

Hidden Cancer Risk Behind Fatty Liver Disease Targets

Blocking the enzyme Caspase-2, thought to protect against fatty liver disease, may instead increase the risk of chronic liver damage and cancer as we age.

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Scientists have discovered that blocking a key cellular enzyme thought to protect against fatty liver disease may instead increase the risk of chronic liver damage and cancer as we age.

In a major [new study](#) published in Science Advances, researchers from Adelaide University have shown that loss of the enzyme Caspase-2 drives abnormal growth in liver cells, triggering inflammation, fibrosis, and a significantly higher risk of liver cancer.

The findings challenge growing interest in Caspase-2 inhibitors as a potential therapeutic strategy to treat and/or prevent fatty liver disease and highlight the need for caution when targeting this pathway.

Caspase-2 plays a critical role in maintaining the genetic stability of liver cells while also having an independent role in controlling fat levels in the liver, according to lead researcher Dr. Loretta Dorstyn from the Centre for Cancer Biology.

“Liver cells normally have extra copies of genetic material—known as polyploidy—and while this feature can help the liver cope with stress, our study shows that without the enzyme Caspase-2, abnormally high levels of polyploidy in the liver can be damaging,” Dr. Dorstyn said.

Using genetically modified mouse models, the researchers found that in mice lacking the enzyme, or had a version of it that no longer worked, liver cells were abnormally large with excessive amount of genetic and cellular damage.

“Over time, these mice developed chronic liver inflammation and characteristics of hepatitis-like liver disease including, scarring, oxidative damage and a type of cell death linked to inflammation. As the animals aged, they were much more likely to develop liver cancer.”

Ageing mice lacking functional Caspase-2 enzyme developed spontaneous liver tumours at much higher rates than normal mice, with up to four times the incidence of liver cancer, characteristic of hepatocellular carcinoma.

Dr. Dorstyn said the findings also overturn assumptions that inhibiting Caspase-2 is universally beneficial.

“While inhibiting this enzyme can be protective in young animals or may help prevent fatty liver disease in the short term, our study shows that its long-term loss is clearly detrimental.

“Our study demonstrates that Caspase-2 is essential for removing damaged and abnormal liver cells as we age. Without it, these cells accumulate, and can become cancerous, while also creating an environment that predisposes the liver to cancer.”

Senior author Professor Sharad Kumar said the research has important implications for drug development.

“There has been significant interest in targeting Caspase-2 to treat metabolic liver disease and reduce liver cancer risk,” Prof Kumar said. “Our data shows that this approach could have serious unintended consequences later in life, increasing susceptibility to chronic liver inflammation, fibrosis and cancer.”

Liver disease is a growing health burden, driven by ageing populations, obesity and metabolic disorders. Liver cancer accounted for almost [760,000 deaths worldwide in 2022](#), according to the World Cancer Research Fund, making it the 6th most common cancer globally.

Caspase- 2 deficiency drives pathogenic liver polyploidy and increases age- associated hepatocellular carcinoma in mice is published in Science Advances (DOI: [10.1126/sciadv.aeb2571](#)).

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