Hep C Clearly Drives Liver Cancer, but What About Other Cancers?

A new systematic review and meta-analysis indicates that hepatitis C is most notably also associated with B-cell non–Hodgkin lymphoma.

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When it comes to malignancies, hepatitis C virus (HCV) is most clearly associated with an increased risk of hepatocellular carcinoma (HCC), the commonest form of liver cancer. In fact, the virus is one of the biggest drivers of that disease. (Treating hep C with direct-acting antivirals, or DAAs, lowers the risk of liver cancer, although those individuals who have already developed cirrhosis by this point still face an elevated risk.) But the virus's potential carcinogenic effects are not limited to its host organ, as research indicates hep C is linked to numerous other cancers as well.

Seeking clarity and more updated scientific information on associations between hep C and various malignancies, researchers at the Internal Medicine and Hepatology Unit at the University of Salerno in Italy conducted a systematic review and meta-analysis of a host of studies. Publishing their findings in Liver International, the investigators found links between HCV and various non-liver cancers. The association was particularly strong between the virus and B-cell non–Hodgkin lymphoma (NHL), a cancer that centers around antibody-producing white blood cells. Treating the virus, whether with DAAs or older interferon-based treatments, was powerfully linked to better NHL outcomes.

Previous research had already identified a connection between HCV and NHL, a finding that has led to proposals that curative therapy for the virus be used as a first-line treatment for low-grade malignant cases of lymphoma.

The new study's authors identified 27 studies that evaluated the rate of hep C infection among just over 33,000 people with NHL and compared this group with nearly 420,000 control subjects. They found that hep C was 3.36 times more common among those with NHL compared with those who did not have the lymphoma.

Since the findings of these studies were rather heterogenous, meaning the strength of the association between hep C and NHL varied quite a bit between studies, the researchers divided the papers into subgroups to look for patterns. In the 15 studies conducted in Europe, HCV was 3.81 times more common among people with NHL. The corresponding association was 3.99 in the

five studies from Asia and 2.11 in the seven studies from North America.

Breaking down the findings by the severity of NHL, the investigators found that in the 16 studies that included data on low-grade NHL, hep C was 3.28-fold more common among such individuals compared with control individuals. In the 12 studies with data on intermediate-grade NHL and the 15 studies with data on high-grade cases of the lymphoma, hep C was respectively 3.37-fold and 4.2-fold more common among those with these two grades of severity.

The good news is that treating HCV among people with NHL was associated with positive health outcomes. Supporting this finding were 13 studies with data on 523 people with both diseases, including 274 people who were cured of hep C and 250 who were either never treated for hep C or treated and not cured. Nine of these studies were conducted during the interferon era of hep C treatment while the other four were conducted more recently, during the current era in which much more tolerable and effective DAAs are available. Overall, curing hep C, compared with not curing the virus, was associated with a 9.34-fold increased likelihood of progression-free survival—meaning not experiencing a worsening of NHL or dying—during study follow-up.

In the three studies focusing on NHL health outcomes that used DAA treatment, curing HCV was tied to an 8.97-fold increased likelihood of progression-free survival. The three studies that included data on people with aggressive lymphomas and the 10 studies with data on those with indolent lymphomas (which advance more slowly) found that curing the virus was associated with a respective 13.73-fold and 6.76-fold greater chance of progression-free survival.

The paper's authors also looked at the connection between HCV and non-HCC tumors, in particular cholangiocarcinoma, which is a cancer of the bile duct that can develop either inside or outside the liver, and pancreatic adenocarcinoma, the most common form of pancreatic cancer.

Between them, 13 studies indicated that having hep C, compared with not having the virus, was associated with a 3.95-fold greater chance of having intrahepatic cholangiocarcinoma. Breaking down the results by geographical area, the study authors found that in eight studies conducted in Asia and the Middle East, two studies in Europe and three studies in North America, the associated risk increased by 2.9-fold, 5.71-fold and 5.87-fold, respectively.

Five studies provided information about pancreatic carcinoma risk, finding that the disease was 1.78-fold more common among those with HCV compared with those who did not have the virus in three Asian studies and 1.75-fold more common among those with HCV versus those without in the four studies that were case controlled—meaning they were retrospective studies in which the two groups under comparison, in this case those with and without the virus, are clearly defined from the outset.

The paper references two large studies that compared the prevalence of almost all types of neoplasms (abnormal cell growth) between people with hep C and the general population. One U.S. study, which included 1.6 million cases of neoplasms and 200,000 matched controls, found a significant association between HCV and cholangiocarcinoma, pancreatic carcinoma, lymphoproliferative disorders (various forms of lymphoma, leukemia and other immune cell

disorders) and liver cancer. Another study conducted in Denmark found a link between hep C and cancers of the pancreas, lung, head and neck, kidney and liver as well as NHL but did not find the virus was associated with other tumor types.

As to how hep C may drive NHL in particular, research findings indicate that the virus may cause lymphocytes to proliferate. Genetic factors that influence the natural history of both diseases may also play a role. Additionally, the virus may drive the production of tumors by promoting harmful inflammation in the body. Hep C is also associated with insulin resistance, which itself can drive cancer cell proliferation.

Preliminary data has indicated that treating HCV with DAAs appears safe for use with chemotherapy for cancer. Information about the safety of DAA treatment in those with tumors outside of the liver is scarce, so more research is needed.

Summing up their paper, the study authors wrote, “Although not all these findings are supported by known pathophysiological mechanisms, and some of them are still controversial, it is clear that extrahepatic neoplasms are a significant problem in patients affected by HCV.”
