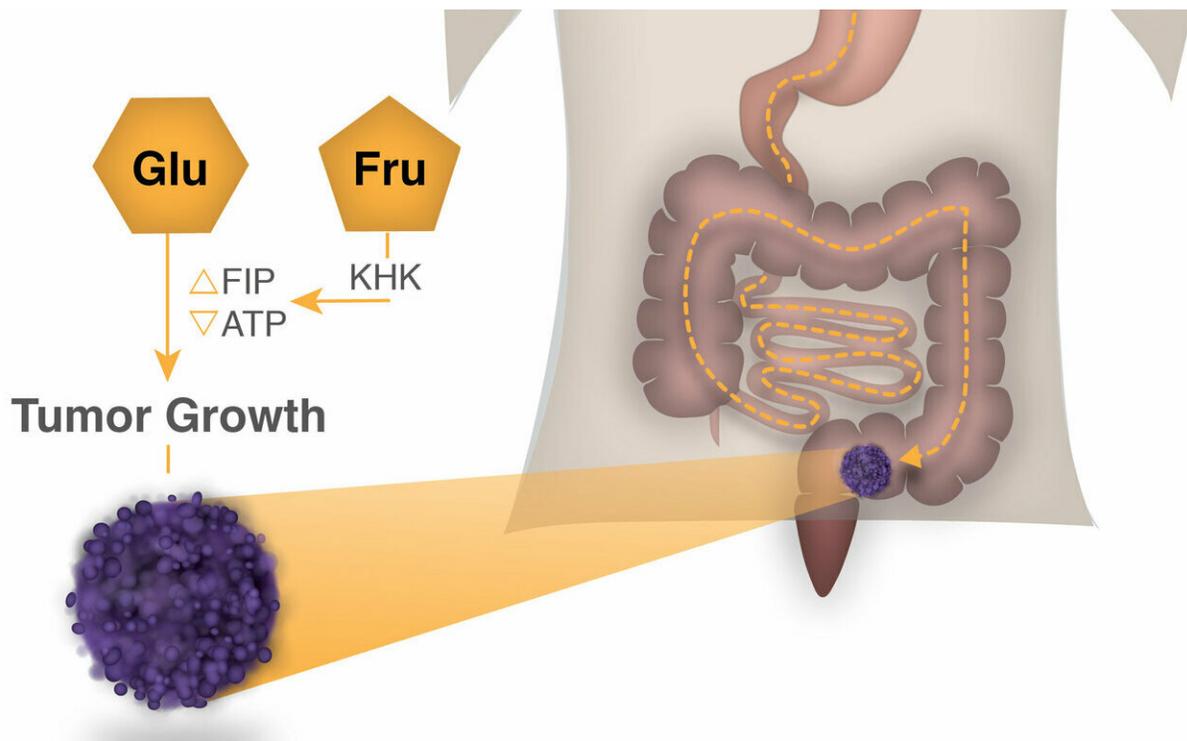


High-fructose corn syrup boosts intestinal tumor growth in mice

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Sugar-sweetened beverages (SSBs) containing a mixture of glucose (Glu) and fructose (Fru), flow through the gastrointestinal tract after consumption. Goncalves et al. show that Glu and Fru are directly absorbed by intestinal tumors, and daily dosing of SSBs accelerates tumor growth. This growth promoting effect is dependent on the enzyme, ketohexokinase (KHK), which produces fructose 1-phosphate (F1P) from Fru, and results in the depletion of adenosine triphosphate (ATP). Both of these metabolic changes promote the conversion of Glu to the building blocks needed for tumor growth. Credit: Vincent Dittmer

Does sugar directly feed cancers, boosting their growth? The answer seems to be 'Yes' at least in mice according to a study led by researchers at Baylor College of Medicine and Weill Cornell Medicine. Their study, published in *Science*, showed that consuming a daily modest amount of high-fructose corn syrup—the equivalent of people drinking about 12 ounces of a sugar-sweetened beverage daily—accelerates the growth of intestinal tumors in mouse models of the disease, independently of obesity. The team also discovered the mechanism by which the consumption of sugary drinks can directly feed cancer growth, suggesting potential novel therapeutic strategies.

"An increasing number of observational studies have raised awareness of the association between consuming [sugary drinks](#), obesity and the risk of [colorectal cancer](#)," said co-corresponding author Dr. Jihye Yun, assistant professor of molecular and [human genetics](#) at Baylor. "The current thought is that sugar is harmful to our health mainly because consuming too much can lead to obesity. We know that obesity increases the risk of many types of cancer including colorectal cancer; however, we were uncertain whether a direct and causal link existed between sugar consumption and cancer. Therefore, I decided to address this important question when I was a postdoc in the Dr. Lewis Cantley lab at Weill Cornell Medicine.

First, Yun and her colleagues generated a mouse model of early-stage colon cancer where APC gene is deleted. "APC is a gatekeeper in colorectal cancer. Deleting this protein is like removing the breaks of a car. Without it, normal intestinal cells neither stop growing nor die, forming early stage tumors called polyps. More than 90 percent of colorectal cancer patients have this type of APC mutation", Yun said.

Using this mouse model of the disease, the team tested the effect of consuming sugar-sweetened water on tumor development. The sweetened water was 25 percent high-fructose corn syrup, which is the

main sweetener of sugary drinks people consume. High-fructose corn syrup consists of glucose and fructose at a 45:55 ratio.

When the researchers provided the sugary drink in the water bottle for the APC-model mice to drink at their will, mice rapidly gained weight in a month. To prevent the mice from being obese and mimic humans' daily consumption of one can of soda, the researchers gave the mice a moderate amount of sugary water orally with a special syringe once a day. After two months, the APC-model mice receiving sugary water did not become obese, but developed tumors that were larger and of higher-grade than those in model mice treated with regular water.

"These results suggest that when the animals have early stage of tumors in the intestines—which can occur in many young adult humans by chance and without notice—consuming even modest amounts of high-fructose corn syrup in liquid form can boost tumor growth and progression independently of obesity," Yun said. "Further research is needed to translate these discovery to people; however, our findings in animal models suggest that chronic consumption of sugary drinks can shorten the time it takes cancer to develop. In humans, it usually takes 20 to 30 years for colorectal cancer to grow from early stage benign tumors to aggressive cancers."

"This observation in animal models might explain why increased consumption of sweet drinks and other foods with high sugar content over the past 30 years is correlating with an increase in colorectal cancers in 25 to 50-year-olds in the United States," said Cantley, co-corresponding author, former mentor of Yun and professor of cancer biology in medicine and director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine.

The team then investigated the mechanism by which this sugar promoted tumor growth. They discovered that the APC-model mice receiving

modest high-fructose corn syrup had high amounts of fructose in their colons. "We observed that sugary drinks increased the levels of fructose and glucose in the colon and blood, respectively and that tumors could efficiently take up both fructose and glucose via different routes."

Using cutting-edge technologies to trace the fate of glucose and fructose in tumor tissues, the team showed that fructose was first chemically changed and this process then enabled it to efficiently promote the production of fatty acids, which ultimately contribute to tumor growth.

"Most previous studies used either glucose or fructose alone to study the effect of sugar in animals or cell lines. We thought that this approach did not reflect how people actually consume sugary drinks because neither drinks nor foods have only glucose or fructose. They have both glucose and fructose together in similar amounts," Yun said. "Our findings suggest that the role of fructose in tumors is to enhance glucose's role of directing fatty acids synthesis. The resulting abundance of fatty acids can be potentially used by cancer cells to form cellular membranes and signaling molecules, to grow or to influence inflammation."

To determine whether fructose metabolism or increased fatty acid production was responsible for sugar-induced tumor growth, the researchers modified APC-model mice to lack genes coding for enzymes involved in either fructose metabolism or fatty acid synthesis. One group of APC-model mice lacked an enzyme KHK, which is involved in fructose metabolism, and another group lacked enzyme FASN, which participates in fatty acid synthesis. They found that mice lacking either of these genes did not develop larger tumors, unlike APC-model mice, when fed the same modest amounts of high-fructose corn syrup.

"This study revealed the surprising result that colorectal cancers utilize [high-fructose corn syrup](#), the major ingredient in most sugary sodas and many other processed foods, as a fuel to increase rates of [tumor](#) growth,"

Cantley said. "While many studies have correlated increased rates of colorectal cancer with diet, this study shows a direct molecular mechanism for the correlation between consumption of sugar and colorectal cancer."

"Our findings also open new possibilities for treatment," Yun said. "Unlike glucose, fructose is not essential for the survival and growth of normal cells, which suggests that therapies targeting [fructose](#) metabolism are worth exploring. Alternatively, avoiding consuming sugary drinks as much as possible instead of relying on drugs would significantly reduce the availability of sugar in the colon."

While further studies in humans are necessary, Yun and colleagues hope this research will help to raise public awareness about the potentially harmful consequences consuming sugary drinks has on human health and contribute to reducing the risk and mortality of colorectal [cancer](#) worldwide.

More information: M.D. Goncalves et al., "High-fructose corn syrup enhances intestinal tumor growth in mice," *Science* (2019). [science.sciencemag.org/cgi/doi ... 1126/science.aat8515](https://science.sciencemag.org/cgi/doi/10.1126/science.aat8515)

Provided by Baylor College of Medicine

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