How Does Curing Hepatitis C Affect Long-Term Liver Cancer Risk?

Scientists aren’t sure, but they know that the risk that a previous case of liver cancer will return remains high for those cured of hep C.

October 25, 2018 By Benjamin Ryan

A primary reason for curing hepatitis C virus (HCV) virus is to reduce the risk of liver-disease progression. That said, it may come as a surprise to many people living with the virus that scientists still don’t necessarily have a firm grasp on exactly how beating HCV affects the risk of certain major health outcomes, in particular hepatocellular carcinoma (HCC, the most common form of liver cancer).

In 2017, a team of researchers published a Cochrane review of 157 trials in which they concluded that they “could not reliably determine” the effect of direct-acting antiviral (DAA) treatment for HCV on the risk of various illnesses and death. The paper met with a storm of controversy and criticism, as other scientists in the field slammed its authors for relying on studies with relatively short follow-up periods.

There was indeed evidence, such critics adamantly stated, indicating that achieving sustained virologic response 12 weeks after completing DAA therapy (SVR12, considered a cure) provides the kind of benefits the Cochrane investigators said they could not detect.

On the subject of liver cancer risk, researchers published a paper in 2017 that seemed to debunk previous theories that being cured of HCV with interferon treatment was associated with a lower risk of developing HCC than beating the virus with DAA medications.

But even if there is no difference in the risk of HCC based on the type of HCV treatment received, what liver cancer risk do those cured of the virus face in the long term? According to a systematic review of 42 studies recently published in Frontline Gastroenterology, the risk of a first diagnosis of liver cancer remains relatively low for this population. However, among those who had HCC before starting curative hep C treatment, the chance of a recurrence of the disease remains very high.

Seeking findings that were as robust as possible, the study authors limited their review of papers reporting on post-hep C cure first diagnoses of HCC to those that included cohorts of more than 100 people. They had no such restriction for studies looking at diagnoses of recurrent liver cancer.
The average age of participants in these studies ranged from 50 to 72 years old. They were followed for an average of three to 70 months.

The lead author of the systematic review, Sonal Singh, MD, an internist in the Department of Family Medicine and Community Health at the University of Massachusetts School of Medicine in Worcester, says his paper did not set out to determine how curing hep C affected the risk of a first diagnosis of liver cancer. However, a meta-analysis he and his team conducted of three studies showed that achieving an SVR lowered the risk of recurrent liver cancer by 50 percent; nevertheless, this finding was not statistically significant, meaning it might have occurred by chance.

Singh says hep C researchers haven’t produced the kind of lengthy follow-up data needed to conduct a proper assessment of the relationship between SVR and HCC risk.

After looking at eight studies that had a control group and 36 that did not, Singh and his coauthors found that, of study participants who had not had liver cancer prior to hep C treatment, 1.5 percent of those in uncontrolled studies and 3.3 percent of those in controlled studies were diagnosed with HCC. As for those who had already had HCC before receiving hep C therapy, a respective 16.7 percent and 20.1 percent of those in the uncontrolled and controlled studies saw their cancer recur post–HCV cure.

In other words, the probability of a liver cancer diagnosis within several years of curing HCV was about 1 in 67 for those who had not already been diagnosed with HCC and 1 in 6 for those who had.

By comparison, the diagnosis rate of liver cancer among people with chronic hep C is about 1 to 3 percent per year and is higher among those with cirrhosis.

“I’m not trying to scare patients,” Singh says. Speaking of DAAs, he says, “I think these are very effective treatments. And I’m treating my patients; everybody’s treating them. But it does mean that I’m following my patients very closely” after they are cured of hep C.

Singh and his coauthors did not express their findings in a more generalizable annual diagnosis rate because they lacked enough data to reliably determine how long researchers in the various studies had tracked study members.

The authors also noted that the overall quality of the evidence backing their findings was low. So without high-quality controlled cohort studies of people cured of HCV and without longer follow-up of such individuals, the review authors “can neither confirm nor rule out an increase or decrease in the risk of incident or recurrent HCC after oral DAA therapy.”

According to Singh, it’s possible that for a certain period after hep C, the act of curing the virus, compared with not doing so, actually temporarily raises the risk of liver cancer; and then later, the risk drops below pre–HCV cure levels such that the lifetime risk is indeed lower thanks to beating hep C.
Theories about why curing hep C may—rather counterintuitively—lead to a temporary boost in the likelihood of liver cancer focus on the possibility that because the virus may actually attack precancerous cells, the sudden lack of HCV thanks to a cure may allow those cells to flourish. Also, quickly altering the balance between liver inflammation and anti-inflammatory forces with hep C treatment could affect the development of malignant cells.

Considering such theories and the uncertainty about how treating HCV affects liver cancer risk, Singh advocates greater ongoing, possibly indefinite, medical monitoring of people who have achieved an SVR. He also calls for more research to provide clear answers to address such uncertainty. His paper stresses that studies should look at how other variables may influence the risk of HCC among people treated for HCV, including viral genotype, alcohol use, hepatitis B virus coinfection, levels of alpha-fetoprotein and cirrhosis stage.