Published in final edited form as:
Nutrition. 2012 October ; 28(10): 1036. doi:10.1016/j.nut.2012.07.004.

Sugar free, cancer free?

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The impact of diet on the prevention and treatment of cancer is an important area of investigation and the differential effects of caloric source—carbohydrates, protein, or fat—has been an area of particular interest. Carbohydrates provide energy but, unlike proteins and fat, also stimulate insulin signals that can be potent mitogens.

Epidemiologic studies have identified associations between diet and serum levels of insulin with cancer incidence and cancer-related morbidity in humans. Obesity increases the risk for certain types of cancers and diabetic patients treated with insulin have an increased risk of developing cancers, relative to those treated with metformin [1,2]. Experiments performed with cell culture and mouse cancer models have shown causal relations among carbohydrate availability, insulin stimulation, and cancer growth [3]. It is tempting to infer that these well-studied insulin-signaling pathways underlie these clinical observations and interventional studies to explore this are underway (www.clinicaltrials.gov). However, the causal relationship of insulin to cancer development and progression in patients is not fully established.

In a recent issue of *Nutrition*, Fine et al. [4] described a pilot study that lays the groundwork for testing the hypothesis that a carbohydrate-restricted diet will slow cancer growth in patients by decreasing the secretion and circulating levels of insulin. This was a small study but has some notable results. First, the dietary restriction of carbohydrates to less than 10% of total calorie intake is feasible in a population of patients with cancer for at least 4 wk. Importantly, the expected physiologic effect of the diet was demonstrated in participants by measuring β-hydroxybutyrate, a marker of ketosis. Second, there were no toxicities that required patients to be removed from the study, although fatigue (defined as tiredness that is not relieved with rest and that limits daily activities) was noted in half the study participants, and all participants lost weight despite the intent of a calorie-neutral diet. Third, and perhaps most intriguing, an association between the degree of ketosis and ^{18}F-2-fluoro-2-deoxyglucose tumor uptake as measured by positron emission tomography (PET) was observed. The patients who had PET progression at 1 mo had a significantly lower relative increase of β-hydroxybutyrate compared with those who had disease that was stable or responsive by PET. The PET response is defined by a decreased ^{18}F-2-fluoro-2-deoxyglucose uptake and not of tumor shrinkage and it should be noted that this does not reflect clinical benefit. However, this result is proof of concept that tumor glucose uptake can be stabilized and occasionally decreased with a carbohydrate-restricted diet.

There are many avenues of investigation to explore from the results of this study. Is this diet safe for extended periods in patients with cancer? Can it be combined safely with other cancer therapeutics? Will PET stable and responsive disease translate into clinical benefit? If so, can we prospectively identify these patients with biomarkers such as tumor insulin receptor expression? Insulin growth factor-1 and -2 levels were not consistently altered in

this study, although it would have been useful to quantify serum levels of insulin growth factor binding proteins which act to suppress the function of these mitogens. How will diet-induced suppression of insulin levels differ from treatment with metformin or other pharmacologic agents that decrease insulin production or inhibit the insulin receptor? Will tumors with activating mutations in proteins that are downstream of insulin signals such as phosphoinositide 3-kinase (PI3K) fail to respond? Building on this well-designed clinical experiment should help us to better understand the impact of dietary changes on cancer growth and guide us to more effective treatment and prevention strategies.

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