Can simple blood tests predict liver cancer?

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Today in high-income countries such as Canada, hepatitis C virus (HCV) is most commonly spread by sharing unsterilized equipment for substance use. However, HCV (and HIV and other germs) can also be transmitted by exposure to unsterilized equipment used for tattooing or body piercing. Cases of sexually transmitted HCV have also been reported where blood-to-blood contact occurs, particularly among men who have sex with men. In previous decades HCV was also transmitted through contaminated blood or blood products such as clotting factors. Today the blood supply in high-income countries is considerably safer.

HCV infects the liver, and as the immune system fights this virus, inflammation occurs. After acute infection, HCV becomes embedded in the liver and chronic infection results. Over time, the interaction between the immune system and HCV results in ongoing inflammation, and so liver cells become less functional and die. Dead cells are replaced with scar tissue in a process known as fibrosis. Over years, as fibrosis spreads, the liver becomes increasingly dysfunctional and a range of complications occurs. If left untreated, HCV infection can lead to liver failure. The ongoing inflammation caused by chronic HCV infection can incite liver cells to develop abnormally and, in some cases, become cancers. In people co-infected with HIV and HCV, HIV infection appears to speed up the degradation of the liver caused by HCV. Co-infected people are also at risk for liver cancer. Spontaneous recovery from HCV infection is uncommon in people co-infected with HIV, as their immune systems are weakened.

Treatment for HCV is a combination of once weekly interferon-alpha and a broad-spectrum antiviral drug called ribavirin. New drugs specifically designed to attack HCV are under development. Two of these new drugs, boceprevir (Victrelis) and telaprevir (Incivik), are approved for use in combination with interferon and ribavirin in people infected with HCV alone (mono-infection), but not yet in people infected with both HIV and HCV, at least in Canada at present.

Monitoring

People with HCV infection undergo many tests so that doctors can assess their general health and, in particular, the health of their liver. Some of these tests, such as liver biopsy, are invasive and can, in rare cases, cause complications. Increasingly, liver specialists are opting to use ultrasound scans of the liver—called FibroScan—with their specialized scanning devices.

Enter FIB-4

In the time before FibroScan technology was widely available in high-income countries, a team of researchers in Brazil, North America and Western Europe tested a formula called FIB-4 into which they inputted the results of simple blood tests. The results of FIB-4 were one tool that doctors could use to help them estimate the degree of liver damage (fibrosis) caused by HCV infection.

Now researchers at Yale University and elsewhere in the U.S. have completed a study with nearly 23,000 HIV-positive men, some of whom were co-infected with hepatitis B virus (HBV) and HCV and were therefore at high risk for developing liver cancer. In general, they found that the greater the FIB-4 result, the greater the likelihood that a person would develop liver cancer. As FIB-4 requires a scientific calculator and simple blood tests, if the findings from the Yale study are confirmed, FIB-4 could represent a relatively cheap and simple way of screening people with HBV, HCV and other risk factors for the possibility of liver cancer.
Study details

The Yale-led research team used data collected from 22,980 HIV-positive U.S. veterans who were enrolled in the Veterans Affairs database between 1996 and 2008. As 98% of participants in this database were male, researchers decided to exclude female volunteers because of their relatively small numbers.

FIB-4 scores were calculated using a complex equation that needed the following factors; all have some relationship to inflammation and liver damage in the setting of HCV infection:

**Age**

Many people infected with HCV may not know exactly when they were infected. However, a person’s age provides some insight into the HCV-disease process. In general, the older a person is, the greater the likelihood that they have been infected with HCV for some time and therefore are more likely to have a greater degree of liver damage than a younger person.

**Platelet count**

Platelets are tiny cells involved in inflammation and helping blood to clot. The amount of platelets in blood, called the platelet count, is somewhat related to the degree of liver damage and elevated pressure within the liver’s blood vessels.

**INR (international normalized ratio)**

This test provides information about how fast a person’s blood clots. Previous studies have linked changes in INR to liver fibrosis.

**AST (aspartate aminotransferase)**

This is an enzyme made by the liver. Higher-than-normal levels of AST in the blood suggest liver injury.

Results—Liver cancer

In the Veterans Affairs database of 22,980 HIV-positive men, there were 122 who had been diagnosed with liver cancer. These 122 cases of cancer occurred an average of seven years after the men had been enrolled in the VA database.

The research team graded the FIB-4 scores of participants as follows:

- low – less than 1.45
- intermediate - between 1.45 and 3.25
- high – greater than 3.25

The researchers made adjustments to their calculations, taking into account factors such as CD4+ cell counts, HIV viral load, use of antiretroviral therapy, co-infection with HBV and/or HCV, as well as alcohol addiction and diabetes. Despite these adjustments, FIB-4 scores had a strong and statistically significant relationship with the development of liver cancer. In general, the researchers found that the greater the FIB-4 score, the greater the risk of developing liver cancer. For instance, people who had a high FIB-4 score were 10 times more likely to develop liver cancer than people with a low score. People with moderately elevated FIB-4 scores were about four times more likely to develop liver cancer than people with low scores.

The strong relationship between FIB-4 scores and subsequent development of liver cancer persisted even when researchers removed a person’s age from the formula.

People who had moderate or elevated FIB-4 scores were at increased risk for liver cancer even if they did not have HBV or HCV and were not addicted to alcohol—factors that all place people at risk for liver cancer.

The present study had data from a huge number of people, lab test results to assess HCV infection and data from a cancer registry to confirm most diagnoses of liver cancer. These make its findings noteworthy.
However, the study was retrospective in nature, but perhaps this is understandable given the relatively low rate of liver cancer (fewer than 1%). The study did not contain data on body mass index (a value obtained by dividing a person’s weight by the square of their height). This could have helped researchers determine if some of the participants who had liver cancer were also obese. This may have been important because obesity appears to be an emerging risk factor for liver cancer. A final weakness of the study was the lack of women.

**Women and FIB-4**

In a separate study, researchers at the University of Cincinnati assessed blood samples from 1,227 women—some were HIV and HCV negative but at high risk for infection with these viruses, some were HCV positive or HIV positive, and others were co-infected with HCV and HIV.

The researchers found that women who did not have HIV or HCV had the lowest FIB-4 levels, while those women who were co-infected with both HIV and HCV had the highest FIB-4 scores. Liver biopsies or ultrasound scans or diagnoses of liver cancer were not available in the Cincinnati study. However, the findings are suggestive of a greater degree of liver damage among co-infected women.

**Next steps**

The Yale-led team has proposed that FIB-4 or a modified FIB-4 formula has potential for predicting which HIV-positive people are at high risk for liver cancer. Now research teams in other countries need to confirm if high FIB-4 levels are associated with liver cancer among HIV-positive people co-infected with hepatitis viruses. Such studies need to include women.

**A more complicated score**

Other research teams are exploring the effect of other markers suggestive of inflammation and assessing their relationship to liver cancer. One of these other scoring systems uses a ratio of two different groups of cells of the immune system found in the blood—neutrophils and lymphocytes. Researchers in Italy have found that the neutrophil-to-lymphocyte ratio can predict the recurrence of liver cancer in HIV-negative people who have undergone a liver transplant as part of their treatment for liver cancer.

— Sean R. Hosein

**REFERENCES:**

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