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An Evolutionary and Mechanistic Perspective on Dietary Carbohydrate Restriction in Cancer Prevention

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An Evolutionary and Mechanistic Perspective on Dietary Carbohydrate Restriction in Cancer Prevention

Abstract
The confluence of basic cell biochemistry, epidemiological and anthropologic evidence points to high dietary carbohydrate and the associated disruption of the glucose-insulin axis as causes of the current increase in metabolic disorders, metabolic syndrome, hypertension and cardiovascular disease. This hyperinsulinemic state likely contributes, as well, to an increased mutagenic microenvironment, with increased risk for cancer. This critical review discusses these risks in their historical and evolutionary context. The evidence supports the benefits of lowering the glycemic load of the diet as a preventive measure against the development of cancer.

Keywords
carbohydrate restriction, calorie restriction, cancer, cancer prevention, evolution, ketogenic diet, nutrtional environment

This perspective is available in Journal of Evolution and Health: http://jevohealth.com/journal/vol1/iss1/15

Editor's note:

Dear Journal of Evolution and Health Reader,

Prior to 1944, the entire scientific community "knew" that proteins had to be the units of heredity. No other macromolecule could possibly be responsible for the enormous diversity of expression in life. Certainly, DNA couldn't have been responsible. After all, there were only four bases! Even the word, protein, was designated to mean "primary."

However, three men, Oswald Avery, Colin MacLeod, and Maclyn McCarty, published a paper in February 1944 in the Journal of Experimental Medicine that clearly demonstrated that the entire scientific community was simply wrong: DNA was the "transforming" genetic material, not protein. Consequently, this landmark paper drove the race for the discovery of the structure of DNA and spurred the discovery of the mechanisms that underlie heredity, cell expression and evolution.

Similarly, this paper presents an alternate hypothesis that is in contrast to the conventional wisdom of cancer mechanisms and therapies. As such, the reader should be aware that some of the literature the author's used for references were speculative in nature. Caloric restriction and carbohydrate restriction are not the same yet are difficult to separate in the literature. Therefore, keep a healthy skepticism as you read. Indeed, the word "Perspective" in the title demonstrates that the authors are themselves aware that the article needs to be tested for its validity!

An evolutionary basis for cancer mechanisms is a unique perspective not seen elsewhere. It is the Journal of Evolution and Health's hope that the article will result in further testing of this interesting hypothesis.

Sincerely,

David C Pendergrass, PhD

Editor-in-Chief

INTRODUCTION

The multiple genetic changes [1,2] that characterize the cancerous state limit the ability to target isolated molecular pathways. At the same time, diet as an effective treatment, widely and often enthusiastically held in popular and social media, holds limited influence in medicine, at least as a sole treatment. In practice, diet is considered an option which usually fails and therefore must be subservient to pharmacology. Nutrition as cancer prevention may, however, be better received.

Calorie restriction (CR) as cancer prevention was proposed and tested in animal models more than 55 years ago [3-5]. Studies of CR in humans have generally addressed cancer treatment [6–9] but, most recently, carbohydrate-restricted diets, ketogenic diets, and so-called paleo diets which have *de facto* reduction of carbohydrate (CHO) as a common feature, have shown much promise for prevention [10]. It is understood, however that the discussion has outstripped both understanding of underlying mechanisms and the limited experimental support [11]. In this critical review, we provide background and recent results supporting the interest in CHO restriction in cancer prevention.

RATIONALE

The rationale for diets based on limiting CHOs and/or generating a ketogenic environment derives first, from our evolutionary past which provided greater variation in the availability of total nutritional sources. However, even in times of plenty, our ancestors had limited access to dietary sugar or purified starch, a circumstance made worse during times of intermittent starvation, quite likely during the ice ages in northern Europe or on the Asian Steppes [12.] The evolutionary pressure for maintaining physiologic stability under extremes of dietary deprivation is evident.

Total caloric restriction has shown efficacy in the treatment of cancers in animal models [7,13,14] but the studies raise questions of the extent to which outcomes are due to *de facto* limitation of CHO. If CHO is 70% of total calories, for example, calorie restriction is primarily CHO restriction

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and will be associated with the changes in the insulin and/or ketosis that may accompany CHO deprivation. While there are numerous intracellular control mechanisms, the insulin-glucose axis exerts a predominant effect and provides a stimulus for excessive growth and mutagenesis [15] as well as support for excessive biomass production required during the progression of cancer [16]. The hyperinsulinemic/hyperglycemic state also may appear as increased mitochondrial reactive oxygen species which, in turn, are likely to have a mutagenic effect [17–19]. Reduced insulin signaling, therefore, is expected to have beneficial effects in tumor suppression and is not excluded as the effect of total caloric restriction.

Support for the importance of insulin signaling comes from epidemiologic associations between several types of cancers and obesity, hyperinsulinemia, and hyperglycemia. In studies of intracellular signaling pathways, insulin is consistently found to modulate tumorigenesis [20]. Reduction in insulin signaling may also provide a parallel approach to cancer inhibition *via* the systemic effects of ketosis which develops only under low systemic insulin levels. KBs in cell culture studies have been demonstrated to act as metabolic inhibitors of glycolytic ATP production and cell growth in several cancer lines [21,22] and also have demonstrable action as signaling molecules with broad cancer inhibiting effects [23–25].

EPIDEMIOLOGIC ASSOCIATIONS OF CANCER, OBESITY, AND DIABETES

Historically, obesity as a major health problem is recent. It can be argued that excessive, cheap sources of CHO, coupled with the recommendations by health agencies to consume high carbohydrate diets, have contributed to hyperinsulinemia and accompanying widespread metabolic syndrome, obesity, type 2 diabetes and lipid disorders. (The U.S. Department of Agriculture, the American Diabetes Association, and the American Heart Association have advised consuming CHOs at about 55-70% of total caloric intake until recently, now revised slightly downward).

However, obesity, hyperglycemia, and hyperinsulinemia have now also been associated with an increased risk of a variety of cancers [26–31]. Obesity has even surpassed smoking as the greatest behavioral risk factor for cancers in the U.S. Multiple studies have now established CHO restriction as an effective, if not superior, way to treat obesity and type 2 diabetes [32–38].

Obesity leads to several physiologic states that accommodate cancer induction and growth. Excess adipose tissue behaves as an endocrine organ, secreting inflammatory factors and hormones that create a hospitable environment for malignant cells both locally and systemically. Adipose cells secrete tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6), and both are inflammatory mediators that have been shown to promote cancer progression through activation of pro-malignant pathways, including PI3-K/Akt, MAPK, and nuclear factor-kappa β [39,40]. The inflammatory state produced by adipose tissue can increase cellular proliferation, tumor survival, and metastases [41]. Systemically, the increase in inflammation can blunt the normal immune response to cancer cells while released cytokines up-regulate fibroblasts, vascular endothelial cells, and macrophages in the extracellular matrix [42]. Finally, high level of C-reactive protein (CRP), another marker of adipose tissue-derived inflammation, is predictive for poor survival in patients with metastatic cancer [43].

The global effect of excess adipose tissue also inhibits the body's ability to effectively modulate insulin and glucose levels. Obesity is accompanied by decreased insulin sensitivity, insulin resistance, and corresponding elevated levels of insulin and serum glucose [44]. Obese individuals also experience a parallel increase in insulin-like growth factor 1 (IGF-1) [45]. As data reveal that cancer cells exhibit increased glucose consumption, [46] it is not surprising that this metabolic state corresponds with poor outcomes in cancer patients [47–50]. Elevated serum glucose and corresponding elevated levels of insulin and IGF-1 provide both stimulus and sustenance for tumor proliferation, and altered glucose metabolism predisposes patients to metabolic dysregulation, favoring a malignant phenotype [16,51], as well as stimulating cellular proliferation while providing cancer cells protection from apoptosis [50,52].

Along these lines, residents of mainland Japan, who consume a more Western diet consisting of an abundance of food experience significantly higher rates of cancer and shorter life span when compared to residents of Okinawa [53]. Furthermore, the Mongolian population has an extraordinarily low incidence of breast cancer even compared to other Asian countries which is particularly interesting given their almost exclusive reliance on red meat and dairy products for energy intake [54]. Also of interest, while data are mixed, some studies in anorexic patients and

those who encounter intervals of minimal food consumption – similar to those of our ancient ancestors – reveal a lower risk of cancer [55,56] even when correcting for the overall reduction in life expectancy. Patients with a history of food overconsumption experience a decrease in cancer incidence and mortality after undergoing a surgical intervention to limit food intake [57–60].

Thus these data indicate that energy restriction and traditional diets that do not promote obesity can have an impact on cancer development.

THE GLUCOSE-INSULIN AXIS IN METABOLISM

The modern "Western diet" is generally considered to consist of highly refined sugars and starches. The key factor is the rate of absorption and low-glycemic-index carbohydrates and added dietary fiber are widely recommended. In practice, these are secondary considerations since approximately 90% or more of the CHOs in the Western diet, i.e. between 250 and 400 grams per day, represent highly absorbable and digestible starches and sugars. At these levels of intake, what follows may be understood to refer to essentially all ingested CHOs.

Dietary CHOs elevate serum glucose concentration, thus stimulating insulin release from the beta cells of the pancreas. A primary effect of insulin secretion – kinetically and thermodynamically – is the repression of fat breakdown (lipolysis) in fat cells (adipocytes). Insulin is generally tissue building or anabolic, and stimulates protein, CHO and lipid synthesis. As is more widely appreciated, insulin represses hepatic production of glucose, the process of gluconeogenesis [38-40], directly or indirectly by the inhibition of glucagon [61]. This is likely the major mechanism for the clearance of blood glucose while the generally appreciated recruitment of GLUT4 receptors to the cell surface of peripheral cells is likely secondary [62]. As shown in Figure 1, glucose itself provides the substrate for re-synthesis of triglyceride (TAG) in adipocytes. Because adipocytes do not express glycerol kinase, the glycerol-3-phosphate must be provided by anaerobic glucose metabolism or glycolysis and glyceroneogenesis, a truncated form of gluconeogenesis, from protein [63].

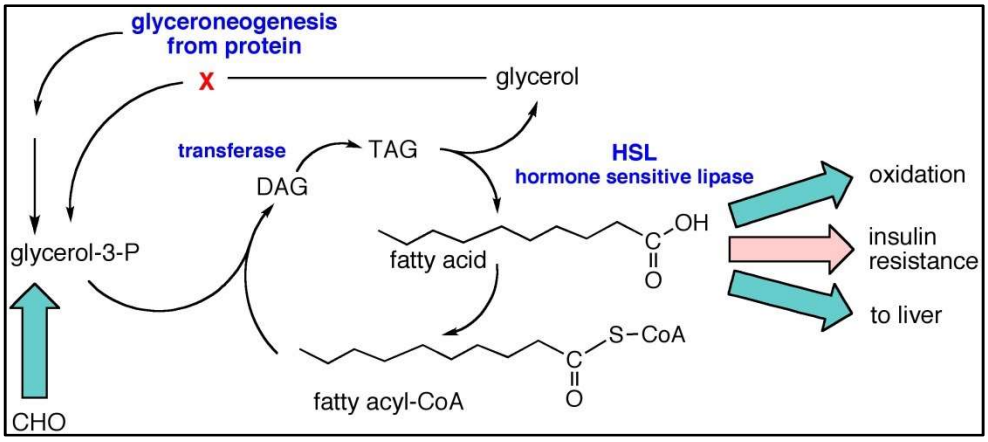

Figure 1: Triacylglycerol (TAG)-fatty acid cycle in adipocytes. Glycerol from lipolysis cannot be re-cycled because adipocytes do not express glycerol kinase. Glycerol-3-phosphate, the substrate for the fatty acyl-CoA transferase must be generated from glycolysis or glyceroneogenesis.

From an overall perspective, excess dietary CHO sets insulin into a state of overdrive to synthesize excess fat and to store the fat in adipocytes, thereby increasing and maintaining adiposity.

EVOLUTION POINTS TO LIMITED CARBOHYDRATE CONSUMPTION

The evolution of the genus *Homo* in East Africa took place during a period characterized by high seasonal and longer-term climate variability, associated fluctuations between wood- and grasslands, arid and moisture climates, and food resources [64]. Unstable food resources and changing climates required the exploitation of new foods. Accordingly, the appearance of early *hominids* coincides with an increasing supplementation of a primarily frugivorous (plant-eating) diet with animal meat. Hints of butchering of animals and use of stone tools are currently dated back to more than 3 million years ago [65-66] preceding even the oldest known *Homo* fossils. About 1.9 million years ago [64], early *Homo* gave rise to the species *Homo erectus*, better adapted for walking longer distances and covering larger areas in search of food. The first human species leaving Africa and colonizing greater Eurasia, *Homo erectus* continued to incorporate meat into the diet as inferred from the production of bifacial hand axes used to butcher animal carcasses.

The emergence of modern humans, *Homo sapien*s, around 200,000 years ago saw a dramatic shift in dietary preference. Although the evidence is sparse, archaeological data indicate the

appearance, about 100,000 years ago, of a wide range of new food sources, including birds, fish, and shellfish [67]. It is estimated that modern humans left Africa and began colonizing Europe, Asia, and Australia approximately 50,000 years ago. And it was only 10,000 years ago that sedentary agriculture developed in some human groups. Over several millennia, this lifestyle diffused widely from centers in the Near East, China and Mesoamerica. According to this perspective, we were hunter-gatherers for 95% of our early evolution. Although the data are limited, the best evidence suggests CHO consumption in this period represented only 20-35% of total caloric intake [68]. There was no bread on the table, there were no cakes, puddings, pies, chips, or pasta. Wild fruits or tubers gathered were available only seasonally. In addition, it has been argued that gathered fruits did not measure up in either size or abundance to fruits now available year round. Such fruits may, in addition, have contained significantly less sugar and more fiber [69]. Looking at this pattern against a likely background of frequent periods of intermittent or longer-term fasting, one would have to conclude that low blood glucose and low insulin levels were characteristic features of humans for most of our evolutionary history.

INSULIN AND KETONE BODY METABOLISM

Under modern conditions of CHO intake, in the well-fed state, the brain uses about 130 grams of glucose per day [70]. During the initial stages of dietary CHO restriction or during fasting, the brain continues to be supplied with glucose by hepatic glycogenolysis and gluconeogenesis, primarily from amino acids from protein breakdown, and to a lesser degree, by glycerol from lipolysis. Continued breakdown of endogenous proteins for gluconeogenesis, however, carries the risk of severe protein loss from muscle, causing ongoing and ultimately fatal damage to the heart and diaphragm. The evolution of ketone body (KB) metabolism promotes a selective survival advantage sparing body protein loss by providing an alternate energy substrate, initially for muscle and, in a few days, for the brain. The KBs, β-hydroxybutyrate, acetoacetate, and the non-enzymatic breakdown product, acetone, derive from acetyl-CoA, primarily from lipolysis of fat tissue. These KBs are synthesized primarily in the liver and are transported to peripheral cells where they are incorporated into the TCA-cycle via reactions catalyzed by a CoA transferase and thiolase:

succinyl-CoA + acetoacetate → succinate + acetoacetyl-CoA

acetoacetyl-CoA + CoA → 2 acetyl-CoA

In essence, KBs provide a method of transporting acetyl-CoA from the liver to other organs, including the brain. The availability of free fatty acid for ketogenesis depends on releasing insulin's inhibition of lipolysis which is accomplished by dietary CHO restriction. Feedback control is exerted by KBs which stimulate pancreatic insulin secretion, albeit to a much smaller extent than glucose, thus controlling fatty acid generation. Loss of this control due to the absence of insulin gives rise to the ketoacidosis of uncontrolled type 1 diabetes).

BACKGROUND ON CANCER

Current theories on cancer describe an initial injurious event leading to a series of genetic mutations. Over-activation of oncogenes and/or loss of function in tumor suppressor genes must accumulate in order to transform a normal cell into one which displays rapid cell-division, growth, and immortality, the hallmarks of cancer. While we think of growth and proliferation as the major characteristics of life, the real demands on the living state come from keeping these processes under control. Hanahan & Weinberg's widely cited hallmarks of cancer [2,1], all describe a failure to control growth and replication (Figure 2).

Classical hallmarks:

- Limitless replicative potential
- Sustained angiogenesis
- Evading apoptosis
- Self-sufficiency in growth signals
- Insensitivity to empty growth signals
- Tissue invasion & metastasis

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Figure 2: Acquired Capabilities of Cancer as described by Hanahan & Weinberg [1] and Hanahan & Weinberg [2]

From an evolutionary perspective, the genetic mutations in pre-cancerous cells can be thought of as re-activating an ancient genetic program that has been switched off, regulated or silenced in contemporary animals. In this sense, tumors can be viewed as an atavism, an evolutionary back-transition towards the first simple multi-cellular organisms [71]. In the context of this paper, cancers adopt an abnormal metabolic reprogramming: reduced mitochondrial function and increased reliance on glycolytic metabolisms. Not included in the original hallmarks, the dependence of glycolytic mechanisms has emerged as a key feature of many cancers. Fermentation of glucose represents an ancient biochemical mechanism employed by prokaryotes at least 3.5 billion years ago [72] when oxygen concentrations in the atmosphere were low [73]. Some authors have argued that this feature alone explains most if not all, the other hallmarks, thereby classifying cancer as a metabolic disease [74]. The theory is supported by evidence that the metabolic environment drives the evolution from mutations within mitochondrial DNA toward a cancerous state [75].

In addition to avoidance of initiating events, repair of unavoidable random cellular damage and removable of potentially cancerous cells becomes critical in prevention. Adaptive mechanisms in humans include the various DNA damage repair methods and ultimately, the cellular suicide process known as apoptosis. Given an order of 10^{13} cells in our body, however, errors in repair are inevitable and will be passed on to subsequent generations of cells, accumulating DNA mutations as we age. Indeed, careful organ autopsies of people who have died from non-cancer causes have revealed high rates of indolent tumors that remained quiescent, causing no symptoms in the patient's life [76,77]. It should be noted, however, that factors permitting and provoking tumors toward aggressive behavior, removing the “brakes” on cell growth, proliferation and metastasis, are hyperglycemia and the associated hyperinsulinemia [78–81].

Metabolic abnormalities appear to contribute to genomic mutation and instability. High blood glucose concentrations – especially those experienced during spikes in poorly-controlled type 2 diabetics – stimulate production of free radicals and especially reactive oxygen species (ROS)

[18,19,82]: Figure 3). Hyperglycemia induces increased ROS in breast cancer cell lines [17,83] presumably contributing to genomic instability. Cancer cells appear to protect themselves from intrinsically high steady state levels of ROS by increasing the rate of glycolysis and activation of the pentose phosphate pathway, both resulting in production of high levels of the anti-oxidative pyruvate and lactate as well as NADPH, stabilizing reduced glutathione [84,85]. Starving such cells of glucose breaks down this defense mechanism and leads to cell death via ROS [86,87]. The overexpression of uncoupling protein 2 in cancer cells has also been proposed as a mechanism to mitigate ROS damage (see section on uncoupling proteins below).

THE WARBURG EFFECT AND MITOCHONDRIAL FUNCTION

Warburg's original observations that rapidly growing cancers produced lactate even in the presence of oxygen led him to believe that this was a universal feature of all cancers [88–90]. While not true in all instances of cancer — most prostate cancers, for example represent an exception [91,92] — the Warburg effect has provided a crystallizing point in research into energy metabolism, mitochondrial function, reactive oxygen species, and the utility of PET scanning in cancer. While it is unlikely that the glycolytic profile that appears in different tumors has a single cause, several important hypotheses based on disruption in mitochondrial function and/or uncoupling of mitochondrial activity from energy production, have been proposed to explain the origin of the Warburg effect [16,93,94].

Mitochondrial DNA (mtDNA; 16,569 base pairs) codes for many of the components of oxidative phosphorylation including subunits of three proton translocases, complexes I, III and IV and complex V, the ATP synthase. Mutations, depletions or abnormalities in mtDNA have been identified in many cancers [75, 95–105]. Mitochondrial dysfunction further enhances production of the free radicals and ROS that are by-products of the redox reactions of electron transport (Figure 3)

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Redox reactions can produce a variety of chemically reactive free radical compounds, the most abundant being ROS, which may be increased by mitochondrial dysfunction. See Figure 3.

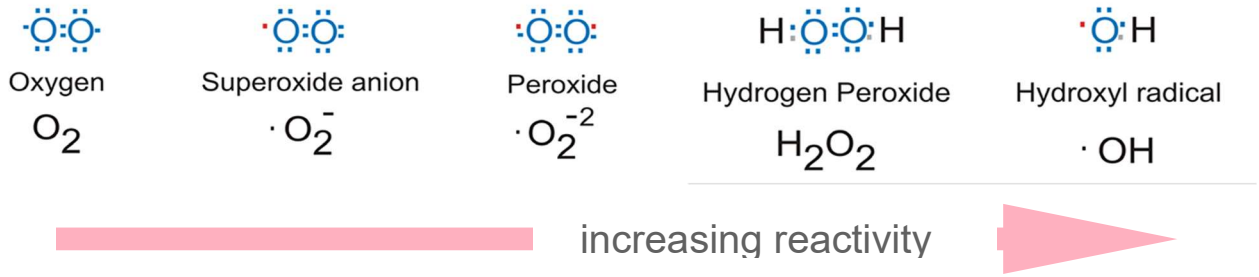

Figure 3: Common forms of reactive oxygen species

The role of uncoupling proteins

In addition to mitochondrial components that are directly involved in aerobic energy production, mechanisms of mitochondrial coupling and metabolic responses are candidates for explaining the tendency of rapidly growing cancers to by-pass aerobic oxidation even under aerobic conditions.

The free energy of aerobic oxidation is captured as a proton gradient across the inner mitochondrial membrane. Dissipation of the gradient is coupled to synthesis of ATP *via* the complex V, the ATP synthase. The process is not perfectly efficient and the loss of usable energy is described as proton leak or uncoupling, analogous to the action of small molecule uncouplers such as 2, 4-dinitrophenol or FCCP, which are protein ionophores. Uncoupling *in vivo* is mediated by several (currently 5) uncoupling proteins [106]. The wasted energy is dissipated as heat and the uncoupling protein 1 (UCP1) – the first discovered in mammals – functions as a mediator of non-shivering thermogenesis in brown adipose tissue. Brown adipose tissue is widely distributed in mammals and newborn humans [107].

The biological roles of UCP 3, 4 and 5 are quite speculative at present. UCP2, while ubiquitous in human cells, is measured at very low levels in most normal tissues, but is expressed at higher

levels in regions of infection, inflammation [108,109] and malignant transformation [22,110–112]. It has been proposed that UCP2 acts in response to elevated levels of ROS, moderating and reducing their chemical reactivity [113,114]. Co-incubation of KBs with glucose-medium in cultured fibroblast lines (RFP3, MCH 064 and MCH065) induces a 30% decline in UCP2 expression compared with glucose medium alone [21]. ROS were not directly measured, but these data are consistent with KB-induced suppression of ROS in normal tissues and a reduced mutagenic microenvironment. It should be noted that cancer lines had much greater variability after the addition of KBs, with reduced UCP2 seen in MDA MB 231 and MCF 7 (40% and 15%, respectively), but increased UCP2 in some colon cancer lines (LoVo CaCO2), and reductions in others (RKO, SW48 and SW480). The significance of these findings is less clear. The most consistent description is that the response of UCP2 to ROS must be as complex as the ROS response itself. Since ROS function as normal signaling molecules as well as toxic free radical species, as modulators of both growth and death it should not be surprising that this will remain an interesting avenue of investigation moving forward.

Cell signaling pathways

Recent studies have shown a direct role for elevated blood glucose levels in promoting oncogenic transformation of cells through the WNT/β-catenin pathway [78] or the EPAC/RAP1 and O-GlcNAc pathways [79]. High blood glucose also acts indirectly as a growth stimulus through its effect on insulin release that in turn increases the bioavailability of IGF-1 and IGF-2 through hepatic down-regulation of IGF binding proteins [20]. The direct effect of insulin/IGF signaling is activation of the insulin receptor, IGF-1 receptor and hybrid insulin/IGF-1 receptors. These in turn activate the PI3K−AKT−mTOR pathway as well as the Ras-Raf-MEK-ERK pathway (Figure 4), both of which stimulate cell growth, proliferation and cell survival [20,115]. Multiple modulators of these pathways exist, including calorie intake, CHO and protein restriction or drugs such as metformin, which down-regulates PI3K signaling through AMP kinase stimulation [116].

The regulatory effect of metformin has led to several current clinical trials testing its combination with chemotherapy and radiation therapy. Metformin has been quite safe in most clinical applications, but nonetheless poses a small risk of hypoglycemia and lactic acidosis.

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However, from the perspective of the data presented here, the same effects could be achieved with a ketogenic diet without adverse side effects and without the need for a medication.

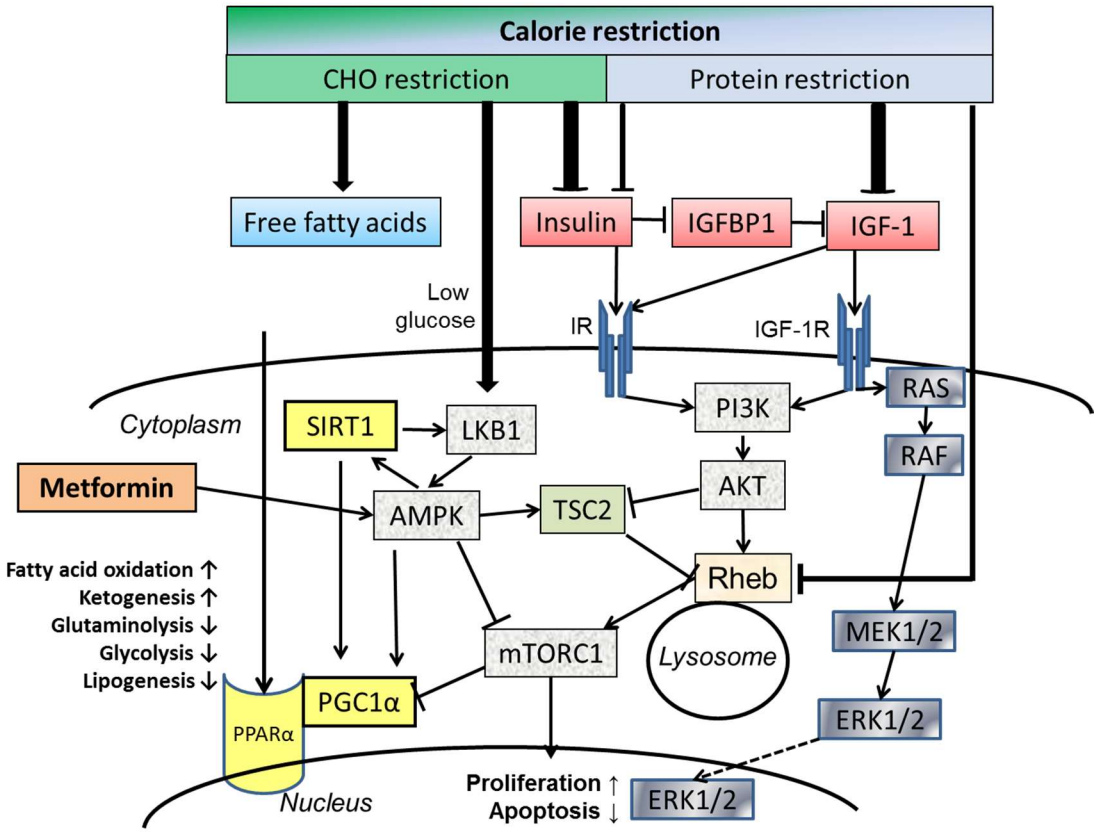

Figure 4: Multiple tumor progression and survival pathways are activated via the Insulin/IGF axis. Dietary restriction in the form of overall CR or specific restriction of CHO or protein has specific effects on the insulin/ IGF-1 system that transduces cellular signals through its insulin and IGF-1 tyrosine kinase receptors. This picture only provides a partial overview of the complexity of this signaling network. The classical action of activated ERK1 and ERK2 is their translocation into the nucleus where they activate mitogenic transcription factors. Similarly mTORC1 targets transcription factors that increase proliferation and counteract apoptosis. Activation of mTORC1 via IR/IGF-1R–PI3K–AKT converges with its activation by amino acids at the lysosomal membrane. There, the guanosine triphosphatase (GTPase) Rheb stimulates activity of mTOR which belongs to the mTORC1 complex. In contrast, a lack of growth signals activates the tumor suppressor tuberin (TSC2) which translocates to the lysosomal membrane and inhibits the Rheb-stimulated activation mTORC1. High insulin levels activate AKT which phosphorylates and inactivates TSC2, whereas CR or glucose withdrawal induce energy stress, decrease the intracellular ATP/AMP ratio

and activate TSC2 through liver kinase B1 (LKB1) – adenosine monophosphate-activated protein kinase (AMPK) signaling. AMPK can also directly inhibit mTORC1 by phosphorylating the regulatory-associated protein of mTOR (Raptor). AMPK has similar actions to the class III histone deacetylase SIRT1 which is a NAD^+ - dependent enzyme that is also activated under calorie or CHO restriction-induced energy stress through an increase in the NAD^+/NADH ratio. AMPK and SIRT1 amplify each other and both activate the peroxisome proliferator activated receptor gamma 1α co-activator (PGC-1α) protein that cooperates with peroxisome proliferator activated receptor α (PPARα) to induce major metabolic shifts such as up-regulation of lipid oxidation and down-regulation of glycolysis. mTORC1, stimulated by insulin/IGF-1 signaling, inhibits these actions. Taken and modified from Ref. [20]

CALORIC AND CARBOHYDRATE RESTRICTION IN CANCER PREVENTION

As early as 1909, it was shown that under-feeding could inhibit the growth of a transplanted tumor in mice [3]. In 1914, not long after he had discovered that an avian sarcoma was caused by a virus, Peyton Rous, using dietary calorie restriction (CR), was able to repress spontaneous tumor development in mice, along with reduced growth of transplanted tumors [117].

Over the next century, the effect of CR on cancer as a preventative means and potential treatment has gone in and out of fashion. In 1945 Tannenbaum found that the appearance of sarcoma induced in mice by addition of the carcinogen benzpyrene was repressed by CR of all macronutrients [5] (Figure 5). If the calories were reduced by restricting CHO alone, the effect was even more pronounced [4,118].

The impressive cancer preventive effects of CR in animal models have been confirmed through a meta-analysis [119] evaluating studies on spontaneous breast tumors in mice published between 1942 and 1995. CR led to an average decrease of 55% in tumor development in CR fed mice compared to *ad libitum* fed controls. A recent meta-analysis estimated a pooled odds ratio of 0.2 (95% confidence interval 0.12-0.34) for a lower tumor incidence after carcinogenic interventions in CR fed mice compared to *ad libitum* feeding [120]. In total, 40 out of 44 studies (90.9%) revealed the tumor-inhibitory effect of CR in laboratory animals with respect to tumor incidence, progression or metastasis. Interestingly, eight out of nine preclinical studies evaluated in this meta-analysis showed that a ketogenic diet was also able to slow down tumor growth, often even as monotherapy.

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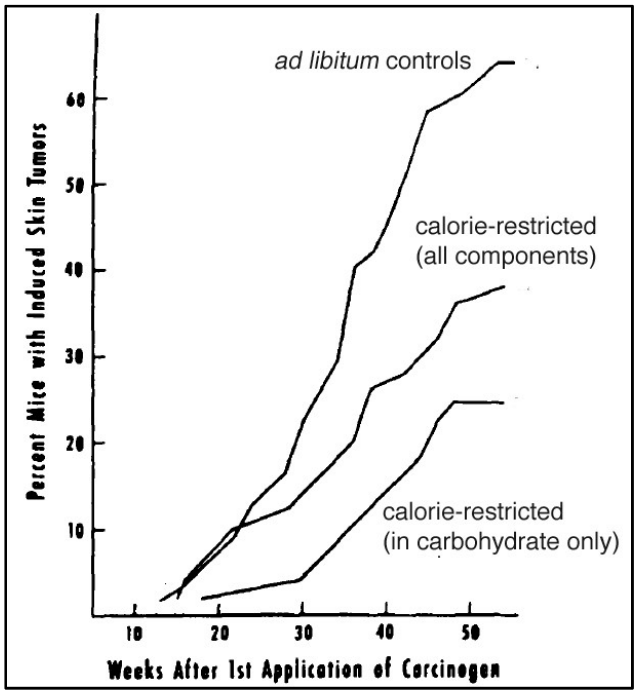

Figure 5: The formation of induced skin tumors and the effect of under-feeding. Modified from Tannenbaum (1945) [4].

Traditional experimental studies described as calorie-restriction (CR) or as, energy-restriction take the reduction in calories as the *cause* of the cancer inhibition. This is unfortunate and inherently misleading because CR can be accomplished in many ways, permitting manipulation of any or all of the *three* macronutrients – proteins, CHOs, and fat. Numerous studies describing cancer inhibition as due to energy or calorie restriction, achieved this goal by exclusively limiting CHO [121–124] or protein [125,126] consumption. The rationale of carbohydrate restriction, however, follows the idea that glucose, directly or indirectly, through the effect of insulin and other hormones, plays a dominant catalytic role biasing the disposition of other nutrients. In the case of energy utilization, the level of carbohydrate will determine how much of all the substrates are oxidized or stored. So, as described above, a hyperglycemic, hyperinsulinemic state is likely to exert substantial control over the emergence of the cancerous state. The impression that CR,

i.e. the reduction of calories themselves, “caused” the inhibition is therefore inaccurate and misleading.

More explicitly, calorie (or energy) restriction has been accomplished by proportional reduction of all macronutrients [97], or, in some cases, an absence of specification is usually taken to signify proportional reduction [127,128]. This experimental design has hazards, as proportional macronutrient reduction is an ambiguous concept whose effects cannot be assumed to be independent of the macronutrient *baseline constituents*. A diet composed of 55-70% CHO composition, recommended by the USDA until only recently, is quite different from one of 10-35% CHO, and even further removed from a ketogenic diet (of less than 10% CHO). Most of these proportional trials have been performed in mice and rats, where total CR of standard chow (55-70% CHO for rodents) represents *de facto* limitation of CHO, the predominant macronutrient.

Kalaany et. al. [97] reported that cancer proliferation was inhibited in wild-type mice after CR (proportional). Further they showed that this inhibition was reversed in genetically altered mice resulting in constitutive activation of the PI3K pathway. Since the PI3K pathway is directly downstream of the insulin receptor, the data strongly point to the dominant role of insulin inhibition by dietary CHO restriction in the wild-type cancer results. Unfortunately, this was not mentioned in the discussion of this article, and the semantics of nutrient and dietary restriction continue.

Ambiguities continue to propagate in the literature. As a result, ‘calorie restriction’ remains popular among approaches to cancer control [129]. We therefore re-emphasize that the insulin/IGF-1 pathway is activated principally by dietary consumption of CHO, and glucose is most often the preferred energy substrate for cancer cells due to metabolic dysfunction, as described above [90,130,10]. Protein consumption also stimulates this pathway albeit to a lesser extent than glucose in humans [20]. Mechanisms of protein activation of this pathway include the stimulation of pancreatic insulin and hepatic glucose production [131,132] as well as a general activation of mTORC1 by amino acids [133]. Intermittent fasting, a low-CHO or low-protein diet, or a ketogenic diet – all dietary elements which humans have often experienced over hundreds of thousands of years of evolution – all reduce insulin/IGF1 signaling. A reduction in blood glucose

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levels via CHO restriction has been shown in cancer patients with *ad libitum* eating [134]. However, other studies failed to observe such an effect in cancer patients [135]. We point out that dietary CHO restriction results in normal range glucose concentrations (60-100 mg/dl) for the vast majority of people. Since most cancers over-express glucose 1 transporters, whose rate of glucose uptake is saturated at levels of 45 mg/dl, it is unlikely that blood glucose reduction has a direct effect on limiting cancer growth, so indirect effects via insulin/IGF1 signaling appear much more important.

For instance, a reciprocal association between blood glucose and KB levels has been shown in both mice [136] and human cancer patients [135]. The significance of high KBs lies in their ability to retard tumor growth [137–140]. For example, KBs inhibit glycolysis in both normal and cancer cells, but while normal tissues easily switch to KBs and fatty acids for fuel when glucose is limited, cancer cells in general cannot compensate for energy loss when glycolysis is impaired [21,22]. This is supported by a clinical trial showing that strict CHO restriction with ketosis can result in the down-regulation of glycolysis in some cancer patients with associated slower tumor growth as measured by imaging procedures [141].

β-hydroxybutyrate, the principle KB manufactured by the liver – and to a lesser extent acetoacetate – has also recently been shown to be a histone deacetylase (HDAC1, 3 and 4) inhibitor [23]. Through this action, β-hydroxybutyrate promotes the hyperacetylation of histone proteins and induces a stress response which promotes autophagy and inhibits mTOR signaling [25].

Thus it becomes clear that methods to minimize circulating insulin and spikes of glucose as well as mediators of chronic inflammation may help to decrease the occurrence and progression of cancer. One such method emphasized in this paper is the reduction of dietary CHO intake to levels that are more in line with the likely human diet in the past.

CONCLUSIONS: MOVING FORWARD BASED ON THE PAST

For over 95% of human evolution, the human diet was largely affected by periods of limited or no food consumption, intermixed with periods of plenty but limited CHO intake compared to

contemporary diets. As the evolutionary biologist Theodosius Dobzhansky stated in 1973: "Nothing in biology makes sense except in the light of evolution." Over a century of accumulated data appears to confirm that this statement applies to the effect of diet on cancer prevention.

CR – and more specifically CHO restriction – which were experienced throughout human evolution as normal periods without food and seasonal variation, appears to have been ingrained within human biology as a method to prevent cancer. Support for this hypothesis has been illustrated in ecologic data, epidemiologic data, preclinical and animal data, and more recently in human data.

Such evidence is encouraging both for treating and, more importantly, for preventing cancer. As described throughout this manuscript, a diet that more closely mimics the ancient human diet appears to result in metabolic changes and cellular pathway modulation favoring a physiologic state that is not conducive to cancer induction or growth. These dietary effects should be incorporated and tested in future clinical trials as they may stand as a potent weapon in the fight against cancer.

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REFERENCES

[1] Hanahan D, Weinberg RA. The Hallmarks of Cancer. Cell 2000;100:57–70.

[2] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.

[3] Moreschi C. Beziehungen zwischen Ernahrung und Tumorwachstum. Zeitschrift Für Immunitätsforsch 1909;2:651–75.

[4] Tannenbaum A. The Dependence of Tumor Formation on the Composition of the Calorie-Restricted Diet as Well as on the Degree of Restriction. Cancer Res 1945;5:616–25.

[5] Tannenbaum A. The Dependence of Tumor Formation on the Degree of Caloric Restriction. Cancer Res 1945;5:609–15.

[6] Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, et al. Fasting and cancer treatment in humans: A case series report. Aging (Albany NY) 2009;1:988–1007.

[7] Longo VD, Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. Trends Pharmacol Sci 2010;31:89–98.

[8] Oshakbayev KP, Alibek K, Ponomarev IO, Uderbayev NN, Dukenbayeva BA. Weight change therapy as a potential treatment for end-stage ovarian carcinoma. AM J Case Rep 2014;15:203–11.

[9] de Groot S, Vreeswijk MP, Welters MJ, Gravesteijn G, Boei JJ, Jochems A, et al. The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study. BMC Cancer 2015;15:652.

[10] Klement RJ, Kämmerer U. Is there a role for carbohydrate restriction in the treatment and prevention of cancer? Nutr Metab (Lond) 2011;8:75.

[11] Champ CE, Volek JS, Siglin J, Jin L, Simone NL. Weight Gain, Metabolic Syndrome, and Breast Cancer Recurrence: Are Dietary Recommendations Supported by the Data? Int J Breast Cancer 2012;2012:506868.

[12] Ben-Dor M, Gopher A, Barkai R. Neandertals Large Lower Thorax May Represent Adaptation to High Protein Diet. Am J Phys Anthropol 2016.

[13] Saleh AD, Simone BA, Savage J, Sano Y, Jin L, Champ C, et al. Caloric restriction augments radiation efficacy in breast cancer. Cell Cycle 2013;12:1955–63.

[14] Simone BA, Champ CE, Rosenberg AL, Berger AC, Anne RP, Monti DA, et al. Selectively starving cancer cells through dietary manipulation: methods and clinical implications. Futur

Oncol 2013;9:959–76.

[15] Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr 2007;86:836S – 842.

[16] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science (80-) 2009;324:1029–33.

[17] Turturro F, Friday E, Welbourne T. Hyperglycemia regulates thioredoxin-ROS activity through induction of thioredoxin-interacting protein (TXNIP) in metastatic breast cancer-derived cells MDA-MB-231. BMC Cancer 2007;7:96.

[18] Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res 2010;107:1058–70.

[19] Yao D, Brownlee M. Hyperglycemia-induced reactive oxygen species increase expression of the receptor for advanced glycation end products (RAGE) and RAGE ligands. Diabetes 2010;59:249–55.

[20] Klement RJ, Fink MK. Dietary and pharmacological modification of the insulin/IGF-1 system: exploiting the full repertoire against cancer. Oncogenesis 2016;5:e193.

[21] Fine EJ, Miller A, Quadros E V, Sequeira JM, Feinman RD. Acetoacetate reduces growth and ATP concentration in cancer cell lines which over-express uncoupling protein 2. Cancer Cell Int 2009;9:14.

[22] Fine E, Feinman Ri, Miller A. Acetoacetate is a metabolic inhibitor of cancer growth. FASEB J 2015;29:725.22 – .

[23] Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, Le Moan N, et al. Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science (80-) 2013;339:211–4.

[24] Newman JC, Verdin E. Ketone bodies as signaling metabolites. Trends Endocrinol Metab 2014;25:42–52.

[25] Rojas-Morales P, Tapia E, Pedraza-Chaverri J. β-Hydroxybytate: A signaling metabolite in starvation response? Cell Signal 2016.

[26] Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 2009;101:48–60.

[27] Kabat GC, Kim M, Caan BJ, Chlebowski RT, Gunter MJ, Ho GYF, et al. Repeated

DOI: 10.15310/2334-3591.1036

measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int J Cancer 2009;125:2704–10.

[28] Kabat GC, Kim MY, Strickler HD, Shikany JM, Lane D, Luo J, et al. A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women. Br J Cancer 2012;106:227–32.

[29] Lann D, LeRoith D. The role of endocrine insulin-like growth factor-I and insulin in breast cancer. J Mammary Gland Biol Neoplasia 2008;13:371–9.

[30] Sparano JA, Wang M, Zhao F, Stearns V, Martino S, Ligibel JA, et al. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. Cancer 2012;118:5937–46.

[31] Stoll BA. Upper abdominal obesity, insulin resistance and breast cancer risk. Int J Obes Relat Metab Disord 2002;26:747–53.

[32] Volek J, Phinney S, Forsythe C, Quann E, Wood R, Puglisi M, et al. Carbohydrate Restriction has a More Favorable Impact on the Metabolic Syndrome than a Low Fat Diet. Lipids 2009;44:297–309.

[33] Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 2003;88:1617–23.

[34] Forsythe CE, Phinney ÆSD, Luz ÆM, Quann EE, Wood ÆRJ, Bibus ÆDM, et al. Comparison of Low Fat and Low Carbohydrate Diets on Circulating Fatty Acid Composition and Markers of Inflammation. Lipids 2008;43:65–77.

[35] Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA 2007;297:969–77.

[36] Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074–81.

[37] Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359:229–41.

[38] Volek JS, Sharman MJ, Love DM, Avery NG, Gómez AL, Scheett TP, et al. Body

composition and hormonal responses to a carbohydrate-restricted diet. Metabolism 2002;51:864–70.

[39] Rivas MA, Carnevale RP, Proietti CJ, Rosemblit C, Beguelin W, Salatino M, et al. TNF alpha acting on TNFR1 promotes breast cancer growth via p42/P44 MAPK, JNK, Akt and NF-kappa B-dependent pathways. Exp Cell Res 2008;314:509–29.

[40] Zhang GJ, Adachi I. Serum interleukin-6 levels correlate to tumor progression and prognosis in metastatic breast carcinoma. Anticancer Res 1999;19:1427–32.

[41] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.

[42] Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.

[43] Albuquerque K V, Price MR, Badley RA, Jonrup I, Pearson D, Blamey RW, et al. Pre-treatment serum levels of tumour markers in metastatic breast cancer: a prospective assessment of their role in predicting response to therapy and survival. Eur J Surg Oncol 1995;21:504–9.

[44] Ros Perez M, Medina-Gomez G. Obesity, adipogenesis and insulin resistance. Endocrinol Nutr 2011.

[45] Nam SY, Lee EJ, Kim KR, Cha BS, Song YD, Lim SK, et al. Effect of obesity on total and free insulin-like growth factor (IGF)-1, and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. Int J Obes Relat Metab Disord 1997;21:355–9.

[46] Nolop KB, Rhodes CG, Brudin LH, Beaney RP, Krausz T, Jones T, et al. Glucose utilization in vivo by human pulmonary neoplasms. Cancer 1987;60:2682–9.

[47] Erickson K, Patterson RE, Flatt SW, Natarajan L, Parker BA, Heath DD, et al. Clinically Defined Type 2 Diabetes Mellitus and Prognosis in Early-Stage Breast Cancer. J Clin Oncol 2011;29:54–60.

[48] Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 2002;20:42–51.

[49] Railo MJ, von Smitten K, Pekonen F. The prognostic value of insulin-like growth factor-I in breast cancer patients. Results of a follow-up study on 126 patients. Eur J Cancer 1994;30A:307–11.

DOI: 10.15310/2334-3591.1036

[50] Turner BC, Haffty BG, Narayanan L, Yuan J, Havre PA, Gumbs AA, et al. Insulin-like growth factor-I receptor overexpression mediates cellular radioresistance and local breast cancer recurrence after lumpectomy and radiation. Cancer Res 1997;57:3079–83.

[51] Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444:840–6.

[52] Macaulay VM. Insulin-like growth factors and cancer. Br J Cancer 1992;65:311–20.

[53] Kagawa Y. Impact of Westernization on the nutrition of Japanese: changes in physique, cancer, longevity and centenarians. Prev Med (Baltim) 1978;7:205–17.

[54] Troisi R, Altantsetseg D, Davaasambuu G, Rich-Edwards J, Davaalkham D, Tretli S, et al. Breast cancer incidence in Mongolia. Cancer Causes Control 2012;23:1047–53.

[55] Mellemkjaer L, Emborg C, Gridley G, Munk-Jorgensen P, Johansen C, Tjonneland A, et al. Anorexia nervosa and cancer risk. Cancer Causes Control 2001;12:173–7.

[56] Michels KB, Ekbom A. Caloric restriction and incidence of breast cancer. JAMA 2004;291:1226–30.

[57] Adams TD, Stroup AM, Gress RE, Adams KF, Calle EE, Smith SC, et al. Cancer incidence and mortality after gastric bypass surgery. Obes (Silver Spring) 2009;17:796–802.

[58] Brolin RL, Robertson LB, Kenler HA, Cody RP. Weight loss and dietary intake after vertical banded gastroplasty and Roux-en-Y gastric bypass. Ann Surg 1994;220:782–90.

[59] Dias MC, Ribeiro AG, Scabim VM, Faintuch J, Zilberstein B, Gama-Rodrigues JJ. Dietary intake of female bariatric patients after anti-obesity gastroplasty. Clin (Sao Paulo) 2006;61:93–8.

[60] Trostler N, Mann A, Zilberbush N, Avinoach E, Charuzi I. Weight Loss and Food Intake 18 Months following Vertical Banded Gastroplasty or Gastric Bypass for Severe Obesity. Obes Surg 1995;5:39–51.

[61] Unger RH. Minireview: weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. Endocrinology 2003;144:5159–65.

[62] Sonksen P. Insulin: understanding its action in health and disease. Br J Anaesth 2000;85:69–79.

[63] Reshef L, Olswang Y, Cassuto H, Blum B, Croniger CM, Kalhan SC, et al. Glyceroneogenesis and the triglyceride/fatty acid cycle. J Biol Chem 2003;278:30413–6.

[64] Antón SC, Potts R, Aiello LC. Evolution of early *Homo*: An integrated biological

perspective. Science (80-) 2014;345:1236828–1.

[65] McPherron SP, Alemseged Z, Marean CW, Wynn JG, Reed D, Geraads D, et al. Evidence for stone-tool-assisted consumption of animal tissues before 3.39 million years ago at Dikika, Ethiopia. Nature 2010;466:857–60.

[66] Harmand S, Lewis JE, Feibel CS, Lepre CJ, Prat S, Lenoble A, et al. 3.3-million-year-old stone tools from Lomekwi 3, West Turkana, Kenya. Nature 2015;521:310–5.

[67] Broadhurst CL, Wang Y, Crawford MA, Cunnane SC, Parkington JE, Schmidt WF. Brain-specific lipids from marine, lacustrine, or terrestrial food resources: potential impact on early African *Homo* sapiens. Comp Biochem Physiol Part B Biochem Mol Biol 2002;131:653–73.

[68] Cordain L, Miller JB, Eaton SB, Mann N, Holt SH, Speth JD. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. Am J Clin Nutr 2000;71:682–92.

[69] Milton K. Nutritional characteristics of wild primate foods: do the diets of our closest living relatives have lessons for us? Nutrition 1999;15:488–98.

[70] Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF. Brain metabolism during fasting. J Clin Invest 1967;46:1589–95.

[71] Davies PCW, Lineweaver CH. Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors. Phys Biol 2011;8:015001.

[72] Webster KA. Evolution of the coordinate regulation of glycolytic enzyme genes by hypoxia. J Exp Biol 2003;206:2911–22.

[73] Cloud PJ. Atmospheric and Hydrospheric Evolution on the Primitive Earth. Science (80-) 1968;160:729–36.

[74] Seyfried TN, Shelton LM. Cancer as a metabolic disease. Nutr Metab (Lond) 2010;7:7.

[75] Chatterjee A, Mambo E, Sidransky D. Mitochondrial DNA mutations in human cancer. Oncogene 2006;25:4663–74.

[76] Manser RL, Dodd M, Byrnes G, Irving LB, Campbell DA. Incidental lung cancers identified at coronial autopsy: implications for overdiagnosis of lung cancer by screening. Respir Med 2005;99:501–7.

[77] Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA. Breast cancer and atypia among young and middle-aged women: A study of 11 medicological autopsies. Brit J

Cancer 1987;56:814–9.

[78] Garcı-Jiménez C, Garcia-Martínez JM, Chocarro-Calvo A, De la Vieja A, García-Jiménez C, García-Martínez JM. A new link between diabetes and cancer: enhanced WNT/β-catenin signaling by high glucose. J Mol Endocrinol 2014;52:R51–66.

[79] Onodera Y, Nam J-M, Bissell MJ. Increased sugar uptake promotes oncogenesis via EPAC/RAP1 and O-GlcNAc pathways. J Clin Invest 2014;124:367–84.

[80] Lopez R, Arumugam A, Joseph R, Monga K, Boopalan T, Agullo P, et al. Hyperglycemia enhances the proliferation of non-tumorigenic and malignant mammary epithelial cells through increased leptin/IGF1R signaling and activation of AKT/mTOR. PLoS One 2013;8:e79708.

[81] Bissell MJ, Hines WC. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med 2011;17:320–9.

[82] El-Osta A, Brasacchio D, Yao D, Pocai A, Jones PL, Roeder RG, et al. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. J Exp Med 2008;205:2409–17.

[83] Singh S, Pandey S, Bhatt AN, Chaudhary R, Bhuria V, Kalra N, et al. Chronic Dietary Administration of the Glycolytic Inhibitor 2-Deoxy-D-Glucose (2-DG) Inhibits the Growth of Implanted Ehrlich's Ascites Tumor in Mice. PLoS One 2015;10:e0132089.

[84] Hirschhaeuser F, Sattler UGA, Mueller-Klieser W. Lactate: A metabolic key player in cancer. Cancer Res 2011;71:6921–5.

[85] Meijer TWH, Kaanders JHAM, Span PN, Bussink J. Targeting Hypoxia, HIF-1, and Tumor Glucose Metabolism to Improve Radiotherapy Efficacy. Clin Cancer Res 2012;18:5585–94.

[86] Allen BG, Bhatia SK, Buatti JM, Cancer C, Published R, June O. Ketogenic Diets Enhance Oxidative Stress and Radio-Chemo-Therapy Responses in Lung Cancer Xenografts Ketogenic Diets Enhance Oxidative Stress and Radio- Chemo-Therapy Responses in Lung Cancer Xenografts. Clin Cancer Res 2013;19:3905–13.

[87] Aykin-Burns N, Ahmad IM, Zhu Y, Oberley LW, Spitz DR. Increased levels of superoxide and H2O2 mediate the differential susceptibility of cancer cells versus normal cells to glucose deprivation. Biochem J 2009;418:29–37.

[88] Warburg O, Wind F, Negelein E. Über den Stoffwechsel der Tumoren im Körper. Klin

Wochenschr 1926;5:829–38.

[89] Warburg O. Über den Stoffwechsel der Carcinomzelle. Klin Wochenschr 1925;4:12–8.

[90] Warburg O. On the origin of cancer cells. Science (80-) 1956;123:309–14.

[91] Fanti S, Nanni C, Ambrosini V, Gross MD, Rubello D, Farsad M. PET in genitourinary tract cancers. Q J Nucl Med Mol Imaging Off Publ Ital Assoc Nucl Med [and] Int Assoc Radiopharmacol (IAR), [and] Sect Soc Radiopharm 2007;51:260–71.

[92] Reinicke K, Sotomayor P, Cisterna P, Delgado C, Nualart F, Godoy A. Cellular distribution of Glut-1 and Glut-5 in benign and malignant human prostate tissue. J Cell Biochem 2012;113:553–62.

[93] Ashrafian H. Cancer's sweet tooth: the Janus effect of glucose metabolism in tumorigenesis. Lancet (London, England) 2006;367:618–21.

[94] Denko NC. Hypoxia, HIF1 and glucose metabolism in the solid tumour. Nat Rev Cancer 2008;8:705–13.

[95] Cheung LWT, Hennessy BT, Li J, Yu S, Myers AP, Djordjevic B, et al. High frequency of PIK3R1 and PIK3R2 mutations in endometrial cancer elucidates a novel mechanism for regulation of PTEN protein stability. Cancer Discov 2011;1:170–85.

[96] Eng C, Kiuru M, Fernandez MJ, Aaltonen LA. A role for mitochondrial enzymes in inherited neoplasia and beyond. Nat Rev Cancer 2003;3:193–202.

[97] Kalaany NY, Sabatini DM. Tumours with PI3K activation are resistant to dietary restriction. Nature 2009;458:725–31.

[98] Kulawiec M, Safina A, Desouki MM, Still I, Matsui S-I, Bakin A, et al. Tumorigenic transformation of human breast epithelial cells induced by mitochondrial DNA depletion. Cancer Biol Ther 2008;7:1732–43.

[99] Mariadason JM. Making sense of HDAC2 mutations in colon cancer. Gastroenterology 2008;135:1457–9.

[100] McGranahan N, Favero F, de Bruin EC, Birkbak NJ, Szallasi Z, Swanton C. Clonal status of actionable driver events and the timing of mutational processes in cancer evolution. Sci Transl Med 2015;7:283ra54.

[101] Mouradov D, Sloggett C, Jorissen RN, Love CG, Li S, Burgess AW, et al. Colorectal cancer cell lines are representative models of the main molecular subtypes of primary cancer. Cancer Res 2014;74:3238–47.

DOI: 10.15310/2334-3591.1036

[102] Nelson WG, De Marzo AM, Isaacs WB. Prostate Cancer 2009.

[103] Simpson L, Parsons R. PTEN: life as a tumor suppressor. Exp Cell Res 2001;264:29–41.

[104] Turajlic S, McGranahan N, Swanton C. Inferring mutational timing and reconstructing tumour evolutionary histories. Biochim Biophys Acta 2015;1855:264–75.

[105] Carew JS, Huang P. Mitochondrial defects in cancer. Mol Cancer 2002;1:9.

[106] Ricquier D, Bouillaud F. The uncoupling protein homologues: UCP1, UCP2, UCP3, StUCP and AtUCP. Biochem J 2000;345 Pt 2:161–79.

[107] Hao R, Yuan L, Zhang N, Li C, Yang J. Brown adipose tissue: distribution and influencing factors on FDG PET/CT scan. J Pediatr Endocrinol Metab 2012;25:233–7.

[108] Caruso C, Lio D, Cavallone L, Franceschi C. Aging, longevity, inflammation, and cancer. Ann N Y Acad Sci 2004;1028:1–13.

[109] Emre Y, Hurtaud C, Nübel T, Criscuolo F, Ricquier D, Cassard-Doulcier A-M. Mitochondria contribute to LPS-induced MAPK activation via uncoupling protein UCP2 in macrophages. Biochem J 2007;402:271–8.

[110] Harper M-E, Antoniou A, Villalobos-Menuey E, Russo A, Trauger R, Vendemelio M, et al. Characterization of a novel metabolic strategy used by drug-resistant tumor cells. FASEB J 2002;16:1550–7.

[111] Horimoto M, Resnick MB, Konkin TA, Routhier J, Wands JR, Baffy G. Expression of uncoupling protein-2 in human colon cancer. Clin Cancer Res 2004;10:6203–7.

[112] Savagner F, Franc B, Guyetant S, Rodien P, Reynier P, Malthiery Y. Defective mitochondrial ATP synthesis in oxyphilic thyroid tumors. J Clin Endocrinol Metab 2001;86:4920–5.

[113] Giardina TM, Steer JH, Lo SZY, Joyce DA. Uncoupling protein-2 accumulates rapidly in the inner mitochondrial membrane during mitochondrial reactive oxygen stress in macrophages. Biochim Biophys Acta 2008;1777:118–29.

[114] Valle A, Oliver J, Roca P. Role of uncoupling proteins in cancer. Cancers (Basel) 2010;2:567–91.

[115] Fine EJ, Feinman RD. Insulin, carbohydrate restriction, metabolic syndrome and cancer. Exp Rev Endocrin Metab 2014;10:15–24.

[116] Nowak K, Eldredge-Hindy H, Champ CE. Metformin: The sweet link between tumor genetics and metabolism? OA Cancer 2014;2:7.

[117] Rous P. The Influence of Diet on Transplanted and Spontaneous Mouse Tumors. J Exp Med 1914;20:433–51.

[118] Tannenbaum A. Effects of Varying Caloric Intake Upon Tumor Incidence and Tumor Growth. Ann New York Acedemy Sci 2006;49.

[119] Dirx MJM, Zeegers MPA, Dagnelie PC, Van Den Bogaard T, Van Den Brandt PA. Energy restriction and the risk of spontaneous mammary tumors in mice: A meta-analysis. Int J Cancer 2003;106:766–70.

[120] Lv M, Zhu X, Wang H, Wang F, Guan W. Roles of Caloric Restriction, Ketogenic Diet and Intermittent Fasting during Initiation, Progression and Metastasis of Cancer in Animal Models: A Systematic Review and Meta-Analysis. PLoS One 2014;9:e115147.

[121] Zhu Z, Jiang W, McGinley JN, Price JM, Gao B, Thompson HJ. Effects of dietary energy restriction on gene regulation in mammary epithelial cells. Cancer Res 2007;67:12018–25.

[122] Zhu Z, Jiang W, Thompson HJ. An experimental paradigm for studying the cellular and molecular mechanisms of cancer inhibition by energy restriction. Mol Carcinog 2002;35:51–6.

[123] Tannenbaum A, Silverstone H. The genesis and growth of tumors; effects of varying the proportion of protein (casein) in the diet. Cancer Res 1949;9:162–73.

[124] Tannenbaum A. The dependence of the genesis of induced skin tumors in the caloric intake during different stages of carcino- genesis. Cancer Res 1944;4:673–9.

[125] Fontana L, Adelaiye RM, Rastelli AL, Miles KM, Ciamporcero E, Longo VD, et al. Dietary protein restriction inhibits tumor growth in human xenograft models. Oncotarget 2013;4:2451–61.

[126] Lamming DW, Cummings NE, Rastelli AL. Restriction of dietary protein decreases mTORC1 in tumors and somatic tissues of a tumor-bearing mouse xenograft model. Oncotarget 2015;6:31233–40.

[127] Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. Annu Rev Med 2003;54:131–52.

[128] Zhu Z, Jiang W, Thompson HJ. Mechanisms by which energy restriction inhibits rat mammary carcinogenesis: in vivo effects of corticosterone on cell cycle machinery in mammary carcinomas. Carcinogenesis 2003;24:1225–31.

DOI: 10.15310/2334-3591.1036

[129] Hursting SD, Smith SM, Lashinger LM, Harvey AE, Perkins SN. Calories and carcinogenesis: lessons learned from 30 years of calorie restriction research. Carcinogenesis 2010;31:83–9.

[130] Seyfried TN, Sanderson TM, El-Abbadi MM, McGowan R, Mukherjee P. Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. Br J Cancer 2003;89:1375–82.

[131] Larivière F, Chiasson JL, Schiffrin A, Taveroff A, Hoffer LJ. Effects of dietary protein restriction on glucose and insulin metabolism in normal and diabetic humans. Metabolism 1994;43:462–7.

[132] Linn T, Santosa B, Grönemeyer D, Aygen S, Scholz N, Busch M, et al. Effect of long-term dietary protein intake on glucose metabolism in humans. Diabetologia 2000;43:1257–65.

[133] Abraham RT. Cell Biology. Making sense of amino acid sensing. Science (80-) 2015;347:128–9.

[134] Champ CE, Palmer JD, Volek JS, Werner-Wasik M, Andrews DW, Evans JJ, et al. Targeting metabolism with a ketogenic diet during the treatment of glioblastoma multiforme. J Neurooncol 2014;117:125–31.

[135] Klement RJ, Sweeney R. Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. BMC Res Notes 2016;9:143.

[136] Kesl SL, Poff AM, Ward NP, Fiorelli TN, Ari C, Putten AJ Van, et al. Effects of exogenous ketone supplementation on blood ketone, glucose, triglyceride, and lipoprotein levels in Sprague – Dawley rats. Nutr Metab (Lond) 2016;13:9.

[137] Patel MS, Russell JJ, Gershman H. Ketone-body metabolism in glioma and neuroblastoma cells. Proc Natl Acad Sci U S A 1981;78:7214–8.

[138] Demetrakopoulos GE, Brennan MF. Tumoricidal potential of nutritional manipulations. Cancer Res 1982;42:756s – 765s.

[139] Magee BA, Potezny N, Rofe AM, Conyers RA. The inhibition of malignant cell growth by ketone bodies. Aust J Exp Biol Med Sci 1979;57:529–39.

[140] Maurer GD, Brucker DP, Bähr O, Harter PN, Hattingen E, Walenta S, et al. Differential utilization of ketone bodies by neurons and glioma cell lines: a rationale for ketogenic diet as experimental glioma therapy. BMC Cancer 2011;11:315.

[141] Fine EJ, Segal-Isaacson CJ, Feinman RD, Herszkopf S, Romano MC, Tomuta N, et al. Targeting insulin inhibition as a metabolic therapy in advanced cancer: a pilot safety and feasibility dietary trial in 10 patients. Nutrition 2012;28:1028–35.