ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 08, pp.19154-19159, August, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

DIABETES INCREASES THE RISK OF CHRONIC LIVER DISEASE AND HEPATOCELLULAR CARCINOMA

[1]Dr. Korada Saradamba and [2,*]Dr. BhagyaLakshmi, V.

[1]Department of Biochemistry, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India
[2]Department of Biochemistry, Rangaraya Medical College, Kakinada, Andhra Pradesh, India

ARTICLE INFO

Article History:
Received 08th May, 2015
Received in revised form
08th June, 2015
Accepted 03rd July, 2015
Published online 21st August, 2015

Key words:
CNLD (Chronic NonAlcoholic fatty liver disease),
HRR (Hazard Risk Ratio),
HCC (Hepatocellular Carcinoma),
cirrhosis. DM (diabetes mellitus).

ABSTRACT

Background and Aims: An association of diabetes with chronic liver disease has been reported, even though the temporal relationship between hese two conditions is not established.
Methods: We identified all patients with a hospital discharge diagnosis of diabetes between 2005 and 2013 from the Hospital records of the King George Hospital, Visakhapatnam, Andhra Pradesh, India. We randomly assigned patients without diabetes and with diabetes. We excluded patients with concomitant liver disease. The remaining cohort was followed through 2005 for the occurrence of chronic nonalcoholic liver disease (CNLD) and hepatocellular carcinoma (HCC). Hazard rate ratios (HRR) were determined in Cox proportional hazard survival analysis. Using the Hospital records of the Departments of Gastroenter-ology and general Medicine. We randomly assigned 3 patients without diabetes for every patient with diabetes. We excluded patients with concomitant liver disease. The remaining cohort was followed through 2005 for the ccurrence of chronic nonalcoholic liver disease (CNLD) and hepato-cellular carcinoma (HCC). Hazard rate ratios (HRR) were determined in Cox proportional hazard survival analysis.
Results: The study cohort comprise 243 patients with diabetes and 620 patients without diabetes. Most were men (98%). Patients with diabetes were older (62 vs. 54 years) than patients without diabetes. The incidence of chronic nonalcoholic liver disease(CNLD) was significantly higher among patients with diabetes (incidence rate: 18.13 vs. 9.55 per 100 person-years, respectively, $P < 0.0001$). Similar results were obtained for HCC (incidence rate: 2.39 vs. 0.87 per 100 person-years, respectively, $P < 0.0001$). Diabetes was associated with an HRR of 1.98 (95% CI: 1.88 to 2.09, $P < 0.0001$) of CNLD and an HRR of 2.16 (1.86 to 2.52, $P < 0.0001$) of hepatocellular carcinoma. Diabetes carried the highest risk among patients with longer than 10 years of follow-up.
Conclusions: Among men with diabetes, the risk of CNLD and HCC is doubled. This increase in risk is independent of alcoholic liver disease, viral hepatitis, or demographic features.

Citation: Dr. Korada Saradamba and Dr. BhagyaLakshmi, V. 2015. "Diabetes increases the risk of chronic liver disease and Hepatocellular carcinoma", *International Journal of Current Research*, 7, (8), 19154-19159.

INTRODUCTION

Chronic liver disease, including cirrhosis, is a major cause of death in many areas of the world, including the United States. Most cases of hepatocellular carcinoma (HCC) develop in persons with advanced chronic liver disease. Evidence of the rising incidence of HCC in the United States and several other countries in Europe and Asia has recently emerged (El-Serag, 2000; Ruhl, 2003). Major risk factors of chronic liver disease that are relatively common include hepatitis C virus (HCV), hepatitis B virus, heavy alcohol consumption, and nonalcoholic fatty liver disease (NAFLD) (Greeve *et al.,* 1993). Rare risk factors include hemochromatosis, _-1 anti-trypsin deficiency, and Wilson's disease.

Corresponding author: Dr. BhagyaLakshmi, V.,
Department of Biochemistry, Rangaraya Medical College, Kakinada, Andhra Pradesh, India.

However, previous studies in the United States evaluating risk factors of chronic liver disease or HCC failed to identify specific risk factors in a large proportion of patients. The so-called cryptogenic cirrhosis has been estimated to account for 5% to 30% of patients with end-stage liver disease. (Lee, 1989) NAFLD has been identified as a possible cause of cryptogenic cirrhosis (Powell *et al.,* 1990; Angulo *et al.,* 1999). Previous studies also failed to identify specific risk factors in 15% and 50% of HCC cases and Di Bisceglie *et al*., 1998). This suggests that there might be other risk factors for chronic liver disease and HCC. Diabetes mellitus (DM) has been proposed as a risk factor for both chronic liver disease and HCC. DM has been associated with NAFLD, including its most severe form, nonalcoholic steatohepatitis (NASH) (Matteoni *et al.,* 1999; Marchesini *et al.,* 1999; Belfiore, 1998; Falck-Ytter *et al.,* 2001). NASH is a chronic necro-inflamatory

condition that can lead to liver fibrosis, cirrhosis, and subsequently to HCC (Cotrim *et al.,* 2000; Zen *et al.,* 2001; Shimada *et al.,* 2002). Earlier epidemiologic studies showed no association between DM and HCC, (Kessler, 1970; Ragozzino *et al.,* 1982; Lu *et al.,* 1988) whereas several more recent studies indicate a significant association between HCC and DM (El-Serag *et al.,* 2001; Kingston *et al.,* 1984; Lawson *et al.,* 1986; La Vecchia *et al.,* 1990; Yu *et al.,* 1991; Adami *et al.,* 1991; La *et al.,* 1994; Adami *et al.,* 1996; La Vecchia *et al.,* 1997; Braga *et al.,* 1997; Wideroff *et al.,* 1997; Hashem, 2004).

However, the temporal association between DM and HCC in these studies is unclear. Because the development of chronic liver disease may lead to glucose intolerance and occasionally diabetes, the study of the risk of chronic liver disease and HCC from DM requires longitudinal cohort studies that exclude most cases of chronic liver disease at the time the identification of diabetes is made. Most previous reports on the association between DM and HCV were case control studies. Most also predated and hence did not adjust for the presence of HCV (El-Serag *et al.,* 2001; Lu *et al.,* 1998; La *et al.,* 1994; La Vecchia *et al.,* 1997; La Vecchia *et al.,* 1997; Wideroff *et al.,* 1997) Among the cohort studies, most had a relatively small number of cases of HCC as well as limited expo-sure to DM because of small sample size and/or short followup.[19,32,33] The largest cohort study that examined the role of DM in HCC was carried out in Denmark and had no internal control group. In that study, the standardized incidence ratios of primary liver cancer including HCC were 4.0 (95% CI: 3.5– 4.6) in men and 2.1(95% CI: 1.6 –2.7) in women with diabetes as compared with the general population (Braga *et al.,* 1997). It remains unclear whether DM precedes the development of significant chronic liver disease and HCC. Moreover, there have been no large cohort studies among multiethnic groups in the United States that evaluated the association between DM and chronic liver disease and HCC. We carried out a large prospective cohort study, using the computerized national databases of the Department of Veterans Affairs (VA) to examine the risk according to preceding diabetes status of 2 conditions: HCC and chronic nonalcoholic liver disease (CNLD).

MATERIALS AND METHODS

Databases

The study population was assembled from hospitalized old patients registered in old Patient Register. The inpatient register comprises a contain discharge summaries and diagnoses recorded for each hospitalization since 2000. Individual patients can be traced through the inpatient register though their unique inpatient numbers. Each hospitalization record contains 1 primary discharge diagnosis and up to 3 or 4 second admissions. The Patient inpatient File does contain information about drug treatment and procedures like biopsy and aspiration with laboratory test results. IP (inpatient) Reg. file has a date of admission, Date of Discharge and Date of Death (if any) recorded.

Study Population

The study population included all hospitalized patients with diabetes as defined by discharge diagnosis codes (ICD-9 250 [1–9] [0–4]) during the 8-year period between October 2005 and October 2013. We included only adults (older than 20 years of age). A method of random selection without replacement was employed to ensure that no individual control subject was selected more than once. Patients in the comparison group who had a prior diagnosis of diabetes between 2005 and 2013 were then excluded. The sampling frame for both groups of patients with and without diabetes was individual patients rather than hospitalizations. Patients with multiple hospitalizations were counted only once, and their earliest hospitalization date was chosen to be the index hospitalization. Using the inpatient registered number as a unique identifier, the patients were prospectively followed File until October 2013. These files were searched for the occurrence of 3 outcomes: diagnoses of CNLD including cirrhosis and death. We also excluded all patients who had any diagnosis of acute or chronic liver disorder during the first year that followed their index hospitalization. In addition to the 3 outcomes described above, during subsequent follow-up (after the first year), we identified the presence of alcohol-related liver disease, viral hepatitis (B and C), and fatty liver. The time at risk of CNLD including cirrhosis was measured from 1 year following the index hospitalization until the development of this condition, HCC, death, or October 2005. The time at risk of HCC was measured from one year following the index hospitalization until the development of HCC, death, or October 2000.

RESULTS

We identified 257,649 patients with diabetes and 772,947 patients without diabetes who were hospitalized in VA facilities between October 1985 and October 1990. Of these, 216,831 patients with diabetes and 765,853 patients without diabetes did not have liver disease in their hospitalization records as far back as 1980. After excluding all patients in whom liver disease was recorded during the first year of follow-up after the index hospitalization, 173,643 patients with diabetes and 650,620 patients without diabetes remained and were included in the principal analyses of HCC and CNLD including cirrhosis and HCC. A greater proportion of patients with diabetes (32.6%) than without diabetes (15.8%) was excluded for liver disease in the past or during the first year of follow-up. The demographic features for these patients are shown in Table 1. Patients with diabetes were older by an average of 7 years. The majority (99.5%) of diabetic patients had type 2 diabetes mellitus. Among patients with diabetes, 1.7% had DM-related Renal manifestations, 3.74% had Ophthalmopathy, 5.01% had Neuropathy. In general, there was no significant difference between cases and controls in co morbid conditions at the initial hospitalization.

CNLD Including Cirrhosis

The Kaplan–Meier survival analysis showed a significantly higher cumulative incidence of CNLD among patients with diabetes as compared with those without diabetes (P _ 0.0001) (Figure 1). During follow-up of 243 person with diabetes, 29 patients developed CNLD (incidence rate: 18.13 per 10,000 person years), The incidence rate ratio was 1.90. Consistent with this increased incidence among patients with diabetes, the relative risk of CNLD in the Cox proportional hazard analysis among persons with diabetes was 1.98 (95% CI: 1.88–2.09,

P _ 0.0001). This adjusted relative risk was obtained while controlling for differences in age, gender, ethnicity, disease co morbidity index, and period of service (Table 2).

This adjusted relative risk was obtained while controlling for differences in age, gender, ethnicity, disease comorbidity index, and period of service (Table 3).

Table 1. A Comparison of Demographic and Clinical Characteristics Between Cases With Diabetes and Controls

Variable	Without Diabetes	Patients with diabetes	
	N: 243	n: 620	*P* value
Age in years, mean(±SD)	61.7 (±10)	54.5 (±12)	0.0001
Women 69	(1.6) 56	(2.4) 28	0.0001
Mean duration of (±SD)*a*	5.3 (4.2)	7.3 (4.04)	0.0001
follow-up in years	89 (58.2)	142 (37.5)	0.0001
Death during follow-up	62 (0.4)	26 (0.4)	0.39
Rheumatologic disease	35 (5.02)	97(4.98)	0.46
Chronic pulmonary disease	68 (0.99)	211 (1.00)	0.30
Hemiplegia or paraplegia	31 (1.83)	92 (1.83)	0.98
Myocardial infarction	23 (1.78)	57 (1.79)	0.74
Congestive heart failure	14 (1.43)	69 (1.40)	0.35
Peripheral vascular disease	28 (2.23)	113 (2.20)	0.45
Cerebro vascular disease	9 (0.58)	39 (0.57)	0.70
Renal disease			
Any malignancy	23 (3.09)	56 (3.04)	0.30

NOTE. All of these patients had no liver disease prior to index hospitalization and during the first year of follow-up. *a*Follow-up ended at death or at developing CNLD or HCC.

Table 2. Risk Factors for Chronic Nonalcoholic Liver Disease: Results of the Cox Proportional Hazard Analysis in a Cohort of 620,243 Hospitalized patiens During 2005 to 2013

Variable	Adjusted hazard ratio	95% Confidence interval	*P* value
Diabetes	1.98	1.88–2.09	<0.0001
Older age (per 10 years)	1.15	1.13–1.18	<0.0001
Women (vs. men)	0.99	0.83–1.18	0.88
Fatty liver	1.89	1.60–2.24	<0.0001
Comorbidity index*	0.99	0.97–1.01	0.33

NOTE. All of these patients had no liver disease prior to hospitalization and during the first year of follow-up. All covariates included in the model are shown in the table.
*Comorbidity index includes 14 disease categories described fully in the Materials and Methods section

The HRR for CNLD increased over time. There was a trend toward higher risk of CNLD with diabetes among patients with longer duration of follow-up. The HRR was 1.30 (1.20–1.42), 1.24 (1.14–1.34), and 1.96 (1.78–2.17) for patients with less than 5 years, 5 years, and more than 5 years of follow-up, respectively. To further disentangle the effects of age and duration of follow-up, this analysis was repeated for patients with and without diabetes between ages 50 and 60 (n _173,643) years.

The trend toward higher risk of CNLD with diabetes among patients with longer duration of follow-up persisted. The HRR was 1.22 (1.01–1.46) and 2.03 (1.7–2.4) for patients with less than 5 years and more than 10 years of follow-up, respectively. In the sensitivity analysis, we constructed a similar model that excluded patients with new diagnoses of HCV (58), hepatitis B (167), alcohol use (663), alcoholic liver disease (462) or fatty liver (697) recorded after the first year of follow-up.

In contrast to the full model in which Hispanic race was associated with a slight significant increase in the risk of CNLD, it became no longer significant in the model with exclusions. On the other hand, black race was not associated with a significant risk in the full model and became associated with a slight but significant increase in the risk of CNLD in the model with exclusions. In that model, diabetes remained an independent risk for CNLD with an adjusted relative risk of 2.13 (95% CI: 1.99–2.28, *P* _ 0.0001) controlling for age, gender, ethnicity, era of military service, and disease comorbidity index. Results were essentially the same if patients with fatty liver were not excluded (HRR _ 2.15, 95% CI: 2.00–2.30). The Kaplan–Meier survival analysis showed a significantly higher cumulative incidence of HCC among patients with diabetes as compared with those without diabetes (*P* _ 0.0001) During follow-up of patient with diabetes, 19 patients were hospitalized with a diagnosis of HCC (incidence rate: 2.39 per 10,000 person-years), whereas, during follow- up of patients without diabetes, 11 patients were hospitalized

with a diagnosis of HCC (incidence rate: 0.87 per 10,000 person-years); the incidence ratio was 2.75. Diabetes was also associated with a greater than 2-fold increase in relative risk of HCC This adjusted relative risk was obtained while controlling for differences in age, gender, ethnicity. Approximately 10% of patients with diabetes had recorded diabetes-related neuropathy, ophthalmopathy, or retinopathy by the time of their index hospitalization. This further supports the argument for a temporal relationship in which diabetes precedes the onset of chronic liver disease. Few studies examined the association between diabetes and liver disease in U.S. populations. In 2000, Poonawala *et al*. showed a higher prevalence of type 2 DM (47%) among 49 patients with advanced cirrhosis in comparison with 22% prevalence in 98 age- and sex-matched controls.41 In 2002, Amarapurkar and Das demonstrated that the prevalence of diabetes in cryptogenic cirrhosis was 57% vs. 30% in noncryptogenic cirrhosis.42 In 1991, Yu *et al*. reported in a case-control study of 74 cases of HCC that DM was associated with a 3.4-fold increase in risk of HCC. This study predated and did not control for the presence of HCV.24 Recently, Hassan *et al*. reported in a case-control study among 115 HCC patients and 230 nonliver cancer patients that the odds ratio was 4.3 (95% CI: 1.9–9.9) for DM.34 We also previously reported in a case-control study of 823 patients with HCC and 3459 controls that DM increased the risk of HCC only in the presence of hepatitis B, HCV, and alcoholic cirrhosis.10 However, a potential bias in epidemiologic studies, especially case-control studies, is discerning the correct temporal relationship between exposure (diabetes) and outcome (HCC). This problem is even more relevant here because 10% to 20% of patients with cirrhosis may have overt DM and a larger percentage may have impaired glucose tolerance.

To minimize this bias in the current study, we excluded all subjects with liver disease recorded before the inception point for follow-up as well as those recorded during the first year of follow-up. In case-control studies including our previous study,10 the prevalence of the strong HCC risk factors (hepatitis B, HCV, and alcoholic liver disease) is very high among cases with HCC, thus making it difficult to isolate an effect for diabetes. Therefore, in the present cohort study, we excluded patients with any prior history of significant liver disease. That initial step of exclusion because of liver disease affected a greater proportion of patients with diabetes, thus further confirming the increased association between diabetes and liver disease.

Furthermore, we carried out additional analyses in which the incidence of HCC and CNLD was calculated after excluding all patients with diagnosis of hepatitis B, HCV, and alcoholism at any time during follow-up. In these analyses, the relative risk with diabetes was slightly reduced but remained highly significant statistically. This indicates that diabetes is a risk factor of CNLD and HCC, independent of other well-recognized risk factors. The latter set of exclusions affected Hispanics disproportionately, thus rendering insignificant the slightly increased risk observed in the full model. On the other hand, the risk of cirrhosis was slightly increased in blacks compared with whites; no clear reason can be ascribed for this finding. In general, the ethnic differences were small.

We found a high relative risk of HCC for preexisting diabetes even with exclusion of persons with overt liver disease as determined by hospitalization with a chronic liver disease or alcohol diagnosis. This does not necessarily mean that persons with diabetes who develop HCC do not have underlying liver disease. Rather, it suggests that the chronic liver disease associated with diabetes is usually insidious and asymptomatic and goes undetected until a severe manifestation such as HCC occurs. Last, the trend toward a duration-response relationship between the risk of HCC and the duration of follow-up of recognized diabetes further supports a causal association. There are several strengths to the present study. It is the largest cohort study to evaluate the relationship between DM and each of CNLD and HCC. The use of the national VA databases allowed the identification of a large cohort of patients with diabetes and the random identification of controls without diabetes. By including more than 800,000 patients with a follow-up of more than 10 million person-years in the analysis, we were able to detect the increased risk of CNLD and HCC that might be over- or underestimated in a smaller study. The study examined hospitalized patients (mostlymale veterans), which limits its generalization regarding women and nonveterans. We did not have accurate data on the onset of diabetes; the inception point for follow-up in this study was the index hospitalization with diabetes, which is likely to underestimate the duration of diabetes.40 However, there is no reason to believe that diabetes detection or treatment has changed significantly during the enrollment period (1985–1990) to make systematically persons enrolled during certain times of the study more or less likely to have a different actual duration of diabetes.

Misclassification of both the risk factor of interest (diabetes) and the outcome of CNLD or HCC is of concern in large administrative data sets, in which diagnoses cannot be verified. Although the majority of patients with a recorded diagnosis of DM are likely to actually have DM, the disease is frequently underrecognized and is underreported in medical records. Therefore, patients in the nondiabetic control group may have had diabetes. This misclassification bias would tend to diminish the true effect of diabetes. One study evaluated the reliability of inpatient information in 1995 in the Patient Treatment File as compared with medical charts and found high reliability for the diagnosis of diabetes whether recorded as a principal diagnosis or secondary diagnosis. 47 In our previous studies, the use of ICD-9 code 155.0 to examine the temporal trends of hospitalization with HCC in the VA system has produced identical results to the incidence rates of histologically confirmed HCC in national cancer registries, thus indicating the validity of using this code as an indicator of HCC. The validity of ICD-9 codes in the Patient Treatment File as indicators of CNLD is not known. However, the same codes were used to define these conditions in both groups of patients with and without diabetes. Therefore, errors in coding or recording because of misclassification are likely to occur at random, thus having little effect on the calculated risk ratio. Our inability to directly measure exposure to viral hepatitis or alcohol intake could have underestimated these conditions; this might have biased our results if patients with diabetes were more likely to have these conditions than those without diabetes.

Differences in co-morbidities between patients with and without diabetes could affect the calculated incidence ratio for HCC or cirrhosis by affecting the survival time. For every patient in the study, we calculated the Deyo co-morbidity index, which is a modification of the Charlson comorbidity index. There were no statistically significant differences between the 2 groups in the composite score of the co-morbidity index.

The pathophysiology underlying the increased risk of CNLD and HCC with diabetes is not certain. DM is known to be associated with NAFLD, including nonalcoholic steatohepatitis (NASH) (Matteoni *et al.,* 1999; Marchesini *et al.,* 1999; Belfiore, 1998; Falck-Ytter *et al.,* 2001). NAFLD patients demonstrate significantly increased insulin resistance compared with control subjects.[12] Insulin resistance facilitates peripheral lipolysis and accumulation of free fatty acids in the liver, thus leading to NAFLD. High serum insulin level decreases mitochondrial _-oxidation of fatty acids.50 Hepatocellular injury, inflammation, and, eventually, hepatic fibrosis can result. HCC as a late consequence of DM-related NASH has been recently described (Cotrim *et al.,* 2000; Zen *et al.,* 2001; Shimada *et al.,* 2002). In our study, although the relative risk changed little when fatty liver patients were excluded from the analysis, NAFLD, including NASH, was underreported because the significance of these disease entities has only recently been recognized.

Lastly, there are potentially important variables related to diabetes that were not captured by our study, and these include body mass index, triglyceride level, and the severity and treatment of diabetes. Although the absolute risks of HCC and CNLD were low among patients with diabetes, the findings in this study are significant for the following reasons. First, DM is a very common disease; the estimated number of persons with diabetes is 16 million in the United States alone and increasing.[51] Second, although HCC is less common in developed countries, its incidence in these areas of the world has been rising. For example, the incidence in the United States has doubled since the early 1980s.[2] For these compelling reasons, the epidemiologic association between DM and HCC cannot be ignored. In summary, DM was found to be an independent risk factor for chronic liver disease and HCC among U.S. veterans. Further studies are needed to examine these associations in women and in nonveterans and to clarify the mechanisms of development of chronic liver disease in patients with diabetes (Hashem *et al*., 2004)

REFERANCES

Adami, H. O., Chow, W. H., Nyren, O., Berne, C., Linet, M. S., Ekbom, A., Wolk, A., McLaughlin, J. K., Fraumeni, J. F. Excess risk of primary liver cancer in patients with diabetes mellitus. *J Natl Cancer Inst*., 1996; 88: 1472–1477.

Adami, H. O., McLaughlin, J., Ekbom, A., Berne, C., Silverman, D., Hacker, D., Persson, I. 1991. Cancer risk in patients with diabetes mellitus. *Cancer Causes Control*, 2:307–314.

Angulo, P., Keach, J., Batts, K., Lindor, K. 1999. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology*, 30:1356–1362.

Belfiore, F., Iannello, S. 1998. Insulin resistance in obesity: metabolic mechanisms and measurement methods. *Mol Genet Metab*., 65:121–128.

Braga, C., La Vecchia, C., Negri, E., Franceschi, S. 1997. Attributable risks for hepatocellular carcinoma in Northern Italy. *Eur J Cancer*, 33:629–634.

Cotrim, H., Parana, R., Braga, E., Lyra, L. 2000. Nonalcoholic steato-hepatitis and hepatocellular carcinoma: natural history? *Am J Gastroenterol*, 95:3018–3019.

Di Bisceglie, A. M., Carithers, R. L. Jr, Gores, G. L. 1998. Hepatocellular carcinoma. Hepatology, 28:1161–1165.

El-Serag, H. B., Mason, A. C. 1999. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745–750.

El-Serag, H. B., Richardson, P. A., Everhart, J. E. 2001. The role of diabetes in hepatocellular carcinoma: a case-control study among United States veterans. *Am J Gastroenterol*, 96:2462–2467.

Falck-Ytter, Younossi Z, Marchesini, G., McCullough, A. 2001. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver Dis., 21:17–26

Greeve, M., Ferrell, L., Kim, M., Combs, C., Robert, J., Ascher, N., Wright, T. L. 1993. Cirrhosis of undefined pathogenesis: absence of evidence for unknown or autoimmune processes. Hepatology, 17:593–598.

Hashem, B. 2004. EL–Searag, Thomas Tran, and James E. Everhart Gastroenterology,126: 460–468.

Kessler, I. I. Cancer mortality among diabetics. *J. Natl Cancer Inst.,* 44:2051–2055.

Kingston, M. E., Ali, M. A., Atiyeh, M., Donnelly, R. J. 1984. Diabetes mellitus in chronic active hepatitis and cirrhosis. Gastroenterology, 87:688–694.

La Vecchia, C., Negri, E., D'Avanzo, B., Boyle, P., Franceschi, S. D. 1990. Medical history and primary liver cancer. Cancer Res., 50:6274–6277.

La Vecchia, C., Negri, E., DeCarli, A., Franceschi, S. D. 1997. Diabetes mellitus and the risk of primary liver cancer. *Int J Cancer,* 73:204–207.

La Vecchia, C., Negri, E., Franceschi, S. D., D'Avanzo, B., Boyle, P. 1994. A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 70: 950–953.

Lawson, D. H., Gray, J. M., McKillop, C., Clarke, J., Lee, F.,D., Patrick, R. S. 1986. Diabetes mellitus and primary hepatocellular carcinoma. *Q J Med*., 61:945–955.

Lee, R. 1989. Nonalcoholic steatohepatitis: a study of 49 patients. Hum Pathol, 20:594–598.

Lu, S. N., Lin, T. M., Chen, C. J., Chen, J. S., Liaw, Y. F., Chang, W. Y., Hsu, S. T. 1988. A case-control study of primary hepatocellular carcinoma in Taiwan. Cancer, 62:2051–2055.

Marchesini, G., Brizi, M., Morselli-Labate, A., Bianchi, G., Bugianesi, E., McCullough, A., Forlani, G., Melachionda, N. 1999. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med*., 107:450–455.

Matteoni, C., Younossi, Z., Gramlich, T., Bopari, N., Liu, Y., McCullough, A. 1999. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology, 116:1413–1419.

Powell, E., Cooksley, W., Hanson, R., Searle, J., Halliday, J., Powell, L. 1990. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology,* 11:74–80.

Ragozzino, M., Melton, L. J. III, Chu, C. P., Palumbo, P. J. 1982. Subsequent cancer risk in the incidence cohort of Rochester, innesota, residents with diabetes mellitus. *J Chronic Dis*., 35:13–19.

Ruhl, C. E., Everhart, J. E. 2003. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology, 124:71–79.

Shimada, M., Hashimoto, E., Taniai, M., Hasegawa, K., Okuda, H., Yayashi, N., Takasaki, K., Lugwig, J. 2002. Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *J. Hepatol*., 37: 154–160.

Wideroff, L., Gridley, G., Mellemkjaer, L., Chow, W. H., Linet, M., Keehn, S., Borch-Johnsen, K., Olsen, J. H. 1997. Cancer incidence in a population based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst*, 89:1360–1365.

Yu, M. C., Tong, M. J., Govindarajan, S., Henderson, B. E. 1991. Non-viral risk factors for hepatocellular carcinoma in a low-risk population, the non-Asians of Los Angeles County, California. *J Natl Cancer Inst1.,* 83:1820–1826.

Zen, Y., Katayanagi, K., Tsuneyama, K., Harada, K., Araki, I., Nakanuma, Y. 2001. Hepatocellular carcinoma arising in non-alcoholic steatopathtis. *Pathol Int*., 51:127–131.

****