World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v7.i12.1708

World J Hepatol 2015 June 28; 7(12): 1708-1717
ISSN 1948-5182 (online)

SYSTEMATIC REVIEWS

Hepatocellular carcinoma in Asia: Prevention strategy and planning

Sara Ashtari, Mohamad Amin Pourhoseingholi, Afsaneh Sharifian, Mohamad Reza Zali

Sara Ashtari, Mohamad Amin Pourhoseingholi, Afsaneh Sharifian, Mohamad Reza Zali, Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran 1985717413, Iran

Author contributions: Sharifian A and Zali MR designed the research; Pourhoseingholi MA designed and checked an edited the paper as a correspondence; Ashtari S performed the research and write the paper.

Supported by Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences.

Conflict-of-interest: The authors declared do not have anything to disclose regarding funding of conflict-of-interest with respect to this manuscript.
Data sharing: No additional data are available.

Correspondence to: Mohamad Amin Pourhoseingholi, PhD, Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tabnak St, Yaman Ave, Velenjak, Tehran 1985717413, Iran. amin_phg@yahoo.com
Telephone: +98-21-22432515
Fax: +98-21-22432517

Received: September 17, 2014
Peer-review started: September 20, 2014
First decision: November 27, 2014
Revised: December 31, 2014
Accepted: May 26, 2015
Article in press: May 27, 2015
Published online: June 28, 2015

Abstract

AIM: To review all of epidemiological and etiological aspects of hepatocellular carcinoma (HCC) and examined the prevention of this disease in Asia.

METHODS: We conducted a systematic review according to the PRISMA guidelines. We were chosen articles that published previously, from PubMed (MEDLINE), the Cochrane database and Scopus. The key words used in this research were as follows: HCC in Asia and the way of prevention of this disease, with no language limitations. We selected those papers published before 2014 that we considered to be most important and appropriate. All relevant articles were accessed in full text and all relevant materials was evaluated and reviewed.

RESULTS: More than 70% of all new cases of liver cancer were diagnosed in Asia, a region that 75% of all those chronically infected with hepatitis B virus (HBV) in the world. Chronic HBV infection is the main cause of HCC in Asia, where the virus is endemic and vertical transmission is common. Japan, Saudi Arabia, Egypt and Pakistan are exception because of high prevalence of HCV infection in these regions. The prevalence of this cancer is high in Eastern and South-Eastern Asia, But Middle Eastern countries are characterized as moderate prevalence rate of HCC region and Central Asia and some part of Middle Eastern countries are known as low prevalence rate of HCC. In addition of HBV and HCV the other factors such as aflatoxin, alcohol, obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) might be responsible for a low prevalence of HCC in Asian countries. Currently available HCC therapies, chemotherapy, surgical are inefficient, mainly due to usually late diagnosis and high recurrence rates after surgical resection, and usually end with treatment failure. Liver transplantation also remains as a difficult strategy in patients with HCC. Thus prevention of HCC by treating and prevention HBV and HCV infection, the major causative agents of HCC, and the other risk

factors such as aflatoxin, alcohol, obesity, diabetes and NAFLD is of a great medical importance.

CONCLUSION: The main challenge which still present in Asia, is the high prevalence of chronic hepatitis. So, prevention of HBV and HCV is the key strategy to reduce the incidence of HCC in Asia.

Key words: Hepatocellular carcinoma; Viral hepatitis; Prevention strategy; Asian countries

Core tip: In this current review, the burden and incidence of hepatocellular carcinoma (HCC) in Asian countries, risk factors and prevention of HCC are discussed. Infection of hepatitis B virus (HBV) is the main cause of HCC in Asia continent, where the virus is endemic and vertical transmission is common. Japan, Saudi Arabia, Egypt and Pakistan are exception due to of high prevalence of HCV infection. The main challenge which still present in Asia, is the high prevalence of chronic hepatitis. So, HBV and HCV prevention is the key strategy to decrease the incidence and burden of HCC in Asia.

Ashtari S, Pourhoseingholi MA, Sharifian A, Zali MR. Hepatocellular carcinoma in Asia: Prevention strategy and planning. *World J Hepatol* 2015; 7(12): 1708-1717 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i12/1708.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i12.1708

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. HCC is the fifth most common cancer in men (554000 cases, 7.5% of the total) and the ninth in women (228000 cases, 3.4% of the total), with 782000 new cases occurring in 2012 and approximately 746000 persons die each year from this[1-3]. The rate of incidence and mortality are similar because most HCCs are diagnosed at an advanced stage[4]. HCC is the second most common cause of death from cancer in the world[1,5]. Its distribution geographically related to the hepatitis B virus (HBV) and/or HCV prevalence, which are HCC's main risk factors[6]. Its burden is the highest in the South-East Asia and Sub-Saharan Africa due to HBV infection's endemic[7] and most new cases (up to 80%) occur in theses area with the age-standardized incidence (> 20 per 100000), compared to low-incidence areas with (< 5 per 100000) in South and Central America, and the some part of Europe[6,8,9]. For men, high incidence regions are Eastern and South-Eastern Asia (> 20 per 100000). Intermediate rates occur in Southern Europe and Northern America (5-10 per 100000) and the lowest rates are in Northern Europe and South-Central Asia (< 5 per 100000)[1]. For women, the rates are much lower, the highest rate are in Eastern Asia and Western Africa (5-10 per 100000), the lowest in Northern Europe and Micronesia (< 5 per 100000)[1,3]. In Asian and African countries, HBV is the most common cause of HCC, while HCV is the most common cause in regions with a low prevalence of HBV (*e.g.,* America, Northern Europe and Australia)[10].

This cancer is generally affecting men more than women, although this difference varies across the world[4,7,11]. According to the GLOBOCON estimates for 2002, the overall male to female ratio was 2.4 and this ratio was even higher in regions with high incidence rate of HCC[9,12]. High rate of HCC in men (compare to women) may be related to higher consume of alcohol and smoking, or/and it has been related to the estrogen and androgens activities[13-15].

The age distribution of HCC varies by incidence rate, sex and region[16]. In low-risk countries (*e.g.,* United States, Canada, and United Kingdom), and also in high-risk Asian countries (*e.g.*, Hong Kong and China) the highest age-specific rates are among persons aged 75 and older[13] and this is despite the fact that, the age-specific rates occur among male aged 60 and 65 before declining in high-risk African countries (*e.g.*, Gambia, Mali), whereas the peak of female's rates are between 65 and 70 before declining[8,13].

MATERIALS AND METHODS

We conducted a systematic review according to the PRISMA guidelines. All searches for writing this review is based on the papers was found in PubMed (MEDLINE), Cochrane database and Scopus in August and September 2014 for topic of HCC in Asia and the way of prevention of this disease, with no language limitations. All relevant articles were accessed in full text and all relevant materials was evaluated and reviewed. We extracted data on epidemiology of HCC, burden and prevalence of HCC, risk factors characteristics association HCC, and prevention of HCC. All findings were reviewed and analyzed, then reported as results in the tables and text.

RESULTS

Burden of liver cancer in Asia

Asian continent covers approximately 4.3 billion people (60% of the world's current population). More than 70% (50% in China alone) of all new cases of liver cancer were diagnosed in Asia, a region that 75% of all those chronically infected with HBV in the world[17]. HBV is the main cause of HCC in Asia, where the virus is endemic and vertical transmission is common[5,18]. In Japan (68%), Saudi Arabia (39.5%), Egypt (69%) and Pakistan (45%) infected with HCV is the main risk factor for HCC[19-22].

Incidence rate of HCC is high in Eastern and South-Eastern Asia (*e.g.,* China, Hong Kong, Taiwan, South Korea, Thailand, and Philippines)[6]. It is less in the

Table 1 Incidence rate for males and females, and common cause of hepatocellular carcinoma in some Asian countries[6,10]

Country	Incidence rate (per 100000 persons)		Common cause of HCC
	Males	Females	
China	58	22	HBV
Hong Kong	29.9	8.3	HBV
India	0.9-3.4	0.2-1.8	HBV
Japan	8	6	HCV
South Korea	45	33.6	HBV
Malaysia	3.6	1.6	HBV
Philippines	13.4	4.8	HBV
Singapore	7.1	1.5	HCV
Taiwan	53	21	HBV
Thailand	33.4	12.3	HBV
Egypt	21.9	4.5	HCV
Iran	1.4	1.9	HBV
Kuwait	8.1	3.6	HBV
Oman	7.4	3.2	HBV
Saudi Arabia	5.9	2.2	HCV
Bahrain	5.3	3.1	HBV
Lebanon	3.5	2.2	HBV
Qatar	3.4	1.8	HBV
Palestine	2.6	0.7	HBV
Tunisia	2.2	0.7	HBV
Jordan	1.9	1.3	HBV

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Middle-East countries (*e.g.,* Iran, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, Bahrain, and Lebanon) compared to high incidence countries in South-East Asia, except in Egypt because of higher incidence of HCC in Middle-East region[10]. Central Asia and some part of Middle East regions (Kazakhstan, Kyrgyzstan, Tajikistan, and Turkmenistan) are characterized by a low incidence rate of HCC[1]. The summery of incidence rate of HCC for males and females and also common cause of HCC in some countries of Asia are shows in Table 1.

Risk factors of HCC: HCC is a complex disease associated with many risk factors and cofactors[12,23]. Main risk factors for HCC include HBV/HCV infection, alcohol, aflatoxin exposure, obesity, non-alcoholic fatty liver disease (NAFLD) and diabetes[12,24,25]. In developing countries, chronic HBV with or without aflatoxin exposure in most cases, is the major cause of HCC. Besides, in these countries, HBV infection is transmitted from mother to newborn and in these infected children, 90% experienced developing chronic HBV[23,26]. In developed countries, in contrast, 90% of HCC cases occur in cirrhosis patients (with chronic HCV or alcohol abuse) and in this regions HCV infection spreads mainly through sexual and other horizontal transmission an adulthood, and if that the HBV vaccination is widely effective in this countries[27-29].

Hepatitis B in Asia: In general, the 350 million people diagnosed with HBV worldwide, and it is estimated that HBV is responsible for (50% to 80%) cause of HCC[24,30]. Although HBV would be the cause HCC in the absence of cirrhosis, the majority of HCC patients (70%-80%) who infected with HBV-related, have cirrhosis too. The increased HCC risk associated with HBV. Thus, the HCC's incidence increases with the prevalence of hepatitis B surface antigen (HBsAg) in all areas, particularly in endemic HBV region[31,32]. Similar to the world distribution of HBV, Asian countries also divided in to the low (< 2%), intermediate (2%-8%) and high endemic areas (> 8%) of HBV[33]. Although the region of South-East Asia previously has classified as a high endemicity area, China is now the only country, classified as high endemic area with 8%-20% prevalence of HBV[34]. Oman, Yemen and Jordan in the Middle East are characterizes by a moderate to high prevalence rate of HBV in their own populations[34,35]. Countries with intermediate endemicity in Asia includes; India, Taiwan, Thailand, Philippines, Korea, Iraq and United Arab Emirates, and countries with low endemicity including Japan, Pakistan, Singapore, Sri Lanka, Bangladesh, Malaysia, Iran, Kuwait and Bahrain[36,37].

Because of hepatitis B prevention programs (vaccination), the epidemiological pattern of HBV prevalence changes with time in most Asian countries. In Taiwan due immunization program of HBV, the percentage of HBV-related HCC in children and adolescents decreased[38,39]. In Saudi Arabia and Malaysia, the prevalence of HBV infection in children have declined since the beginning of the vaccination[40,41]. Iran is located in low risk area and characterized as low incidence rate of HCC (< 5 per 100000)[42]. According to a recent study designed in Southern Iran, HBV was the main HCC's risk factor, accounts for of 52.1% of cases[43]. After setting the HBV National Vaccination Program for all newborns and high risk groups since 1992 in Iran, the prevalence of the virus decreased dramatically[35,44]. According to World Health's report in 2001 and Centers for Disease

Control and Prevention's in 2005, prevalence of chronic hepatitis B (CHB) infection in Iran ranges between 2%-7%[35,45]. Factors which increased the risk of HCC in persons with chronic HBV infection include; male, age, long time infected, family history of HCC, aflatoxin exposure, alcohol, tobacco, and infected with HBV genotype C[46].

Hepatitis C in Asia: 170-200 million people are infected with HCV worldwide and its play an important role in HCC especially in regions where CHB is less common[47,48]. In contrast, HCC in HCV patients almost occurs in people with cirrhosis[49,50]. The estimated risk of HCC in patients with HCV is 15 to 20 times higher in healthy persons, and also increased the risk of HCC in patients with advanced hepatic fibrosis or cirrhosis[51]. Prior to anti-HCV screening tests for blood donors (in 1990/1991 in Europe and United States), blood transfusion and injection drug use (IDU) were recognized as the leading cause of HCV, but after the implementation of routine blood donor screening, IDU is the main risk factor (only in developed countries)[10,52]. According to World Health Organization's (WHO) Global Database for Blood Safety. It is calculated that 43% of blood donors (in developing countries) are not properly screened for prevent the transfer of infections, including HCV[53]. Therefore, in developing countries blood transfusion is a highly main risk for HCV transmission. Sexual and maternal-infant HCV transmission can occur but it is rare[54]. Generally, the population at risk for HCV infections who are exposed to infected blood, hemodialysis, IDU, prisoners, tattooing, and during medical and dental care[55].

The most high prevalence rate of HCV occurs in African and Asian countries (5.3% in Africa and 2.15%-3.9% in Asia)[56,57]. The prevalence of HCV infection in Asian countries varies geographically, In Japan, Saudi Arabia, Egypt and Pakistan, HCV is the cause of HCC. The markers of Hepatitis C infection (positive anti-HCV) are found in 80%-90% HCC patients in Japan, 70% in Egypt, 40%-50% in the Pakistan and 35%-40% in Saudi Arabia[10,58-61].

According to the population-based study of Merat *et al*[62] the prevalence of HCV in Iran was 0.3%, 1.6% and 1.0% in Tehran, Hormozgan, and Golestan provinces, respectively. After HBV, HCV infection is the main risk factor of HCC in Iran with an incidence of 8.5%[43].

Factors which increased the risk of HCC in persons with chronic HCV include; male, elderly, co-infected with human immunodeficiency virus and HBV infection, heavy alcohol intake, diabetes and obesity[63-66].

Concept of carcinogens in HBV and HCV

HBV is members of hepadnaviruses that can cause transient or chronic infections. And finally chronic infections can lead to liver failure with cirrhosis and HCC[67]. Multiple factors are involved in the hepatocarcinogenesis of HBV infection. A main factor is chronic necroinflammation and subsequent fibrosis/liver cell proliferation. In spite of that, HCC only occurs in a small proportion of HBsAg carriers. Because the hepatocarcinogenic process includes the interplay between hepatitis B and host hepatocytes, both genomes could contribute to the final pathogenic outcomes, individually or synergistically[68].

HBV contains a double stranded genomic DNA that may encode oncogenic viral proteins which is possibly contributed to hepatocarcinogenesis[69]. For example, protein HBx (which is a well-known viral non-structural gene) operates as a multifunctional regulator modulating gene transcription, cell responses to oxidative stress, protein degradation, apoptosis, and several signaling pathways[70]. Due to this fact that, the specific mechanism is still unknown, its role in liver malignant transformation has been clearly demonstrated by HBx[71]. In addition to viral oncogenic proteins, several viral factors, including genotype, BCP mutation, and viral load have been confirmed to be associated with hepatocarcinogensis. In Asia, it is revealed that, genotype C is more commonly associated with liver cirrhosis and HCC compared with genotype B[23,72].

Hepatitis C is member of the flaviviruses, which it forms its own genus, hepacivirus. HCV is a small, enveloped positive-sense, single stranded RNA virus, and its life cycle is predominantly cytoplasmic[73]. Therefore, this virus is likely to predispose to cancer by alteration of cell signaling and metabolism as similar as by inducing immune responses[74]. Modulation of cellular immunity and metabolism are processes that establish a liver microenvironment which characterized by chronic inflammation, oxidative stress and repair processes that lead to liver fibrosis, cirrhosis and HCC[75-78].

Other environmental and genetic risk factors of HCC

HBV and HCV infections are the major causes of more than 75% of the HCC in the world, with an even more in developing countries[16]. HBV infection is most common in Asia, except in Japan, Saudi Arabia, Egypt and Pakistan, where HCV instead, is the main cause of primary HCC. In addition, exposure to aflatoxin in Asia is a significant risk factor, especially in China and Taiwan[18,79]. On the other hand, other factors such as alcohol, obesity, diabetes and NAFLD might be responsible for a low prevalence of HCC in Asian countries[6,10].

Aflatoxin: Aflatoxin is a mycotoxin produced by the Aspergillus fungus. This fungus grows easily on foodstuffs including; peanuts, corn, pistachio, *etc*., which stored in warm and damp conditions[80]. Studies have been done in sub-Saharan Africa and South-East Asia revealed the association between aflatoxin and HCC[81]. Also, some studies in Asia, Shanghai and Taiwan, indicated the interaction between aflatoxin exposure and hepatitis B infection and a study in Taiwan reported that in HBsAg carriers, who were susceptible to aflatoxin, were more likely to develop HCC[82-86]. Besides, in most regions where aflatoxin exposure is high, HBV infection also is highly prevalent[13]. A recent study in Taiwan[87]

reported the relationship between aflatoxin and HCV with advanced liver disease. Unfortunately we don't have any study in Middle East countries that worked on association between of aflatoxin and HCC.

Alcohol: Alcohol generally contributed to 15% to 45% of HCC cases in developed countries due to its significant role in cirrhosis[13,88]. Many studies have shown the association of heavy alcohol intake (> 50-70 g/d for several years) and HCC[89-91]. Men tend to consume more alcohol than women[10]. The annual incidence of HCC due to alcohol cirrhosis is 1%-4%[92]. Alcohol consumption in Asian countries, in contrast to American and European countries, plays a minor role for HCC development. Especially in Middle Eastern countries, rather than to south Eastern countries in Asia the consumption of alcohol is very low[6,10,43].

Obesity, diabetes and non-alcoholic fatty liver: Epidemiological studies have shown that obesity is a risk factor for HCC. Similar studies further indicate that type 2 of diabetes milieus (T2DM) is also a major risk factor. Both obesity and T2DM are often related to NAFLD. Case reports have shown progression of NAFLD to cirrhosis and HCC[93,94]. A Danish study indicated that, the chance of HCC is more in obese people than general population (RR = 1.9)[65]. The risk of HCC in obese Patients (with body mass index greater than 30) is increasing more than cirrhotic patients[95]. The prevalence of obesity in Asian countries varies geographically. This prevalence is 19.4% in Iran, 33.3% in Saudi Arabia, 33.2% in Qatar, 33.1% in Egypt, 32.9% in Bahrain, 5.7% in China, 5.0% in Japan, 14.0% in Malaysia[96]. The highest prevalence belongs to Kuwait with 42.0% and lowest prevalence belongs to Bangladesh with 1.1%[96] (data adjusted for 2008 for comparability). Prevalence of overweight and obese people based on several national health surveys in Asia has increased[97]. The prevalence of obesity in adults in South-East Asian countries is usually low, compared to developed countries like as the United State, but in contrast to South-East Asian countries, the prevalence of obesity in Middle-East countries is high and almost is equal to developed countries. In the future, obesity may be play as an important role of HCC because of the high prevalence in Middle-East countries[98].

Comparative Prevalence of diabetes in Asian countries also, varies geographically. This prevalence is 9.94% in Iran, 23.09% in Kuwait, 22.87% in Qatar, 16.80% in Egypt, 17.30% in Bahrain, 9.02% in China, 12.28% in Singapore, 10.85% in Malaysia[99]. The highest prevalence belongs to Saudi Arabia with 23.87% and lowest prevalence belongs to Japan with 5.12%[99]. The prevalence of diabetes in countries located in South-east Asia is quite low but, in contrast, this prevalence is high in Middle-East countries. In the future, the high incidence rate of diabetes in countries of Middle-East might become it as the major risk factor for HCC in this region.

According to community-based cohort studies in the United States, Scandinavia, Taiwan, and Japan[64,65,93], the occurrences of HCC was 1.5 to 2.0 times higher in obese persons than in people with normal weight. Also some case-control studies and a few cohort studies indicated that, occurrence of HCC in persons with T2DM than in non-diabetics persons is double[100,101]. NAFLD is clearly linked with obesity and T2DM, that is way it is recognizes as a possible risk factor for HCC[102]. NAFLD may started as simple steatosis (NAFLD), to non-alcoholic steatohepatitis (NASH) or cirrhosis and HCC (due to obesity), T2DM associated to metabolic derangements[103]. NASH is a more advanced stage of NAFLD, so that about 20% of NASH patients usually progress to liver cirrhosis or even some patients with NASH show HCC with or without liver cirrhosis[104,105]. NASH is the first damage caused by a buildup of fat in the liver (NAFLD), NASH can progress and get worse with scar and severe inflammation and fibrosis. With 5-year follow-up of patients with NASH, observed that the progression of fibrosis can lead to cirrhosis[104]. Some factors such as abnormal glucose regulation, obesity, T2DM and triglyceride can increase the risk of NASH[106]. Generally the whole fibrogenesis develops of NASH from NAFLD due to multiple factors, including; oxidative stress, insulin resistance, lipotoxicity, pro-inflammatory cytokine and hepatic stem cells[107].

DISCUSSION

The main challenge which still present in Asia, is the high prevalence of chronic hepatitis. So, prevention of infection with hepatitis B and hepatitis C is the key to reduce the burden of HCC in Asia[108,109].

Prevention of HBV

HBV vaccination is the most effective methods to prevent HBV in both newborn and adult infections with HBV[110]. National HBV vaccination program reduces the prevalence of HBV and also the incidence of HCC dramatically[24]. However, more time is needed to reach the final results, because this program were introduced between 1982 and 1990 in the world and most cases of HCC occur after the age of 40 years[111,112].

Antiviral treatment of HBV

The results of many studies suggested that antiviral therapy is very effective to controls HBV infection. In a study has been done in China, cirrhosis and fibrosis HBV patients randomly assigned in two groups; first received 100 mg of lamivudine per day and second received placebo for up to 5 years. According to the results, the incidence of HCC was significantly reduced in the lamivudine group (3.9% *vs* 7.4%; HR = 0.49; *P* = 0.047)[113].

Prevention of HCV

HCV's prevention, in absence of an effective vaccine, is more challenging than the HBV's and requires a fundamental and comprehensive strategy, including;

blood donations screening, safe injection and systematic avoidance of unnecessary injections[22].

Antiviral treatment of HCV

Combination antiviral therapy helps to prevent the HCV and followed by HCC. Combination therapy decreases the risk of HCC in patients with HCV-related cirrhosis, even without complete biochemical and virological clearing[60]. The current treatments for HCV are combination therapy of pegylated interferon with ribavirin[114-117].

Other strategy and remaining challenge to prevent HBV and HCV infection: In most Asian countries, HBV is usually transmitted from mother to newborn[118]. In order to avoid of maternal-child transmission, WHO is recommending HBV vaccination at birth, but unfortunately less than half of member states have policy to provide HBV vaccination at birth and only 27% of newborns globally received this vaccine[119,120].

Raising awareness and knowledge about the viral hepatitis B and C infection help reduce transmission in the community, also increasing awareness among policy-makers, health professionals and decision- makers in society can help to make better decision and planning to prevent viral hepatitis[120]. Implementation of blood safety strategies is one of the best ways to prevent transmission of hepatitis C infection[24,108], screening blood donation is really effective but in low-income countries where data available, only 35% of donated blood samples were screened in a quality assured manner in 2008[120].

Early detection of HBV and HCV cases provides the best opportunity for effective medical support and prevention of further spread[22,108].

Most new cases of HCV and HBV infections in Asia (or elsewhere) are due to IDU. Needle and syringe sharing practices between Injecting drug users, largely increase the risk of HCV and HBV. Generally, about 60%-80% (about 10 million people) of injecting drug users is positive for HCV and 5%-10% positive for HBV. Controlling this social problem is important in prevention of HCV and HBV cirrhosis related to HCC[121-123].

Prevention of HCC associated with other risk factors: The proportion of HCC cases due to other causes (except HBV and HCV) is usually between 10% and 20% in Asia[108]. Such cases include aflatoxin, alcohol consumption, obesity, type 2 diabetes and NAFLD. Therefore abstaining from alcohol and toxin exposure is very effective for reducing the risk of HCC.

NAFLD in synergy with other risk factors such as obesity, diabetes and metabolic syndrome, is becoming one of the other risk factors for HCC. Due to the lack of understanding of the pathogenesis of the disease, the prevention of NAFLD remains as a difficult problem. So prevention of the risk factors of NAFLD such as obesity, insulin resistance, diabetes and metabolic syndrome is the key strategy to reduce the incidence of NAFLD in the world[124]. Therefore, changing the life style such as weight loss and regular physical activity is directed towards reducing HCC risk factors. Based on the epidemiologic evidence, obesity and T2DM are associated to NAFLD and they are independent risk factors of HCC. In addition, early detection and treatment of diabetes and hyperinsulinemia are very essential and critical to prevent of HCC associated with diabetes and NAFLD. Several studies showed that the use of insulin-sensitizing (metformin and thiazolidinediones) agents in diabetes could reduce the risk of HCC[125-127]. Insulin-sensitizing drugs and avoiding from treatments contributing to hyperinsulinemia would be helpful to prevent HCC and to improve disease outcomes[103].

COMMENTS

Background

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and the second cause of cancer death. Hepatitis B virus (HBV) and HCV infections are the major cause of HCC in the Asian countries, where the virus is endemic and vertical transmission is common. In addition of HBV and HCV the other factors such as aflatoxin, alcohol, obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) might be responsible for a low prevalence of HCC in Asian countries.

Research frontiers

The objective of this study was to review systematically all of aspects of HCC in Asia, provides updated epidemiological data on HCC and its etiology and also this study have examined the current and future possibilities of prevention of this disease in Asian countries.

Innovations and breakthroughs

Unfortunately, most previous studies only focused on South-East countries on Asia. However, in this study the authors have tried to consider all the countries is located in Asia. And generally the authors collected useful information.

Applications

Based on this systematic review obesity, diabetes and NAFLD is growing in Asian countries, which can increase the risk of HCC. An also aflatoxin should be more considered.

Terminology

HCC, also called malignant hepatoma, is the most common type of liver cancer. Most cases of HCC are due to HBV, HCV or cirrhosis.

Peer-review

This is a well-written comprehensive review of the epidemiology of HCC in Asia.

REFERENCES

1 **IARC**. Liver Cancer: Estimated Incidence, Mortality, Prevalence Worldwide in 2012. [Accessed 2013 Dec 12]. Available from: URL: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx 2012

2 **Flores A**, Marrero JA. Emerging trends in hepatocellular carcinoma: focus on diagnosis and therapeutics. *Clin Med Insights Oncol* 2014; **8**: 71-76 [PMID: 24899827 DOI: 10.4137/CMO.S9926]

3 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

4 **Yang JD**, Roberts LR. Hepatocellular carcinoma: A global view. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 448-458 [PMID: 20628345 DOI: 10.1038/nrgastro.2010.100]

5 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

6 **Yuen MF**, Hou JL, Chutaputti A. Hepatocellular carcinoma in the

Asia pacific region. *J Gastroenterol Hepatol* 2009; **24**: 346-353 [PMID: 19220670 DOI: 10.1111/j.1440-1746.2009.05784.x]
7 **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]
8 **Nordenstedt H**, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis* 2010; **42** Suppl 3: S206-S214 [PMID: 20547305 DOI: 10.1016/S1590-8658(10)60507-5]
9 **Ferlay J**, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. Lyon: IARC Press, 2001
10 **Poustchi H**, Sepanlou S, Esmaili S, Mehrabi N, Ansarymoghadam A. Hepatocellular carcinoma in the world and the middle East. *Middle East J Dig Dis* 2010; **2**: 31-41 [PMID: 25197510]
11 **McGlynn KA**, Tsao L, Hsing AW, Devesa SS, Fraumeni JF. International trends and patterns of primary liver cancer. *Int J Cancer* 2001; **94**: 290-296 [PMID: 11668511]
12 **Venook AP**, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist* 2010; **15** Suppl 4: 5-13 [PMID: 21115576 DOI: 10.1634/theoncologist.2010-S4-05]
13 **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]
14 **Naugler WE**, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, Karin M. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 2007; **317**: 121-124 [PMID: 17615358 DOI: 10.1126/science.1140485]
15 **Nagasue N**, Ogawa Y, Yukaya H, Ohta N, Ito A. Serum levels of estrogens and testosterone in cirrhotic men with and without hepatocellular carcinoma. *Gastroenterology* 1985; **88**: 768-772 [PMID: 2981753]
16 Cancer incidence in five continents. Volume VIII. *IARC Sci Publ* 2002; (**155**): 1-781 [PMID: 12812229]
17 **Lai CL**, Ratziu V, Yuen MF, Poynard T. Viral hepatitis B. *Lancet* 2003; **362**: 2089-2094 [PMID: 14697813 DOI: 10.1016/S0140-6736(03)15108-2]
18 **Bosch FX**, Ribes J, Cléries R, Díaz M. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2005; **9**: 191-211, v [PMID: 15831268 DOI: 10.1016/j.cld.2004.12.009]
19 **Salim EI**, Moore MA, Al-Lawati JA, Al-Sayyad J, Bazawir A, Bener A, Corbex M, El-Saghir N, Habib OS, Maziak W, Mokhtar HC, Seif-Eldrin IA, Sobue T. Cancer epidemiology and control in the arab world - past, present and future. *Asian Pac J Cancer Prev* 2009; **10**: 3-16 [PMID: 19469617]
20 **Umemura T**, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. *J Gastroenterol* 2009; **44** Suppl 19: 102-107 [PMID: 19148802 DOI: 10.1007/s00535-008-2251-0]
21 **But DY**, Lai CL, Yuen MF. Natural history of hepatitis-related hepatocellular carcinoma. *World J Gastroenterol* 2008; **14**: 1652-1656 [PMID: 18350595 DOI: 10.3748/wjg.14.1652]
22 **Franceschi S**, Raza SA. Epidemiology and prevention of hepatocellular carcinoma. *Cancer Lett* 2009; **286**: 5-8 [PMID: 19070421 DOI: 10.1016/j.canlet.2008.10.046]
23 **Gomaa AI**, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. *World J Gastroenterol* 2008; **14**: 4300-4308 [PMID: 18666317 DOI: 10.3748/wjg.14.4300]
24 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]
25 **Kim do Y**, Han KH. Epidemiology and surveillance of hepatocellular carcinoma. *Liver Cancer* 2012; **1**: 2-14 [PMID: 24159567 DOI: 10.1159/000339016]
26 **Parikh A**, Taouli B. Imaging of hepatocellular carcinoma: current concepts. *Recent Results Cancer Res* 2013; **190**: 33-55 [PMID: 22941012 DOI: 10.1007/978-3-642-16037-0_3]
27 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917 [PMID: 14667750 DOI: 10.1016/S0140-6736(03)14964-1]
28 **Montalto G**, Cervello M, Giannitrapani L, Dantona F, Terranova A, Castagnetta LA. Epidemiology, risk factors, and natural history of hepatocellular carcinoma. *Ann N Y Acad Sci* 2002; **963**: 13-20 [PMID: 12095924 DOI: 10.1111/j.1749-6632.2002.tb04090.x]
29 **Seeff LB**, Hoofnagle JH. Epidemiology of hepatocellular carcinoma in areas of low hepatitis B and hepatitis C endemicity. *Oncogene* 2006; **25**: 3771-3777 [PMID: 16799618 DOI: 10.1038/sj.onc.1209560]
30 **El-Serag HB**. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res* 2007; **37** Suppl 2: S88-S94 [PMID: 17877502 DOI: 10.1111/j.1872-034X.2007.00168.x]
31 **Simonetti RG**, Cammà C, Fiorello F, Politi F, D'Amico G, Pagliaro L. Hepatocellular carcinoma. A worldwide problem and the major risk factors. *Dig Dis Sci* 1991; **36**: 962-972 [PMID: 1649041 DOI: 10.1007/BF01297149]
32 **Sherman M**. Hepatocellular carcinoma: epidemiology, risk factors, and screening. *Semin Liver Dis* 2005; **25**: 143-154 [PMID: 15918143 DOI: 10.1055/s-2005-871194]
33 **World Health Organization**. Global Alert and Response (GAR): Hepatitis B. Available from: URL: http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index1.html
34 **Zidan A**, Scheuerlein H, Schüle S, Settmacher U, Rauchfuss F. Epidemiological pattern of hepatitis B and hepatitis C as etiological agents for hepatocellular carcinoma in iran and worldwide. *Hepat Mon* 2012; **12**: e6894 [PMID: 23233864 DOI: 10.5812/hepatmon.6894]
35 **Smolle E**, Zöhrer E, Bettermann K, Haybaeck J. Viral hepatitis induces hepatocellular cancer: what can we learn from epidemiology comparing iran and worldwide findings? *Hepat Mon* 2012; **12**: e7879 [PMID: 23233866 DOI: 10.5812/hepatmon.7879]
36 **Qirbi N**, Hall AJ. Epidemiology of hepatitis B virus infection in the Middle East. *East Mediterr Health J* 2001; **7**: 1034-1045 [PMID: 15332746]
37 **André F**. Hepatitis B epidemiology in Asia, the Middle East and Africa. *Vaccine* 2000; **18** Suppl 1: S20-S22 [PMID: 10683538 DOI: 10.1016/S0264-410X(99)00456-9]
38 **Lu SN**, Su WW, Yang SS, Chang TT, Cheng KS, Wu JC, Lin HH, Wu SS, Lee CM, Changchien CS, Chen CJ, Sheu JC, Chen DS, Chen CH. Secular trends and geographic variations of hepatitis B virus and hepatitis C virus-associated hepatocellular carcinoma in Taiwan. *Int J Cancer* 2006; **119**: 1946-1952 [PMID: 16708389 DOI: 10.1002/ijc.22045]
39 **Chen CH**, Su WW, Yang SS, Chang TT, Cheng KS, Lin HH, Wu SS, Lee CM, Changchien CS, Chen CJ, Sheu JC, Chen DS, Lu SN. Long-term trends and geographic variations in the survival of patients with hepatocellular carcinoma: analysis of 11,312 patients in Taiwan. *J Gastroenterol Hepatol* 2006; **21**: 1561-1566 [PMID: 16928217 DOI: 10.1111/j.1440-1746.2006.04425.x]
40 **Al-Faleh FZ**, Ayoola EA, Al-Jeffry M, Arif M, Al-Rashed RS, Ramia S. Integration of hepatitis B vaccine into the expanded program on immunization: The Saudi Arabian experience. *Ann Saudi Med* 1993; **13**: 231-236 [PMID: 17590667]
41 **Ng KP**, Saw TL, Baki A, Rozainah K, Pang KW, Ramanathan M. Impact of the Expanded Program of Immunization against hepatitis B infection in school children in Malaysia. *Med Microbiol Immunol* 2005; **194**: 163-168 [PMID: 15834754 DOI: 10.1007/s00430-004-0231-4]
42 **Pourhoseingholi MA**, Fazeli Z, Zali MR, Alavian SM. Burden of hepatocellular carcinoma in Iran; Bayesian projection and trend analysis. *Asian Pac J Cancer Prev* 2010; **11**: 859-862 [PMID: 21133591]
43 **Hajiani E**, Masjedizadeh R, Hashemi J, Azmi M, Rajabi T. Risk factors for hepatocellular carcinoma in Southern Iran. *Saudi Med J* 2005; **26**: 974-977 [PMID: 15983686]
44 **Alavian SM**, Fallahian F, Lankarani KB. The changing epidemiology of viral hepatitis B in Iran. *J Gastrointestin Liver Dis* 2007; **16**: 403-406 [PMID: 18193122]
45 **Poorolajal J**, Majdzadeh R. Prevalence of chronic hepatitis B infection in Iran: a review article. *J Res Med Sci* 2009; **14**: 249-258

[PMID: 21772891]
46 **Yang HI**, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, Wang LY, Lu SN, You SL, Chen DS, Liaw YF, Chen CJ. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 1134-1143 [PMID: 18695135 DOI: 10.1093/jnci/djn243]
47 **Bruix J**, Barrera JM, Calvet X, Ercilla G, Costa J, Sanchez-Tapias JM, Ventura M, Vall M, Bruguera M, Bru C. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet* 1989; **2**: 1004-1006 [PMID: 2572739 DOI: 10.1016/S0140-6736(89)91015-5]
48 **Chen DS**. Hepatitis C virus in chronic liver disease and hepatocellular carcinoma in Taiwan. *Princess Takamatsu Symp* 1995; **25**: 27-32 [PMID: 8875606]
49 **Fattovich G**, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW, Realdi G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; **112**: 463-472 [PMID: 9024300 DOI: 10.1053/gast.1997.v112.pm9024300]
50 **Tan A**, Yeh SH, Liu CJ, Cheung C, Chen PJ. Viral hepatocarcinogenesis: from infection to cancer. *Liver Int* 2008; **28**: 175-188 [PMID: 18251977 DOI: 10.1111/j.1478-3231.2007.01652.x]
51 **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]
52 **Touzet S**, Kraemer L, Colin C, Pradat P, Lanoir D, Bailly F, Coppola RC, Sauleda S, Thursz MR, Tillmann H, Alberti A, Braconier JH, Esteban JI, Hadziyannis SJ, Manns MP, Saracco G, Thomas HC, Trépo C. Epidemiology of hepatitis C virus infection in seven European Union countries: a critical analysis of the literature. HENCORE Group. (Hepatitis C European Network for Co-operative Research. *Eur J Gastroenterol Hepatol* 2000; **12**: 667-678 [PMID: 10912488 DOI: 10.1097/00042737-200012060-00017]
53 **World Health Organization**. Global database on blood safety summary report: 1998-1999. Available from: URL: http://www.who.int/bloodsafety/global_database/en/
54 **Ohto H**, Terazawa S, Sasaki N, Sasaki N, Hino K, Ishiwata C, Kako M, Ujiie N, Endo C, Matsui A. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *N Engl J Med* 1994; **330**: 744-750 [PMID: 8107740 DOI: 10.1056/NEJM199403173301103]
55 **Sarkari B**, Eilami O, Khosravani A, Sharifi A, Tabatabaee M, Fararouei M. High prevalence of hepatitis C infection among high risk groups in Kohgiloyeh and Boyerahmad Province, Southwest Iran. *Arch Iran Med* 2012; **15**: 271-274 [PMID: 22519374]
56 **Shepard CW**, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; **5**: 558-567 [PMID: 16122679 DOI: 10.1016/S1473-3099(05)70216-4]
57 **Sy T**, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006; **3**: 41-46 [PMID: 16614741 DOI: 10.7150/ijms.3.41]
58 **Miyakawa Y**, Iino S. Toward prevention of hepatocellular carcinoma developing in chronic hepatitis C. *J Gastroenterol Hepatol* 2001; **16**: 711-714 [PMID: 11446875 DOI: 10.1046/j.1440-1746.2001.02543.x]
59 **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]
60 **Sievert W**, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, Amarapurkar D, Chen CH, Dou X, El Khayat H, Elshazly M, Esmat G, Guan R, Han KH, Koike K, Largen A, McCaughan G, Mogawer S, Monis A, Nawaz A, Piratvisuth T, Sanai FM, Sharara AI, Sibbel S, Sood A, Suh DJ, Wallace C, Young K, Negro F. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int* 2011; **31** Suppl 2: 61-80 [PMID: 21651703 DOI: 10.1111/j.1478-3231.2011.02540.x]
61 **Fakeeh M**, Zaki AM. Hepatitis C: prevalence and common genotypes among ethnic groups in Jeddah, Saudi Arabia. *Am J Trop Med Hyg* 1999; **61**: 889-892 [PMID: 10674665]
62 **Merat S**, Rezvan H, Nouraie M, Jafari E, Abolghasemi H, Radmard AR, Zaer-rezaii H, Amini-Kafiabad S, Maghsudlu M, Pourshams A, Malekzadeh R, Esmaili S. Seroprevalence of hepatitis C virus: the first population-based study from Iran. *Int J Infect Dis* 2010; **14** Suppl 3: e113-e116 [PMID: 20362479 DOI: 10.1016/j.ijid.2009.11.032]
63 **Davis GL**, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138**: 513-521, 521.e1-6 [PMID: 19861128 DOI: 10.1053/j.gastro.2009.09.067]
64 **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]
65 **Møller 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]
66 **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]
67 **Bréchot C**. Pathogenesis of hepatitis B virus-related hepatocellular carcinoma: old and new paradigms. *Gastroenterology* 2004; **127**: S56-S61 [PMID: 15508104 DOI: 10.1053/j.gastro.2004.09.016]
68 **Amit S**, Jorge A M. Screening for hepatocellular carcinoma. *Gastroenterol Hepatol* (N Y) 2008; **4**: 201-208 [PMID: 21904498]
69 **Miller JC**, Hahn PF, Chung RT, Thrall JH, Lee SI. Screening for hepatocellular carcinoma in cirrhotic patients. *J Am Coll Radiol* 2008; **5**: 1012-1014 [PMID: 18755444 DOI: 10.1016/j.jacr.2008.01.017]
70 **Murakami S**. Hepatitis B virus X protein: a multifunctional viral regulator. *J Gastroenterol* 2001; **36**: 651-660 [PMID: 11686474 DOI: 10.1007/s005350170027]
71 **Liu CJ**, Kao JH. Hepatitis B virus-related hepatocellular carcinoma: epidemiology and pathogenic role of viral factors. *J Chin Med Assoc* 2007; **70**: 141-145 [PMID: 17475593 DOI: 10.1016/S1726-4901(09)70346-6]
72 **Shlomai A**, de Jong YP, Rice CM. Virus associated malignancies: the role of viral hepatitis in hepatocellular carcinoma. *Semin Cancer Biol* 2014; **26**: 78-88 [PMID: 24457013 DOI: 10.1016/j.semcancer.2014.01.004]
73 **Moradpour D**, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol* 2007; **5**: 453-463 [PMID: 17487147 DOI: 10.1038/nrmicro1645]
74 **Bartosch B**, Thimme R, Blum HE, Zoulim F. Hepatitis C virus-induced hepatocarcinogenesis. *J Hepatol* 2009; **51**: 810-820 [PMID: 19545926 DOI: 10.1016/j.jhep.2009.05.008]
75 **Friedman SL**. Mechanisms of hepatic fibrogenesis. *Gastroenterology* 2008; **134**: 1655-1669 [PMID: 18471545 DOI: 10.1053/j.gastro.2008.03.003]
76 **McGivern DR**, Lemon SM. Tumor suppressors, chromosomal instability, and hepatitis C virus-associated liver cancer. *Annu Rev Pathol* 2009; **4**: 399-415 [PMID: 18928409 DOI: 10.1146/annurev.pathol.4.110807.092202]
77 **Koike K**. Pathogenesis of HCV-associated HCC: Dual-pass carcinogenesis through activation of oxidative stress and intracellular signaling. *Hepatol Res* 2007; **37** Suppl 2: S115-S120 [PMID: 17877471 DOI: 10.1111/j.1872-034X.2007.00173.x]
78 **Bartosch B**. Hepatitis B and C viruses and hepatocellular carcinoma. *Viruses* 2010; **2**: 1504-1509 [PMID: 21994691 DOI: 10.3390/v2081504]

79 **Ananthakrishnan A**, Gogineni V, Saeian K. Epidemiology of primary and secondary liver cancers. *Semin Intervent Radiol* 2006; **23**: 47-63 [PMID: 21326720 DOI: 10.1055/s-2006-939841]

80 **Wild CP**, Montesano R. A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and prevention. *Cancer Lett* 2009; **286**: 22-28 [PMID: 19345001 DOI: 10.1016/j.canlet.2009.02.053]

81 **IARC**. Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins. Lyon: IARC Press, 1993

82 **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]

83 **Wu W**. Occupational cancer epidemiology in the People's Republic of China. *J Occup Med* 1988; **30**: 968-974 [PMID: 3068337 DOI: 10.1097/00043764-198812000-00017]

84 **Wang JS**, Huang T, Su J, Liang F, Wei Z, Liang Y, Luo H, Kuang SY, Qian GS, Sun G, He X, Kensler TW, Groopman JD. Hepatocellular carcinoma and aflatoxin exposure in Zhuqing Village, Fusui County, People's Republic of China. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 143-146 [PMID: 11219772]

85 **Wang LY**, Hatch M, Chen CJ, Levin B, You SL, Lu SN, Wu MH, Wu WP, Wang LW, Wang Q, Huang GT, Yang PM, Lee HS, Santella RM. Aflatoxin exposure and risk of hepatocellular carcinoma in Taiwan. *Int J Cancer* 1996; **67**: 620-625 [PMID: 8782648 DOI: 10.1002/(SICI)1097-0215(19960904)67:5<620::AID-IJC5>3.0.CO;2-W]

86 **Wu HC**, Wang Q, Yang HI, Ahsan H, Tsai WY, Wang LY, Chen SY, Chen CJ, Santella RM. Aflatoxin B1 exposure, hepatitis B virus infection, and hepatocellular carcinoma in Taiwan. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 846-853 [PMID: 19273485 DOI: 10.1158/1055-9965.epi-08-0697]

87 **Chen CH**, Wang MH, Wang JH, Hung CH, Hu TH, Lee SC, Tung HD, Lee CM, Changchien CS, Chen PF, Hsu MC, Lu SN. Aflatoxin exposure and hepatitis C virus in advanced liver disease in a hepatitis C virus endemic area in Taiwan. *Am J Trop Med Hyg* 2007; **77**: 747-752 [PMID: 17978082]

88 **Abdel-Hamid NM**. Recent insights on risk factors of hepatocellular carcinoma. *World J Hepatol* 2009; **1**: 3-7 [PMID: 21160959 DOI: 10.4254/wjh.v1.i1.3]

89 **Hassan MM**, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002; **36**: 1206-1213 [PMID: 12395331 DOI: 10.1053/jhep.2002.36780]

90 **Braga C**, La Vecchia C, Negri E, Franceschi S. Attributable risks for hepatocellular carcinoma in northern Italy. *Eur J Cancer* 1997; **33**: 629-634 [PMID: 9274446 DOI: 10.1016/S0959-8049(96)00500-X]

91 **Donato F**, Tagger A, Chiesa R, Ribero ML, Tomasoni V, Fasola M, Gelatti U, Portera G, Boffetta P, Nardi G. Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case-control study in Italy. Brescia HCC Study. *Hepatology* 1997; **26**: 579-584 [PMID: 9303486 DOI: 10.1002/hep.510260308]

92 **Jepsen P**, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. *Ann Intern Med* 2012; **156**: 841-847, W295 [PMID: 22711076 DOI: 10.7326/0003-4819-156-12-201206190-00004]

93 **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]

94 **Caldwell SH**, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S97-S103 [PMID: 15508109 DOI: 10.1053/j.gastro.2004.09.021]

95 **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]

96 **World Health Organization**. Global status report on non-communicable diseases 2010. [Accessed 2011 April]. Available from: URL: http://www.who.int/nmh/publications/ncd_report_full_en.pdf

97 **Ramachandran A**, Snehalatha C. Rising burden of obesity in Asia. *J Obes* 2010; **2010**: pii: 868573 [PMID: 20871654 DOI: 10.1155/2010/868573]

98 **Yoon KH**, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, Zimmet P, Son HY. Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006; **368**: 1681-1688 [PMID: 17098087 DOI: 10.1016/s0140-6736(06)69703-1]

99 **International Diabetes Federation**. IDF Diabetes Atlas. 6th ed. Brussles, Belgium: International Diabetes Federation, 2013

100 **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]

101 **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]

102 **Neuschwander-Tetri BA**, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; **37**: 1202-1219 [PMID: 12717402 DOI: 10.1053/jhep.2003.50193]

103 **Baffy G**, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol* 2012; **56**: 1384-1391 [PMID: 22326465 DOI: 10.1016/j.jhep.2011.10.027]

104 **Starley BQ**, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010; **51**: 1820-1832 [PMID: 20432259 DOI: 10.1002/hep.23594]

105 **Ertle J**, Dechêne A, Sowa JP, Penndorf V, Herzer K, Kaiser G, Schlaak JF, Gerken G, Syn WK, Canbay A. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *Int J Cancer* 2011; **128**: 2436-2443 [PMID: 21128245 DOI: 10.1002/ijc.25797]

106 **van der Poorten D**, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, London R, Peduto T, Chisholm DJ, George J. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology* 2008; **48**: 449-457 [PMID: 18627003 DOI: 10.1002/hep.22350]

107 **Okazaki I**, Noro T, Tsutsui N, Yamanouchi E, Kuroda H, Nakano M, Yokomori H, Inagaki Y. Fibrogenesis and Carcinogenesis in Nonalcoholic Steatohepatitis (NASH): Involvement of Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinase (TIMPs). *Cancers* (Basel) 2014; **6**: 1220-1255 [PMID: 24978432 DOI: 10.3390/cancers6031220]

108 **Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma**. Prevention of hepatocellular carcinoma in the Asia-Pacific region: consensus statements. *J Gastroenterol Hepatol* 2010; **25**: 657-663 [PMID: 20492323 DOI: 10.1111/j.1440-1746.2009.06167.x]

109 **Fazeli Z**, Pourhoseingholi MA, Vahedi M, Zali MR. Burden of Hepatocellular Carcinoma in Aisa. *Asian Pacific J Cancer Prevention* 2012; **13**: 5955-5958 [DOI: 10.7314/APJCP.2012.13.12.5955]

110 **Zanetti AR**, Van Damme P, Shouval D. The global impact of vaccination against hepatitis B: a historical overview. *Vaccine* 2008; **26**: 6266-6273 [PMID: 18848855 DOI: 10.1016/j.vaccine.2008.09.056]

111 **Chen DS**. Toward elimination and eradication of hepatitis B. *J Gastroenterol Hepatol* 2010; **25**: 19-25 [PMID: 20136972 DOI: 10.1111/j.1440-1746.2009.06165.x]

112 **Lim SG**, Mohammed R, Yuen MF, Kao JH. Prevention of hepatocellular carcinoma in hepatitis B virus infection. *J Gastroenterol Hepatol* 2009; **24**: 1352-1357 [PMID: 19702903 DOI: 10.1111/j.1440-1746.2009.05985.x]

113 **Liaw YF**, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J. Lamivudine for patients with chronic hepatitis B and

advanced liver disease. *N Engl J Med* 2004; **351**: 1521-1531 [PMID: 15470215 DOI: 10.1056/NEJMoa033364]

114 **Ashtari S**, Vahedi M, Pourhoseingholi MA, Karkhane M, Kimiia Z, Pourhoseingholi A, Safaee A, Moghimi-Dehkordi B, Zali MR, Alavian SM. Direct medical care costs associated with patients diagnosed with chronic HCV. *Hepat Mon* 2013; **13**: e8415 [PMID: 23930132 DOI: 10.5812/hepatmon.8415]

115 **Coppola N**, Pisaturo M, Tonziello G, Sagnelli C, Sagnelli E, Angelillo IF. Efficacy of Pegylated interferon α-2a and α-2b in patients with genotype 1 chronic hepatitis C: a meta-analysis. *BMC Infect Dis* 2012; **12**: 357 [PMID: 23245594 DOI: 10.1186/1471-2334-12-357]

116 **Singal AK**, Singh A, Jaganmohan S, Guturu P, Mummadi R, Kuo YF, Sood GK. Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *Clin Gastroenterol Hepatol* 2010; **8**: 192-199 [PMID: 19879972 DOI: 10.1016/j.cgh.2009.10.026]

117 **Ashtari S**, Vahedi M, Pourhoseingholi MA, Pourhoseingholi A, Safaee A, Moghimi-Dehkordi B, Zali MR. Estimation of average diagnosis and treatment costs of hepatitis C. *Gastroenterol Hepatol Bed Bench* 2012; **5**: 139-145 [PMID: 24834215]

118 **McMahon BJ**, Alberts SR, Wainwright RB, Bulkow L, Lanier AP. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. *Arch Intern Med* 1990; **150**: 1051-1054 [PMID: 2158773 DOI: 10.1001/archinte.150.5.1051]

119 **World Health Organization**. Global Immunization Data. [Accessed 2012 March]. Available from: URL: http://www.who.int/immunization/monitoring_surveillance/global_immunization_data.pdf

120 **World Health Organization**. Prevention and control of viral hepatitis infection: framework for global action. [Accessed 2012]. Available from: URL: http://www.who.int/csr/disease/hepatitis/GHP_Framework_En.pdf

121 **McCaughan GW**, Omata M, Amarapurkar D, Bowden S, Chow WC, Chutaputti A, Dore G, Gane E, Guan R, Hamid SS, Hardikar W, Hui CK, Jafri W, Jia JD, Lai MY, Wei L, Leung N, Piratvisuth T, Sarin S, Sollano J, Tateishi R. Asian Pacific Association for the Study of the Liver consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. *J Gastroenterol Hepatol* 2007; **22**: 615-633 [PMID: 17444847 DOI: 10.1111/j.1440-1746.2007.04883.x]

122 **Farrell GC**. New hepatitis C guidelines for the Asia-Pacific region: APASL consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. *J Gastroenterol Hepatol* 2007; **22**: 607-610 [PMID: 17444844 DOI: 10.1111/j.1440-1746.2007.04969.x]

123 **Li L**, Fan HB, Yang DL. [An introduction of the consensus statements on the diagnosis, management and treatment of hepatitis C virus infection from the Asian Pacific Association for the Study of the Liver]. *Zhonghua Gan Zang Bing Za Zhi* 2007; **15**: 955-957 [PMID: 18171543]

124 **Zelber-Sagi S**, Lotan R, Shlomai A, Webb M, Harrari G, Buch A, Nitzan Kaluski D, Halpern Z, Oren R. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. *J Hepatol* 2012; **56**: 1145-1151 [PMID: 22245895 DOI: 10.1016/j.jhep.2011.12.011]

125 **Donadon V**, Balbi M, Mas MD, Casarin P, Zanette G. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int* 2010; **30**: 750-758 [PMID: 20331505 DOI: 10.1111/j.1478-3231.2010.02223.x]

126 **Nkontchou G**, Cosson E, Aout M, Mahmoudi A, Bourcier V, Charif I, Ganne-Carrie N, Grando-Lemaire V, Vicaut E, Trinchet JC, Beaugrand M. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *J Clin Endocrinol Metab* 2011; **96**: 2601-2608 [PMID: 21752887 DOI: 10.1210/jc.2010-2415]

127 **Hassan MM**, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, Javle M, Moghazy DM, Lozano RD, Abbruzzese JL, Vauthey JN. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. *Cancer* 2010; **116**: 1938-1946 [PMID: 20166205 DOI: 10.1002/cncr.24982]

P- Reviewer: Fujino Y, Mihaila RG, Tomizawa M **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com