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Introductory Chapter: Etiology and Pathogenesis of Hepatocellular Carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent malignant tumor of the liver with hundreds of thousands of new cases diagnosed each year. Men are up to 3 times more likely to develop HCC compared to women. HCC encounters a higher incidence in countries with low socio-economic status and with improper access to healthcare. These countries also associate high alcohol intake among the population as well as increased incidence of hepatotropic viruses or human immunodeficiency virus (HIV). On the other hand, screening and surveillance of patients at risk have determined the upturn of survivability in HCC patients.

2. Risk factors

HCC has several well-known risk factors, which have been proven to strongly associate with the development of HCC. The most common etiological risk factors are hepatotropic viruses: hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) and a suggestive evidence is revealed by similar distribution of HCC in areas where these viruses also encounter increasing incidence and it is considered that up to 90% of the diagnosed HCCs develop in context of hidden cirrhosis [1, 2]. Other risk factors that are highly involved in the hepatocellular carcinogenesis also include autoimmune hepatitis, nonalcoholic fatty liver disease (NAFLD), obesity and diabetes, tobacco and alcohol abuse, environmental toxins, and iron overload.

2.1. Cirrhosis

Cirrhosis is the main underlying cause for most HCC cases, with HBV, and HCV infection often involved in the development of cirrhosis. Approximately 70–90% of liver cancers occur on cirrhosis, and in Western countries, the HCC ratio on cirrhosis exceeds 90%. The likelihood of developing HCC in viral B cirrhosis is 2.4% per year, and viral C cirrhosis is 5–7% per year. In Europe, HCC incidence is 1.5–3/100 cirrhosis per year. Male gender, advanced age, long duration of the disease and the severity of the disease are the main risk factors for developing cancer in cirrhosis alongside etiology of cirrhosis [3].

The progression from cirrhosis to HCC is a complex process. Cirrhosis is the outcome of any chronic hepatic illness and it is outlined by debilitation of regenerative capacity of the liver through declining proliferation of the hepatocytes [4]. Telomere dysfunction and alterations of cellular micro- and macroenvironment have been proven to enhance cellular proliferation [5]. Telomerase dysfunctions determine chromosomal instability and reduced regenerative liver capacity with decreased hepatocyte regeneration. It has been proven that telomeres are shorter in hepatocytes from a cirrhotic liver compared to a normal liver. Also, shorter telomeres are associated with the progression of liver fibrosis [6].

Several mouse models studies have suggested that telomerase dysfunctions have been associated with early-stage liver cancers but not with high-grade HCCs, which tends to indicate that telomere dysfunction cannot determine alone the development and progression of HCC in cirrhotic livers [7]. Van Gijssel et al. supported this idea by using a rat model in which they decreased hepatocyte proliferation with various hepatotoxic compounds that also increased carcinogen-induced tumor forming [8]. Activation of stellate cells in liver cirrhosis can increase products of oxidative stress, several growth factors as well as cytokines with further roles in reducing hepatocyte regeneration, and development of HCC [9]. Outbreaks of dysplasia occur in regeneration nodules, followed by neoplastic transformation. HCC rarely develops on the noncytotoxic liver and this is particularly common in HBV infection, hemochromatosis or HCV infection. The existence of viral infection or portal hypertension can increase the odds of developing HCC for patients with primary biliary cirrhosis [10].

2.2. HBV infection

HBV is regarded as the main etiological factor that generates multiple pathological changes inside the liver structure, being responsible for the development of HCC over time [11]. However, in order to correctly assess the risk of carcinogenesis triggered by chronic HBV infection, multiple variables need to be considered, like a virus or host-related factors and also the patient's lifestyle [12]. A major study published Chen CJ et al. evaluated the risk of developing HCC in 3653 patients who were positive HBV infection and negative for hepatitis C antibodies. The authors concluded that recorded serum levels of HBV DNA higher or equal to 10,000 copies/mL are a significant risk predictor for the development of HCC, no matter the Hepatitis B antigen level and liver cirrhosis [13].

In highly endemic regions, HBV is mainly transmitted from mother to child during birth (perinatal exposure). In developed countries, HBV infection is primarily contracted through parental contact with infected blood or through sexual contact [14]. Co-infection with HBV

is found in 9% HIV-infected patients, resulting in an increased risk of developing HCC compared to chronic HBV infection alone [15]. At the time of writing, there are 10 genotypes of human HBV named from A to J. The last genotype (J) was described in 2009 by Tatematsu K et al. [16], while the highest risk of developing HCC is linked with genotype C [17].

The prevalence of HBV carriers associates geographically with the distribution of HCC. Epidemiological studies indicated a 200-fold increase in HCC risk in Taiwanese HBV men compared to HBV-negative men [18]. Cirrhosis developed from chronic HBV infection is globally the most important etiologic factor of HCC.

Hepatocarcinogenesis generated by chronic HBV infection is a multistep process that implies rearrangement of the intracellular DNA leading to inflammation of the hepatocytes, accompanied by an increased rate of proliferation [19]. After the integration of viral DNA into the host's genome, the telomerase reverse transcriptase is altered and multiple genes involved in the malignant process suffer various insertional mutations [20]. If the inflammation process continues to affect the hepatocytes, the liver will respond to injury with necrosis of the affected areas, followed by compensatory regeneration and hepatic fibrosis, therefore, altering the entire hepatic architecture, leading to cirrhosis [21]. Recent studies enhance the importance of HBV X protein, suggesting that pathways like p38MAPK and PI-3 K/AKT are used in order to increase the invasive potential of HBV infection [22, 23]. The association of HBV infection with HCV or HVD or with increased alcohol intake or aflatoxin consumption increases the carcinogenic risk of HBV [24].

2.3. HCV infection

Chronic hepatitis C infection is a major risk factor for developing HCC. In developed countries, HCV is the important risk factor for HCC. HCV-associated HCC patients are usually significantly older than those with HCC associated with HBV infection [16].

The evolution over time of the viral infection in a few countries is pledged for the massive increase of HCC incidence. The major spread of HCV infection took place in Japan around the 1930s and in the US in the 1960s. These assessments are consistent with epidemiological observations and allow the estimate that HCC prevalence will increase in the US over the next 2–3 decades when it is likely to match that in Japan [25]. HBV co-infection, present in 3–13% of patients with viral hepatitis C, is associated with a HCC risk of 3–4 times the incidence of each infection [26]. It is considered that the survivors of the Hiroshima and Nagasaki nuclear bombs that were HCV-positive had a much higher risk of developing HCC in the absence of cirrhosis. It was suggested that the radiation had a mutagenic effect and C virus stimulated cell proliferation in these patients [27]. Almost all HCV-related hepatocarcinomas occur due to cirrhosis or chronic inflammation. It is therefore, believed that HCV is an indirect carcinogenic agent by induced inflammatory and necrotic lesions. Core protein influences various cellular functions, including apoptosis, and suppresses p53 activity [28–30].

2.4. Autoimmune hepatitis

The risk of developing HCC for patients with underlying autoimmune hepatitis still remains unclear. Development of HCC in the absence of cirrhosis or viral hepatitis is rather rare or

isolated [31]. A recent meta-analysis concluded that the risk of HCC is much lower for patients with autoimmune hepatitis and cirrhosis than for patients with cirrhosis from viral hepatitis or primary biliary cholangitis [32, 33]. Development of HCC from autoimmune hepatitis with corticosteroid-therapy should mainly impose searching for associated viral chronic hepatitis or any other HCC risk factors that can promote carcinogenesis [34].

2.5. Tobacco and alcohol abuse

Tobacco and alcohol abuse represent important HCC risk factors and exposure to both risk factors can increase HCC susceptibility. The mechanism involves generation of reactive oxygen species (ROS) and a decrease of antioxidants, which induces oxidative stress [35].

Alcohol chronic intake is associated with HCC development due to the several mechanisms such as creation of acetaldehyde-DNA; formation of cytochrome P450E1-associated ROS species; iron overload, which can lead to further ROS formation and p53 gene mutation or activation of factor-KappaB-involved in the promotion of inflammatory response; oxidative stress promotion; and decreased metabolism of vitamin A, which determines the promotion of hepatocyte proliferation as well as initiation and development of liver fibrosis [36]. Alcohol interferes with hepatocarcinogenesis by inducing an already demonstrated precancerous lesion, such as liver cirrhosis or by modifying carcinogenesis initiated by other agents such as HBV or HCV or environmental carcinogens following hepatic enzyme induction or by altering cell membranes [37].

2.6. Environmental toxins

Aflatoxin b1 derived from a fungus (*Aspergillus flavus*) is a major risk factor in some tropical and subtropical regions. *Aspergillus flavus* is ubiquitous and contaminates cereals (corn, rice, and sorghum), hazelnuts, etc., stored in humidity conditions. Epidemiological data have shown a strong correlation between aflatoxin intake and HCC incidence in some countries in Asia and Africa. Since 1993, the International Agency for Research on Cancer recognized aflatoxins as a human carcinogen (group IA) [38]. Advanced age, smoking, alcohol, and HBV infection may increase the carcinogenic risk of aflatoxin [39].

2.7. Obesity, diabetes and nonalcoholic fatty liver disease (NAFLD)

Obesity represents an important public health problem, with a massive increase in the past years and with staggering estimations of approximately 300 million obese worldwide. Obesity elevates the risk of all types of cancer, including HCC [40]. One study performed in Denmark on a cohort of 43.965 obese patients estimated the relative risk of liver cancer to 1.9 in comparison to the general population [41]. Two Swedish population-based cohort studies also showed an increased risk of HCC among obese [42, 43].

In another US study, Nair et al. evaluated the importance of obesity in over 19,000 patients diagnosed with cirrhosis and liver transplants, with an overall incidence for HCC of 3.5%. The study suggested obesity as a statistically independent risk factor for liver cancer in patients with alcoholic and cryptogenic cirrhosis [44]. Furthermore, a recent case-control study

indicated synergy between increased alcohol intake, smoking, and obesity [45]. In 2014, an American study regarding the incidence of hepatocellular carcinoma in Texas Latinos concluded that the incidence of liver cancer is somehow higher than other regions in the US, suggesting risk factors related to increased obesity and diabetes rates, as well as environmental, cultural and socioeconomic factors, and possibly genetic predisposition [46].

The mechanism by which obesity leads to cancer is unclear; insulin resistance and its subsequent inflammatory cascade, and insulin growth factor (IGF)-1 seem to be implicated [47]. In a study published in 2010, Michael Karin's team addressed the mechanism by which the obesity can lead to cancer by studying the development of HCC induced by diethylnitrosamine (DEN) or fat diet in mice [48, 49].

Although this is not entirely proven, a number of studies indicate that NAFLD is the link between obesity, diabetes, and HCC. In time, NAFLD can lead to fibrosis and finally, cirrhosis. Approximately 60% of patients with obesity have simple steatosis or steatosis with mild inflammation and around 25–30% have nonalcoholic steatohepatitis (NASH) [50].

Further mechanisms involved in the development of HCC at obese patients were addressed by Villanueva et al. by studying the molecular links between inflammation and liver cancer uncovering the reported role of lymphotoxin signaling in HCC development. The involvement of oxidative stress in developing HCC in obese patients was studied by Zhang, Kaufman et al., who underlined that the accumulation of intracellular lipids increases the demand on the endoplasmic reticulum (ER), which integrates several metabolic processes, therefore inducing ER dysfunction that leads to the production of ROS, provoking oxidative stress and activation of inflammatory pathways (NF- κ B and JNK signaling). Another effect of oxidative stress is that can also induce DNA damage that leads to genomic instability that prompts the mutations that favor the development of neoplastic cells [51–53]. Carbohydrate metabolism alterations are frequently encountered at patients with cirrhosis [54].

Since 1986 at least 10 case-control and 5 prior cohort studies from seven different countries reported a connection between diabetes and HCC, promoting the idea that diabetes is an important and consistent risk factor for HCC [55–57]. However, the current studies have not established if diabetes precedes HCC.

The association among obesity, diabetes, NAFLD, and HCC has been assessed by El-Serag et al. in two large studies that substantiated the increased risk of HCC by obtaining results, which showed a doubling number of cases with HCC in patients with diabetes in contrast with nondiabetic patients in a 10–15 year observation period, explaining that the rising incidence of HCC in the US in the past 30 years is connected to an ever-growing prevalence of obesity and diabetes [58, 59].

Since the incidence of obesity and diabetes is in a continuous growth in the world, Kelly, and co. study demonstrated a direct established relationship between diabetes and HCC risk. The biological mechanism of diabetes implicated in hepatocarcinogenesis is not entirely established. Increased serum levels of insulin are at this point the most researched mechanism for the link between diabetes and cancer, though only high levels of insulin are not enough to cause HCC. Levels of insulin-like growth factor-1 (IGF-1) have been linked with increased

risk for pancreatic cancer [60–62]. Most studies indicate that serum IGF-1 levels were linked with the high-risk of HCC, and also that IGF-1 can promote tumor cell growth [63–66]. This was often linked to cell proliferation in pancreatic cancer and similar effects could be observed in HCC [62, 67].

As diabetes and obesity continue to be an ever-growing worldwide concern, we can anticipate a near future increase in the prevalence of NAFLD-related HCC [68]. If liver cirrhosis is present, NAFLD patients have a substantially higher risk to develop HCC [69]. Obesity is linked with a low-grade inflammatory status and also an increased production of cytokines like IL-6 or TNF-alpha [70]. Multiple potential carcinogenic mechanisms are also involved, such as reduced levels of adiponectin [71, 72], hepatic lipid accumulation with possible energy support required for massive tumor growth [73] or normal intracellular signaling means affected by lipotoxicity [74].

2.8. Iron overload

Almost two thirds of the total iron pool is present in hemoglobin while the rest of it is stored, mostly inside the liver, with the help of an intracellular protein called ferritin, which can bind up to 4500 molecules of iron per molecule of ferritin. Transferrin is a glycoprotein responsible for binding the circulating iron within the plasma [75]. Iron overload has been mainly associated with hereditary hemochromatosis (HH) and dietary iron overload (DIO).

Iron overload is frequently linked with an abnormal secretion of hepcidin [76, 77]. Recent studies performed on rats, which underwent a high-iron diet also confirm the possibility to develop HCC in the absence of liver cirrhosis, therefore, excessive iron is capable to generate oxidative tissue damage alone by accelerating the development of free radicals [78, 79]. DIO has been reported in some countries located in the southern and central part of Africa, mainly in the rural parts and highlights the link between the consumption of large volumes of home-brewed alcohol using iron containers, and development of iron overload [79].

3. Conclusion

HCC is a complex pathogenesis link with various risk factors. Liver cirrhosis is, unsurprisingly, an important risk factor for HCC development, regardless of the cause, whereas chronic HBV and HCV infections are the most significant developing factors for liver cancer worldwide. Therefore, frequent causes of cirrhosis are indicated as risk factors for HCC. The common factors affecting the progression to HCC in patients with cirrhosis are host and viral related with the involvement of external risk factors such as smoking, alcohol, and aflatoxins.

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References

- [1] El-Serag HB. Hepatocellular carcinoma. *The New England Journal of Medicine*. 2011; **365**:1118-1127
- [2] Zhang DY, Friedman SL. Fibrosis-dependent mechanisms of hepatocarcinogenesis. *Hepatology*. 2012;**56**:769-775
- [3] Grando-Lemaire V, Guettier C, Chevret S, Beaugrand M, Trinchet JC. Hepatocellular carcinoma without cirrhosis in the west: Epidemiological factors and histopathology of the non-tumorous liver. *Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Journal of Hepatology*. 1999 Sep;**31**(3):508-513
- [4] Delhay M, Louis H, Degraef C, et al. Relationship between hepatocyte proliferative activity and liver functional reserve in human cirrhosis. *Hepatology*. 1996;**23**:1003-1011
- [5] El-Serag HB, Rudolph KL. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;**132**:2557-2576
- [6] Wege H, Brümmendorf TH. Telomerase activation in liver regeneration and hepatocarcinogenesis: Dr. Jekyll or Mr. Hyde? *Current Stem Cell Research & Therapy*. 2007 Jan;**2**(1):31-38
- [7] Farazi PA, Glickman J, Jiang S, et al. Differential impact of telomere dysfunction on initiation and progression of hepatocellular carcinoma. *Cancer Research*. 2003;**63**:5021-5027
- [8] van Gijssel HE, Maassen CB, Mulder GJ, et al. p53 protein expression by hepatocarcinogens in the rat liver and its potential role in mitoinhibition of normal hepatocytes as a mechanism of hepatic tumour promotion. *Carcinogenesis*. 1997;**18**:1027-1033
- [9] Bataller R, Brenner DA. Liver fibrosis. *The Journal of Clinical Investigation*. 2005; **115**:209-218
- [10] Zhang X-X, Wang L-F, Jin L, Li Y-Y, Hao S-L, et al. Primary biliary cirrhosis-associated hepatocellular carcinoma in Chinese patients: Incidence and risk factors. *World Journal of Gastroenterology*. 2015 Mar 28;**21**(12):3554-3563
- [11] Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. *Journal of Carcinogenesis*. 2017;**16**:1. Published online 2017 May 29. DOI: 10.4103/jcar.JCar_9_16
- [12] Philippe J. Zamor, Andrew S. deLemos, and Mark W. Russo. Viral hepatitis and hepatocellular carcinoma: Etiology and management. *Journal of Gastrointestinal Oncology* 2017 Apr; **8**(2): 229-242. DOI: 10.21037/jgo.2017.03.14
- [13] Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. REVEAL-HBV study group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *Journal of the American Medical Association*. 2006 Jan 4;**295**(1):65-73
- [14] Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: Worldwide incidence and trends. *Gastroenterology*. 2004 Nov;**127**(5 Suppl 1):S5-S16

- [15] Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, Zilmer K, Vella S, Kirk O, Lundgren JD, EuroSIDA Group. Hepatitis B and HIV: Prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*. 2005 Mar 24;**19**(6):593-601
- [16] Tatematsu K, Tanaka Y, Kurbanov F, Sugauchi F, Mano S, Maeshiro T, Nakayoshi T, Wakuta M, Miyakawa Y, Mizokami M. A genetic variant of hepatitis B virus divergent from known human and ape genotypes isolated from a Japanese patient and provisionally assigned to new genotype J. *Journal of Virology*. 2009 Oct;**83**(20):10538-10547
- [17] Chan HL, Tse CH, Mo F, Koh J, Wong VW, Wong GL, Lam Chan S, Yeo W, Sung JJ, Mok TS. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. *Journal of Clinical Oncology*. 2008 Jan 10;**26**(2):177-182
- [18] Tabor E. Hepatocellular carcinoma: Global epidemiology. *Digestive and Liver Disease*. 2001 Mar;**33**(2):115-117
- [19] Lee JM, Wong CM, Ng IO. Hepatitis B virus-associated multistep hepatocarcinogenesis: A stepwise increase in allelic alterations. *Cancer Research*. 2008 Jul 15;**68**(14):5988-5996
- [20] Toh ST, Jin Y, Liu L, Wang J, Babrzadeh F, Gharizadeh B, Ronaghi M, Toh HC, Chow PK, Chung AY, Ooi LL, Lee CG. Deep sequencing of the hepatitis B virus in hepatocellular carcinoma patients reveals enriched integration events, structural alterations and sequence variations. *Carcinogenesis*. 2013 Apr;**34**(4):787-798
- [21] Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology*. 2008 May;**134**(6):1655-1669
- [22] Wang WH, Hullinger RL, Andrisani OM. Hepatitis B virus X protein via the p38MAPK pathway induces E2F1 release and ATR kinase activation mediating p53 apoptosis. *The Journal of Biological Chemistry*. 2008 Sep 12;**283**(37):25455-25467. DOI: 10.1074/jbc.M801934200
- [23] Chung TW, Lee YC, Kim CH. Hepatitis B viral HBx induces matrix metalloproteinase-9 gene expression through activation of ERK and PI-3K/AKT pathways: Involvement of invasive potential. *The FASEB Journal*. 2004 Jul;**18**(10):1123-1125
- [24] Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, Schalm S. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. *Gut*. 2000 Mar;**46**(3):420-426
- [25] Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, Alter HJ. A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. *Proceedings of the National Academy of Sciences of the United States of America*. 2002 Nov 26;**99**(24):15584-15589. Epub 2002 Nov 18
- [26] Tagger A, Donato F, Ribero ML, Binelli G, Gelatti U, Portera G, Albertini A, Fasola M, Chiesa R, Nardi G. A case-control study on a novel DNA virus (TT virus) infection and hepatocellular carcinoma. The Brescia HCC study. *Hepatology*. 1999 Jul;**30**(1):294-299

- [27] Sharp GB, Mizuno T, Cologne JB, Fukuhara T, Fujiwara S, Tokuoka S, Mabuchi K. Hepatocellular carcinoma among atomic bomb survivors: Significant interaction of radiation with hepatitis C virus infections. *International Journal of Cancer*. 2003 Feb 10;**103**(4):531-537
- [28] Koike K, Moriya K, Yotsuyanagi H, Shintani Y, Fujie H, Tsutsumi T, Kimura S. Compensatory apoptosis in preneoplastic liver of a transgenic mouse model for viral hepatocarcinogenesis. *Cancer Letters*. 1998 Dec 25;**134**(2):181-186
- [29] Blonski W, Reddy KR. Hepatitis C virus infection and hepatocellular carcinoma. *Clinics in Liver Disease*. 2008;**12**:661-674
- [30] Andrade LJ, D'Oliveira A, Melo RC, et al. Association between hepatitis C and hepatocellular carcinoma. *Journal of Global Infectious Diseases*. 2009 Jan-Jun;**1**(1):33-37
- [31] Geramizadeh B, Nikeghbalian S, Shamsaifar A, Kazemi K, MalekHosseini SA. Hepatocellular carcinoma in two patients with autoimmune hepatitis, a single center experience and review of the literature. *Hepatitis Monthly*. 2013;**13**(4):e7957. DOI: 10.5812/hepatmon.7957
- [32] Hino-Arinaga T, Ide T, Kuromatsu R, Miyajima I, Ogata K, Kuwahara R, et al. Risk factors for hepatocellular carcinoma in Japanese patients with autoimmune hepatitis type 1. *Journal of Gastroenterology*. 2012;**47**(5):569-576
- [33] Wong RJ, Gish R, Frederick T, Bzowej N, Frenette C. Development of hepatocellular carcinoma in autoimmune hepatitis patients: A case series. *Digestive Diseases and Sciences*. 2011;**56**(2):578-585
- [34] Tansel A, Katz LH, El-Serag HB, Thrift AP, Parepally M, Shakhatreh MH, Kanwal F. Incidence and determinants of hepatocellular carcinoma in autoimmune hepatitis: A systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*. 2017 Aug;**15**(8):1207-1217
- [35] Koh W-P, Robien K, Wang R, Govindarajan S, J-M Yuan MCY. Smoking as an independent risk factor for hepatocellular carcinoma: The Singapore Chinese health study. *British Journal of Cancer*. 2011 Oct 25;**105**(9):1430-1435
- [36] Purohit V, Rapaka R, Kwon OS, Song BJ. Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma. *Life Sciences*. 2013 Jan 17;**92**(1):10-1016
- [37] Brooks PJ, Theruvathu JA. DNA adducts from acetaldehyde: Implications for alcohol-related carcinogenesis. *Alcohol*. 2005;**35**:187-193
- [38] Kew MC. Aflatoxins as a cause of hepatocellular carcinoma. *Journal of Gastrointestinal and Liver Diseases*. 2013 Sep;**22**(3):305-310
- [39] Wu HC, Santella R. The role of aflatoxins in hepatocellular carcinoma. *Hepatitis Monthly*. 2012 Oct;**12**(10 HCC):e7238
- [40] Toffanin S, Friedman SL, Llovet JM. Obesity, inflammatory signaling, and hepatocellular carcinoma-an enlarging link. *Cancer Cell*. 2010 Feb 17;**17**(2):115-117

- [41] Moller H, Mellemgaard A, Lindvig K, Olsen J. Obesity and cancer risk: A Danish record-linkage study. *European Journal of Cancer*. 1994;**30A**:344-350
- [42] Wiklund K, Dich J. Cancer risks among female farmers in Sweden. *Cancer Causes & Control*. 1994;**5**:449-457
- [43] Wolk A et al. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes & Control*. 2001;**12**:13-21
- [44] Nair S, Mason A, Eason J, Loss G, Perrillo RP. Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? *Hepatology*. 2002;**36**:150-155
- [45] Marrero JA et al. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. *Journal of Hepatology*. 2005;**42**:218-224
- [46] Amelie G. Ramirez, Edgar Munoz, [...], Lucina Suarez. Incidence of hepatocellular carcinoma in Texas Latinos, 1995-2010: An Update. *PLoS One*. 2014 July 21;**9**(7):e103693
- [47] Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: A weighty connection. *Hepatology*. 2010;**51**:1820-1832
- [48] Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell*. 2010;**140**:197-208
- [49] Rebouissou S, Amessou M, Couchy G, Poussin K, Imbeaud S, Pilati C, et al. Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours. *Nature*. 2009;**457**:200-204
- [50] Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: Summary of an AASLD single topic conference. *Hepatology*. 2003;**37**:1202-1219
- [51] Villanueva A, Savic R, Llovet JM. Lymphotoxins: new targets for hepatocellular carcinoma. *Cancer Cell*. 2009;**16**:272-273
- [52] Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. *Nature*. 2008;**454**:455-462
- [53] Conn HO, Schreiber W, Elkington SG. Cirrhosis and diabetes. II. Association of impaired glucose tolerance with portal-systemic shunting in Laennec's cirrhosis. *The American Journal of Digestive Diseases*. 1971;**6**:227-239
- [54] Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, Wolk A, McLaughlin JK, Fraumeni JF Jr. Excess risk of primary liver cancer in patients with diabetes mellitus. *Journal of the National Cancer Institute*. 1996;**89**:317-318
- [55] Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, Borch-Johnsen K, Olsen JH. Cancer incidence in a population based cohort of patients hospitalized with diabetes mellitus in Denmark. *Journal of the National Cancer Institute*. 1997;**89**:1360-1365
- [56] Lagiou P, Kuper H, Stuver SO, Tzonou A, Trichopoulos D, Adami H-O. Role of diabetes mellitus in the etiology of hepatocellular carcinoma. *Journal of the National Cancer Institute*. 2000;**92**:1096-1099

- [57] Beasley RP. Diabetes and hepatocellular carcinoma. *Hepatology*. 2006;**44**:1408-1410
- [58] El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: A case-control study among United States veterans. *The American Journal of Gastroenterology*. 2001;**96**:2462-2467
- [59] El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology*. 2004;**126**:460-468
- [60] Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *Journal of the National Cancer Institute*. 1999 Apr 7;**91**(7):620-625
- [61] Grimberg A, Cohen P. Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. *Journal of Cellular Physiology*. 2000 Apr;**183**(1):1-9
- [62] Ohmura E, Okada M, Onoda N, Kamiya Y, Murakami H, Tsushima T, Shizume K. Insulin-like growth factor I and transforming growth factor alpha as autocrine growth factors in human pancreatic cancer cell growth. *Cancer Research*. 1990 Jan 1;**50**(1):103-107
- [63] Elsammak MY, Amin GM, Khalil GM, Ragab WS, Abaza MM. Possible contribution of serum activin a and IGF-1 in the development of hepatocellular carcinoma in Egyptian patients suffering from combined hepatitis C virus infection and hepatic schistosomiasis. *Clinical Biochemistry*. 2006;**39**:623-629
- [64] Su WW, Lee KT, Yeh YT, Soon MS, Wang CL, Yu ML, Wang SN. Association of circulating insulin-like growth factor 1 with hepatocellular carcinoma: One cross-sectional correlation study. *Journal of Clinical Laboratory Analysis*. 2010;**24**:195-200
- [65] Barrett JC. Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. *Cancer Research*. 1997;**57**:4667-4672
- [66] Pollak M. Insulin-like growth factor physiology and cancer risk. *European Journal of Cancer*. 2000;**36**:1224-1228
- [67] Le Roith D. Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. *The New England Journal of Medicine*. 1997;**336**:633-640
- [68] Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology*. 2002 Dec;**36**(6):1349-1354
- [69] White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clinical Gastroenterology and Hepatology*. 2012 Dec;**10**(12):1342-1359
- [70] Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H, Karin M. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell*. 2010 Jan 22;**140**(2):197-208

- [71] Marra F, Bertolani C. Adipokines in liver diseases. *Hepatology*. 2009 Sep;**50**(3):957-969. DOI: 10.1002/hep.23046
- [72] Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *The Journal of Clinical Investigation*. 2006 Jul;**116**(7):1784-1792
- [73] Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nature Reviews. Cancer*. 2007 Oct;**7**(10):763-777
- [74] Unger RH, Clark GO, Scherer PE, Orci L. Lipid homeostasis, lipotoxicity and the metabolic syndrome. *Biochimica et Biophysica Acta*. 2010 Mar;**1801**(3):209-214. DOI: 10.1016/j.bbali.2009.10.006 Epub 2009 Nov 27
- [75] Michael C. Kew. Hepatic Iron overload and hepatocellular carcinoma. *Liver Cancer*. 2014 Mar;**3**(1):31-40. Published online 2014 Mar 4
- [76] Ludwiczek S, Aigner E, Theurl I, Weiss G. Cytokine-mediated regulation of iron transport in human monocytic cells. *Blood*. 2003 May 15;**101**(10):4148-4154
- [77] Bradbear RA, Bain C, Siskind V, Schofield FD, Webb S, Axelsen EM, Halliday JW, Bassett ML, Powell LW. Cohort study of internal malignancy in genetic hemochromatosis and other chronic nonalcoholic liver diseases. *Journal of the National Cancer Institute*. 1985 Jul;**75**(1):81-84
- [78] Pietrangelo A. Hereditary hemochromatosis—A new look at an old disease. *The New England Journal of Medicine*. 2004 Jun 3;**350**(23):2383-2397
- [79] Friedman BM, Baynes RD, Bothwell TH, Gordeuk VR, Macfarlane BJ, Lamparelli RD, Robinson EJ, Sher R, Hamberg S. Dietary iron overload in southern African rural blacks. *South African Medical Journal*. 1990 Sep 15;**78**(6):301-305

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