

Popular artificial sweetener may negatively affect cancer immunotherapy



The artificial sweetener sucralose may be linked to reduced effectiveness in immunotherapy for treating some types of cancers. Cavan Images/Getty Images

- Non-sugar, or artificial, sweeteners are widely used to reduce the energy in sweetened foods and drinks, particularly those marketed as diet, or low or no sugar.
- However, concerns about their possible health effects include links to gastrointestinal problems, metabolic effects, and even increased cancer risk.
- Now, a study has found that one of the most widely used artificial sweeteners, sucralose, could adversely affect cancer immunotherapy.
- The researchers suggest that by changing the gut microbiome, sucralose decreases the effectiveness of immunotherapy for several cancers.

Health concerns regarding sucralose have mainly centered around its potential to cause systemic inflammation, metabolic diseases, disruptions in gut microbiota, liver damage, and toxic effects at the cellular level.

Now, a study suggests that people whose diet includes large amounts of sucralose, e.g., from diet drinks, respond less well to cancer immunotherapy than those who consume less or none of the sweetener.

The research, which is published in *Cancer Discovery*, a journal of the American Association of Cancer Research, found that sucralose changed the gut microbiota so bacteria degraded an amino acid, arginine, that immune cells need to be able to destroy cancer cells.

Why are experts worried about sucralose?

Sucralose is one of six non-sugar sweeteners approved by the Food and Drug Administration (FDA) Trusted Source for use as additives in the food and drinks industry — the others are aspartame, advantame, neotame, saccharin, and acesulfame potassium (Ace-K).

It is made by replacing 3 hydroxyl (oxygen and hydrogen) groups in sucrose (table sugar) molecules with chloride atoms.

The resulting sucralose is up to 650 times sweeter than sucrose and, because people cannot digest it, contains no accessible energy.

Therefore, it is widely used to sweeten foods and drinks, as well as being sold as an alternative to sugar for those trying to decrease their energy intake.

However, there are concerns, both about its health effects and its efficacy for helping weight loss. In 2023, the World Health Organization (WHO) Trusted Source advised that non-sugar sweeteners should not be used for weight control, saying that:

“Replacing free sugars with NSS [non-sugar sweeteners] does not help with weight control in the long term. [...] NSS are not essential dietary factors and have no nutritional value. People should reduce the sweetness of the diet altogether, starting early in life, to improve their health.”

Investigating the sucralose-cancer link

Diwakar Davar, MD, associate professor of medicine at the University of Pittsburgh and a medical oncologist and hematologist at UPMC Hillman Cancer Center, senior author of the study, told Medical News Today:

“We think this finding is highly significant as it could have immediate positive impacts on cancer patients receiving immunotherapy. The fact that we not only identified sucralose as a potential problem for those receiving immunotherapy, but that we also found a way to fix this problem through arginine supplementation is exciting and something that could be put into clinical practice easily.”

According to Jack Jacoub, MD, a board certified medical oncologist and medical director of MemorialCare Cancer Institute at Orange Coast and Saddleback Medical Centers in Orange County, CA, who was not involved in this research, the findings were significant.

“Frankly, this is a superb piece of scientific work,” Jacoub told MNT. “The authors were able to study preclinical models (mice) and draw conclusions related to the effect of high sucralose intake on T-cell function tumor response to immunotherapy.”

“They then took this understanding and later tested it in prospective enrolled patients with lung cancer and melanoma. They showed that patients consuming sucralose greater than 0.16 mg/kg/d [milligram per kilogram per day] had inferior response to immunotherapy,” he explained.

“Recognizing the significance of arginine on T cell functions they then went back to the mouse model and proved giving it restored T cell function and benefit to immunotherapy in mice. In my opinion, this is high quality evidence suggesting this absolutely needs more exploration,” added Jacoub.

Sucralose decreased immune response

In their study, the researchers included 132 patients who had undergone immunotherapy or chemoimmunotherapy for advanced/metastatic melanoma or advanced non-small cell lung cancer (NSCLC) Trusted Source. They also included 25 patients who had high-risk resectable melanoma.

All participants had completed a Diet History Questionnaire III (DHQ III), had received at least 3 months of treatment, had at least one post-treatment imaging study evaluable for response and had been followed up for at least 6 months from the start of therapy.

From the diet questionnaire, researchers calculated each patient’s non-nutritive sugar (NNS) intake (mg/day) and divided it by their weight in kg to get a weight-normalized average daily intake of mg/kg/day.

People with melanoma or non-small cell lung cancer who consumed high levels of sucralose (more than 0.16mg/kg/day) had a worse response to immunotherapy, and poorer survival rates, than those with diets low in the artificial sweetener.

Asked whether people undergoing cancer immunotherapy should try to avoid sucralose in their diets, lead author Abby Overacre, PhD, assistant professor in the Department of Immunology at the University of Pittsburgh and UPMC Hillman Cancer Center, told MNT:

“We are working on future prospective clinical trials to ask these sorts of questions for patients undergoing immunotherapy. Based on what we know so far, we would recommend that patients minimize intake of non-nutritive sweeteners, particularly sucralose.”

Jacoub agreed with this assessment, saying that: “This is enough information for me to recommend this to my patients. Frankly, we are talking about cancer and giving up diet soda, etc. is not difficult and directly goes to the question patients and their family commonly ask every day when I see them which is ‘What can I do to help treat my cancer?’.”

It is important to note that the research is still in the early stages, and this may not apply to all cancer types.

Gut microbiota changes reduced T-cell activity

The researchers then carried out tests in two mouse models of cancer to determine how high sucralose consumption reduced the immunotherapy response.

They found that mice fed sucralose were resistant to immunotherapy, had significantly increased tumor growth, less CD8+ T cell Trusted Source infiltration, and were more likely to die.

CD8+ T-cells are immune cells that produce the most powerful anti-cancer response, so their reduced function meant the immunotherapy was less effective.

In the sucralose-fed mice, the researchers discovered changes in the gut microbiota, with greater numbers of gram positive bacteria that degraded arginine, an amino acid that is essential for T-cell production.

“Gram positive bacteria have been associated with poorer immunotherapy efficacy in previous studies. However, we are very focused and interested in the function of these bacteria in hopes to better understand how they may directly contribute to cancer growth and immunotherapy response.”

— Abby Overacre, PhD

Arginine supplements may counteract sucralose’s effects

When researchers fed arginine or citrulline (which is metabolized in the body to arginine) to the mice, immunotherapy became effective again. They suggest that arginine or citrulline supplements could be given to people undergoing cancer immunotherapy to counteract the effect of sucralose in their diet.

But could people undergoing cancer immunotherapy get enough arginine from their diet?

“While there are certainly foods that are higher in arginine, especially in diets associated with better immunotherapy responses (nuts/seeds, poultry, lentils, fruits), a supplement may help those who struggle to achieve a high amount of arginine from diet alone,” Overacre told MNT.

In addition to continuing their research into sucralose and immunotherapy, the researchers hope to investigate whether other non-nutritive sweeteners have similar effects.

“We hope that this study can help patients currently receiving immunotherapy. Importantly, this gives patients something they can do themselves or alongside their physicians to potentially improve their overall care.”

— Abby Overacre, PhD

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