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UNDER EMBARGO UNTIL APRIL 14, 2020, 12:01 AM ET

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New study indicates exercise can help prevent liver cancer

Exercise retards development of liver cancer by direct effects independent of weight control in an animal model that closely resembles humans with fatty liver disease, report scientists in the Journal of Hepatology

Amsterdam, April 14, 2020 – Liver cancer is the fourth most common cause of cancer death worldwide and is growing rapidly due to the "diabesity pandemic." A new study reported in the *Journal of Hepatology*, published by Elsevier, provides strong evidence that voluntary exercise could help prevent the most common type of liver cancer, hepatocellular carcinoma, and identifies the molecular signaling pathways involved.

Fatty liver disease is common with obesity and diabetes and contributes to rapidly increasing rates of liver cancer throughout the world. More than 800,000 people worldwide are diagnosed with this cancer each year. It is also a leading cause of cancer deaths, accounting globally for more than 700,000 deaths each year.

"As yet there are very few effective therapies for liver cancer (the death rate approximates the incidence), so approaches to prevent liver cancer are greatly needed," explained lead investigator Geoffrey C. Farrell, MD, Liver Research Group, ANU Medical School, Australian National University at The Canberra Hospital, Garran, ACT, Australia. "Some population data suggest that persons who exercise regularly are less likely to develop liver cancer but, studies addressing whether this has a real biological basis, and, if so, identifying the molecular mechanism that produces such a protective effect, are few and the findings have been inconclusive."

Investigators studied whether exercise reduces the development of liver cancer in obese/diabetic mice. Mice genetically driven to eat so that they become obese and develop type 2 diabetes as young adults were injected early in life with a low dose of a cancer-causing agent. Half of the mice were allowed regular access to a running wheel; the other half were not and remained sedentary. The mice ran up to 40 kilometers a day as measured by rotations of the exercise wheel. This slowed down the weight gain for three months, but at the end of six months of experiments even the exercising mice were obese. At six months, most of the sedentary mice had liver cancer while none of the exercising mice had developed it.

This research shows that exercise can stop development of liver cancer in mice that have fatty liver disease related to obesity and type 2 diabetes. Specifically, while nearly all obese mice injected with a

low dose of a cancer-causing agent developed liver cancer within six months, mice that regularly exercised failed to do so. They were completely protected against liver cancer development in the timeframe of these experiments. Weight control did not mitigate the development of liver cancer.

Investigators also carried out detailed mechanistic studies that partly clarified how exercise can prevent liver cancer. They showed that the beneficial effects of voluntary exercise were exerted via molecular signaling pathways, two of which were identified as tumor suppressor gene p53 and the stress-activated protein kinase JNK1.

The investigators first demonstrated JNK1 activation to be a key factor that can be "switched off" by exercise and proved its involvement by separate studies in obese mice lacking JNK1. They also demonstrated that activated p53, known as "guardian of the cell" and "policeman of the oncogenes," is important for regulation of the cell cycle inhibitor, p27, thereby stopping the persistent growth of altered cells destined to become cancerous.
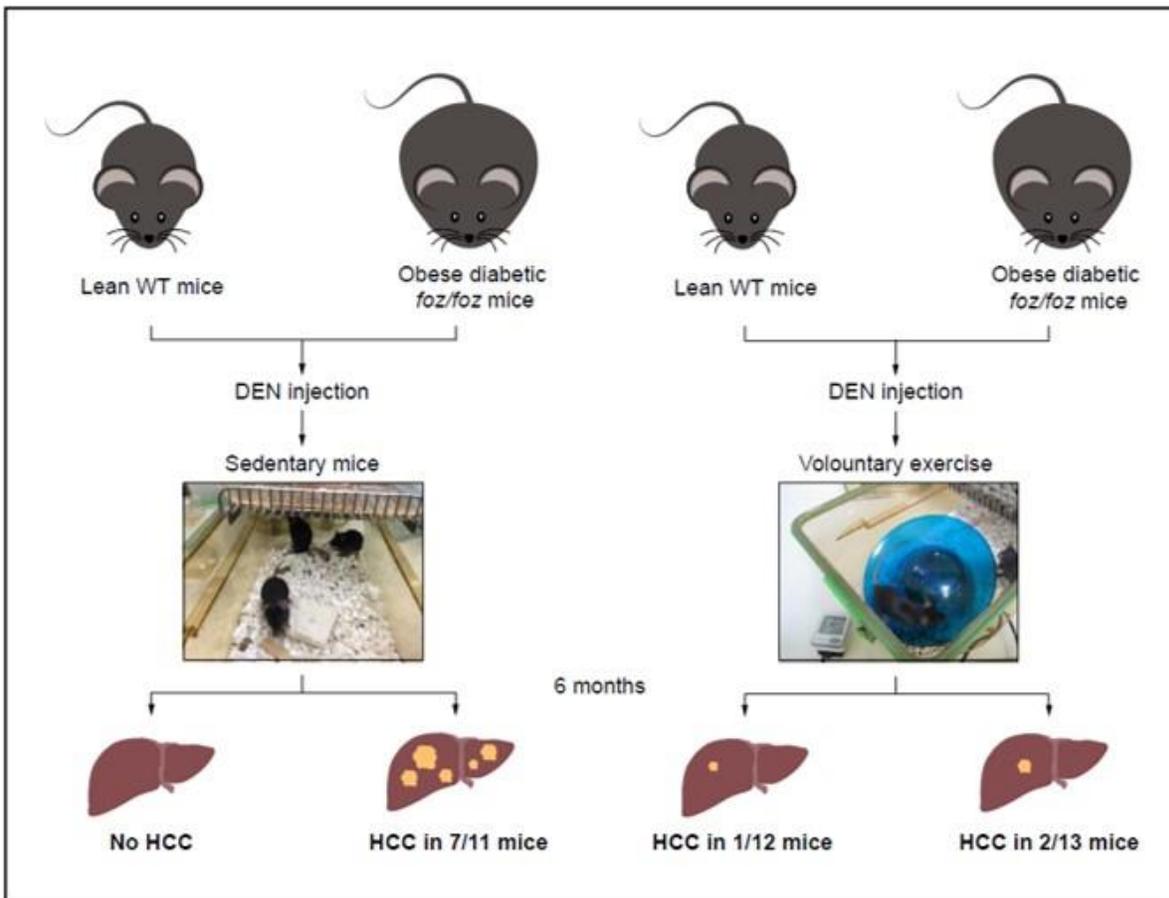
Caption: Scheme illustrating how exercise attenuates liver cancer development in obese and diabetic mice compared with sedentary mice.

"Exercise has already been shown to improve some outcomes for patients with cirrhosis. If the present studies in an animal model that closely resembles humans with fatty liver disease can be replicated in patients, it is likely that exercise could delay onset of liver cancer and mitigate its severity, if not completely prevent it – thereby greatly improving patient outcomes," commented Dr. Farrell. "Also, knowing the molecular pathways involved points to ways that drugs or pharmaconutrients could be employed to harness the powerful protective effect of exercise to lower risk of liver cancer in overweight people with diabetes."

Notes for editors
The article is "Exercise retards hepatocarcinogenesis in obese mice independently of weight control," by Arfianti Arfianti, Sharon Pok, Vanessa Barn, W. Geoffrey Haigh, Matthew M. Yeh, George N. Ioannou, Narci C.-H. Teoh, and Geoffrey C. Farrell (https://doi.org/10.1016/j.jhep.2020.02.006). It will appear in the *Journal of Hepatology*, volume 73, issue 1 (July 2020) published by Elsevier.

Full text of this article is available to credentialed journalists upon request; contact Vicki Wetherell at +44 1865 843193 or hmsmedia@elsevier.com. Journalists wishing to interview the authors should contact Rachel Curtis at 0459 879 726; Rachel.Curtis@anu.edu.au or the ANU Media Team at +61 2 6125 7979 or media@anu.edu.au.

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