PH, Santella RM. Aflatoxin B1 and polycyclic aromatic hydrocarbon adducts, p53 mutations and p16 methylation in liver tissue and plasma of hepatocellular carcinoma patients. *Int J Cancer* 2006; **119**: 985-991 [PMID: 16570275 DOI: 10.1002/ijc.21699]
77 **Qian GS**, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, Wogan GN, Groopman JD. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. *Cancer Epidemiol Biomarkers Prev* 1994; **3**: 3-10 [PMID: 8118382]
78 **Dilber MS**, Phelan A, Aints A, Mohamed AJ, Elliott G, Smith CI, O'Hare P. Intercellular delivery of thymidine kinase prodrug activating enzyme by the herpes simplex virus protein, VP22. *Gene Ther* 1999; **6**: 12-21 [PMID: 10341871]
79 **Hifnawy MS**, Mangoud AM, Eissa MH, Nor Edin E, Mostafa Y, Abouel-Magd Y, Sabee EI, Amin I, Ismail A, Morsy TA, Mahrous S, Afefy AF, el-Shorbagy E, el-Sadawy M, Ragab H, Hassan MI, el-Hady G, Saber M. The role of aflatoxin-contaminated food materials and HCV in developing hepatocellular carcinoma in Al-Sharkia Governorate, Egypt. *J Egypt Soc Parasitol* 2004; **34**: 479-488 [PMID: 15124754]
80 **Chen CJ**, Wang LY, Lu SN, Wu MH, You SL, Zhang YJ, Wang LW, Santella RM. Elevated aflatoxin exposure and increased risk of hepatocellular carcinoma. *Hepatology* 1996; **24**: 38-42 [PMID: 8707279 DOI: 10.1002/hep.510240108]
81 **La Vecchia C**, Tavani A. Coffee and cancer risk: an update. *Eur J Cancer Prev* 2007; **16**: 385-389 [PMID: 17923807 DOI: 10.1097/01.cej.0000243853.12728.76]
82 **Kono S**, Shinchi K, Imanishi K, Todoroki I, Hatsuse K. Coffee and serum gamma-glutamyltransferase: a study of self-defense officials in Japan. *Am J Epidemiol* 1994; **139**: 723-727 [PMID: 7909403]
83 **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 [PMID: 12434283 DOI: 10.1038/sj.bjc.6600582]
84 **Shimazu T**, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, Shibuya D, Tsuji I. Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. *Int J Cancer* 2005; **116**: 150-154 [PMID: 15756689 DOI: 10.1002/ijc.20989]
85 **Bravi F**, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S, La Vecchia C. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology* 2007; **46**: 430-435 [PMID: 17580359 DOI: 10.1002/hep.21708]
86 **Chou YH**, Chiou HJ, Tiu CM, Chiou SY, Lee SD, Hung GS, Wu SC, Kuo BI, Lee RC, Chiang JH, Chang T, Yu C. Duplex Doppler ultrasound of hepatic Schistosomiasis japonica: a study of 47 patients. *Am J Trop Med Hyg* 2003; **68**: 18-23 [PMID: 12556142]
87 **Ezzat S**, Abdel-Hamid M, Eissa SA, Mokhtar N, Labib NA, El-Ghorory L, Mikhail NN, Abdel-Hamid A, Hifnawy T, Strickland GT, Loffredo CA. Associations of pesticides, HCV, HBV, and hepatocellular carcinoma in Egypt. *Int J Hyg Environ Health* 2005; **208**: 329-339 [PMID: 16217918 DOI: 10.1016/j.ijheh.2005.04.003]
88 **McGlynn KA**, London WT. Epidemiology and natural

history of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 2005; **19**: 3-23 [PMID: 15757802 DOI: 10.1016/j.bpg.2004.10.004]
89 **Bull LN**, Carlton VE, Stricker NL, Baharloo S, DeYoung JA, Freimer NB, Magid MS, Kahn E, Markowitz J, DiCarlo FJ, McLoughlin L, Boyle JT, Dahms BB, Faught PR, Fitzgerald JF, Piccoli DA, Witzleben CL, O'Connell NC, Setchell KD, Agostini RM, Kocoshis SA, Reyes J, Knisely AS. Genetic and morphological findings in progressive familial intrahepatic cholestasis (Byler disease [PFIC-1] and Byler syndrome): evidence for heterogeneity. *Hepatology* 1997; **26**: 155-164 [PMID: 9214465 DOI: 10.1002/hep.510260121]
90 **Van Thiel DH**, Ramadori G. Non-viral causes of hepatocellular carcinoma. *J Gastrointest Cancer* 2011; **42**: 191-194 [PMID: 20820946 DOI: 10.1007/s12029-010-9195-3]
91 **Bogdanos DP**, Invernizzi P, Mackay IR, Vergani D. Autoimmune liver serology: current diagnostic and clinical challenges. *World J Gastroenterol* 2008; **14**: 3374-3387 [PMID: 18528935 DOI: 10.3748/wjg.14.3374]
92 **Wong RJ**, Gish R, Frederick T, Bzowej N, Frenette C. Development of hepatocellular carcinoma in autoimmune hepatitis patients: a case series. *Dig Dis Sci* 2011; **56**: 578-585 [PMID: 21046244 DOI: 10.1007/s10620-010-1444-6]
93 **Dawn BM**, Todd S, Kim SI, Glucksman M. Biochemistry and molecular biology. Philadelphia: Wolters Kluwer Health/Lippincott Williams and Wilkins, 2007
94 **Mustajoki P**. Acute intermittent porphyria. *Semin Dermatol* 1986; **5**: 155
95 **Lithner F**, Wetterberg L. Hepatocellular carcinoma in patients with acute intermittent porphyria. *Acta Med Scand* 1984; **215**: 271-274 [PMID: 6328897 DOI: 10.1111/j.0954-6820.1984.tb05005.x]
96 **Mogl MT**, Pascher A, Presser SJ, Schwabe M, Neuhaus P, Nuessler NC. An unhappy triad: hemochromatosis, porphyria cutanea tarda and hepatocellular carcinoma-a case report. *World J Gastroenterol* 2007; **13**: 1998-2001 [PMID: 17461505]
97 **Das SK**, Ray K. Wilson's disease: an update. *Nat Clin Pract Neurol* 2006; **2**: 482-493 [PMID: 16932613 DOI: 10.1038/ncpneuro0291]
98 **Reyes CV**. Hepatocellular carcinoma in Wilson Disease-related liver cirrhosis. *Gastroenterol Hepatol* (N Y) 2008; **4**: 435-437
99 **Guan R**, Oon CJ, Wong PK, Foong WC, Wee A. Primary hepatocellular carcinoma associated with Wilson's disease in a young woman. *Postgrad Med J* 1985; **61**: 357-359 [PMID: 2991870 DOI: 10.1136/pgmj.61.714.357]
100 **Liang Y**, Yang Z, Zhong R. Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis. *Hepatology* 2012; **56**: 1409-1417 [PMID: 22504852 DOI: 10.1002/hep.25788]
101 **Harada K**, Hirohara J, Ueno Y, Nakano T, Kakuda Y, Tsubouchi H, Ichida T, Nakanuma Y. Incidence of and risk factors for hepatocellular carcinoma in primary biliary cirrhosis: National data from Japan. *Hepatology* 2013; **57**: 1942-1949 [PMID: 23197466 DOI: 10.1002/hep.26176]
102 **Muguti G**, Tait N, Richardson A, Little JM. Hepatic focal nodular hyperplasia: a benign incidentaloma or a marker of serious hepatic disease? *HPB Surg* 1992; **5**: 171-176; discussion 176-180 [PMID: 1324705 DOI: 10.1155/1992/25139]
103 **Turati F**, Edefonti V, Talamini R, Ferraroni M, Malvezzi M, Bravi F, Franceschi S, Montella M, Polesel J, Zucchetto A, La Vecchia C, Negri E, Decarli A. Family history of liver cancer and hepatocellular carcinoma. *Hepatology* 2012; **55**: 1416-1425 [PMID: 22095619 DOI: 10.1002/hep.24794]

P- Reviewers Chuma M, Corrales FJ, Vivarelli M
S- Editor Wen LL **L- Editor** A **E- Editor** Li JY