

## Diet and Cancer

Cancer research history was quietly made at an American university in January.

For the first time ever, a randomized controlled trial that uses calorie restriction as a treatment for cancer — and measures a cancer-related outcome — was approved by the institutional review board at Duke University in Durham, North Carolina, and is on its way to the clinic.

"In the entire field of cancer research, there have only been a handful of studies of calorie restriction as a cancer treatment," Stephen Freedland, MD, from Duke, told Medscape Medical News. But none of them were randomized clinical trials.

In what appears to be a manifestation of zeitgeist, the approval at Duke comes when single-group studies of calorie restriction as a cancer treatment are being planned (in breast cancer at Thomas Jefferson University in Philadelphia, Pennsylvania) or are underway (in pancreatic and lung cancer at the University of Iowa in Ames).

Such clinical trials should be seen in a larger research context, explained an expert.

"During the past 10 years or so, interest in the metabolism of cancer cells has seen a dramatic increase, which is surely why interest in dietary interventions...has increased," said Rainer Klement, MD, a radiation oncologist at the University Hospital of Würzburg in Germany.

"The time is definitely ripe to test the various ways of altering cancer patients' metabolism — be it through physical exercise, ketogenic diets, fasting, or calorie restriction. The combination of these lifestyle interventions with the standards of care seems very promising to me," he wrote in an email to Medscape Medical News.

In 2011, Dr. Klement and a colleague published a review of the possible role of carbohydrate restriction in the treatment and prevention of cancer (*Nutr Metab.* 2011;8:75).

The hypothesis that suppressing carbohydrates could suppress or slow cancer growth is supported by a lot of laboratory science. The pair explain that complex carbohydrates are ultimately digested as glucose, which can cause tumor cells to proliferate.

"First, contrary to normal cells, most malignant cells depend on steady glucose availability in the blood for their energy and biomass-generating demands, and are not able to metabolize significant amounts of fatty acids or ketone bodies due to mitochondrial dysfunction," they write. In other words, cancer cells thrive on glucose and starve on fats and ketones, which are food-derived energy units that are plentiful in low-carbohydrate diets.

The commonplace advice to avoid dietary fat is not a good recommendation to give cancer patients. "They should eat a lot of fat and avoid sugar," Dr. Freedland noted.

The Duke study will involve calorie restriction in men with prostate cancer — specifically, cutting down on carbohydrates. The participants will have "failed" primary therapy for prostate cancer, as evidenced by a rising prostate-specific antigen (PSA) score after surgery, and will have experienced disease progression.

"No treatments have been shown to slow prostate cancer progression after radical prostatectomy. We hypothesize that a carbohydrate-restricted diet will slow prostate cancer growth," the Duke researchers write in their trial description.

A projected 60 men will be randomized to either a low-carbohydrate diet (<20 g/day) or usual care. The outcome measure is PSA doubling time or change in PSA over the 6-month study period. The value of PSA in diagnosing prostate cancer is dubious, but in the treatment of men with diagnosed disease it is a well-established measure of disease progression and stabilization.

The Duke study, which is not yet enrolling patients and has a projected end date of 2016, is funded by the National Cancer Institute and the Atkins Foundation, which is a philanthropic outgrowth of the famed Atkins diet enterprise. The study will employ an "Atkinsesque" diet, said Dr. Freedland, which means carbohydrates are severely limited.

#### Calorie Restriction Along With Standard Treatment

The planned trial at Jefferson will employ a different calorie-restriction strategy, according to Nicole Simone, MD, a radiation oncologist.

"I have designed a clinical trial that will open at Thomas Jefferson University in the next few weeks. Early-stage breast cancer patients will undergo caloric restriction concurrent with radiation," she told Medscape Medical News in an email.

In this case, the calorie restriction, which includes fasting, is expected to have a synergistic effect with an established treatment, explained Dr. Simone.

"We hypothesize that caloric restriction may augment the effect of cytotoxic targeted therapies in breast cancer, such as radiation, through an IGF-1R pathway-mediated mechanism," she and her colleagues write in their project proposal.

They expand on just how calorie restriction might prime these breast tumor cells for destruction in a review published in the January issue of the *Oncologist*.

The Jefferson trial design calls for stage 0 and I breast cancer patients who are candidates for breast-conserving therapy to consume a liquid diet 36 hours prior to definitive surgery, and then a diet with a 25% calorie reduction during radiation therapy. Calorie restriction will start the week of radiation planning and continue for the 6 weeks of radiation, for a total of 10 weeks.

The primary end point of this feasibility study, which has the winning name of CAREFOR (Caloric Restriction for Oncology Research), will be acute toxicity. The secondary end points include progression-free and overall survival. If the combination of radiation plus calorie restriction does not add toxicity — Dr. Simone believes it might actually reduce it — the researchers hope to eventually conduct a national multicenter study.

The Jefferson study shares some similarities with research being conducted at the University of Iowa, in which calorie restriction (a ketogenic diet consisting of high fat, adequate protein, low carbohydrates) is being administered at the same time as chemoradiation in separate trials of pancreatic cancer and lung cancer. The phase I trials aim to determine the safety and early efficacy of dietary manipulation during traditional therapy. "Preclinical data from mouse studies indicates a ketogenic diet increases tumor cell killing," write the Iowa researchers in their project descriptions.

The trials are sponsored by the National Cancer Institute, the University of Iowa, and Nutricia North America, and will use the latter's branded ketogenic diet in combination with standard therapy as the intervention.

#### Other Evidence

Extensive research suggests that restricting calories will improve cancer outcomes, according to Dr. Simone and colleagues. More than 100 years ago, lab research first indicated that mice fed a calorie-restricted diet had "significantly slower" tumor growth than those fed their regular diet, they write.

Human data are also suggestive. Dr. Simone and colleagues explain that "multiple population-based studies of underweight patients have revealed a significantly lower cancer incidence than in the general population."

Furthermore, obesity can lead to a higher risk for cancer, and prospective studies have demonstrated an association between obesity and cancer-specific mortality in multiple sites, they note.

The relation between insulin metabolism, obesity, exercise, and cancer has led to a recent surge of interest in dietary intervention during cancer treatment. "This is exemplified with newer trials, such as the National Cancer Institute of Canada MA.32 trial, which is treating early-stage breast cancer patients with standard therapy and randomizes them to placebo or metformin, which affects several metabolic pathways," write Dr. Simone and colleagues.

Although a lot of research is underway or about to be underway, Dr. Simone still has evidence-based advice to share with her breast cancer patients.

"I discuss decreasing weight with all of my breast cancer patients. From recent literature, we know that most breast cancer patients gain weight during cancer treatment, and this has been linked to worse outcomes," she said.

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