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Mini Review

The Sugar-Cancer Connection Revisited: Aren't Obesity, Cardiovascular And Metabolic Disorders, The Main Problems?

Pierre A Guertin*

Department of Psychiatry and Neurosciences, Laval University, Laval University Medical Center, Canada

***Corresponding author**
Pierre A Guertin, Department of Psychiatry and Neurosciences, Laval University, Laval University Medical Center, Quebec City, Quebec, Canada, Email: pierre.guertin@crchudequebec.ulaval.ca

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Abstract

Blood sugar had been proposed a long time ago to promote cancer. Since then, several studies were undertaken to either disprove or confirm that potential causal relationship. Among all forms of sugars - e.g., glucose, carbohydrates, fructose, maltose -, none was shown to increase directly or specifically the risks of cancer. Moreover, a reduction of glucose intake failed to prevent or reduce tumor cell activity. This said, all cells including cancer cells need sugar or more specifically glucose as fuel for their intrinsic cellular metabolism. One thing is clear about sugar or glucose - eating a lot of it generally leads to overstimulation of insulin, insulin growth factor (IGF), and overweight problems. In other words, as of today, scientists have failed to confirm a direct link between sugar and cancer, although an indirect link was found between cancer and all sources of energy such as lipids, proteins, alcohol, and sugar or glucose -i.e., when steadily taken in excess, all forms of energy lead generally to insulin problems, obesity, and type II diabetes which are, in turn, conditions well-known to enhance the risks of several types of cancer.

The main source of energy is sugar - what is it and what does it do?

Sugar, also known as carbohydrate or saccharide, is a water-soluble biomolecule composed of carbon, hydrogen, and oxygen ($C_nH_{2n}O_n$) that comes in many forms - the simplest form molecularly, monosaccharide, includes molecules such as glucose, dextrose, fructose, levulose, ribose, xylose, and galactose. Monosaccharides can also bound as more complex structures - i.e. disaccharides such as sucrose (table sugar or saccharose), lactose, maltose, lactulose, trehalose, cellobiose, and honey as well as polysaccharides such as cellulose, starch, and glycogen.

Monosaccharides have many functions in the body. First and foremost, they are the main source of fuel used to produce energy by each and every single cell of the body (e.g., cells from the brain, heart, and lungs or pathological cells like tumors) - i.e., glucose is 'burnt' in the cytoplasm by mitochondria using glycolysis processes in order to obtain Adenosine Triphosphate (ATP), the ultimate form of energy or energy carrier used per se by living cells. Most cells, under normal conditions, use aerobic glycolysis (a.k.a., aerobic respiration), a metabolic mechanism involving oxygen to get ATP. Cells 'burn' or break down glucose into pyruvate, and obtain in turn ATP, water, and a by-product, carbon dioxide. This said, cellular respiration can also occur in some circumstances without oxygen or anaerobically (see details, below).

Disaccharides (water-soluble) and polysaccharides (insoluble) can also be used to get energy. They are either broken down or hydrolyzed to get glucose and hence ATP or used as building blocks for cellular structure (e.g., starch or cellulose for the cell walls of plants or heterosaccharides for the skin and other connective tissues). They can also be stored to build reserves or stocks of energy (e.g., glycogen made by the liver and muscles to be stocked in them).

When energy demands exceed what can be produced by aerobic glycolysis alone - such as in rapidly contracting skeletal muscle cells during sprinting -, anaerobic glycolysis (i.e., without oxidative phosphorylation) is used instead for a faster production of ATP. On the other hand, when energy demands are low, less intense, and long-lasting - e.g., muscle contraction during jogging -, aerobic processes are used for long-lasting production of ATP. Along the same idea, when there is not enough oxygen for the required need of energy, cells will also choose anaerobic glycolysis (a.k.a., anaerobic respiration) and break down glucose into pyruvate to get ATP and lactic acid as a waste product instead of carbon dioxide.

In some conditions, proteins can also be converted into glucose or triglycerides for supply or energy storage (Merck Manual Home Health Handbook) and lipids such as cholesterol and triglycerides can be metabolized to form glycerol. In turn, glucose can also be transformed into fatty acids, triglycerides, cholesterol, and steroids. In other words, despite levels of stored glycogen or types of ingested food, the body will end up generating glucose to fulfill every cell needs for ATP. If carbohydrates are lacking or no longer being ingested (e.g., a low-carbohydrate 'ketogenic' diet), the liver will indeed generate ketones, a byproduct of lipid breakdown, as well as glucose to meet the demands and to make sure that blood sugar levels remain stable [1].

The origins : The Warburg Hypothesis and Popular Misconceptions

Cancer cells are well-known to be associated with an enhanced rate of glycolysis during periods of fast growth - this phenomenon has been called the Warburg Effect or Warburg Hypothesis. It has indeed been discovered by Otto Warburg who confusingly associated it with aerobic glycolysis. In fact, cancer cells consume more glucose than normal cells. However, they secrete lactic acid (normally associated with lactic fermentation and anaerobic glycolysis rather than aerobic glycolysis) instead of breaking it down completely into carbon dioxide.

In other words, cancer cells produce more lactate than non cancer cells and hence rely more on anaerobic glycolysis and fermentation than on oxygen and oxidative phosphorylation. Since fermentation of glucose produces only 2 ATP per glucose while oxidative phosphorylation produces 36 ATP per molecule of glucose, cancer cells consume more glucose to maintain their pool of ATP. This is based on Warburg's findings made nearly a century ago when discovering that tumor cells growing *in vitro* (i.e., in a petri dish) consume far more glucose than normal cells or non-dividing cells [2,3]. When grown in culture with 13 mM glucose, cancer cells produced indeed a 70-fold increase in lactate accumulation - the byproduct normally associated with anaerobic glycolysis, as mentioned earlier. Higher lactate levels was interpreted as evidence that tumor cells possess dysfunctional mitochondria forcing them to use abnormally anaerobic glycolysis for energy. His finding let some people to believe that sugar is the root of all cancers and that eating more sugar meant stimulation of cancer. However, since then, the theory has been significantly challenged and popular misconceptions have been explained. No statistically significant clinical data in humans has proven the Warburg hypothesis in real life conditions [4] but some findings in animal models kept suggesting the existence of a link, at least indirectly [5].

Evidences Against The Warburg Hypothesis: Tumor Cells Feed on Everything and Most Sources of Energy Can Be Metabolized to Glucose for ATP Production

Firstly, as explained above, simple or complex carbohydrates as well as lipids and proteins can be used by cells to get energy - to achieve that, they are metabolized to form glucose (and ketones, in some conditions) for ATP production. In other words, a person may eat exclusively proteins, his or her cells will nonetheless get the needed glucose to remain alive and functional. Indeed, because the body has this fail-safe system that never lets your blood glucose level go down below a critical level, eating less sugar will just make the body use its other resources, that is lipids and proteins, to produce glucose [6].

Secondly, using modern molecular biology and state-of-the-art genetic techniques, several studies have clearly demonstrated that mitochondria work normally in cancer cells [7,8]. In fact, the concept of abnormal aerobic glycolysis as the paradigm of tumor cell metabolism is untrue since some tumor cells (e.g., glioma, hepatoma, and breast cancer lines) exhibit high rates of oxidative phosphorylation [9]. Some cancer cells can even reversibly switch between fermentation and oxidative phosphorylation, depending on glucose levels, either high or low, and specific cellular conditions [10]. In other words, it is true that sugar feeds every cell of the body- even every cancer cells. But, recent findings have clearly contributed to establish that eating sugar doesn't lead *per se* directly nor specifically to cancer. This said, eating habits or health problems that are associated with an overstimulation of IGF-1 production is generally recognized to be carcinogenic (e.g., colorectal cancer, prostate cancer, breast cancer, 11).

Thirdly, as pointed out by Dr Darren Saunders, an Australian researcher and expert in cancer biology, 'It's actually not the sugar that's evil, it's the volume in which it's eaten and that link to obesity' (www.abc.net.au). In fact, a large epidemiology study with 435,674 participants revealed nearly 10 years ago that no direct association can be established between total sugar ingested and risks of cancer [12]. However, overeating and excessive caloric intake was clearly been associated with several types of cancer - e.g., breast cancer [13]. In fact, the US CDC officially reports that up to 40% of all cancers in the US may be associated with overweight and obesity (cdc.gov/media/releases/2017/p1003-vs-cancer-obesity.html). Among them, there is breast cancer, colon cancer, endometrial cancer, esophageal cancer, gallbladder cancer, kidney cancer, liver cancer, meningioma, multiple myeloma, ovarian cancer, pancreatic cancer, stomach cancer, and thyroid cancer. Accordingly, excessive ingestion of lipids and proteins (e.g., meat) should also be avoided to reduce cancerogenic problems [14,15].

How To Break The Links Between Dietary Problems, Fat Storage, and Cancer

It is correct to say that eating excessive amounts of sugar may result in weight gain. In fact, abundance of all forms of sugar in our diet is one of the main reasons underlying the epidemic of obesity that we know today (www.cdc.gov/nutrition; [16]. As mentioned above, being overweight or obese puts people at a higher risk for cancer among many other life-threatening diseases.

Several methods may be used to reduce dietary problems and risks of cancer. Among them, increasing consciousness levels (often referred to 'mindfulness' or 'relative consciousness', [17-19] may constitute a promising alternative avenue against obesity, bad dietary choices, and cancer. Different techniques such as vagal nerve stimulation, Mindfulness Based Cognitive Therapy, MBSR, transcendantal meditation, and others, already used therapeutically, were shown to elicit multiple benefits on health (e.g., enhancement of attention or memory, reduction of depression, brain size and function, healthy aging and longevity, stress reduction, reduction of cardiovascular risks, and maintenance of normal blood pressure, [20-34]. If better eating habits are possible though increased awareness, then the role of weight problems in cancer shall be significantly reduced by regularly practicing meditative techniques (www.cancer.org/about-cancer; [35-41].

Obviously, increasing education level about food, its constitutive elements, and the effects on hormonal regulation (e.g., GH, IGF, and insulin regulation) would be imperative for reducing the risks of cancer [42-44]. As importantly, the role of regular exercise on health should be explained to the general public in schools and elsewhere. The long-term consequences on health degradation and system/organ dysregulations of physical inactivity and a sedentary lifestyle are indeed undisputable. In able-bodied persons, walking daily more than 30 minutes is generally recognized as the threshold level for preventing life-threatening complications. However, for disabled and particularly for wheelchair-bound persons - e.g., with a severe spinal cord injury -, the threshold for preventing polymorbidities, systemic dysregulations, and overmedication problems remains unclear and is currently being explored [45]. Yet, according to the American Cancer Society, regular exercise could lead to a reduced incidence of several cancers (i.e., most of those already shown to be affected by overweight problems). In fact, an epidemiology study with 1,44 million participants clearly revealed in 2016 that at least 13 different types of cancer are associated with lower risks in physically active people [46].

Take-home message and concluding remarks

Several simple things can easily be implemented to reduce the risks of cancer - 1) avoid excessive calorie intake and too many carbohydrates, especially refined carbohydrates that lack fiber and other foods with added sugars, 2) maintain a balanced diet and avoid excessive ingestion of lipids and proteins, 3) keep body weight down through regular physical activity, and 4) increase awareness about life in general and about the importance of food and exercise more specifically.

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