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A Low Carbohydrate, High Protein Diet May Extend Your Life and Reduce Your Chances of Getting Cancer

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When glucose in our blood enters our cells, it is broken down via glycolysis to pyruvate. Pyruvate can then be converted into lactic acid and secreted, ending glycolysis, or into acetyl–CoA and broken down, with the help of oxygen (O_2), within mitochondria to carbon dioxide (CO_2) and water via oxidative phosphorylation (OXPHOS, i.e., the Kreb's, Citric acid, or tricarboxylic acid cycle).[1] In 1857, Louis Pasteur discovered that in the absence of O_2, normal cells survive by switching from OXPHOS, which generates 36 ATPs/glucose, to glycolysis, which only generates 2 ATPs/glucose. In the 1920s, Otto Warburg found that cancer (CA) cells, unlike normal cells, use glycolysis instead of OXPHOS even when O_2 is present, and this type of metabolism is called aerobic glycolysis or the Warburg effect.[1] Because most tumours use this less efficient energy generating system, they have to take up more blood glucose (BG) than normal cells to survive. This characteristic is the basis for identifying human CAs using PET scans with 18-fluorodeoxyglucose, a glucose analog.[2]

Importantly, every normal cell in our body is within 0.1 mm from a capillary, corresponding to the diffusion limit of O_2.[1] Thus, normal cells are no more than a few cell layers away from O_2 and nutrients.[3] However, glucose can diffuse slightly further than O_2, so when tumours grow beyond 0.1 mm, they can still acquire glucose and switch from OXPHOS to glycolysis by activating the transcription factor hypoxia inducible factor 1 (HIF1), which regulates over 70 different genes.[3] Amongst the genes turned on are cell surface glucose transporters (to increase glucose uptake), angiogenic factors (to induce the formation of new blood vessels), and enzymes (to enhance glycolysis and inhibit OXPHOS).[4,5] But why do CA cells still use glycolysis when O_2 is present? The answer is that many oncogenes, as well as inactivated tumour suppressors, activate HIF1.[4,6-8]

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Given that glycolysis is an inefficient producer of ATP, what advantage do CA cells have in using glycolysis when O_2 is present? The advantage appears to be that, in the presence of an adequate supply of glucose, glycolysis is preferred because it generates ATP faster than OXPHOS,[7] and instead of catabolizing the carbon chains completely to CO_2 for ATP production, it makes them available as building blocks for the synthesis of DNA and RNA, protein, and lipids, all of which are essential for proliferation.[5,9,10] As well, glycolysis generates NADPH via the pentose phosphate pathway, which increases glutathione, an important intracellular reducing agent that prevents reactive oxygen species (ROS)–induced cell death.[11] So, as long as CA cells can get enough glucose, they will maintain a high glycolytic rate because it allows for very rapid proliferation and survival. Also, enhanced glycolysis leads to high levels of lactic acid in the extracellular milieu. This increase in lactic acid can significantly decrease the extracellular pH, especially because poor blood supply to tumours results in sluggish lactic acid removal. This drop in pH is toxic to normal cells, producing space for the tumour cells to proliferate. Tumour cells are unharmed because they evolve resistance to this acid by, for example, inactivating the tumour suppressor p53.[12] Extracellular acid also facilitates metastasis by promoting the breakdown of extracellular matrix and basement membrane, and inhibiting tumour–killing immune responses.[10] Because metastasis is the major cause of mortality from CA, targeting glycolysis may prove very useful.[12]

Because most tumours are highly dependent on glucose for proliferation and survival, while most normal cells are less so because they can use alternate carbon sources like amino acids and fatty acids to drive OXPHOS,[13] we asked if we could lower BG sufficiently, through diet changes alone, to slow or prevent tumour growth.

Our typical Western diet contains 50-60 % (% kcal) carbohydrate (CHO), 10-15 % protein and 30 % fat. This level of CHO can raise our BG levels after a meal into ranges that can lead to advanced glycation end products (AGE). These are a heterogeneous group of sugar–modified proteins that bind to AGE receptors (RAGE) on immune, endothelial, epithelial, and central nervous system cells, leading to oxidative stress, blood vessel damage and subsequent chronic inflammation, and promote CA and other inflammation–based diseases.[14] As well, high BG leads to high blood insulin (a hormone, secreted by the pancreas, that promotes the storage of blood glucose in the form of glycogen in the liver and fat in adipose cells) and insulin-like growth factor 1 (IGF-1) levels, both of which have been linked to a shortened lifespan, obesity, and increased risk of CA.[11,15-20]

While reducing CHO appears beneficial for reducing the growth rate of CA cells, either fat or protein must be increased to maintain an isocaloric diet. Because high fat appears to be detrimental,[21,22] we opted to increase protein instead. Interestingly, protein leads to more rapid satiety than fats or CHOs,[23] and so it lowers the risk of obesity and thus inflammation and CA. In fact, weight loss may be the most positive variable in CA prevention and progression.[15,24] As well, there is evidence that certain amino acids, like arginine and tryptophan, skew the immune system to a CA–fighting phenotype[25,29] and can slow CA growth.[30,31] A high protein diet also provides amino acids that can be converted to glucose to ensure BG levels do not fall below 50 % (which can lead to loss of consciousness) on a low CHO diet. On the other hand, there is evidence that ingesting higher than 35 % protein may lead to renal insufficiency,[14] liver damage, osteoporosis, and prostate and colorectal CAs.[27,32,33] Some of this damage, however, appears to be linked to pre–existing kidney conditions or due to the consumption of red and processed meats,[33] which can be avoided. Moreover, such damage can be further mitigated by the consumption of low CHO or high amylose–containing starch (i.e., resistant starch), which reduces colonic DNA damage induced by diets high in red meat.[34]

> **Avoid regular, sugar–based pops, fruit juices and foods with a high glycemic index.**

> **High carbohydrate diets lead to obesity and an increased cancer risk.**

We first compared the growth rate of mouse or human tumour cells subcutaneously injected into mice on Western or low CHO diets (i.g., 15 % CHO, 58 % protein, 26 % fat), hypothesizing that if we could reduce BG levels, we might force CA cells to die or resort to OXPHOS to survive. A switch to OXPHOS should reduce lactic acid production, which should both increase immune responses to kill tumours and reduce tumour invasiveness, angiogenesis, and metastasis. As expected, we found our low CHO diets resulted in lower BG and insulin levels and, importantly, slower growth rates for both murine and human carcinomas.[35]

We then embarked on synergy studies with a number of known chemotherapeutic agents and found that the combination of our 15 % CHO diet with the cyclooxygenase-2 (Cox-2) inhibitor celecoxib (Celebrex) dramatically reduced the rate of tumour growth, with negligible effects on mouse weights.[35] In relation to this finding, it has been shown that Cox-2 is overexpressed in many human CAs and that Cox inhibitors block tumour–induced angiogenesis[36] and may be beneficial in preventing or slowing colon, breast,[37] and prostate CAs.[38-40]

We then asked if our 15 % CHO diet (without celecoxib [Celebrex]) was safe and efficacious in long term studies using a spontaneous mouse mammary tumour model that mimics human breast CA.[41] These studies revealed that the mice in the 15 % CHO diet group did not gain weight as they aged, unlike the fat–laden mice on the Western diet. This finding is important because, as mentioned earlier, obesity leads to chronic inflammation and thus increases the incidence of CA. At one year of age, almost half the mice on the Western, but none on the low CHO diet, developed tumours. As well, seven out of the ten mice on the Western diet developed tumours over their lifetime, with only one reaching the normal lifespan for this mouse strain.[35] Meanwhile, only three out of the 11 mice on the 15 % CHO diet developed tumours, and more than half reached or exceeded their normal life expectancy.[35] Of

note, the kidneys in the old mice on the 15 % CHO diet appeared to be functioning normally, as assessed by a lack of protein in their urine, in spite of their high protein diet.[42]

Based on our results, as well as epidemiological studies suggesting that high CHO diets lead to obesity and an increased CA risk in humans,[19,20] we recommend diets containing 15-20 % CHO (preferably high in fibre), 40 % protein (preferably not high in red meat), and 40 % fat (preferably high in omega–3 fatty acids and no trans fat) for adult men and women, but not for growing children and pregnant mothers who require higher levels of BG, insulin, and IGF-1.

Specifically, one should avoid regular, sugar–based pops, fruit juices, and foods with a high glycemic index (GI) such as white rice, white bread, and potatoes. Instead, aspartame or sucralose sweetened drinks, whole fruits whose fibre content slows the digestion of CHOs, and whole grain products should be incorporated into the diet. Lastly, the GI of a meal can be lowered by 30 % with the addition of four teaspoons of vinegar or lemon juice: however, to protect tooth enamel, rinse mouth with water after the meal. With simple solutions such as these, we can maintain our health and quality of life.

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