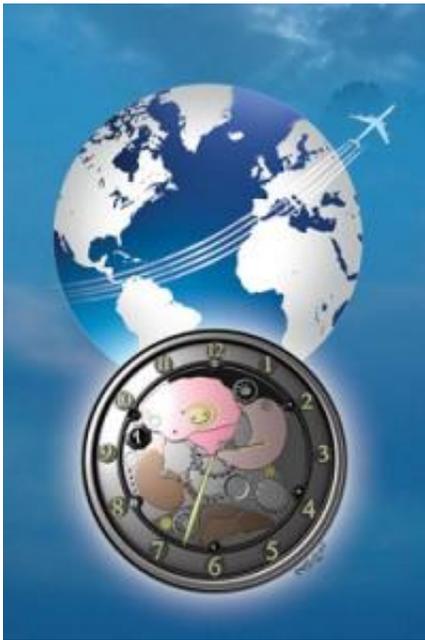


Jet lag and obesity share similar pathways to liver cancer

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Our inner clock goes out of sync after long plane trips. Credit: Image: Max Planck Institute for Biophysical Chemistry / Merve Evren

Since 1980, the incidence of hepatocellular carcinoma, the most common type of liver cancer, has nearly tripled, and obesity related liver disease is one of the driving forces behind the increasing number of cases. Baylor College of Medicine researchers are now examining how other lifestyle factors may affect your health. Using mice, the scientists show that repeated jet lag increases both obesity related liver disease and the risk of liver cancer. The study appears November 23 in *Cancer Cell*.

"Liver cancer is on the rise worldwide, and in human studies we've now seen that patients can progress from fatty [liver disease](#) to [liver cancer](#) without any middle steps such as cirrhosis," says David Moore, a professor of molecular and cellular biology, who led the study with Associate Professor Loning Fu, both at Baylor. "We knew we needed an animal model to examine this connection, and studies in the Fu Lab found that chronically jet-lagged mice developed liver cancer in a very similar way as that described for obese humans."

When we are exposed to light, our bodies' central circadian clock in the brain resets. When we constantly travel through different time zones, work night shifts, or push ourselves to stay awake at the regular sleep time, our central clock is being chronically disrupted. This disruption also extends to clocks in other tissues that are controlled by the central clock.

By changing the times the lights went on and off during the night each week, the researchers modeled the effects of chronic jet lag in normal mice who were fed a healthy diet. They found that the mice gained weight and fat, and developed fatty liver disease, which progressed to chronic inflammation and eventually liver cancer in some cases

The jetlagged mice lost normal control of [liver metabolism](#). This included not only the buildup of fat, but also increased production of bile acids, which are produced by the liver to help us digest our food. Earlier studies have linked high bile acid levels to liver cancer, not only in mice but also in humans.

The researchers found that circadian clock disruption activated two nuclear receptors that help regulate liver bile acid metabolism. Jetlagged mice lacking a receptor called FXR, which keeps bile acid level in the liver within a normal physiological range, had higher bile acid levels and much more liver cancer. Mice lacking a receptor called CAR that

regulates bile acid breakdown and is also known to promote liver cancer, did not get any [liver tumors](#).

In humans, these receptors work in a similar manner. The Baylor College of Medicine scientists didn't directly study jetlag in humans. But there is evidence that sleep disruption increases both [fatty liver disease](#) and liver cancer risk in humans, and they hypothesize that lifestyle changes that generate chronic jet lag can also disrupt the body's internal homeostasis and increase liver cancer risk in humans.

"Recent studies have shown that more than 80 percent of the population in the United States adopt a lifestyle that leads to chronic disruption in their sleep schedules," says Loning Fu. "This has also reached an epidemic level in other developed countries, which is coupled with the increase in obesity and liver cancer risk."

The scientists hope to continue their research to further examine whether drugs interacting with the nuclear receptors can help to prevent jet lag from affecting [bile acid](#) levels in the liver, with the ultimate goal of potentially using them as pharmaceutical strategies to prevent liver cancer in humans.

"This experiment allowed us to take several threads that were already there and put them together to come to this conclusion," says Moore. "We think most people would be surprised to hear that chronic jet lag was sufficient to induce liver cancer."

"To us, our results are consistent with what we already knew about these receptors, but they definitely show that chronic circadian disruption alone leads to malfunction of these receptors," Fu adds. "And thus, maintaining internal physiological homeostasis is really important for liver tumor suppression."

More information: *Cancer Cell*, Kettner et al: "Circadian Homeostasis of Liver Metabolism Suppresses Hepatocarcinogenesis"

[www.cell.com/cancer-cell/fullt ... 1535-6108\(16\)30494-9](http://www.cell.com/cancer-cell/fulltext/S1535-6108(16)30494-9) , DOI: [10.1016/j.ccell.2016.10.007](https://doi.org/10.1016/j.ccell.2016.10.007)

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