The Incidence and Risk Factors of Hepatocellular Carcinoma in Patients with Nonalcoholic Steatohepatitis

Mustafa S. Ascha,1 Ibrahim A. Hanouneh,2 Rocío Lopez,3 Tarek Abu-Rajab Tamimi,1 Ariel F. Feldstein,1 and Nizar N. Zein1

Nonalcoholic steatohepatitis (NASH) is a well-recognized cause of cirrhosis and has been increasingly associated with the development of hepatocellular carcinoma (HCC). The aims of this study were to (1) estimate the incidence of HCC in patients with NASH-related cirrhosis, (2) compare incidence in NASH-related cirrhosis with hepatitis C virus (HCV)-related cirrhosis, and (3) identify risk factors of HCC in patients with NASH-related cirrhosis compared with HCV-related cirrhosis. Adult patients with cirrhosis secondary to chronic HCV (n = 315) or NASH (n = 195) were evaluated at our hepatobiliary clinic between 2003 and 2007. To assess for HCC development, all patients were monitored using serial abdominal computed tomography and serum alpha-fetoprotein every 6 months. Kaplan-Meier analysis was performed to estimate the cumulative incidence of HCC. Descriptive statistics were computed for all factors. Univariate and multivariate Cox regression analysis were used to assess associations between HCC and factors of interest. The median follow-up was 3.2 years (25th percentile [P25], 75th percentile [P75]: 1.7, 5.7) during which 25/195 (12.8%) of NASH-cirrhotic and 64/315 (20.3%) of HCV-cirrhotic patients developed HCC (P = 0.03). Yearly cumulative incidence of HCC was found to be 2.6% in patients with NASH-cirrhosis, compared with 4.0% in patients with HCV cirrhosis (P = 0.09). Multivariate regression analysis revealed that older age (P = 0.006) and alcohol consumption (P = 0.002) were independent variables associated with development of HCC in patients with NASH-cirrhosis. Compared with nondrinkers, patients who reported any regular alcohol consumption were at greater risk for HCC development (hazard ratio: 3.6; P25, P75: 1.5, 8.3). Conclusion: Patients with NASH cirrhosis have a greatly increased risk of liver cancer. Alcohol consumption, a modifiable risk factor, appears to be the most significant factor associated with risk of HCC development in our study population. (HEPATOLOGY 2010;51:1972-1978)
characteristics of metabolic syndrome such as obesity and diabetes mellitus are strongly correlated with NASH and are increasing in prevalence in the United States. Obesity has already been linked to the development of primary liver cancer; both obesity and diabetes mellitus have been closely correlated with increased risk of several malignancies, specifically HCC.\(^4\)\(^\text{9}\)\(^\text{10}\) Despite a lack of strong evidence, it is possible that the associations between obesity/diabetes and HCC are related to the progression of nonalcoholic fatty liver in the setting of cirrhosis. NAFLD and NASH can progress to cirrhosis and liver failure in 3%-15%.\(^9\)\(^\text{10}\) There have been several emerging reports of HCC in the setting of NAFLD.\(^\text{11}\)\(^\text{14}\) However, there is a lack of large population studies regarding the risk of HCC in patients with liver cirrhosis secondary to NASH.

Few factors, including alcohol consumption, are believed to increase the risk of HCC development in patients with liver cirrhosis.\(^\text{15}\)\(^\text{17}\) While heavy alcohol consumption is widely recognized as a significant risk for the development of HCC, the significance of alcohol intake in small quantities and its relationship with the development of HCC in the NASH population is not known.

The aims of this study, therefore, were to (1) estimate the incidence and cumulative annual risk of HCC in patients with NASH cirrhosis, (2) compare it with those with hepatitis C virus (HCV) cirrhosis, and (3) to identify risk factors for HCC in patients with NASH-cirrhosis compared with HCV-cirrhosis.

### Patients and Methods

All adult patients (age ≥18 years) with liver cirrhosis secondary to chronic HCV infection or NASH who were referred to the liver transplant clinic at our institution between January 2003 and June 2007 (N = 664) whose data were prospectively recorded for study were retrospectively identified and reviewed using the Cleveland Clinic Foundation electronic medical records system. Consistent with the American Association for the Study of Liver Diseases Guidelines,\(^\text{18}\) patients with cirrhosis were referred to transplantation in our institution when they developed evidence of hepatic decompensation (Child-Turcotte-Pugh [CTP] score ≥7 or model for end-stage liver disease [MELD] score ≥10), or when they experienced their first major complication (ascites, variceal bleeding, or hepatic encephalopathy). Patients were excluded if they were diagnosed with HCC at their initial visit or had a previous history of HCC (n = 54), were previous orthotopic liver transplant recipients (n = 6), had an unknown date of cirrhosis diagnosis (n = 72), or were lost to follow-up after their initial visit (n = 22).

All patients were followed by protocol serial abdominal computed tomography and serum alpha-fetoprotein every 6 months. Whereas HCC was identified radiologically in all patients (n = 89), histologic confirmation was obtained in only 53 (59%) patients. Radiological diagnosis was defined according to American Association for the Study of Liver Diseases practice guidelines on the management of HCC.\(^\text{19}\) According to these guidelines, radiologic diagnosis of HCC is defined as either (1) the presence of a hepatic lesion ≥2 cm in diameter with typical vascular pattern for HCC on one dynamic imaging technique or alpha-fetoprotein >200 ng/mL or (2) the presence of a lesion 1-2 cm in diameter with typical vascular pattern for HCC on two dynamic imaging techniques. Follow-up time was defined as the number of years from the diagnosis of cirrhosis to the diagnosis of HCC, or from the diagnosis of cirrhosis to the last follow-up visit when protocol surveillance confirmed no HCC.

Demographic data (age, sex, and race), details of metabolic traits—including body mass index (BMI), fasting serum glucose, triglyceride, high-density lipoprotein, and systolic and diastolic blood pressure—were extracted from patients’ records. Additionally, detailed medical history of hypertension, hyperlipidemia, and diabetes and their corresponding therapy was also obtained from medical records. Patient data from the first clinic visit were used to calculate MELD and CTP scores.

Patients with cirrhosis were identified based on histological features of cirrhosis and/or radiological evidence of cirrhosis in the context of portal hypertension (ascites, variceal bleeding, thrombocytopenia or hepatic encephalopathy). NASH was defined according to the histologic features of NASH, when available, or cryptogenic cirrhosis in the presence of metabolic syndrome and without a history of significant alcohol intake. Metabolic syndrome was defined following the National Cholesterol Education Program Adult Treatment Plan III (ATP III) guidelines, the only notable exception being that the waist circumference trait was replaced by BMI >28.8 kg/m\(^2\) in both men and women for the purpose of this study, which has been validated.\(^\text{20}\) The diagnosis of diabetes mellitus was made at the time of transplant evaluation using criteria recommended by the American Diabetes Association and Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (fasting blood glucose value of 126 mg/dL on two separate occasions in those not receiving hypoglycemic agents or corticosteroids). Patients who were receiving insulin or oral hypoglycemia were assumed to have diabetes mellitus. The
presence of HCV was confirmed by qualitative seropositivity for HCV RNA.

Using the standard assessment of patients undergoing liver transplant evaluation, we excluded potentially confounding liver diseases, including: hepatitis B infection (determined by seropositivity for hepatitis B surface antigen and hepatitis B core antigen); hereditary hemochromatosis (by serum iron indices in all patients and genetic testing, if indicated); primary biliary cirrhosis (serum mitochondrial antibody and compatible histology); primary sclerosing cholangitis (by cholangiogram, if suspected); autoimmune hepatitis (based on serum markers and histology); and alpha-1-antitrypsin deficiency (phenotypic analysis).

**Definitions of Alcohol and Tobacco Intake.** Level of alcohol intake was divided into four categories based on published studies. The first category was “never,” which was defined as a lack of alcohol intake altogether. The second category was “social alcohol intake,” which was defined as consumption of no more than two alcoholic drinks daily or three to six drinks daily on weekends. “Significant alcohol intake” was defined as consumption of more than two drinks daily or more than six drinks daily on weekends for the past 5 years. “Formerly significant alcohol intake” was defined as more than “social alcohol intake” within the past 5 years. A patient was considered an ex-smoker if he or she reported not smoking for the past 6 months, with the intention to quit.

**Statistical Analysis.** Descriptive statistics were computed for all variables, including medians and percentiles for continuous variables and frequencies for categorical factors. Time of follow-up was defined as number of years from diagnosis of cirrhosis to HCC diagnosis or last follow-up visit if no HCC. Kaplan-Meier analysis was performed to estimate HCC cumulative incidence from the time of cirrhosis diagnosis, and plots of cumulative events versus years of follow-up were constructed. In order to assess which factors were associated with development of HCC after cirrhosis diagnosis, univariate and multivariate Cox proportional hazard regression analysis was performed; this was done for NASH and HCV separately. An automated stepwise variable selection was performed on 1,000 bootstrap samples to choose the final models. Variables that appeared in more than 20% of the replications were incorporated in the final model. SAS version 9.2 software (SAS Institute, Cary, NC) and R version 2.4.1 software (R Foundation for Statistical Computing) were used for all analyses.

### Table 1. Baseline Characteristics

| Factor                        | Total (N = 510) | HCV (n = 315) | NASH (n = 195) | P Value |
|-------------------------------|----------------|--------------|---------------|---------|
| Age at time of cirrhosis diagnosis, years | 50.5 (45.8, 56.5) | 48.2 (44.6, 51.9) | 56.6 (50.6, 60.8) | <0.001 |
| Male sex                      | 327 (64.1)     | 241 (76.5)   | 86 (44.1)     | <0.001 |
| Caucasian                     | 417/494 (84.4) | 238/308 (77.3) | 179/186 (96.2) | <0.001 |
| BMI (kg/m²)                   | 31.0 (26.3, 35.5) | 28.3 (24.8, 32.0) | 34.6 (31.2, 38.4) | <0.001 |
| Albumin                       | 3.2 (2.8, 3.6)  | 3.2 (2.7, 3.5) | 3.3 (2.8, 3.7)  | 0.15    |
| Creatinine                    | 0.9 (0.7, 1.1)  | 0.8 (0.7, 1.0) | 0.9 (0.7, 1.1)  | 0.027   |
| Bilirubin                     | 1.7 (1.1, 3.0)  | 1.8 (1.2, 3.1) | 1.6 (1.0, 2.6)  | 0.063   |
| International normalized ratio| 1.2 (1.1, 1.3)  | 1.2 (1.1, 1.3) | 1.2 (1.1, 1.2)  | 0.002   |
| CTP score                     | 7.0 (5.0, 8.0)  | 7.0 (5.0, 8.0) | 6.0 (5.0, 8.0)  | 0.23    |
| MELD score                    | 11.6 (9.0, 14.6) | 11.8 (9.2, 14.7) | 11.1 (8.5, 14.3) | 0.17    |
| Systolic blood pressure       | 123.0 (111.0, 138.0) | 123.0 (112.0, 137.0) | 123.0 (110.0, 140.0) | 0.99    |
| Diastolic blood pressure      | 69.0 (62.0, 77.0) | 71.0 (65.0, 79.0) | 64.0 (57.0, 72.0) | <0.001  |
| Diabetes mellitus             | 241 (48.1)     | 100 (32.5)   | 141 (73.1)     | <0.001  |
| Smoking**                     |                |              |               |         |
| Never                         | 170 (33.8)     | 61 (19.6)    | 109 (57.1)     |         |
| Current                       | 148 (29.4)     | 128 (41.0)   | 20 (10.5)      |         |
| Ex-smoker                     | 185 (36.8)     | 123 (39.4)   | 62 (32.5)      |         |
| Alcohol                       |                |              |               | <0.001  |
| Never                         | 179 (35.9)     | 59 (19.0)    | 120 (63.8)     |         |
| Social                        | 103 (20.7)     | 45 (14.5)    | 58 (30.9)      |         |
| Heavy                         | 34 (6.8)       | 34 (11.0)    | 0 (0)          |         |
| Former heavy drinker          | 182 (36.6)     | 172 (55.5)   | 10 (5.3)       |         |
| HCC                            | 89 (17.5)     | 64 (20.3)    | 25 (12.8)      | 0.03    |
| Alpha-fetoprotein level at time of HCC diagnosis | 15.2 (6.9, 35.0) | 15.7 (7.0, 38.6) | 8.3 (6.4, 25.1) | 0.27    |
| Follow-up time, years*        | 3.2 (1.7, 5.7) | 3.4 (1.8, 5.8) | 2.7 (1.4, 5.3) | 0.036   |

Data are expressed as the median (P25, P75) or n (%).

* Number of years from diagnosis of cirrhosis to HCC diagnosis or last follow-up visit if no HCC.

** Missing data in 7 patients.
Results

Baseline Characteristics. Among the 510 patients included in the study, 195 had NASH-cirrhosis and 315 had HCV-cirrhosis (Table 1). The median age for the entire population was 50.5 (25th percentile [P25], 75th percentile [P75]: 45.8, 56.5), of which 327 (64.1%) were men and 417 (84.4%) were Caucasian. NASH patients tended to be older than those with HCV at the time of cirrhosis diagnosis (median 56.6 versus 48.2 years, respectively; \( P < 0.001 \)). Significantly fewer NASH patients were men compared with HCV patients (86/195 [44.1%] versus 241/315 [76.5%], respectively; \( P < 0.001 \)). The HCV group had fewer Caucasians than the NASH group (77.3% versus 96.2%, respectively; \( P < 0.001 \)). Not surprisingly, patients with NASH had a higher BMI than those who had HCV (median [range]: 34.6 [31.2-38.4] kg/m\(^2\) versus 28.3 [24.8-32.0] kg/m\(^2\), respectively; \( P < 0.001 \)) and were more likely to have diabetes mellitus (141 [73.1%] versus 100 [32.5%], respectively; \( P < 0.001 \)).

One hundred forty-eight patients (29%) underwent orthotopic liver transplantation by the end of follow-up (HCV, 93 [63%]; NASH, 55 [37%]; \( P = 0.75 \)). The median MELD and CTP scores at enrollment were 11.6 (P25, P75: 9.0, 14.6) and 7.0 (P25, P75: 5.0, 8.0), respectively. There were no significant differences in the values of MELD and CTP at the time of the enrollment between NASH and HCV groups.

Morphological and histological characteristics of HCC were available in patients with HCC who underwent orthotopic liver transplantation (n = 50). Overall, tumors related to HCV tended to be larger than those associated with NASH (largest nodule, 3.0 [SD: 1.3] cm versus 2.2 [SD: 0.9] cm; \( P = 0.032 \)). Additionally, alpha-fetoprotein levels were higher in HCV patients than in NASH patients (mean [range]: 14.0 [7.4-69.0] versus 6.9 [4.9-12.1], respectively; \( P = 0.02 \)). There were no statistically significant differences between HCV- and NASH-associated HCC, whether related to the number of nodules at diagnosis, the presence of microvascular invasion, or degree of tumor differentiation on histological examination of explanted liver specimens (data not shown). Similarly, the overall survival after orthotopic liver transplantation in those 50 patients was insignificant between HCV and NASH patients.

Never, current, and ex-smokers amounted to 170 (33.8%), 148 (29.4%), and 185 (36.8%), respectively. Tobacco abuse was less common in the NASH group than in the HCV group (20/195 [10.5%] versus 128/315 [41.0%]; \( P < 0.001 \)). Alcohol was a significantly different variable between the populations, because the NASH population was partially defined by a lack of significant alcohol intake. As such, significantly more patients in the NASH group reported never drinking or social drinking compared with the HCV population (\( P < 0.001 \)). By definition, no patients with current or formerly significant drinking habits were in the NASH group.

Cumulative Incidence of HCC. Over a median follow-up time of 3.2 years (P25, P75: 1.7, 5.7 years) after cirrhosis diagnosis, 89 (17.4%) patients of the entire population developed HCC. Twenty-five of 195 (12.8%) NASH-cirrhotic patients developed HCC compared with 64/315 (20.3%) HCV-cirrhotic patients (\( P = 0.03 \)). The yearly cumulative incidence of HCC in patients with NASH cirrhosis was 2.6% per year compared with 4.0% for patients with HCV cirrhosis (\( P = 0.09 \)). Figure 1 shows Kaplan-Meier estimates of the cumulative risk of HCC in the two study groups.

Risk Factors for HCC in Patients with NASH Cirrhosis. On univariate analysis, three factors were
identified to be statistically associated with the development of HCC within the NASH-cirrhosis group (Table 2). The first factor was older age at time of cirrhosis diagnosis (hazard ratio 1.07 [confidence interval 1.02-1.1]; $P = 0.012$). Higher BMI was also negatively associated with the development of HCC (hazard ratio, 0.94 [confidence interval 0.89-0.99]; $P = 0.025$). Among the NASH population, patients who reported any lifetime alcohol consumption were 3.6 (1.5, 8.3) times more likely to develop HCC than those who had no exposure to alcohol, $P = 0.003$. There was a statistical trend towards association between male gender and development of HCC, but the trend did not reach statistical significance ($P = 0.071$).

In multivariate analysis, adjusting for factors of interest based on univariate analysis, only older age at the time of cirrhosis diagnosis (hazard ratio, 1.08 [confidence interval 1.02-1.1]; $P = 0.006$) and any alcohol consumption (hazard ratio, 3.8 [confidence interval 1.6-8.9]; $P = 0.002$) remained independently associated with the development of HCC in the population with NASH-cirrhosis.

**The Cumulative Incidence of HCC by Alcohol Consumption.** Kaplan-Meier estimates of the cumulative risk of HCC development in the entire study population (n = 510) among the four categories of alcohol intake were performed (Fig. 2). Patients who reported never drinking alcohol were significantly less likely to develop HCC compared with those who reported any level of drinking ($P < 0.001$) in both the HCV and NASH groups. The cumulative risk of HCC in patients who reported no alcohol intake was compared with the cumulative risk of HCC in patients who reported only social alcohol intake for both groups (Fig. 3). In both groups, social alcohol intake was associated with increased risk of HCC development compared with nondrinkers (HCV, $P = 0.002$; NASH, $P = 0.001$). Analysis of patients who reported any level of alcohol consumption indicated no significant difference in the annual cumulative risk of HCC among social, heavy, or formerly heavy alcohol drinkers ($P > 0.10$).

**Discussion**

The increasing incidence of HCC in the United States has largely paralleled the epidemic of obesity. Emergent data suggest that NAFLD is a key factor linking obesity and HCC. It is estimated that nearly two-thirds of obese people have some form of fatty liver, ranging from steatosis to NASH. NASH can progress to liver cirrhosis in 3%-15% and subsequently to liver cancer. Despite this link, there is a paucity of data regarding the risk of HCC in patients with liver cirrhosis secondary to NAFLD.

Our study estimated the annual cumulative risk of HCC in patients with NASH. The yearly cumulative incidence of HCC was 2.6% per year in patients with NASH cirrhosis compared with 4.0% per year in those with HCV cirrhosis over a median follow-up time of 3.2 years. These figures suggest that NASH carries a risk of developing HCC that rivals the risk in patients with HCV-cirrhosis. Our results are consistent with other reports. As such, patients with NASH-cirrhosis should be closely monitored for HCC.

Our data represent a population of patients with chronic liver disease who were referred for liver transplant evaluation. These patients are required to comply with clinic visits and a surveillance program. When a
visit or a test is missed, patients are contacted initially by phone and if not successful, by a certified letter where appointment is scheduled. Consequently, patients included in the study were highly motivated individuals who were followed carefully for HCC surveillance.

Our study has several limitations that could introduce the possibility of overestimating or underestimating the risk of HCC. First, our data represented a subset of HCV- and NASH-related cirrhosis patients who were referred for liver transplant evaluation; therefore, patients with compensated liver disease were not included in the study. Second, patients with no pathologic or radiologic diagnosis of cirrhosis and no clinical evidence of portal hypertension were not included in the study. This may introduce the possibility of underestimating HCC incidents. Third, we considered patients with cryptogenic cirrhosis in the setting of metabolic syndrome as having NASH cirrhosis. Although this is potentially a source of bias, this definition has been accepted in recent medical literature.23

The identification of risk factors associated with HCC is of paramount importance for any protective strategy against cancer. With this in mind, one must consider the several factors that have been clearly identified as positively correlated risk factors in the development of HCC, including chronic hepatitis B virus and HCV infection,25,26 obesity,4,6 and type 2 diabetes mellitus.7,8 Although diabetes mellitus has been proposed as a risk factor for HCC,27 the causal association between diabetes and HCC is difficult to study. Diabetes is a known risk factor for NAFLD and NASH, which can lead to cirrhosis and subsequently HCC. On the other hand, cirrhosis itself is associated with glucose intolerance and diabetes. Additionally, HCV has been associated with an increased risk of diabetes.28 Several studies have examined the association between diabetes and HCC with conflicting results.27,29 In fact, these studies failed to identify whether diabetes precedes the development of underlying liver disease or HCC.

Consistent with the literature, this study confirms chronic HCV infection as risk factor for the development of HCC. Obesity was not independently correlated with HCC in multivariate analysis, suggesting that the link between obesity and HCC is probably mediated by the progression of nonalcoholic fatty liver disease to cirrhosis and subsequently to liver cancer. Animal studies have revealed several hepatic carcinogenic components of cigarette smoke.30 However, there are few and inconsistent clinical data to support cigarette smoking as associated with increased risk for HCC,16,17,31 one example being the present study.

The most significant factor recognized in the present study was that of alcohol intake, because it is one of the variables that may have introduced a level of subjectivity into the study. Despite this subjectivity, our findings are consistent with—and also elaborate on—an increasing number of reports that have recognized excessive alcohol intake as a major risk factor for HCC.15,17 In addition to excessive alcohol intake, however, our study supports emerging data16,32 that alcohol intake, even in social quantities, may potentially increase the risk of HCC development in NASH- and HCV-cirrhotic patients to a risk comparable to that of never-drinkers.

In conclusion, patients with NASH cirrhosis have a greatly increased risk of liver cancer. Of particular concern is alcohol consumption, a modifiable risk factor that appears to be the most significant factor associated with HCC in this population.

References

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-2576.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745-750.
3. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817-823.
4. Wolk A, Gridley G, Svensson M, Nyren O, McLaughlin JK,Fraumeni JF, et al. A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control 2001;12:13-21.
5. Møller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. Eur J Cancer 1994;30A:344-350.
6. 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.
7. Polese J, Zucchetto A, Montella M, Dal Maso L, Crispò A, La Vecchia C, et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. Ann Oncol 2009;20:353-357.
8. Regimbeau JM, Colombat M, Moghul P, Durand F, Abdalla E, Degott C, et al. Obesity and diabetes as a risk factor for hepatocellular carcinoma. Liver Transpl 2004;10(Suppl. 1):S69-S73.
9. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221-1231.
10. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Gastroenterology 1999;117:664-669.
11. Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 2002;123:134-140.
12. Haji S, Kubo S, Shuto T, Tanaka H, Tanaka H, Takemura S, Yamamoto T, et al. Hepatocellular carcinoma arising from nonalcoholic steatohepatitis: report of two cases. Surg Today 2006;36:390-394.
13. Mori S, Yamasaki T, Sakaida I, Takami T, Sakaguchi E, Kimura T, et al. Hepatocellular carcinoma with nonalcoholic steatohepatitis. J Gastroenterol 2004;39:409-411.
14. Hashimoto E, Yatsuji S, Tobari M, Tanai M, Torii N, Tokushige K, et al. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. J Gastroenterol 2009;44(Suppl. 19):89-95.
15. Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. Gastroenterology 2004;127(Suppl. 1):S72-S78.

16. Yuan JM, Govindarajan S, Arakawa K, Yu MC. Synergism of alcohol, diabetes, and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. Cancer 2004;101:1009-1017.

17. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol 2005;42:218-224.

18. Murray KF, Carithers RL. Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. HEPATOLOGY 2005;41:1407-1432.

19. Bruix J, Sherman M. Management of hepatocellular carcinoma. Practice Guidelines Committee, American Association for the Study of Liver Diseases. HEPATOLOGY 2005;42:1208-1236.

20. Sattar N, Gaw A, Scherbakova O, Ford I, Ford I, O'Reilly DS, Haffner SM, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003;108:414-419.

21. Metwally MA, Zein CO, Zein NN. Predictors and noninvasive identification of severe liver fibrosis in patients with chronic hepatitis C. Dig Dis Sci 2007;52:582-588.

22. Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. HEPATOLOGY 2006;43:682-689.

23. 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; 36:1349-1354.

24. Ratziz V, Bonyhay L, Di Martino V, Charlotte F, Cavallaro L, Sayegh-Tainturier MH, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. HEPATOLOGY 2002;35:1485-1493.

25. Yeh FS, Yu MC, Mo CC, Luo S, Tong MJ, Henderson BE. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. Cancer Res 1989;49:2506-2509.

26. Kew MC, Yu MC, Keel MA, Coppin A, Sarkin A, Hodkinson J. The relative roles of hepatitis B and C viruses in the etiology of hepatocellular carcinoma in southern African blacks. Gastroenterology 1997;112:184-187.

27. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gastroenterology 2005;54:333-339.

28. Elgouhari HM, Zein CO, Hanouneh IA, Feldstein AE, Zein NN. Diabetes mellitus is associated with impaired response to antiviral therapy in chronic hepatitis C infection. Dig Dis Sci 2009; doi:10.1007/s10620-008-0683-2.

29. 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.

30. International Agency for Research on Cancer. Tobacco Smoking and Involuntary Smoking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83. Lyon, France: International Agency for Research on Cancer; 2004.

31. Hsing AW, McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr. Cigarette smoking and liver cancer among US veterans. Cancer Causes Control 1990;1:217-221.

32. Donato F, Tagger A, Gelarti U, Parrinello G, Boffetta P, Albertini A, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002;155:323-331.