see related article on page 624

Diabetes and Hepatocellular Carcinoma: What Role Does Diabetes Have in the Presence of Other Known Risk Factors?

Jessica A. Davila, PhD[1]

Abstract: Known risk factors for hepatocellular carcinoma (HCC) include hepatitis C, hepatitis B, and alcoholic liver disease. Several studies have examined diabetes as a risk factor for HCC because of its association with fatty liver disease and non-alcoholic steatohepatitis. The current study by Tung *et al.* found that neither diabetes nor overweight was a risk factor for HCC. Results were consistent using both a cross-sectional and a case–control study approach. Findings from this study suggest that diabetes and overweight alone are not adequate to increase the risk of HCC in the absence of concomitant viral hepatitis or liver disease.

Am J Gastroenterol 2010; 105:632–634; doi:10.1038/ajg.2009.715

The incidence of hepatocellular carcinoma (HCC) in the United States has more than doubled over the past two decades (1). Primary known risk factors for HCC are hepatitis C virus (HCV), hepatitis B virus (HBV), and alcoholic liver disease (2,3). Yet previous studies have reported the absence of these risk factors in up to 50% of HCC cases (4). Other potential risk factors for HCC include diabetes and obesity as measured by body mass index (BMI). The proposed mechanism of HCC development for diabetes and obesity is through the development of fatty liver disease and non-alcoholic steatohepatitis (NASH). The pathogenesis of NASH involves insulin resistance, which is associated with both obesity and diabetes (5). Several studies have examined the association between HCC and diabetes. Earlier studies reported no association between diabetes and HCC, while more recent studies have identified diabetes as a risk factor for HCC (6–15). A study conducted among a large cohort of Veterans found that the incidence of HCC was increased more than twofold among patients with diabetes, and that the risk of developing HCC among patients with diabetes was 2.2 times greater than in patients without diabetes (9). Another population-based case–control study using the Surveillance, Epidemiology and End Results Medicare database reported an odds ratio of 2.87 (95% confidence interval (CI): 2.49–3.30) for diabetes among patients without other major risk factors (HCV, HBV, alcoholic liver disease, or hemochromatosis) for HCC (7).

Other studies have focused on the association between HCC and obesity. It is estimated that 90% of people with obesity have fatty liver disease, including NASH and cirrhosis (16). One study of over 19,000 patients found that the incidence of HCC was higher in obese (defined as BMI > 30 kg/m^2) patients than in non-obese patients (4.0% vs. 3.0%, respectively; $P = 0.013$), and that obesity was associated with a 65% increased risk of developing HCC (13). Another large prospective cohort study of more than 900,000 individuals reported that the mortality rate from liver cancer was five times greater among those with a BMI between 35–40 compared with those with a normal BMI (5).

A synergistic relationship has also been reported to exist between diabetes and other known risk factors for HCC, specifically viral hepatitis and alcohol use (11,17). A recent study reported that among HCV-infected patients who were not infected with HBV, those with diabetes had a 3.5-fold increased risk of developing HCC compared with those without diabetes (17). The same study found a lower yet significant increase in the risk of HCC among patients with HBV who were not infected with HCV among those with diabetes compared to those without diabetes (relative risk = 2.17; 95% CI: 1.07–4.43).

In this issue of the *American Journal of Gastroenterology*, Tung *et al.* (18) report the results of a study using both a cross-sectional and a case–control design to examine the association between diabetes and overweight in a dual HBV and HCV endemic area of Taiwan. Data for this study were obtained from a comprehensive health-screening program conducted in 2004 that was offered to all individuals residing in Tainan County, Taiwan who were aged ≥ 40 years. A total of 56,702 adults participated in the

[1]Houston Center for Quality of Care & Utilization Studies, Sections of Health Services Research at Baylor College of Medicine and the Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA. **Correspondence:** Jessica A. Davila, PhD, Baylor College of Medicine, The Michael E. DeBakey VA Medical Center, 2002 Holcombe Boulevard (152), Houston, Texas 77030, USA. E-mail: jdavila@bcm.tmc.edu
Received 10 November 2009; accepted 24 November 2009

screening program. Clinical measurements included hepatitis B surface antigen, anti-HCV, platelet count, BMI, and fasting blood sugar level. All variables were measured at the time when the screening program examination was performed. Diabetes was defined as having a fasting blood sugar level >126 mg/dl and overweight was defined as having a BMI >24 kg/m^2. Among all individuals who participated in the screening program, 72 new cases and 42 known cases of HCC were identified. The 42 known cases of HCC were excluded because BMI collected following diagnosis and treatment for HCC may not accurately reflect the BMI before diagnosis. Three separate analyses were conducted to address the study question. The first analysis was a cross-sectional approach that included all patients with complete information who participated in the screening program. For the second and third analyses, participants were matched in a 1:2 case–control design. Participants were first matched on age, sex, and residence to evaluate the association between HBV, HCV, diabetes, overweight, and HCC. Subsequently, matching was expanded to include HBV and HCV status to allow more focused examination of the association between diabetes, overweight, and HCC.

Neither diabetes nor being overweight was shown to be significantly associated with HCC in any of the analyses. The prevalence of diabetes was 9.7% among patients with HCC compared with 9.6% among controls. The prevalence of overweight was slightly lower among patients with HCC compared with controls (51.4% vs. 54.9%, respectively). However, BMI for patients with HCC was collected at the time of HCC diagnosis, which may not reflect the patients' true BMI years before developing HCC. In the unadjusted analysis comparing the HCC cases with non-matched controls, an odds ratio of 1.0 (95% CI: 0.5–2.2) was reported for diabetes, and an odds ratio of 0.9 (0.5–1.4) was reported for overweight.

As expected, HBV and HCV were associated with HCC. A subanalysis was conducted among only those patients with hepatitis C who were not infected with hepatitis B, as previous studies have reported that patients with HCV and diabetes are at a significantly higher risk of developing HCC compared with patients with HCV alone. Again, diabetes and overweight were not significantly associated with the development of HCC.

Thrombocytopenia was identified as an independent risk factor for HCC, even after adjusting for HBV and HCV. It is likely that the presence and severity of cirrhosis underlying the thrombocytopenia may explain why thrombocytopenia was consistently found to be associated with HCC in all study analyses. Cirrhosis is the main precursor lesion for HCC except among patients with HBV (19–22). Patients with cirrhosis develop HCC at an annual incidence of 2–7% per year (21).

One limitation of this study was that the role of alcohol could not be evaluated. Heavy alcohol intake (more than 50 g/day) has been shown to be associated with an increased risk of HCC (23). Other studies report that alcohol consumption is associated with diabetes as well as HCC. A study by Hassan *et al.* (11) detected a synergistic relationship between diabetes and alcohol, indicating that heavy alcohol consumption and diabetes together may exacerbate the effects of each risk factor individually on the development of HCC.

In summary, findings from this study highlight the importance of considering multiple factors, including diabetes, viral hepatitis, and alcohol consumption, when assessing patients' risk for developing HCC. Although this study did not find an association between diabetes and HCC, other studies have reported that diabetes may significantly increase the risk of developing HCC when other known risk factors are present. These patients should be considered for HCC surveillance, especially following the onset of cirrhosis. Further work is needed to better understand the mechanisms underlying the relationship between diabetes and HCC in the presence of other risk factors, and to develop strategies to best monitor these patients for the development of chronic liver disease and HCC.

CONFLICT OF INTEREST

Guarantor of the article: Jessica A. Davila, PhD.
Financial support: None.
Potential competing interests: None.

REFERENCES

1. El Serag HB, Davila JA, Petersen NJ *et al.* The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817–23.
2. El Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med 2000;160:3227–30.
3. Hassan MM, Frome A, Patt YZ *et al.* Rising prevalence of hepatitis C virus infection among patients recently diagnosed with hepatocellular carcinoma in the United States. J Clin Gastroenterol 2002;35:266–9.
4. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Semin Liver Dis 1995;15:64–9.
5. Calle EE, Rodriguez C, Walker-Thurmond K *et al.* Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
6. Adami HO, Chow WH, Nyren O *et al.* Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88:1472–7.
7. Davila JA, Morgan RO, Shaib Y *et al.* Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut 2005;54:533–9.
8. El Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. Am J Gastroenterol 2001;96:2462–7.
9. El Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126:460–8.
10. El Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4:369–80.
11. Hassan MM, Hwang LY, Hatten CJ *et al.* Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–13.
12. Lai MS, Hsieh MS, Chiu YH *et al.* Type 2 diabetes and hepatocellular carcinoma: a cohort study in high prevalence area of hepatitis virus infection. Hepatology 2006;43:1295–302.
13. Nair S, Mason A, Eason J *et al.* Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? Hepatology 2002;36: 150–5.
14. Wideroff L, Gridley G, Mellemkjaer L *et al.* Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 1997;89:1360–5.
15. Yu MC, Tong MJ, Govindarajan S *et al.* Nonviral risk factors for hepatocellular carcinoma in a low-risk population, the non-Asians of Los Angeles County, California. J Natl Cancer Inst 1991;83:1820–6.
16. Caldwell SH, Crespo DM, Kang HS *et al.* Obesity and hepatocellular carcinoma. Gastroenterology 2004;127 (Suppl 1): S97–103.

17. 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. Gastroenterology 2008;135:111–21.
18. Tung H-D, Wang J-H, Tseng P-L et al. Neither diabetes mellitus nor overweight was a risk factor for hepatocellular carcinoma in a dual HBV and HCV endemic area: community cross-sectional and case-control studies. Am J Gastroenterol 2010;105:624–31.
19. Bralet MP, Regimbeau JM, Pineau P *et al.* Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 2000;32:200–4.
20. De Mitri MS, Poussin K, Baccarini P *et al.* HCV-associated liver cancer without cirrhosis. Lancet 1995;345:413–5.
21. El Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology 2002;36 (Suppl 1): S74–83.
22. Fattovich G. Progression of hepatitis B and C to hepatocellular carcinoma in Western countries. Hepatogastroenterology 1998;45 (Suppl 3): 1206–13.
23. Everhart J, Herion D. Hepatitis C virus infection and alcohol. In: Liang TJ, Hoofnaglw JH (eds). Hepatitis C. Academic Press: San Diego, 2000, pp. 363–88.