REVIEW

Risk Factors of Hepatocellular Carcinoma - Current Status and Perspectives

Jing Gao[1,2], Li Xie[1,2], Wan-Shui Yang[1,2], Wei Zhang[1,2], Shan Gao[3], Jing Wang[1,2], Yong-Bing Xiang[1,2]*

Abstract

Hepatocellular carcinoma is a common disorder worldwide which ranks 5th and 7th most common cancer among men and women. In recent years, different incidence trends have been observed in various regions, but the reasons are not completely understood. However, due to the great public efforts in HCC prevention and alternation of lifestyle, the roles of some well documented risk factors played in hepatocarcinogenesis might have changed. This paper summarizes both the environmental and host related risk factors of hepatocellular carcinoma including well established risk factors such as hepatitis virus infection, aflatoxin and alcohol, as well as possible risk factors such as coffee drinking and other dietary agents.

Keywords: Hepatocellular carcinoma - risk factors - epidemiology

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Introduction

Hepatocellular carcinoma (HCC) is a common disorder worldwide which ranks the 5th and 7th most common cancer among men and women (GLOBOCAN 2008). Among the main risk factors for HCC, chronic infections of hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most important in humans, accounting for more than 70% of HCC cases worldwide (Cougot et al., 2005). Or more aggressively-close to 90% in WHO's perspective (IARC, 2008). The relative importance of HBV and HCV infections in HCC etiology varied greatly from one part of the world to another (Parkin et al., 2005; IARC, 2008; Nordenstedt et al., 2010; Sherman, 2010; Venook et al., 2010; McGlynn et al., 2011). The geographical variability in the incidence of HCC has been attributed to the changing distribution and the natural history of HBV and HCV infections. In high risk areas as most Asian and African countries, HBV is the primary cause of HCC except Japan where HCV is the predominant cause. Whereas in developed countries as United States and European countries, HCV plays a more dominant role. More than half of HCC cases were both HBsAg- and anti-HCV- in areas with low incidence such as United States and some North European countries, where heavy alcohol consumption and, possibly, obesity and diabetes mellitus may be of greater importance.

Some risk factors are region specific. In South China and sub-Saharan Africa, dietary digestions of aflatoxin are of special contributions to the risk of HCC. While among most European populations, HCV infection and alcohol consumption are the leading causes. Additional established risk factors of HCC includes excessive alcohol intake, iron overload, family history of malignant liver tumors, and possibly tobacco, diabetes and obesity. Although these factors have been indicated in the development of HCC, their contributions to the causation remains uncertain (Bartlett, et al., 2005; AICR, 2007).

Environmental risk factors

Cirrhosis

It has been recognized that the most important clinical risk factor for the development of HCC is cirrhosis. In western countries, about 70%-90% of hepatocellular carcinomas develop in patients with macronodular cirrhosis which is characterized by large nodules varying in size surrounded by fibrosis (Okuda et al., 2007; Nordenstedt et al., 2010). In eastern Asia and West Africa, the proportion of patients with pre-existing liver cirrhosis at the time of HCC diagnosis appears to be much lower, perhaps in the range of 25-50% (IARC, 2008). Approximately 80% of HCCs develop in cirrhotic livers. The high rate of co-existing cirrhosis in HCC patients and the emergence of HCC in prospectively followed cirrhosis patients have led to the assumption that pre-existing cirrhosis is an important prerequisite for hepatocarcinogenesis, although some HCCs do arise in the absence of cirrhosis. However, well-designed prospective studies on precursor liver conditions are inadequate

*[1]State Key Laboratory of Oncogene and Related Genes, [2]Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, [3]Department of Infection Management, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China *For correspondence: ybxiang@shsci.org*

in some area. So whether cirrhosis is a pre-neoplasm condition to HCC still need further investigation.

Hepatitis Viral infection

Hepatitis B virus infection: It was estimated that two billion people have been infected with HBV, and more than 350 million have chronic liver infections of which about 75% live in Asia and western pacific (WHO Media centre, 2008). The association of HCC with chronic HBV infection was recognized in the early eighties and is well-established. Chronic HBV infection is the main causal factor for HCC in the world and has been categorized as causing cancer in IARC monograph evaluations (IARC, 1994). In conservative estimation, the proportion of HCC attributed to HBV is about 54% worldwide (IARC, 2008). A national survey conducted in 2002 showed that the rate of HBsAg in the general population was 9% in China (Liang et al., 2005). Around 120 million people in China are carriers of HBV -almost a third of the people infected with HBV worldwide; 30 million people in the country are chronically infected (Liu et al., 2002; Liu et al., 2007).

Numerous epidemiological studies have been published on the relationship between HBV infection and the risk of HCC. Some of which could be traced back to 1950s (Edmondson et al., 1954, Higginson et al., 1957). Relative risk of HCC in hepatitis e-antigen (HBeAg) positive patient is much higher than among inactive hepatitis B surface antigen (HBsAg) carriers. Even patients with hepatitis B core (HBc) antibody or hepatitis B surface (HBs) antibodies are at increase risk of developing HCC but much lower than those with active infection. HBV DNA is the most important predictor of HCC development in HBsAg positive patients. Case-control studies in all regions of the world have showed in consistence that HBV are highly related to HCC with odds ratios ranging from 5 to 65 (IARC, 1994). According to three meta analyses, the combined odds ratio of HBsAg positive compared to HBsAg negative was estimated over 11 in China (Zhao et al., 1993; Luo et al., 2005; Ye et al., 2007). Findings from prospective studies also showed supportive evidence. Chien-Jen Chen used a cohort of more than 1.5 million pregnant Taiwanese women from 1983 to 2000 to study the relationships of HBV infection and parity with risk of HCC. The researchers found that risk for hepatocellular carcinoma during follow-up was statistically significantly higher among pregnant women who had chronic, active, or persistent HBV infections (and even in those who had seroclearance for hepatitis B surface antigen during follow-up) than among women who were not carriers of HBs antigen at study entry. The more children a woman had, the lower her risk appeared to be (Fwu et al., 2009). A study carried in Haimen City in China enrolled 58,545 men (15.0% HBV carriers) and 25,340 women (10.7% HBV carriers) from 1992 to 1993. After eight years follow-up, they found HCC is the major cause of death in the cohort. Among men, the cumulative risks for death from HCC were: 0.5% for HBV uninfected and 8% for HBV carriers. Among women, the cumulative risks were 0.1% for HBV uninfected and 2.0% for HBV carriers (Evans et al., 2002). Moreover, the great decrease of HCC incidence led by anti-HBV vaccine was the best evidence.

However, despite overwhelming epidemiological evidence, the role of HBV in tumor formation remains unclear. The virological aspects of chronic HBV infection are very important for determining the risk of HCC. Differences in HBV genotypes, genetic mutations may have effects on the pathogenic properties as infectivity, mechanism of transmission, capability of integration to the human DNA, and expression of HBV proteins, thus influence the disease phenotypes.

HBV has been classified into eight genotypes known as A-H and subgenotype diversity has also been observed within some genotypes (IARC, 2008). Of the eight genotypes discovered, genotypes B and C are prevalent in Asia, while genotypes A and D are prevalent in Europe, United States and Central Africa (Pujol et al., 2009). Four genotypes have been observed in China mainland and genotype B and C accounts for 95%. Genotype C is dominant in northern china and genotype B is more prevalent in south. (He et al., 2009)

Pujol, et al summarized the genotypic variations of HBV and their clinical implications (Pujol et al., 2009). Of all the genotypic variations of HBV, mutations of pre-core region and basal core promoter (BCP) are the most common ones. Reverse association has been observed between Pre-C A1896G mutation and risk of HCC(Yang et al., 2008), whereas the BCP A1762T/G1764A double mutant has been reported to be associated with an increased risk of HCC and acceleration to death from HCC in cohort studies(Baptista et al., 1999; Chen et al., 2007).

Hepatitis C virus infection: The presence of HCV was identified in 1989, 20 years later than the discover of HBV (Choo et al., 1989). HCV is an enveloped, single stranded, positivesense RNA virus which is different with HBV (Hoofnagle et al., 1999). HCV infection is a major viral cause of HCC in areas with low HBV prevalence.

The distribution of HCV infection also has considerate geographic variations. Higher prevalence was found in countries in the Far East, Latin America, Mediterranean and certain areas in Africa and Eastern Europe. A meta-analysis on the seroprevalence of hepatitis B surface antigen (HBsAg) and antibodies against hepatitis C virus (anti-HCV) from 90 studies covering 36 countries confirmed wide international variations. A predominance of HBsAg was found in HCC from most Asian, African and Latin American countries, but anti-HCV predominated in Europe, North America, Japan, Pakistan, Mongolia, and Egypt. Egypt has the highest prevalence of HCV in the world followed by Japan (Raza et al., 2007). According to the World Health Organization, about 3% of the world's population has been infected with HCV and 170 million are chronic carriers. The proportion of HCC attributable to chronic hepatitis is about 31% for HCV (IARC, 2008).

The incidence of HCC in population with HCV infection varies with the existence of co-factors such as cirrhosis, AFP level and platelet count (Fattovich et al., 2006). Generally, the yearly incidence of HCC in people with cirrhosis is 3-5% (WHO, 2002). HBV co-infection and alcohol intake may increase the incidence approximately 2- to 4-fold (Fattovich et al., 2006).

HCV-related HCCs are on the increase in many

geographical areas as a consequence of an epidemic of community-acquired infections and it's likely to get worse (Castello G et al., 2009). The age adjusted incidence rate doubled in US in the past two decades and at least half of the observed increase could be explained by HCV infection (El-Serag et al., 2003), just as the case in Japan (Umemura et al., 2009). With the wider and quicker spread of HCV, related HCC may become more severe worldwide.

The mechanism of HCC caused by HCV remains unsolved. Unlike HBV, it does not integrate into human genome, and does not seem to encode a transforming protein. Continuous inflammation and hepatocyte regeneration in the setting of chronic hepatitis and subsequent progression to cirrhosis is thought to lead to chromosomal damage and possibly to initiate hepatic carcinogenesis (Gomaa et al., 2008).

Eleven major HCV genotypes with several subtypes for each have been identified throughout the world, namely 1-11. Of all the genotypes, genotypes 1-3 have a worldwide distribution and patients infected with HCV genotype 1b have almost double the risk to develop HCC than those infected with other genotypes (Raimondi et al., 2009). Because of the genetic variation of this virus and its constant mutation, no effective vaccination against HCV is currently available (WHO, 2010).

Co-infection of hepatitis B and hepatitis C: Epidemiological studies have demonstrated that co-infection with HBV and HCV is associated with a higher risk of HCC development than either infection alone. The cumulative risk of developing HCC was 10%, 21%, and 23%, respectively, after 5 years and 16%, 28% and 45%, respectively, after 10 years (Chiaramonte et al., 1999). A meta analysis showed that co-infection with HBV and HCV was associated with an odds ratio of 136 for the development of HCC compared with 20.4 and 23.6 for HBV or HCV infection alone (Donato et al., 1998). However, some evidences from prospective studies are not supportive. To quantify the risk of cancers among persons diagnosed with HBV/HCV infections, a cohort of 39109 HBV, 75834 HCV and 2604 HBV/HCV co-infected persons was established and followed from 1990 to 2002, similar incidences were observed in HBV and HBV/HCV co-infection groups (Amin et al., 2006). Another prospective study in Taiwan obtained similar results (Sun et al., 2003). Studies in China mainland also showed inconsistence. According to Peng, et al. (2008), of the 28 case-control studies related to combined infection of both viruses, 18 observed a synergy effect, and 10 observed a antagonistic effect.

Toxins

Aflatoxin intoxication (AFT): Aflatoxins are a class of mycotoxins produced by moulds of the Aspergillus parasiticus and Aspergillus flavus. Aflatoxin B1 is the major component of these mixtures and was classified as group 1 carcinogen by IARC in 1987 (IARC, 1987). Aflatoxins grow on whole grains such as rice, corn, and wheat, as well as on peanuts, almonds, walnuts, sunflower seeds, and spices such as black pepper and coriander. Aflatoxins can contaminate these food products during processing, storage, or transport when conditions are favorable for mold growth. Humans are exposed to hepatocarcinogenic aflatoxins through ingestion of moldy foods particularly in sub-Sahara Africa, South-East Asia and China (IARC, 2008).

Over the past 40 years there have been extensive efforts to investigate the association between aflatoxin exposure and HCC. However, the quantification of AFT exposure was restricted to dietary estimation until 1980s. Several biomarkers of AFT have been identified afterwards and strong evidence between AFT and HCC has been yield since then. AFT can work independently or as a co-factor for HCC development.

Yeh et al evaluated the roles of HBV and AFB1 in the development of liver cancer in a cohort of 7917 men aged 25-64 years old in Guangxi Autonomous Region in China. A linear relationship was found between AFB1 ingestion level and mortality of liver cancer (Yeh et al., 1989). They also found serum Aflatoxin-serum albumin adducts a dosimeter of exposure. Synergy effect was observed between AFT and HBV infection. A cohort in Shanghai enrolled 18,244 middle aged men during 1986 and 1989 and followed for 70,000 person-years. They found HBsAg positivity and presence of urinary aflatoxins alone were significantly associated with 7.3- and 3.4-fold increases in HCC risk, respectively. There was a strong interaction of these two risk factors on HCC risk- individuals positive for both biomarkers exhibited a 59.4-fold elevation in HCC risk compared with those who were negative for both markers. And the author indicated that DNA adduct AFB-N7-gua formation was the best urinary marker for assessing individual exposure of AFT (Qian et al., 1994). Studies in the high-AFB1 contamination area of Qidong, China also reported similar results (Ming et al., 2002). Decreased aflatoxin contamination in the food may partly contribute to the decreasing burden of liver cancer in some areas such as China and Singapore (Yu and Yuan, 2004). With incessant economic development and increasing of living conditions in these areas, the contribution of AFT in the development of HCC may gradually fade away.

Drinking water contamination: The hypothesis of some types of drinking water as risk factor for liver cancer was first raised by Su De-long in 1972 (Su et al., 1979) and series of studies were conducted since then. In 1970s, he noticed that in epidemic areas such as Qidong, Haimen, Fusui, and Taixing in China, the incidence difference could not be explained totally by HBV and AFT. Further epidemiological studies in Qidong, Haimen and Nanhui county indicated that people who drank surface water (pond, ditch, river versus well water or deep well) had increased risk of HCC. In Qidong-Haimen area people who drank pond-ditch water had a HCC mortality of 100/100,000, while those who drank water from Yangtze River or deep water got HCC mortality about 20/l00,000 and l0/l00,000, respectively (Yu et al., 1989). Meta-analysis of 6 case-control studies in China showed an summarized OR of 2.46 (95%CI: 1.69~2.59) (Yu et al., 2001). Changing from pond/ditch to deep well (at least 200 m) water had led to a subsequent decrease in the mortality rate from HCC (Yu et al., 1986; Huang et al., 1992).

Several contaminants had been isolated from the

surface water, including blue-green algae toxins, nitrite, organochlorine pesticides, and some microelements. Among these possible carcinogens, the most convincing one is microcystins (MCs). There is a wide spectrum of cyanotoxins of which the hepatotoxins are cyclic peptides, predominantly microcystins, nodularins, and cylindrospermopsin. MCs are able to induce proliferation at low doses, induce severe intrahepatic haemorrhages, liver necrosis and may have possible synergistic effect with aflatoxins (Ueno et al., 1996; Yu et al., 2001; Clark et al., 2008). Therefore, it was defined by IARC as possibly carcinogenic to human (Cogliano et al., 2008).

Fleming et al carried a ecological study in Florida, US and observed a significantly increased risk for HCC with residence within the service area of a surface water treatment plant was found compared to persons living in areas contiguous to the surface water treatment plants. However, this increased risk was not seen in comparison to persons living in randomly selected ground water treatment service areas or compared to the Florida cumulative incidence rate for the study period (Fleming et al., 2002).

Nowadays, more and more people drink tap water. And as the water eutrophycation which could lead to cyanobacteria bloom keeps increasing, contaminants in drinking water deserves more attention.

Alcohol

Alcohol drinking was found to be related to both HCC incidence and mortality in ecological studies in mid-80s. Nanji, et al investigated the correlation of alcohol consumption and mortality of HCC in eighteen different countries and found a correlation coefficient of 0.4 (Nanji et al., 1985). Qiao, et al explored the relationships between the prevalence of HBsAg, mean annual per capita alcohol consumption and PLC death rates in 30 countries. There was a logarithmic linear relationship between per capita alcohol consumption and the PLC death rate after adjustment for the prevalence of HBsAg (partial correlation coefficient = 0.38, $p < 0.05$) (Qiao et al., 1988). Alcohol consumption was also regarded as a major risk factor for the rise in liver cancer mortality rates in Japanese men since1970 (Makimoto et al., 1999).

In areas with low prevalence of HBV and HCV infection, alcohol is an important risk factor of HCC and this has been defined as a causal relationship by IARC early to 1988 (IARC, 1988). In high incidence areas, alcohol may exacerbate viral liver damage and promote tumor development. Alcohol could lead to hepatocarcinogenesis through three possible means-causing alcohol induced cirrhosis, playing as a carcinogen, or working synergistically with other risk factors.

Alcohol is a significant cause of cirrhosis and may contribute to 15% to 45% of HCC cases in Western countries. Three population-based cohort studies in Sweden found that the standard incidence ratios (SIR) were 3.1 for alcoholic patients, 35.1 for patients with cirrhosis, and 34.3 for both diagnoses (Adami et al., 1992). In the United States, alcohol abuse is five times more prevalent than HCV infection, and is responsible for more HCC than HCV infection. The population attributable risks (PARs) of HCC in US were 16% for HBV, 22% for HCV, and 32% for alcohol. And in Italy, the proportions were 22%, 36% and 46%, respectively (Morgan et al., 2004). In Mediterranean area, the PARs were 28.8% for alcohol, 21.6% for HCV, and 16.2% for alcohol and HCV combined (Donato et al., 2006).

Case-control studies have shown that chronic, heavy ethanol consumption is associated with an approximately 2-fold increased odds ratio for HCC. The risk of HCC increased with the amount of ethanol intake and some regarded that the risk remained elevated several years after abstinence (Morgan et al., 2004), although the latter is still in controversial. Longitudinal studies also show that chronic alcohol use increases the risk for HCC. A cohort study of totally 11,837 male residents in Taiwan observed a moderate risk between alcohol drinking and HCC, with a RR of 1.46 (Wang et al., 2003). A dose-response relationship was also observed in several studies, which was summarized in a meta-analysis that the RR for liver cancer were 1.19 (95% CI: 1.12-1.27), 1.40 (95% CI:1.25-1.56), and 1.81 (95% CI:1.50-2.19) for 25, 50, and 100 g of alcohol intake per day, respectively (Corrao et al., 2004). However, some studies have showed that there may be a threshold for the effect of alcohol on liver cancer. A case-control study by Yuan, et al in US demonstrated that compared with subjects who never consumed alcohol on a weekly basis, those who consumed <2 drinks per day had an approximately 40% reduction in risk of HCC, whereas who drank > 4 drinks a day had a 3-fold increase in risk of HCC after adjustment for potential confounders (Yuan et al., 2004). A hospital-based case-control study in Brescia, Italy observed a steady increasing risk of HCC for an alcohol intake of more than 60 g/day for both men and women (Donato et al., 2002).

Studies of alcohol intake and risk of HCC were inconsistent in Chinese population. A cohort study in Sichuan province found that accumulative alcohol consumption was strongly associated to the risk of liver cancer in both men and women (Fan et al., 1996), while studies in Taixing and Huaian didn't observe a significant relationship between alcohol and liver cancer (Huang et al., 2005; Yu et al., 2008). The discordant may due to relatively small sample size or incomplete study design. In addition, a meta-analysis concluded that alcohol was a risk factor for HCC in China with a pooled OR of 1.87 (Pei et al., 2008).

Furthermore, synergistic interactions have been noticed between alcohol intake and risk factors such as hepatitis virus, diabetes, obesity, and smoking (Wang et al., 2003; Yuan et al., 2004; Singal et al., 2007; Chuang et al., 2009). As the consumption of alcohol beverages keep increasing in some parts of the world (Morgan et al., 2004) alcohol related HCC may became a more critical issue in these areas.

Tobacco

Over the past 30 years, the association of tobacco smoking with the risk of HCC has been extensively studied. However, the results were far from consistent in regard to different populations and potential confounders. Of more than 40 studies that examined the association

between 1983 and 2002, the number of studies which reported positive results was almost equal to the number with no associations (Schottenfeld et al., 2006). Although it was defined as a causal relationship by the IARC in 2004 (IARC, 2004), the US Office of the Surgeon General concluded that the evidence is suggestive but not sufficient in the same year (US Department of Health and Human Services, 2004). In order to clarify the confusion, well designed large scale case-control and cohort studies were carried out thereafter and several systematic literature reviews were conducted based on them.

Gandini, et al. reviewed 254 epidemiological studies from 1961 to 2003 and reported a pooled RR of 1.56 (95% CI: 1.29-1.87) for current smokers versus nonsmokers and a RR of 1.49 (95% CI: 1.06-2.10) for former smokers versus nonsmokers (Gandini et al., 2008). Another meta analysis by Lee, et al got an overall RR of 1.51 (95% CI: 1.37-1.67) and 1.12 (95% CI: 0.78-1.60), respectively. And the increased risk among current smokers was consistent when stratified by region, design, sample size and publication period and a positive dose-response relationship was also observed (Lee et al., 2009).

Synergistic interactions have been reported between tobacco smoking and other existing risk factors including HBV, HCV, alcohol, obesity and diabetes (Mori et al., 2000; Yuan et al., 2004; Marrero et al., 2005; Hassan et al., 2008), but the relationships are still inconclusive.

Oral contraceptives

Oral contraceptives (OCs) were first demonstrated to have relationship with benign liver tumors such as hepatic adenoma and focal nodular hyperplasia (Kenya et al., 1990; Korula et al., 1991). Transition from benign hepatic adenoma to HCC was documented (Gyorffy et al., 1989; Korula et al., 1991) and cumulative evidence indicated that there was a relationship between OC and HCC.

Most case-control studies in developed countries with low HBV prevalence consistently reported that long-term use of OC (>5 years) could increase the risk of HCC, the summary OR was 2.5 (95% CI: 1.7-3.5) in ever- vs. never- users of OCs and 5.8 (95% CI: 3.0 -11.0) for the longest duration of use (Yu et al., 2004 Schottenfeld et al., 2006). However, in populations with high prevalence of hepatitis virus infection, no significant relationship was found (WHO, 1989; Kew et al., 1990). A recent meta-analysis of 12 case-control studies indicated no association between short term OC use and risk of HCC, but the author did mention the possibility of a causal relationship in non-hepatitis B endemic areas with long-term OC use (Maheshwari et al., 2007).

Only few cohort studies were conducted on this issue and failed to find a significant association (Colditz et al., 1994; Hannaford et al., 1997). But these studies had relatively small number of case which could result in low statistical power. Based on the existing evidence, IARC concluded there was sufficient evidence that OCs were carcinogenic to human but did not make clear conclusion between OCs and HCC (IARC, 2008). More research is needed on the formulation and duration of OCs use and the risk of HCC in the existence of other important risk factors.

Dietary factors

Coffee: Many studies have reported an inverse association between coffee consumption and HCC risk as well as a favorable effect on liver function and cirrhosis. In a meta-analysis (Bravi et al., 2007) of 6 case-control studies (from Japan, Italy and Greece) and 4 cohort studies (all of these from Japan), a 41% (95%CI: 0.49-0.72) reduction of HCC risk was observed in coffee drinkers, compared to non-drinkers. The overall OR for coffee drinkers versus non-drinkers was 0.54 (95%CI: 0.38-0.67) for case-control studies and 0.64 (95%CI: 0.56-0.74) for cohort studies. However, all of the cohort studies were from Japan where coffee consumption was less frequent and did not control for HBV/HCV infections. A prospective study in Finland confirmed the association (Hu et al., 2008) and a dose-response relation was also documented (Gellati et al., 2005; Inoue et al., 2005; Hu et al., 2008).

Despite the consistency of epidemiological studies, the reason for this relationship remains unsolved. Regular coffee consumption was inverse related to serum gamma-glutamyltransferase (GGT) activity, which was widely used as a marker of cirrhosis, and other liver enzymes such as Alanine aminotransferase (ALT) and alkaline phosphatase which were markers of liver injury (La Vecchia, 2005). Various components of coffee have been related to such a favourable effect, including caffeine, coffee oils kahweol of cafestol, and antioxidant substances from coffee beans, but no definite evidence is available for any of these components (He et al., 2001; Scharf et al., 2001; Huber et al., 2002; La Vecchia, 2005).

Tea: Many studies detected that green tea consumption reduce the risk of HCC in animal model. Few reported in epidemiological studies and the results were inconsistent. A studies in China discovered a protective effect of green tea against HCC, with relative risk of 0.8 (95%CI: 0.7-1.0) for current drinkers (Yu et al., 2002). And another study found a 43% and 78% decreased risks of liver cancer among smokers or alcohol drinkers, respectively (Mu et al., 2003). But study in Qidong, China failed to find a significant association (Zhu et al., 2001). Two prospective researches conducted in Japan obtained different results. Akane Ui et al found that green tea consumption was inversely associated with the incidence of liver cancer, with HR of 0.63 (95%CI: 0.41-0.98) and 0.5 (95%CI: 0.27-0.90) for ≥5 cups/day in men and women (Ui, 2009). While no association was observed by Inoue et al. (2009). A meta-analysis also confirmed the protective effect of green tea on development of liver cancer (Fon Sing et al., 2011).

Other dietary factors: Of the 6 case-control studies related to vegetable and fruits consumption and HCC (Lam et al., 1982; Negri et al., 1991; Srivatanakul et al., 1991; Kuper et al., 2000; Yu et al., 2002; Talamini et al., 2006), three studies reported a significant inverse association between fruit intake and HCC (Negri et al., 1991; Srivatanakul et al., 1991; Talamini et al., 2006). Cohort studies from Taiwan and Japan observed a significant inverse association between vegetable and fruits consumption and risk of HCC (Yu et al., 1995; Sauvaget et al., 2003; Pham et al., 2006; Kurahashi et al.,

2009). Based on available evidence, the World Cancer Research Fund (WCRF) concluded in 2007 that there was limited suggestive evidence for the protective effect of fruit against liver cancer and limited non-conclusive evidence for vegetables (WCRF, 2007).

A study in Italy found a protective effect from milk and yoghurt (OR=0.28, 95% CI: 0.13-0.61), white meats (OR=0.44, 95% CI: 0.20-0.95) and eggs (OR=0.31, 95% CI: 0.14-0.69) (Talamini et al., 2006). Study in Haimen, China also found a favorable effect of egg, as well as other foods rich in protein (Yu et al., 2002), while a recent prospective study in US reached an opposite result (Ioannou et al., 2009). Sharp et al reported a reduced risk of HCC in Japanese atomic bomb survivors with frequent soya food consumption (Sharp et al., 2005). The relation between some nutrients intake and HCC risk were investigated, among which favorable effect were reported including flavonoid (Lagiou et al., 2008), β-carotene (Polesel et al., 2007), retinoids (Yuan et al., 2006), selenium (Yu et al., 1991), etc.

Host-related risk factors

Metabolic syndrome

Obesity: Growing evidence showed that obesity was related to both HCC incidence and mortality and the impact of obesity on HCC was greater in men than women. Calle, et al carried a prospective study of more than 900,000 US adults from 1982, compared with adults with normal weight, adults with a body-mass index (BMI) of at least 35.0 had significantly elevated relative risk of live cancer, with a RR of 4.52 (95% CI: 2.94-6.94) for men and 1.68 (95%CI: 0.93-3.05) for women (Calle, et al., 2003). Two studies from Sweden and Denmark found an excess incidence of HCC in obese patients, with a RR of 2.0-4.0 (Mokker et al., 1994; Wolk et al., 2001). A meta-analysis of 10 cohort studies found that compared with persons of normal weight, the summary relative risks of liver cancer were 1.17 (95% CI: 1.02-1.34) for those who were overweight and 1.89 (95% CI: 1.51-2.36) for those who were obese (Larsson et al., 2007)

As Asian population usually has different body composition, environmental exposures, genetic background, and socio-economic circumstances compared to western population, the effect of obesity on HCC may also be different. However, most studies with regard to this issue were carried in western countries and studies in Asian population are less convincing. In order to figure out this issue, Batty, et al examined this association using data from the Asia Pacific Cohort Studies Collaboration which has pooled individual participant data from over forty studies and a total population of 405,799. No strong evidence was found between obesity or overweight and liver cancer mortality after adjustment for age, sex and alcohol (Batty et al., 2009). However, this analysis did not adjust for hepatitis virus infection because of the lack of such information. Whether obesity is an independent risk factor for HCC is still uncertain. Further investigations on excess body weight and HCC risk are needed, especially in Asian population.

Obesity may lead to HCC through the development of non-alcoholic fatty liver disease (NAFLD), accumulation of fat in the liver to non-alcoholic steatohepatitis (NASH), cirrhosis, and liver cancer. A recent study demonstrated that obesity was a genuine promoter of HCC in a mice model depending on enhanced production of the tumor promoting cytokines IL-6 and TNF, which cause hepatic inflammation and activation of the oncogenic transcription factor STAT3 (Park et al., 2010).

Diabetes mellitus: Most epidemiological studies of Diabetes mellitus (DM) and HCC have reported a positive association so far. A study in US identified 173,643 patients, mostly man, discharged from the Department of Veterans Affairs medical system with diabetes and followed up to 2000, the incidence rate for HCC was 2.39 in diabetic patients compared with 0.87 in nondiabetic patients ($P < 0.0001$), with a hazard rate ratio of 2.16 for the development of HCC (El-Serag et al., 2004). In a systematic review of typeIIdiabetes and HCC, the pooled OR of 13 case-control studies was 2.5 (95% CI: 1.8-3.5) and the pooled RR of 17 cohort studies was also 2.5 (95% CI: 1.9-3.2). Although there was evidence that diabetes might have synergistic effects with alcohol and hepatitis virus (Hasson et al., 2002; Yuan et al., 2004), the author found it independent from these factors in his review (El-Serag et al., 2006). Two large-scale studies conducted in USA, found that metabolic syndrome increases the risk of primary liver cancer (Welzel et al., 2011; Borena et al., 2012).

A possible explanation for the association is diabetes is part of the metabolic syndrome, which increases the risk of NASH, then leads to liver cancer (El-Serag et al., 2007). Despite the possibility of a causal association, several arguments have been raised in the study of DM and HCC. One is that the relation between diabetes and HCC might be a consequence of HCV infection (White et al., 2008). Other studies suggested that diabetes might also be a consequence of cirrhosis or other chronic liver disease. Results in different populations were quite conflicting. Whether diabetes is an independent risk factor for HCC is still under question.

Furthermore, among the cohort studies, most of the reports came from US, European, or Japan, where HCV infection is common. Only one of them was conducted in a general Chinese population (Lai et al., 2006). Regarding the difference in the etiology, more study in Chinese population is needed to define a conclusive association between diabetes and risk of HCC. Other potential confounders should be included such as diet, physical activity and obesity which are highly related to diabetes. Other metabolic disorders that may increase the risk of HCC include tyrosinaemia, alpha-1-trypsin deficiency, hypercitrullinaemia, porphyria cutanea tarda and glycogen storage disease (IARC, 2008).

Iron overload: The liver is the main organ of iron storage and metabolism in the body. Therefore, abnormal iron metabolism would bring damage to liver tissue at the first place. Some metabolic disorders such as hereditary hemochromatosis (HH) are important causes of excess iron accumulation. Patients with HH were reported to have a 200-fold increased risk of HCC (Niederau et al., 1985; Kowdley et al., 2004) in earlier studies. A population-bases

study in US showed a 24-fold increased risk (Yang et al., 1998) and a study in Sweden obtained a standardized incidence ratio of 1.7 (95% CI: 1.5-2.0) (Elmberg et al., 2003).

Dietary iron overload was first described by Strachan in 1929 (Strachan AS, 1929) and was later found common in many countries in sub-Sahara Africa. People there used to consume a certain kind of home-brewed beer which had high iron content. Case-control studies showed a relative risk of dietary iron overload to HCC from 3.1 to 23.5 (Gordeuk et al., 1996; Mandishoma et al., 1998; Moyo et al., 1998).

Most commonly, iron overload led to HCC through cirrhosis, but there was evidence that iron overload could cause HCC independent of it (Blumberg et al., 1988). Moreover, iron overload may interact with HBV, HCV, alcohol and many other known HCC risk factors and act as a co-factor in the pathogenesis of HCC (Kew et al., 2009).

In conclusion, in confirmed risk factors of HCC, cirrhosis, hepatitis viral infection such as HBV and HCV are still playing important roles in hepatocarcinogenesis. However, with wider use of Hepatitis B vaccination, the importance of HBV will decrease in the future. Also, with incessant economic development and increasing of living conditions, the contribution of AFT in the development of HCC may gradually fade away in certain areas. As HCV-related HCCs are on the increase in many geographical areas, a safe and effective vaccine that prevents and treats HCV infection is urgently required. The consumption of alcohol beverages and tobacco keep increasing in some parts of the world, therefore related HCC may became a more critical issue in these areas. In possible risk factors of HCC, DM and obesity deserve more concern for their rapid increasing worldwide.

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