# Who Is at Risk for Liver Cancer After Hepatitis C Treatment?

Hepatocellular carcinoma can still occur after hepatitis C is cured, and risk factors differ for people with and without cirrhosis.

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Some people with liver cirrhosis remain at risk for developing liver cancer even after hepatitis C treatment, according to study results presented at the AASLD Liver Meeting. Unsuccessful treatment that did not lead to a cure is the biggest risk factor. A related study found that among people who were cured, risk factors differ for people with and without cirrhosis.

Over years or decades, chronic hepatitis C virus (HCV) infection can lead to the development of cirrhosis and hepatocellular carcinoma (HCC), the most common type of liver cancer. People who are successfully treated for hepatitis C are less likely to develop HCC, but some risk remains, especially for those who have already progressed to advanced fibrosis or cirrhosis. Liver cancer is often diagnosed late, when it is more difficult to treat, and being able to predict who is at risk could enable targeted surveillance and prompt treatment.

## Liver Cancer and Cirrhosis

In the first study, Loreta Kondili, MD, PhD, of Istituto Superiore Di Sanità in Rome, and colleagues evaluated the medium- to long-term impact of direct-acting antiviral (DAA) treatment on the development of liver cancer in hepatitis C patients with cirrhosis.

This analysis included 2,214 participants in the Italian PITER cohort who were treated with DAAs after they had developed cirrhosis and were followed for at least one year. Most (93%) achieved a sustained virological response (SVR), which is considered a cure. The median age was 64. People who had received a liver transplant or had previously been diagnosed with HCC were excluded.

Over a median 30 months of follow-up after the end of treatment, 149 people (6.7%) developed HCC for the first time, including 119 (5.8%) who had achieved SVR and 30 (20%) who had not. This meant that those who were not cured had a more than seven-fold higher risk of new liver cancer. What's more, people without SVR developed liver cancer sooner after completing treatment. At two years post-treatment, 98% of people who achieved SVR were still alive without HCC, compared with just 65% of those who were not cured.

Among people who did achieve SVR, other liver cancer risk factors included HCV genotype 3, low

platelet counts, low albumin levels and older age. Male sex, hepatitis B coinfection and diabetes were also linked to increased HCC risk, but these associations did not reach statistical significance. No association was seen with liver stiffness (a measure of fibrosis severity), body mass index, alcohol use, HIV coinfection, liver fat, use of sofosbuvir or ribavirin, or previous treatment with interferon-based therapy.

At the time of diagnosis, 80% of people with liver cancer had intermediate to advanced liver cancer. During follow-up, 26% of patients with HCC died and 7.6% received a liver transplant. Having more advanced fibrosis before DAA treatment, as determined by liver stiffness measurements, was an independent predictor of death.

"Failure to achieve SVR after DAA treatment is significantly associated with the probability of development of de novo HCC in the first two years," the researchers concluded, stressing the importance of ongoing monitoring and prompt cancer treatment.

Liver Cancer After SVR

A second study, by Jennifer Kramer, PhD, MPH, of the Center for Innovations in Quality, Effectiveness and Safety, and colleagues looked at liver cancer risk factors among people who were cured of hepatitis C, assessed at one year and two years after treatment.

This analysis included 98,612 U.S. veterans with hepatitis C who achieved SVR with DAA treatment between January 2014 and December 2018. Almost all were men, half were white, 39% were black and the mean age was 61. Nearly a third had cirrhosis at the time of treatment. People with and without cirrhosis were demographically similar but the former group had higher bilirubin and albumin levels and higher rates of diabetes, hypertension and obesity.

A total of 2,298 people developed HCC during the study period. Annual incidence rates for people with cirrhosis were 1.6% during the first year after treatment and 1.9% during the second year, compared with 0.21% and 0.27%, respectively, for those without cirrhosis.

The researchers found that liver cancer risk factors differed according to cirrhosis status.

Among people with cirrhosis, HCC predictors at 12 months included male sex, white race, HCV genotype 3, longer cirrhosis duration, higher bilirubin levels and the presence of esophageal varices (enlarged veins). Changes in albumin levels and worsening fibrosis also predicted HCC risk. However, race, HCV genotype and bilirubin were no longer significant predictors at 24 months while changes in hemoglobin became a significant factor. Nonsmokers had a lower risk of liver cancer.

Among people without cirrhosis, in contrast, metabolic factors such as diabetes and hypertension, as well as worsening fibrosis, were strongly associated with liver cancer risk at both time points.

“In a cohort of patients with virologically cured HCV infection, risk factors for HCC were different in

patients with and without cirrhosis," the researchers concluded. "In patients with cirrhosis, they were mostly disease-severity-related, whereas metabolic traits were important in patients without cirrhosis."

These findings, they added, could inform decisions about liver cancer surveillance in people cured of hepatitis C. Because risk factors can change over time, they suggested that repeated assessment at two years "is practical and can improve risk stratification" regardless of their cirrhosis status.

Click here to read Kondili's abstract.

Click here to read Kramer's abstract.

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