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Diabetes Mellitus is a Risk Factor for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Virus Infection in China

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Study Design A
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Statistical Analysis C
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Background: This study aimed to investigate whether diabetes mellitus (DM) increased the risk of developing hepatocellular carcinoma (HCC) in patients with chronic hepatitis B virus (HBV) infection.

Material/Methods: Individuals with a confirmed diagnosis of HCC and chronic HBV infection (n=112), and non-diabetic individuals with both chronic HBV infection and HCC (n=210), were matched by age, sex, and degree of liver cirrhosis. Demographic, lifestyle, and clinical data were reviewed. Data were analyzed by univariate and multiple logistic regression analysis to identify the risk factors for HCC.

Results: Of the 112 patients with HCC (median age, 52.0 years; range, 46.3–56.0 years), 18.8% were men, and the prevalence of cirrhosis was 90.2%. Of the 210 patients without HCC (median age, 51.0 years; range, 47.0–58.0 years), 26.2% were men, and the prevalence of cirrhosis was 91.9%. Diabetes mellitus was more prevalent among individuals with HCC (16.1%) compared with those without HCC (7.6%) and increased the risk for HCC by two-fold to three-fold (adjusted odds ratio [AOR]: 2.402; 95% confidence interval [CI], 1.150–5.018). Multivariate analysis showed that cigarette smoking significantly increased the risk of HBV-related HCC (AOR: 1.665; 95% CI, 1.031–2.690), as did increased levels of HBV DNA (≥10^3 IU/mL) (AOR: 1.753; 95% CI, 1.079–2.849).

Conclusions: In a Chinese population with chronic HBV infection, DM increased the risk of HCC, as did cigarette smoking and high levels of HBV DNA. Screening patients with known risk factors for HCC might improve early detection rates and treatment to prevent tumor progression.

MeSH Keywords: Carcinoma, Hepatocellular • Diabetes Mellitus • Hepatitis B virus

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Background

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and is the second leading cause of cancer-related deaths worldwide [1]. Approximately 750,000 new cases of HCC are diagnosed each year [2], and Chinese patients account for 55% of the global incidence of HCC. The causes of HCC include chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, primary autoimmune hepatitis, hemochromatosis, Budd-Chiari syndrome, and chronic alcohol consumption, which can lead to liver cirrhosis [3]. Globally, 257 million individuals are infected with HBV [4], which is associated with 50–80% of all cases of HCC [5,6]. In China, HBV is the leading cause of HCC, where it accounts for 70% of cases [7,8].

Diabetes mellitus (DM) is a significant global health issue that shares risk factors with several types of cancer [9]. The incidence of DM among adults in China reached 11.7% in 2010 [10], and more recent reports have identified a relationship between DM and HCC. Epidemiologic studies have now shown that that DM is an independent risk factor that is associated with an approximately two-fold increase in the risk of developing HCC risk when compared with non-diabetic individuals [11–14]. Also, DM has been reported to be a possible risk factor for both the recurrence of HCC [15–18] and increased mortality in patients with HCC [19,20].

Previously published studies on the epidemiology of HCC have mainly focused on the association with HBV, HCV, and alcohol, including fatty liver disease associated with alcohol [14,21]. However, the link between DM and HBV-related HCC remains to be investigated, particularly in China, where the prevalence of chronic HBV infection is high.

Therefore, this case-controlled study aimed to investigate whether DM increased the risk of developing HCC in patients with chronic HBV infection in a Chinese patient population while controlling for other known risk factors for HCC.

Material and Methods

Patients and study design

A retrospective study was conducted of patients diagnosed and treated at The First Hospital of Jilin University in China, between January 2016 to January 2017. Patients with a diagnosis of chronic hepatitis B virus (HBV) infection diagnosis whose complete medical records were available were included in the study. The study protocol was approved by the Independent Institutional Review Board of The First Hospital of Jilin University. Each patient enrolled in the study provided written informed consent to participate.

The study inclusion criteria were confirmed chronic HBV infection, and in the patients with type 2 diabetes mellitus, a confirmed diagnosis of diabetes. Patients who had hepatocellular carcinoma (HCC) and liver cirrhosis also had confirmatory diagnostic tests. The study exclusion criteria included a known negative test for HBV surface antigen (HBsAg), co-infection with human immunodeficiency virus (HIV) or hepatitis C virus (HCV), a history of any other malignancy, and a history or signs of infection or other causes of liver disease, including autoimmune hepatitis and alcoholic or non-alcoholic fatty liver disease (NAFLD).

Diagnosis of chronic HBV infection, cirrhosis, and HCC

The diagnosis of HBV infection was based on a periodical or consistently high alanine transaminase (ALT) level (≥ twice the upper limit of normal), and the presence of serum HBsAg and HBV DNA for more than six months [22]. Liver cirrhosis was diagnosed by combined radiological and histological findings. HCC was diagnosed by liver biopsy and histology following computerized tomography (CT) and magnetic resonance imaging (MRI), which also included a portal venous contrast-enhanced scan showing increased arterial vascularization within the tumor, or positive imaging associated with an alpha-fetoprotein (AFP) level >400 ng/mL.

Diagnosis of diabetes mellitus (DM)

Patients with a known history of diabetes who were on being treated for diabetes were included or individual who had one or more of the following: a fasting blood glucose level ≥7.0 mmol/L; a random blood glucose level ≥11.1 mmol/L; or a two-hour post-prandial plasma glucose ≥11.1 mmol/L [23].

Demographic and clinical variables

From a review of the clinical records, data were obtained and analyzed on the following variables: gender, age, the presence of cirrhosis, the presence of gallstones, a family history of HCC, cigarette smoking, the history of DM, levels of ALT, aspartate aminotransferase (AST), HBV DNA, and glucose.

Statistical analysis

Data analysis of continuous variables used non-parametric tests, including the medians (25^{th} and 75^{th} percentiles), numbers and percentages, and categorical variables including the chi-squared (χ^2) test. All tests were two-tailed with $P<0.05$ indicating statistical significance. Multivariate logistic regression analysis was used to account for possible confounding variables and adjusted odds ratios (AORs) were obtained with 95% confidence intervals (CIs). All statistical analysis was performed using SPSS version13.0 (SPSS, Inc., Chicago, IL, USA) for Windows.

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Table 1. Demographic and clinical characteristics of study participants.

Variable	CHB + HCC N=112		CHB only N=210		*P* value
Male, N (%)	21	(18.8)	55	(26.2)	0.134
Age (years)	52.00	(46.25, 56.00)	51.00	(47.00, 58.00)	0.341
Cigarette smoking, N (%)	55	(49.1)	76	(36.2)	0.025
Family history of HCC, N (%)	16	(14.3)	19	(9.0)	0.150
Diabetes mellitus, N (%)	18	(16.1)	16	(7.6)	0.019
Gallstones, N (%)	24	(21.4)	31	(14.8)	0.130
Cirrhosis, N(%)	101	(90.2)	193	(91.9)	0.601
HBV DNA	3370.00	(338.75; 852,750.00)	1485.00	(20.00; 639,250.00)	0.018
AST (IU/L)	45.65	(34.45, 79.55)	43.00	(30.10, 71.40)	0.199
ALT (IU/L)	49.85	(29.80, 81.75)	36.45	(23.38, 61.80)	0.002
Glucose (mmol/L)	5.10	(4.67, 7.23)	5.03	(4.49, 5.91)	0.106

AST – aspartate aminotransferase; ALT – alanine aminotransferase; HCC – hepatocellular carcinoma; CHB – chronic hepatitis B; HBV – hepatitis B virus; HBsAg – HBV surface antigen. Continuous variables are expressed as the median (25th and 75th percentiles). Categorical variables are expressed as numbers and percentages.

Results

Patient demographic and clinical data

Table 1 shows the demographic and clinical features of the study participants. We initially recruited 980 patients with chronic hepatitis B virus (HBV) infection but excluded 310 patients, due to incomplete medical records, and excluded a further 120 patients based on the exclusion criteria described above. Individuals with a confirmed diagnosis of HCC and chronic HBV infection (n=112), and non-diabetic individuals with both chronic HBV infection and HCC (n=210) were matched by age, sex, and degree of liver cirrhosis.

Among the 112 patients with HCC, the median age was 52.0 years (range, 46.3–56.0 years), 18.8% were men, and the prevalence of cirrhosis was 90.2%. Among the 210 patients without HCC matched by sex, age, and cirrhosis status, the median age was 51.0 years (range, 47.0–58.0), 26.2% were men, and the prevalence of cirrhosis was 91.9% (Table 1).

There were no significant differences between the controls and the patients with HCC in terms of demographic characteristics, including gallstones and family history of HCC. Patients with HCC were significantly more likely to have DM when compared with patients without HCC (16.1% versus 7.6%) (P=0.019) and had significantly increased serum HBV DNA (or viral load) (3370.0 IU/mL) compared with patients without HCC (1485.0 IU/mL) (P=0.018). Cigarette smoking was also more common among patients with HCC (49.1%) compared with controls (36.2%) (P=0.025). Serum alanine transaminase (ALT) levels were significantly increased in patients with HCC compared with controls without HCC (P=0.002), but aspartate transaminase (AST) and glucose levels were similar between the two groups (P=0.199 and P=0.106, respectively).

Factors associated with HCC in patients with chronic HBV infection

Univariate analysis showed that cigarette smoking, DM, and increased serum levels of HBV DNA were more common in patients with HCC than in control participants without HCC (Table 2). Adjusting for potential confounders, including gender, age, cigarette smoking, family history of HCC, cirrhosis, high levels of HBV DNA, and DM, using multivariate analysis, confirmed the findings from univariate analysis. The diagnosis of DM increased the risk of HCC by two-fold to three-fold (AOR: 2.402; 95% CI, 1.150–5.018), and high serum HBV DNA levels increased the risk for HCC by nearly two-fold (AOR: 1.753; 95% CI, 1.079–2.849), while cigarette smoking increased HCC risk by between one-fold to two-fold (AOR: 1.665; 95% CI, 1.031–2.690).

Discussion

The findings of this study showed that in patients with chronic hepatitis B virus (HBV) infection, diabetes mellitus (DM)

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Table 2. Univariate and multivariate analyses of factors associated with HBV-related HCC.

Variable	CHB + HCC N=112	CHB only N=210	*P*#	AOR (95% CI)*	*P***
Sex			0.134		
Female, N (%)	91 (81.3)	155 (73.8)			
Male, N (%)	21 (18.8)	55 (26.2)			
Age			1.000		
≤50	48 (42.9)	90 (42.9)			
>50	64 (57.1)	120 (57.1)			
Diabetes			0.019	2.402 (1.150–5.018)	0.020
No, N (%)	94 (83.9)	194 (92.4)			
Yes, N (%)	18 (16.1)	16 (7.6)			
Cigarette smoking			0.025	1.665 (1.031–2.690)	0.037
No, N (%)	57 (50.9)	134 (63.8)			
Yes, N (%)	55 (49.1)	76 (36.2)			
Family history of HCC			0.150		
No, N (%)	96 (85.7)	191 (91.0)			
Yes, N (%)	16 (14.3)	19 (9.0)			
Cirrhosis			0.601		
No, N (%)	11 (9.8)	17 (8.1)			
Yes, N (%)	101 (90.2)	193 (91.9)			
HBV DNA			0.018	1.753 (1.079–2.849)	0.023
$<10^3$ IU/mL, N (%)	39 (34.8)	102 (48.6)			
$\geq 10^3$ IU/mL, N (%)	73 (65.2)	108 (51.4)			

AOR – adjusted odds ratio; CI – confidence interval; HBV – hepatitis B virus; HCC – hepatocellular carcinoma. # *P* value for univariate analysis; * Adjusted for gender, age, cigarette smoking, family history of HCC, liver cirrhosis, HBV DNA level, and diabetes mellitus; ** *P* value for multivariate analysis.

doubled the risk of developing hepatocellular carcinoma (HCC) in Chinese patients, which is consistent with the findings from previously published studies [12,24–26]. A long-term study of a community-based cohort showed that DM combined with HBV infection increased the risk of developing HCC by between two-fold to three-fold [12]. Similarly, Gao et al. studied the role of DM in patients with chronic HBV infection and liver cirrhosis and found that DM independently increased the likelihood that their cirrhosis would progress to HCC [27]. Zheng et al. also conducted a hospital-based case-control study to explore the possible association between DM and HCC and found a significant synergistic association between DM and HBV infection and the incidence of HCC [8].

However, there have also been some studies that have not established this association. In 2017, a Chinese case-control study of 91 patients with chronic HBV infection, liver cirrhosis, and DM, and 91 patients with liver cirrhosis without DM reported no association between DM and an increased risk for developing HCC [28]. In 2013, a retrospective cohort study explored the risk factors associated with the development of HCC in 5,6231 patients aged more than 40 years and did not find an association between DM and the development of HCC [29]. Because there are conflicting epidemiological findings, prospective studies involving more geographical and ethnic groups and studies that include investigations into the possible mechanisms involved in the liver in DM, chronic HBV infection, and HCC are warranted.

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One mechanism by which DM increases the risk of HBV-associated HCC might involve the effects of increased levels of insulin and insulin-like growth factor-1 (IGF-1) in adipose tissue, liver, and muscle tissues that result from insulin resistance, as several previously published studies have shown that increased levels of IGF-1 levels may have a role in carcinogenesis in the liver and other tissues [30–35]. Another potential mechanism by which DM may increase the risk of HBV-associated HCC involves obesity, which might trigger carcinogenic effects by the secretion of pro-inflammatory cytokines from visceral adipose tissues [36].

Also, hyperglycemia in poorly controlled DM might also have a carcinogenic effect, rather than hyperinsulinemia [36,37]. Cancer cells, which are rapidly dividing, have been shown to require more glucose than normal cells [38]. Direct carcinogenic effects of hyperglycemia combined with activation of the Wnt signal transduction pathway were recently proposed to promote carcinogenesis, resulting in nuclear beta-catenin accumulation and aberrant acetylation of beta-catenin [39].

In adults with chronic HBV infection, DM may influence the progression of liver cirrhosis and lead to severe liver-related outcomes [40,41]. Also, patients with diabetes and HCC have been shown to suffer from dysregulation of bile acid homeostasis and of the intestinal microbiome. Dietary obesity induces alterations of gut microbiota, thereby increasing the levels of deoxycholic acid, a gut bacterial metabolite known to cause DNA damage [42,43]. In mice models, the enterohepatic circulation of deoxycholic acid provokes senescence-associated secretory phenotype in hepatic stellate cells (HSCs), which then secrete inflammatory and tumor-promoting factors in the liver, thus facilitating HCC development in mice after exposure to chemical carcinogen [42,43]. Notably, blocking the deoxycholic acid production or reducing gut bacteria efficiently prevents the development of HCC development in obese mice. but the molecular pathways remain unknown [42,43].

The findings of the present study showed that cigarette smoking also increased the risk for developing HCC in patients with chronic HBV infection, although previous studies have shown conflicting results regarding the link between smoking and liver cancer [44,45]. However, due to the carcinogenic nature of some tobacco metabolites, such an association is likely. For example, some smokers have high blood levels of 4-aminobiphenyl DNA adducts, which are associated with an increased risk for HCC [46–48]. Also, N-nitrosodimethylamine, a common chemical byproduct of tobacco smoke, can potentially cause liver tumors in mice, rats, monkeys, and other species [49]. Vinyl chloride, a component of tobacco smoke, can also cause HCC and angiosarcoma in humans [50]. In the present study, patients who had HBV DNA levels $\geq 10^3$ IU/mL had a significantly increased risk for HCC compared with other patients with chronic HBV infection and low levels of HBV DNA, which is supported by the findings of previous studies [51,52].

This study had several limitations, including its retrospective design, the reliance on adequate and accurate patients details from clinical records, and the lack of details regarding the treatments the patients received for their DM. These limitations indicate that future prospective studies might provide further information on the association between specific hypoglycemic agents and the development of HCC. Also, because the study was conducted in a single center, which restricted the patient sample size, it was not possible to divide the study population with DM into smokers and non-smokers or to further clarify the role of smoking and diabetes in the occurrence or progression of HCC. The patient sample size was also limited due to the matching required of cirrhosis status between the study group and the control group, and the application of the necessary patient exclusion criteria.

Conclusions

The findings of this study showed that, in a Chinese population with chronic hepatitis B virus (HBV) infection, diabetes mellitus (DM) increased the risk of hepatocellular carcinoma (HCC). Cigarette smoking and high levels of HBV DNA were also associated with HCC. These findings highlight the importance of screening patients with known risk factors for HCC, which may improve early detection rates and treatment to prevent tumor progression.

References:

1. Ferlay J, Soerjomataram I, Dikshit R et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015; 136(5): E359–86
2. Ferlay J, Shin HR, Bray F et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer, 2010; 127(12): 2893–917
3. Nagaoki Y, Hyogo H, Aikata H et al: Recent trend of clinical features in patients with hepatocellular carcinoma. Hepatol Res, 2012; 42(4): 368–75
4. World Health Organization (WHO): Hepatitis B. Available from: URL: *http://www.who.int/mediacentre/factsheets/fs204/en/*
5. Bruix J, Sherman M: Management of hepatocellular carcinoma: An update. Hepatology, 2011; 53(3): 1020–22
6. Zhu RX, Seto WK, Lai CL, Yuen MF: Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. Gut Liver, 2016; 10(3): 332–39
7. Jemal A, Bray F, Center MM et al: Global cancer statistics. Cancer J Clin, 2011; 61(2): 69–90
8. Zheng Z, Zhang C, Yan J et al: Diabetes mellitus is associated with hepatocellular carcinoma: A retrospective case-control study in hepatitis endemic area. PLoS One, 2013; 8(12): e84776

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9. Huang MY, Chung CH, Chang WK et al: The role of thiazolidinediones in hepatocellular carcinoma risk reduction: a population-based cohort study in Taiwan. Am J Cancer Res, 2017; 7(7): 1606–16
10. Xu Y, Wang L, He J et al: Prevalence and control of diabetes in Chinese adults. JAMA, 2013; 310(9): 948–59
11. Balkau B, Kahn HS, Courbon D et al: Hyperinsulinemia predicts fatal liver cancer but is inversely associated with fatal cancer at some other sites: The Paris Prospective Study. Diabetes Care, 2001; 24(5): 843–49
12. Chen CL, Yang HI, Yang WS et al: Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Gastroenterol, 2008; 135(1): 111–21
13. Lee MS, Hsu CC, Wahlqvist ML et al: Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: A representative population prospective cohort study of 800,000 individuals. BMC Cancer, 2011; 11: 20
14. Elkrief L, Chouinard P, Bendersky N et al: Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. Hepatology, 2014; 60(3): 823–31
15. Ikeda Y, Shimada M, Hasegawa H et al: Prognosis of hepatocellular carcinoma with diabetes mellitus after hepatic resection. Hepatology, 1998; 27(6): 1567–71
16. Huo TI, Wu JC, Lui WY et al: Diabetes mellitus is a recurrence-independent risk factor in patients with hepatitis B virus-related hepatocellular carcinoma undergoing resection. Eur J Gastroenterol Hepatol, 2003; 15(11): 1203–8
17. Komura T, Mizukoshi E, Kita Y et al: Impact of diabetes on recurrence of hepatocellular carcinoma after surgical treatment in patients with viral hepatitis. Am J Gastroenterol, 2007; 102(9): 1939–46
18. Kawamura Y, Ikeda K, Arase Y et al: Diabetes mellitus worsens the recurrence rate after potentially curative therapy in patients with hepatocellular carcinoma associated with nonviral hepatitis. J Gastroenterol Hepatol, 2008; 23(11): 1739–46
19. Coughlin SS, Calle EE, Teras LR et al: Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol, 2004; 159(12): 1160–67
20. Landman GW, van Hateren KJ, Kleefstra N et al: The relationship between glycaemic control and mortality in patients with type 2 diabetes in general practice (ZODIAC-11). Br J Gen Pract, 2010; 60(572): 172–75
21. Li X, Xu H, Gao Y et al: Diabetes mellitus increases the risk of hepatocellular carcinoma in treatment-naive chronic hepatitis C patients in China. Medicine, 2017; 96(13): e6508
22. Martin P, Lau DT, Nguyen MH et al: A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2015 Update. Clin Gastroenterol Hepatol, 2015; 13(12): 2071-87.e16.
23. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med, 1998; 15(7): 539–53
24. Lai MS, Hsieh MS, Chiu YH, Chen TH: Type 2 diabetes and hepatocellular carcinoma: A cohort study in high prevalence area of hepatitis virus infection. Hepatology, 2006; 43(6): 1295–302
25. Inoue M, Kurahashi N, Iwasaki M et al: Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: A large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). Cancer Causes Control, 2009; 20(5): 741–50
26. Ko WH, Chiu SY, Yang KC, Chen HH: Diabetes, hepatitis virus infection and hepatocellular carcinoma: A case-control study in hepatitis endemic area. Hepatol Res, 2012, 42(8): 774–81
27. Gao C, Fang L, Zhao HC et al: Potential role of diabetes mellitus in the progression of cirrhosis to hepatocellular carcinoma: A cross-sectional case-control study from Chinese patients with HBV infection. Hepatobiliary Pancreat Dis Int, 2013; 12(4): 385–93
28. Han H, Deng H, Han T et al: Association between hepatocellular carcinoma and type 2 diabetes mellitus in Chinese hepatitis B virus cirrhosis patients: A case-control study. Med Sci Monit, 2017; 23: 3324–34
29. Chen CT, Chen JY, Wang JH et al: Diabetes mellitus, metabolic syndrome and obesity are not significant risk factors for hepatocellular carcinoma in an HBV- and HCV-endemic area of Southern Taiwan. Kaohsiung J Med Sci, 2013; 29(8): 451–59
30. Ish-Shalom D, Christoffersen CT, Vorwerk P et al: Mitogenic properties of insulin and insulin analogues mediated by the insulin receptor. Diabetologia, 1997; 40(Suppl. 2): S25–31
31. Ford ES, Cogswell ME: Diabetes and serum ferritin concentration among U.S. adults. Diabetes Care, 1999; 22(12): 1978–83
32. Niedernhofer LJ, Daniels JS, Rouzer CA et al: Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells. J Biol Chem, 2003; 278(33): 31426–33
33. Rosenfeld RG: Insulin-like growth factors and the basis of growth. N Engl J Med, 2003; 349(23): 2184–86
34. Calle EE, Kaaks R: Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer, 2004; 4(8): 579–91
35. Bowker SL, Majumdar SR, Veugelers P, Johnson JA: Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin: Response to Farooki and Schneider. Diabetes Care, 2006; 29(8): 1990–91
36. Fujita K, Iwama H, Miyoshi H et al: Diabetes mellitus and metformin in hepatocellular carcinoma. World J Gastroenterol, 2016; 22(27): 6100–13
37. Warburg O: On the origin of cancer cells. Science, 1956; 123(3191): 309–14
38. Miles KA, Williams RE: Warburg revisited: Imaging tumour blood flow and metabolism. Cancer Imaging, 2008; 8: 81–86
39. Chocarro-Calvo A, Garcia-Martinez JM, Ardila-Gonzalez S et al: Glucose-induced beta-catenin acetylation enhances Wnt signaling in cancer. Mol Cell, 2013; 49(3): 474–86
40. Moreau R, Delegue P, Pessione F et al: Clinical characteristics and outcome of patients with cirrhosis and refractory ascites. Liver Int, 2004; 24(5): 457–64
41. Younossi Z, Kochems K, de Ridder M et al: Should adults with diabetes mellitus be vaccinated against hepatitis B virus? A systematic review of diabetes mellitus and the progression of hepatitis B disease. Hum Vaccin Immunother, 2017; 13(11): 2695–706
42. Holmes E, Li JV, Athanasiou T et al: Understanding the role of gut microbiome-host metabolic signal disruption in health and disease. Trends Microbiol, 2011; 19(7): 349–59
43. Shackel NA, Vadas MA, Gamble JR, McCaughan GW: Beyond liver fibrosis: Hepatic stellate cell senescence links obesity to liver cancer by way of the microbiome. Hepatology, 2014; 59(6): 2413–15
44. Chuang SC, Lee YC, Hashibe M et al: Interaction between cigarette smoking and hepatitis B and C virus infection on the risk of liver cancer: A meta-analysis. Cancer Epidemiol Biomarkers Prev, 2010; 19(5): 1261–68
45. Abdel-Rahman O, Helbling D, Schob O et al: Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: An updated systematic review of 81 epidemiological studies. J Evid Based Med, 2017; 10(4): 245–54
46. International Agency for Research on Cancer (IARC): Monograph on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1–42. IARC Monographs Supplement 7, 1987
47. Wang LY, Chen CJ, Zhang YJ et al: 4-Aminobiphenyl DNA damage in liver tissue of hepatocellular carcinoma patients and controls. Am J Epidemiol, 1998; 147(3): 315–23
48. Chen SY, Wang LY, Lunn RM et al: Polycyclic aromatic hydrocarbon-DNA adducts in liver tissues of hepatocellular carcinoma patients and controls. Int J Cancer, 2002; 99(1): 14–21
49. International Agency for Research on Cancer (IARC): IARC monograph on the evaluation of the carcinogenic risk of chemicals to humans: Some N-nitroso compounds. 1978; 17: 1–349
50. Grosse Y, Baan R, Straif K et al: Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. Lancet Oncol, 2007; 8(8): 679–80
51. Chen CJ, Yang HI, Su J et al: Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA, 2006; 295(1): 65–73
52. Chen CJ, Yang HI, Iloeje UH: Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology, 2009; 49(5 Suppl.): S72–84

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