The high-fat, low-carbohydrate diet known as the ketogenic diet has become an established treatment for intractable epilepsy over the last decade, but it has also gained widespread popular attention as a regimen for weight loss. Attention has now moved to the diet as a possible cancer therapy. “Many cancer patients now come in and ask about diet, because of the media coverage,” says Kevin Fontaine, Professor of Health Behavior at the University of Alabama at Birmingham, in the USA. But according to oncologist Matthew Vander Heiden, director of the Koch Institute for Integrative Cancer Research at MIT (Cambridge, Massachusetts), “It is almost entirely conjecture that it is useful in cancer.” He urges the cancer community to be extremely cautious about the value of these dietary principles. So far, he says, “there is almost zero clinical evidence that this is beneficial for patients with cancer.”

In the 1920s and 1930s, doctors commonly prescribed the ketogenic diet for epilepsy in children, but the idea can be traced as far back as ancient Greece, and stems from the observation that starvation seemed to stop seizures. A low-carb, high-fat diet is thought to mimic fasting. With the advent of new anti-epilepsy drugs, the diet went out of fashion, but in the past decade it has been reintroduced for a significant proportion of patients whose epilepsy does not respond to medication.

## Principles rationale and evidence

The therapeutic ketogenic diet is an extreme version of popular low-carb diets. It requires that at least three-quarters of calorie intake should come from fats, with the remainder coming from proteins and carbohydrates. All foods have to be carefully weighed and calories calculated to make sure the ratio is correct. The idea is to reach a state of ketosis, at which point, instead of metabolising glucose, the liver metabolises fatty acids into the ketones β-hydroxybutyrate, acetoacetic acid and acetone.

The proposition that the diet might be useful in treating cancer has been raised most widely with regard to brain cancers, possibly due to its use in controlling epilepsy, which also involves the brain. “Brain, breast and colorectal cancer are probably the three where there is some interest in the ketogenic diet out there,” says Fontaine, who adds that there are also anecdotal reports that patients on a ketogenic diet undergoing cancer treatment have fewer severe side effects.

One rationale for its use comes from the fact that cancer cells are highly glycolytic – they take up more glucose than normal cells. This principle is exploited in oncology in the technique of fluorodeoxyglucose (FDG)-positron emission tomography (PET), which visualises tumours through imaging injected radioactive glucose, which will be present in higher concentrations in cancer cells.

A direct link between glucose and cancer cell proliferation was proposed in the 1920s by German physiologist Otto Warburg, who suggested that cancer cells promote growth by increasing glucose uptake. Known as the Warburg effect, he observed cancer cells undergoing a type of fermentation known as ‘aerobic glycolysis’, in which glucose is converted into lactate, even in the presence of oxygen.

> “Even on the most extreme ketogenic diet, glucose levels only fall by half, which still provides enough glucose to saturate cells”

The theory that cancer proliferation could be slowed if cancer cells were ‘starved’ of glucose developed based on this principle – and the ketogenic diet was seen as one way of doing this.

However, as Vander Heiden points out, “The thinking here is actually a bit oversimplified, and flawed. It’s very hard to starve your tumour of glucose simply by diet.” Our bodies are designed to maintain very constant glucose levels, he explains, and even on the most extreme ketogenic diet, glucose levels only fall by half, which still provides enough glucose to saturate cells.

Nevertheless, a growing body of animal studies show that the ketogenic diet can impact cancer progression. For example, a 2016 study looking at mice implanted with human-derived glioblastoma cells found that a ketogenic diet consisting of 90% fat reduced tumour progression and increased life expectancy by 50% compared to the control mice, who were given a standard 55% fat diet.

Such results have prompted small-scale trials in humans, adding a ketogenic diet to standard treatments. Currently there are at least 30 clinical trials registered on clinicaltrials.gov – most of them treating brain, breast and pancreatic cancers. The majority are taking place in the US, but at least six trials have been conducted in Europe. So far, these have been small scale and designed to test the tolerability of the diet and levels of some biochemical markers. None have yet provided any direct evidence of increased survival.

## Potential mechanisms

One factor that may better explain how the diet could be beneficial is its ability to reduce insulin levels. Insulin has a role in regulating blood glucose levels but is also a growth factor, which seems to have a role in cancer growth. “Lowering blood glucose to half means insulin levels in your body are very low, and this could be a potential benefit,” says Vander Heiden.

In 2018, Fontaine, with colleagues at the University of Alabama, looked at insulin levels in a study of the ketogenic diet in women diagnosed with ovarian or endometrial cancers. “We became interested in gynaecological cancers because it seemed like those cells were very glycolytic,” says Fontaine. In the 12-week trial, led by Professor of Nutrition Sciences Barbara Gower, 45 participants were randomised to either a ketogenic or standard recommended diet (roughly 40–60% carb, 15% protein and less than 20% fat). They found that those on the ketogenic diet had lower fasting insulin levels, and they also found a negative correlation between ketone levels and insulin growth factor 1 (IGF1), which is known to drive cancer proliferation. “Our hypothesis is this reduction in insulin is where [the ketogenic diet] could provide a favourable environment, in the sense of reducing cancer proliferation and growth,” says Fontaine.

But the trial did not find any significant reductions in another cancer marker, CA125, a protein found in greater concentration in ovarian cancer cells. Fontaine points to shortcomings in the trial design as a possible explanation for this finding. “The problem was that these women were at different stages of treatment, some of them were still undergoing chemo. So our speculation is that, although the diet had favourable effects on body fat and insulin and IGF1, the effects on cancer were just overshadowed by the fact that they were still undergoing very invasive chemotherapy.” He hopes ultimately that a large multi-centre study, starting directly after diagnosis but before the start of standard treatments, could isolate the impact of the diet alone. But as he adds, “Logistically, pulling that kind of trial off is going to be a real challenge.”

> “There are many lines of evidence that the specific metabolism of cancers varies across different cancers”

Vander Heiden agrees that controlling insulin levels may be the key, but to understand this more fully more work is needed on the relationship between cancer and metabolism. “There are many lines of evidence that the specific metabolism of cancers varies across different cancers,” says Vander Heiden. “In some cases [the ketogenic diet] maybe is beneficial, in other cases, it’s maybe not.”

## Where the ketogenic diet might play a role

One area where evidence is mounting is for its use is in improving the performance of phosphatidylinositol-3 (PI3) kinase inhibitors. These drugs were designed to inhibit insulin-activated growth factor enzymes, and in doing so limit cancer proliferation, but have so far failed to live up to expectations. “The PI3 kinase inhibitors have been a very disappointing class of drugs in the clinic… they’re not the game changing drugs many thought they would be,” says Vander Heiden. The reason seems to be that when a PI3K inhibitor blocks insulin signalling in cancer cells, it causes glucose levels to be elevated in normal cells, which in turn stimulates more insulin production from the pancreas, balancing out any initial advantage.

In 2018, Lewis Cantley at the Cornell Weil Medical School in New York, showed that PI3K inhibitors are more effective in preventing cancer proliferation in mice when combined with a ketogenic diet, to lower blood glucose levels. The diet was found to be more effective than using glucose-lowering drugs such as metformin. Cantley is now planning trials in patients with breast and endometrial cancer, leukaemia or lymphomas, using both the diet and PI3K inhibitors. It is important to note, however, that in cancer cells where growth was not linked to the PI3K pathway or insulin, the ketogenic diet had little effect, and in the case of some leukaemias, it actually caused faster progression.

Another possible role for the diet is in its ability to sensitise cancer cells to radiation. This was recently investigated by Rekha Chaudhary, an oncologist specialising in brain cancers and professor of medicine at the University of Cincinnati. She became interested in using the diet as an adjunct to the treatment of glioblastoma multiforme (GBM), the most aggressive form of primary brain tumour (grade IV astrocytoma), with a five-year survival rate of only 3%.

> “My hypothesis was that the ketogenic diet was making the cancer cells more sensitive to radiation”

Her interest had been sparked by mouse studies performed 2012, in the laboratory of neuro-oncologist Adrienne Scheck at St Joseph’s Hospital and Medical Center, Phoenix Arizona. The studies had shown that, while placing mice with malignant gliomas on a ketogenic diet increased their median survival by five days, when given with radiation, 9 out of 11 animals showed undetectable tumour signals after treatment, and no recurrences in 200 days. “The ketogenic diet seems to cause mTor inhibition [a kinase that belongs to the PI3K family], and [mTor inhibition] often leads to radiation sensitivity. So my hypothesis was that actually [the ketogenic diet] was making the cancer cells more sensitive to radiation,” says Chaudhary.

In a retrospective study of 29 patients with grades II–IV astrocytoma, patients followed a modified Atkins diet – a variant of the ketogenic diet with a 1:1 ratio of fat to protein and carbohydrate – throughout radiation and chemotherapy. Chaudhary saw some promising signs compared to the control group. Among the 19 patients diagnosed with grade IV astrocytoma (glioblastoma), she

observed increases in the extent of pseudoprogression on MRI scan in 11 (58%). This temporary increase in lesion size on MRI images often occurs after radiation therapy, prior to improvements. Chaudhary has not yet been able to analyse survival data, but she acknowledges that a much bigger study would be needed to reach conclusions, which could be difficult to do with patients suffering from these types of cancers.

## How tolerable are ketogenic-type diets?

Whilst eating almost unlimited fat may sound appealing at first glance, in reality eating fat without carbohydrates can be difficult and unappealing, says Vander Heiden. “It’s really important to point [this] out for people who are considering doing this,” he says, particularly given the current lack of clinical evidence. “If you’re facing end-stage cancer, and there’s probably no diet that’s going to cure you… I think one has to be really careful recommending some of these things to people.”

Chaudhary says she received some similar push-back, with some people asking whether it is fair to burden patients who are dying from brain tumours with an unpalatable diet. Her view is that the desire to contribute in some way to fighting the cancer outweighs issues of palatability. “I think that patients don’t care about that, they want to be able to do something.” She found her patients were able to tolerate the diet, and says their quality-of-life markers looked similar to other patients with brain cancer. “I remember, [the husband of one patient] was an engineer… and he was so happy to calculate all the carbs every day and measure the ketones… to feel like they are actively doing something.”

Fontaine’s patients also responded positively to the diet, he says, with no-one dropping out because they couldn’t tolerate it. “The biggest adjustment is actually psychological, because it’s been drilled into [patients] that eating a lot of fat is not good for you. Once they get over that barrier, it’s highly satisfying… hunger is not really an issue,” he says. People also tend to lose weight – in his study they observed a 21% loss of visceral fat in patients on the ketogenic diet, compared with 5% on the standard control diet.

He also saw reductions in lipid levels, but says that the concerns that this diet can lead to seriously high levels of LDL cholesterol are not supported by current evidence. “It’s increasingly clear that the criticism around the effects of a high-fat diet on lipids is probably not justified, certainly not supported by the preponderance of the data.”

But with a perceived reduction in the variety of foods, the diet can get monotonous, he accepts, and some patients did experience what is known as ‘keto flu’. “It’s a bit of a fatigue, that sets in usually within two to three days of starting this diet. We can manage that usually with an increase in salt intake, and magnesium seems to help… But paradoxically, once they get rolling with the diet, they often report an increase in their energy level,” says Fontaine.

## An open mind

Fontaine is a supporter of the diet on account of the health benefits it provides from weight loss and lowering of insulin levels, and he could see it becoming a permanent change for some patients: “If there is a role that this diet will play in cancer, apart from being an adjunct to traditional treatment, it may actually be more important in preventing a recurrence. I really see its value there.” He adds that any reduction in carbohydrate consumption, particularly processed foods, is probably beneficial, even if they chose not to follow a ketogenic diet (which requires the patient to be in ketosis).

Vander Heiden believes there is a clear need for more research and particularly clinical trials: “I think diet can be a powerful adjuvant to some of our therapies or some of our approaches, and

clearly patients care about this, but we need better data… the trials need to be done if we're going to really actualise this and help people." But he also cautions that we need to keep an open mind over whether the ketogenic diet or any other dietary intervention will ultimately be shown to provide a survival advantage: "People need to be open to the fact that unproven therapies might be effective, but they also might be harmful… we just have to be careful. People get, for lack of a better word, somewhat 'religious' about diet sometimes."

> Today a number of researchers are looking at cancer as a metabolic disease, rather than one driven by genomic instability

When it comes to the relationship between diet and cancer growth, our understanding is still quite limited, says Vander Heiden. "Patients ask about diet all the time, and we don't really know what to say. There is a lot of evidence of what a heart-healthy diet should be, and the heart-healthy diets are often extrapolated to be good in all cases. But again, it's not clear that this is the case."

Today a number of researchers are looking at cancer as a metabolic disease, rather than one driven by genomic instability, and Vander Heiden feels that diet will probably play a role in future cancer treatment – in some way. "In my view, in the end the dietary interventions aren't going to be as simple as just the ketogenic diet," he says, pointing, as an example, to studies suggesting that some colon cancers need the amino acid serine to proliferate, in which case a diet low in serine could be helpful.

Chaudhary is also optimistic that we will gain a better understanding of how diet impacts cancer progression, and we will be able to select from a variety of diet options for patients in the same way that we now select cancer treatments: "Eventually, we're going to come to a time where you're going to walk in and [your clinician] is going to say, for this condition, and for your family history, and for your genetics, you're going to have this diet."