

RISING RATES OF NONALCOHOLIC FATTY LIVER DISEASE DRIVE UP HEPATOCELLULAR CARCINOMA CASES

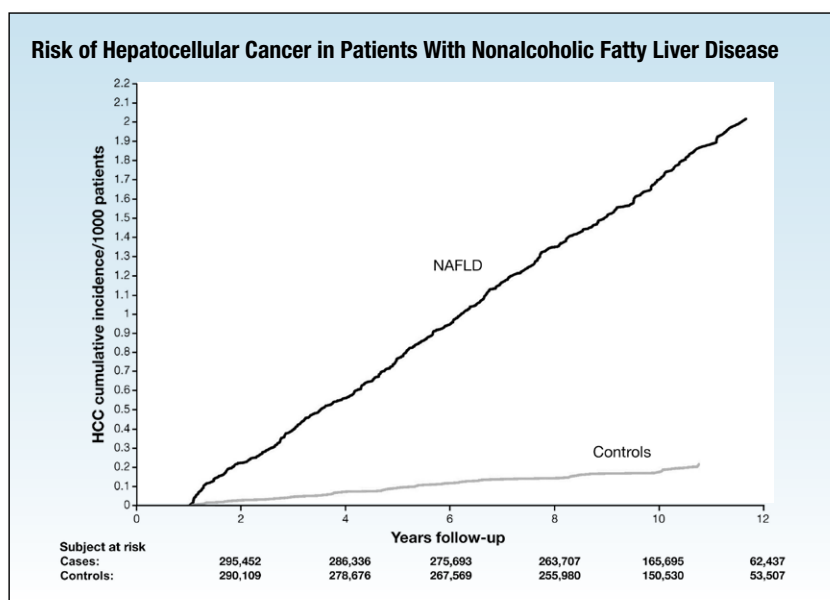
HOUSTON—A new epidemic appears poised to overtake hepatitis C as the leading cause of hepatocellular carcinoma.

“Nonalcoholic fatty liver disease is the next big thing in the epidemiology of liver cancer,” said Fasiha Kanwal, MD, MSHS, an investigator in the Clinical Epidemiology & Comparative Effectiveness Program at the Center for Innovations in Quality, Effectiveness and Safety at the Michael E. DeBakey VAMC in Houston.

Nonalcoholic fatty liver disease is a subtype of liver steatosis, which is characterized by fat that accounts for more than 5% of the liver mass. When steatosis occurs without evidence of excessive alcohol consumption, specific hereditary disorders or medications known to increase fat buildup in the liver, it is classified as NAFLD.

NAFLD appears closely connected to metabolic syndrome, affecting up to 75% of patients with diabetes, 80%-90% of obese patients and 90% of individuals with hyperlipidemia. NAFLD develops asymptotically in many patients, and 80% of patients with NAFLD have normal alanine transaminase values, the most common liver function test.

Just how many Americans have nonalcoholic fatty liver disease



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remains a matter of some debate. According to the American Liver Foundation, nearly one-third of adults and 10% of children have NAFLD, about twice the rate seen in 2000.

Research conducted at the Brooke Army Medical Center at Fort Sam Houston in Texas, however, suggests that nearly half of all adults in the United States actually might have it.¹

The Army study enrolled 400 adult outpatients, and ultrasound examination found that 46% had NAFLD. Nearly three-quarters of diabetic patients had NAFLD, and almost a quarter of them had

progressed to nonalcoholic steatohepatitis, in which the liver becomes inflamed.

Even the high rate of NAFLD seen in this study could represent an underestimation. Recent guidelines note that “steatosis at 30% is the accepted lower limit where steatosis can be detected reliably by ultrasound (currently the most commonly used diagnostic test for fatty liver).”²

Researchers agreed, though, that NAFLD has become the most common chronic liver disease in the world and that its increasing prevalence will contribute to rising rates of hepatocellular carcinoma.

“While patients with nonalcoholic fatty liver disease have a smaller risk of HCC than patients with hepatitis C, it affects so many more people,” Kanwal told *U.S. Medicine*.

The rising rates will hit the VA especially hard. The VA’s success in treating hepatitis C means VA “will be seeing HCV less and less, while fatty liver disease will be more and more of a problem,” predicted David Ross, MD, PhD, MBI, national director of the VA’s HIV, Hepatitis, and Related Conditions Programs and associate clinical professor of Medicine at the George Washington University School of Medicine and Health Sciences in Washington, DC.

EIGHTFOLD RISK

Research by Kanwal and her colleagues at the VA and Baylor found that veterans with biochemically apparent NAFLD had almost eight times the risk of developing HCC as veterans who did not have fatty liver.³

Their retrospective study compared the risk of HCC in 296,707 veterans diagnosed with NAFLD at 130 VA facilities between Jan. 1, 2004, and Dec. 31, 2008, to a sex- and age-matched cohort of 296,707 veterans without NAFLD. Only 0.4% of NAFLD patients had a diagnosis of cirrhosis at the start of the study, and just 1.4% were diagnosed with cirrhosis during the study.

As of Dec. 31, 2015, 545 patients developed HCC, 490 in the NAFLD group and 55 in the control group. On an unadjusted basis, “patients with NAFLD had an 8.6-fold

higher risk of HCC than controls,” which persisted on multivariable analysis, according to the study led by Kanwal, who is also chief of the Gastroenterology and Hepatology Section at the Baylor College of Medicine in Houston, and editor-in-chief of *Clinical Gastroenterology and Hepatology*.

In addition, the authors found some subgroups of NAFLD patients had significantly higher risk than others. The incidence of HCC was more than five times higher in men than women (0.22 vs. 0.04 per 1,000 person years) and more common in Hispanic veterans across all age groups than in non-Hispanic patients. Risk of HCC increased substantially after age 65.


Per 1,000 patient years, the annual incidence of HCC in NAFLD patients with cirrhosis was 10.63 compared to 0.08 for veterans with NAFLD but no cirrhosis and 0.02 for veterans without NAFLD. Hispanics with cirrhosis faced the greatest risk, with an annual incidence of 23.76 per 1,000 patient years. Twenty percent of the veterans who developed HCC, however, had no cirrhosis.

High levels of fibrosis as indicated by high FIB-4 scores were associated with a nearly 10-fold increase in HCC risk in the absence of a cirrhosis diagnosis. The researchers determined that the highest risk occurred in patients with high FIB-4 and cirrhosis (13.55 per 1,000 patient years).

Based on these findings, the researchers suggested that FIB-4 scores and presence of cirrhosis “can be easily applied in clinical practice to identify the at-risk

groups for targeted evaluation and risk modification among the masses of individuals with NAFLD.”

That might be a direction the VA pursues as it retools its advanced liver disease program to reflect the changing needs of patients, particularly in light of some evidence that NAFLD-related HCC is 20% more deadly than HCC of other etiologies.⁴

“NAFLD is coming of age, not just in the VA, but nationally,” Ross told *U.S. Medicine*. We are expanding the scope of what we are doing in terms of advanced liver disease and focusing on how do we connect with veterans with risk of liver disease. We want to ensure we don’t lose the gains seen against hepatocellular carcinoma by putting into place an integrated system not seen in other healthcare systems.” 

¹ Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, Landt CL, Harrison SA. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*. 2011 Jan;140(1):124-31.

² National Guideline Centre (UK). Non-Alcoholic Fatty Liver Disease: Assessment and Management. London: National Institute for Health and Care Excellence (UK); 2016 Jul. (NICE Guideline, No. 49.) 6, Diagnosis of NAFLD.

³ Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, Li L, Desiderio R, Thrift AP, Asch SM, Chu J, El-Serag HB. Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease. *Gastroenterology*. 2 Dec;155(6):1828-1837.e2.

⁴ Zoler ML. VIDEO: NAFLD increasingly causing U.S. hepatocellular carcinomas. *Diabetes:HUB*. MDedge. April 27, 2015.