

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Association of Extrahepatic Cancers With Chronic Hepatitis C Virus Infection



Anders H. Nyberg, MD, PhD
Hepatologist
Division of Gastroenterology/Hepatology
Kaiser Permanente Southern California
San Diego, California

G&H How common is hepatitis C virus infection in the general US population?

AN Approximately 2.7 million (range, 2.2-3.2 million) Americans are estimated to be chronically infected with hepatitis C virus (HCV). This is the most-cited estimate based upon data from the National Health and Nutrition Examination Survey (NHANES). The majority of persons with chronic HCV were born between 1945 and 1965 (ie, baby boomers), and the peak incidence was in the 1970s and 1980s.

A recent editorial by Dr Robert Gish and colleagues suggested that the prevalence of chronic HCV is vastly underestimated in the United States, as the NHANES data do not include institutionalized people, homeless people, and people living on Native American reservations who have chronic HCV infection. Thus, the authors suggest that the actual number of people with chronic HCV infection may be as high as 5 to 7 million. I believe that the true prevalence of HCV in the United States is likely closer to the higher estimate.

G&H What are the most common extrahepatic manifestations and comorbidities associated with HCV infection?

AN Approximately 40% to 70% of people with chronic HCV infection will experience extrahepatic manifestations. It is important to recognize these conditions when they are present. Mixed cryoglobulinemia with vasculitis has been described in up to 40% of patients, while

fatigue, arthralgias, and myalgias have been seen in up to 50% of patients. Membranous glomerulonephritis, purpura, neuropathy, and Sicca syndrome are other manifestations. Possible dermatologic manifestations include lichen planus and porphyria cutanea tarda. Patients with chronic HCV infection also have an increased risk of insulin resistance, type 2 diabetes, cardiovascular disease, and lymphoproliferative disorders (most often non-Hodgkin lymphoma).

Many patients report poor quality of life with cognitive impairment, poor memory, and difficulties with concentration and focus as well as depression. However, this group of patients often has multiple other comorbidities that can cause these symptoms; thus, all of the manifestations are not necessarily related to HCV only.

G&H How prevalent is hepatocellular carcinoma in HCV patients?

AN In the United States, the incidence of hepatocellular carcinoma (HCC) is approximately 7 per 100,000 people. There is considerable geographic variation as well as gender and race differences, with the highest rates in California and Texas. The highest incidence of HCC is seen in Asians and Pacific Islanders, although recent data have shown an increase of HCC in African Americans, Hispanics, and whites belonging to the baby boomer generation. The next generation has lower rates of HCC, suggesting that the predominant risk factor for HCC in the United States is chronic HCV infection. It is estimated that in 2016 there will be 39,000 new cases of HCC in the

United States with 27,000 deaths. In chronic HCV infection, HCC is primarily diagnosed in those with cirrhosis, and the annual rate of developing HCC is estimated to be in the range of 1% to 5% per year.

G&H What is the current understanding of the relationship between HCV and extrahepatic cancers?

AN The association between HCV and HCC is well established. The majority of HCC cases are diagnosed in patients with advanced fibrosis or cirrhosis. The main carcinogenic factor is likely chronic necroinflammation resulting from long exposure to HCV leading to cirrhosis.

However, it is not well understood why extrahepatic cancer rates may be increased in patients with chronic HCV infection. Chronic HCV has been shown to affect a number of cellular signaling pathways promoting cancer formation as well as inhibiting tumor suppressor genes. In addition, patients with chronic HCV often have multiple cofactors such as high rates of alcohol use, tobacco use, diabetes, and obesity. These factors are also associated with an increased risk of cancer. Hence, the increased cancer rates in HCV infection may not be solely attributed to HCV but, instead, may be due to multiple factors.

G&H Thus far, how common does the association between HCV infection and extrahepatic cancers appear to be?

AN At the 2015 European Association for the Study of the Liver (EASL) meeting, my colleagues and I presented data from a retrospective analysis of all new cancer cases reported between 2008 and 2012 in the Kaiser Permanente Southern California database. We calculated cancer rates in patients with and without a diagnosis of chronic HCV infection. Patients who were younger than 18 years of age, who were HIV-positive, or who had a history of bone marrow or solid organ transplant were excluded. We stratified the data for alcohol use, tobacco use, diabetes, and obesity. The study included approximately 34,000 patients with HCV infection who were compared with more than 5 million patients without HCV infection. Unadjusted cancer rates were 2 to 3 times higher in the HCV population for head-and-neck, lung, esophageal, stomach, pancreatic, prostate, and renal cancers, as well as myeloma and non-Hodgkin lymphoma. The rate of liver cancer was 68 times higher in the HCV population, and the risk of having any cancer was more than twice as high in the HCV population. After stratification, the cancer rates remained significantly increased for total cancer cases, liver cancer, and non-Hodgkin lymphoma. Multivariate analysis showed a strong association between cirrhosis and an increased cancer risk.

G&H Were these findings surprising?

AN We certainly expected to find an increased rate of HCC in the HCV population. However, the increase of more than 60-fold was much higher than expected. We did not expect that there would be so many different types of cancer with increased rates. However, after stratification, only the total cancer, liver cancer, and lymphoma rates were significantly increased. We were also surprised to see that cirrhosis was so strongly associated with so many cancer types.

G&H What are the strengths and limitations of this study?

AN The main strength of this study is that it was a large database analysis of real-world patients. Additionally, we used the Kaiser Permanente Southern California Surveillance, Epidemiology, and End Results Program–affiliated cancer registry, in which all cancer cases are fully validated.

The main limitations are the retrospective nature of the study and the fact that we have not established a causal relationship between HCV and extrahepatic cancer. In addition, we may not have recorded the confounders (tobacco use, alcohol abuse, etc) accurately, or we may have omitted an important confounder.

G&H How do these study findings compare with findings of earlier studies?

AN The increased rate of HCC in patients with chronic HCV infection agrees with findings from earlier studies. Previous studies performed in different parts of the world have reported increased cancer rates of various types in patients with HCV infection. Dr Stuart Gordon's group recently described increased unadjusted rates of liver, pancreatic, and renal cancers as well as non-Hodgkin lymphoma in a US population. Increased rates of non-Hodgkin lymphoma and myeloma were seen in a Swedish study. A South American study found an increased rate of HCV antibody among patients with prostate cancer. These results are in agreement with ours. However, most of the studies only reported crude (unadjusted) cancer rates. In our study, using multivariable analysis, the majority of the increased cancer rates were explained by confounders. However, all cancers, liver cancer, and non-Hodgkin lymphoma were significantly increased in the multivariable model.

At Digestive Disease Week 2015, Dr Lisa Nyberg presented data on the natural history of HCV. In this population of HCV patients, achieving sustained virologic response (SVR) was associated with decreased liver-related and non-liver-related mortality, thus supporting

the concept of HCV as a systemic disease rather than only a liver disorder. The study showed a strong relationship between cirrhosis and HCC. Furthermore, patients who were treated and cured of HCV prior to developing cirrhosis had no liver-related mortality.

G&H Are there any plans for follow-up studies?

AN Since effective and well-tolerated HCV treatment is now available for most patients, it will be interesting to find out if the eradication of HCV infection will result in a decrease in cancer rates. Some case studies have shown that successful HCV treatment is associated with the regression of myeloma and non-Hodgkin lymphoma. A long-term, prospective study could validate the findings of Dr Lisa Nyberg's retrospective natural history study—that is, to find out whether patients treated and cured of HCV infection who are followed prospectively have decreased cancer rates and decreased mortality.

G&H Are all HCV patients at increased risk for cancer?

AN Patients with advanced fibrosis and cirrhosis are at increased risk of developing HCC. We found a strong correlation between cirrhosis and extrahepatic cancers, but we cannot predict who will be at increased risk of developing these malignancies. As already discussed, the cancer risk is multifactorial, and many of the HCV patients have other risk factors for cancer, such as alcohol and tobacco use and obesity. More research is needed on this issue.

G&H Should HCV patients undergo screening for cancer?

AN All HCV patients with advanced fibrosis and cirrhosis should undergo HCC surveillance. Many patients with HCV infection have had the disease for 30 to 40 years and even longer. Some of these patients may be at increased risk of developing cancer even after achieving

SVR. A recent presentation by Dr Hashem El-Serag also suggested that patients who are older than 65 years, those with diabetes, and those with HCV genotype 3 infection may be at increased risk of developing HCC even after clearing the virus. Thus, these patient groups may also benefit from HCC surveillance.

G&H Are there any preventive measures that can be undertaken in these patients?

AN I believe that the most important prevention is to treat and eradicate HCV infection while recognizing that HCV is a systemic disease with a number of extrahepatic manifestations. However, this patient population also has many other modifiable risk factors. HCV patients should work on lifestyle improvements, particularly in terms of smoking, obesity, alcohol abuse, diet, and diabetes. Left unaddressed, these lifestyle issues may lead to comorbidities in the future.

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Suggested Reading

Allison RD, Tong X, Moorman AC, et al; Chronic Hepatitis Cohort Study (CHeCS) Investigators. Increased incidence of cancer and cancer-related mortality among patients with chronic hepatitis C infection, 2006-2010. *J Hepatol*. 2015;63(4):822-828.

El-Serag H, Richardson P, Kanwal F, et al. Incidence and predictors of hepatocellular cancer following sustained virological response: a natural cohort study [abstract 90]. Presented at: AASLD Liver Meeting 2015; November 13-17, 2015; San Francisco, California.

Gish RG, Cohen CA, Block JM, et al. Data supporting updating estimates of the prevalence of chronic hepatitis B and C in the United States. *Hepatology*. 2015;62(5):1339-1341.

Nyberg AH, Chung JW, Shi JM, et al. Increased cancer rates in patients with chronic hepatitis C: an analysis of the cancer registry in a large US health maintenance organization [abstract O058]. Presented at: The 50th European Association for the Study of the Liver meeting; April 22-26, 2015; Vienna, Austria.

Nyberg L, Li X, Yang S-J, et al. The association of sustained virological response and mortality after interferon-based therapy for chronic hepatitis C (HCV) in a large U.S. community-based health care delivery system [abstract 809]. Presented at: Digestive Disease Week 2015; May 16-19, 2015; Washington, DC.