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Translating Mechanism-Based Strategies to Break the Obesity-Cancer Link: A Narrative Review

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Abstract

Prevalence of obesity, an established risk factor for many cancers, has increased dramatically over the past 50 years in the United States and across the globe. Relative to normoweight cancer patients, obese cancer patients often have poorer prognoses, resistance to chemotherapies, and are more likely to develop distant metastases. Recent progress on elucidating the mechanisms underlying the obesity-cancer connection suggests that obesity exerts pleomorphic effects on pathways related to tumor development and progression, and thus there are multiple opportunities for primary prevention and treatment of obesity-related cancers. Obesity-associated alterations, including systemic metabolism, adipose inflammation, growth factor signaling and angiogenesis, are emerging as primary drivers of obesity-associated cancer development and progression. These obesity-associated host factors interact with the intrinsic molecular characteristics of cancer cells, facilitating several of the hallmarks of cancer. Each is considered in the context of potential

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preventive and therapeutic strategies to reduce the burden of obesity-related cancers. Additionally, this review focuses on emerging mechanisms behind the obesity-cancer link as well as relevant dietary interventions, including calorie restriction, intermittent fasting, low-fat diet, and ketogenic diet, that are being implemented in preclinical and clinical trials, with the ultimate goal of reducing incidence and progression of obesity-related cancers.

Keywords

obesity; cancer; risk biomarkers; calorie restriction; ketogenic diet

Introduction

Over the past half century in the United States the prevalence of obesity, defined as body mass index (BMI) of 30 kg/m^2 or greater, has tripled with nearly 40% of adults and 20% of children burdened by the disease.[1] Not only epidemic to the United states, more than 600 million adults are obese worldwide with and additional 2.1 billion are considered overweight.[2] Increasing prevalence of obesity signifies a major public health problem as obesity increases risk of several chronic diseases and comorbidities including type II diabetes (T2DM), cardiovascular disease (CVD), hypertension, chronic inflammation and, as discussed in this review, many types of cancer.[3]

As illustrated in Figure 1, and based on the recent report from the International Agency for Research on Cancer, risk of 13 distinct cancer types is increased with excess body fatness: breast (in postmenopausal women), ovarian, liver, gallbladder, kidney, colon, pancreatic, gastric, esophageal, endometrial, thyroid, multiple myeloma, and meningioma.[4] Overall, an estimated 13% of incident cases worldwide, and approximately 20% of incident cases in Europe and North America, are attributable to obesity.[5] Aside from higher risk of developing cancer, obese individuals are more likely to have reduced response to anticancer therapies,[6] and obesity is implicated in approximately 20% of all cancer-related mortalities.[7] This includes prostate cancer, for which obesity increases progression but not incidence.[8] Here, we discuss (with a focus on developing mechanism-based intervention strategies) mechanisms through which obesity affects normal tissue homeostasis and cancer development and/or progression, including alterations in systemic metabolism, growth factor signaling, inflammation and angiogenesis.

Methods

A traditional literature review was performed to describe the multiple mechanisms underlying the obesity-cancer link, as well as dietary interventions targeting those mechanisms for primary cancer prevention and treatment. Searches were completed using PubMed and Google Scholar. A variety of key words were searched including obesity, metabolic reprogramming, secretome, cell signaling, inflammation, adipose, angiogenesis, cancer prevention, cancer treatment, calorie restriction, intermittent fasting, low fat diet and ketogenic diet.

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Obesity-Associated Systemic Alterations Impact the Hallmarks of Cancer

Hanahan and Weinberg identified essential biological capabilities acquired by all cancer cells during the multistep development of tumors in their classic article titled “The Hallmarks of Cancer”[9] first published in 2000 and updated in their 2011 “Hallmarks of Cancer: the Next Generation.”[10] These essential aberrations of cancer cells are sustaining proliferative signaling, insensitivity to anti-growth signals, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating processes related to invasions and metastasis. Conceptual progress in the decade between these two articles led to identification of additional hallmarks: deregulation of cellular energy metabolism, evading immune destruction, tumor-promoting inflammation and genomic instability. Extensive research on the obesity-cancer link supports the concept of obesity-associated systemic alterations, including 1) obesity-associated metabolic reprograming, 2) dysregulation of growth factor signaling, 3) adipose tissue inflammation and 4) induction of angiogenesis, facilitating several hallmarks of cancer.[11]

Obesity-Associated Metabolic Reprogramming—Metabolic reprogramming has long been known as a feature of cancer cells since the ‘Warburg effect,’ whereby cancer cells readily utilize glycolysis under normoxic conditions, was first described in 1924.[12] Increased attention in the last two decades has led to inclusion of metabolic reprogramming as a true hallmark of cancer cells.[10] Cancer cells can alter their metabolism including glycolytic, mitochondrial, and anapleurotic pathways to adapt to changing environments[13,14] and progress to more aggressive disease.[15–18] Many of these pathways converge on the tricarboxylic acid(TCA) cycle, with β-oxidation of fatty acids generating acetyl-CoA, glutaminolysis producing α-ketoglutarate and pyruvate being converted to oxaloacetate.[13] Selective pressure to proliferate in cancer cells drives these intermediates to be shuttled from the mitochondria and utilized as precursors for synthetic pathways including lipid, nucleotide and amino acid synthesis, rather than ATP production via the electron transport chain.[13,19] As a result, cancer cells may become more reliant on glucose for ATP generation, and amino acids and fatty acids for TCA intermediates. Overnutrition increases provisions of - glucose and fat, all of which can feed into this metabolic reprogramming to fuel cancer cell proliferation. Moreover, glycolysis has been shown to be enhanced in cancer cells in the context of obesity.[20,21] In addition, obesity is often associated with metabolic syndrome and diabetes,[22,23] conditions characterized by hyperglycemia and/or hypertriglyceridemia,[24] providing ample circulating nutrients to a developing tumor, even between feeding periods.[25] Both elevated serum glucose and triglyceride[26,27] levels have been associated with increased cancer risk.

In many cancers autophagy forms part of metabolic reprogramming. Autophagy. the process in which cells digest and recycle their cellular contents during low nutrient availability, can provide cancer cells with lipids, amino acids and nucleotides needed for proliferation.[28] Recent studies have shown high dependence on autophagy for tumor microenvironment cells that adopt senescence-associated secretory phenotype, which supports neighboring cancer cells through provision of digested contents, growth factors and inflammatory factors.[29,30] Obesity has been shown to induce autophagy, particularly in adipocytes.[31–33] Inhibition of autophagy combined with calorie restriction has been shown to reduce tumor growth.[34]

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These obesity-associated metabolic adaptations facilitate the development of cancer hallmarks including *insensitivity to anti-growth signals, resistance to cell death, and deregulation of cellular energetics*.[11] Interactions between cancer cell energetics and systemic metabolism highlight novel therapeutic strategies and interventions, particularly in obese individuals, as cancer cells may be more sensitive to metabolic perturbation, having already committed to a metabolic reprogram.

Dysregulation of Growth Factor Signaling—As depicted in Figure 2, obesity and metabolic syndrome are associated with aberrations in insulin signaling, growth factor signaling, and glucose metabolism.[35] One growth factor implicated in cancer risk and progression is insulin-like growth factor (IGF)-1. Produced primarily following growth hormone stimulation in the liver, IGF-1 functions as a regulator of growth and developmental processes.[36] IGF binding proteins bind circulating IGF-1 and limit its bioavailability to bind to its receptor and initiate downstream signals promoting growth and/or survival.[37] Hyperglycemia and hyperinsulinemia, hallmarks of metabolic syndrome, increase IGF-1 production and bioavailability. Hyperglycemia suppresses IGF-1 binding protein synthesis and hyperinsulinemia promotes expression of growth hormone receptor and subsequent IGF-1 synthesis.[35] Growth and survival functions of IGF-1 give it the potential to impact many hallmarks of cancer, including *sustained proliferative signaling, insensitivity to anti-growth signals, induction of angiogenesis and metastatic potential*.[38] As a result, elevated IGF-1 is established as a risk factor for multiple cancer types including breast, prostate, lung and colorectal.[37,39]

In response to elevated blood glucose levels, pancreatic β-cells release insulin, a peptide hormone that stimulates peripheral uptake of glucose, glucose metabolism, and energy storage pathways. IGF-1 receptor and insulin receptor stimulate the same downstream activation of phosphoinositide 3-kinase (PI3K)/Akt pathway (Figure 2), a pathway frequently altered in epithelial cancers.[40] In response to these growth factors and nutrient availability, PI3K/Akt produces lipid messengers that initiate Akt signaling,[40] activating mammalian target of rapamycin (mTOR)-associated signaling cascade which promotes cell growth, proliferation and survival.[41] Oncogenic signals or loss of tumor suppressors can also activate mTOR signaling, while low nutrient conditions activate AMP-activated protein kinase (AMPK), an energy responsive pathway that inhibits mTOR.[42] Obesity-induced activation of mTOR can contribute to several hallmarks of cancer including: *sustained proliferative signaling, insensitivity to anti-growth signals, induction of angiogenesis, and activation of processes related to invasion and metastasis*.[43] In preclinical models, blocking mTOR signaling with drugs such as rapamycin (mTOR inhibitor)[44–46] and metformin (AMPK activator),[46–48] block tumor-enhancing effects associated with the obese phenotype.[49] Interestingly, rapamycin has exhibited anti-inflammatory attributes, attenuating inflammation as well as tumor promotion, suggesting crosstalk between mTOR-related growth and survival signals and inflammatory signals.[50]

Adipose Tissue Inflammation—Mammals, including humans, have 2 major fat depots: subcutaneous and visceral (intra-abdominal). These adipose depots contain white adipose tissue (WAT) that stores energy in the form of triacylglycerol and brown adipose tissue

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(BAT) that dissipates energy by burning fatty acids to generate heat. WAT and BAT have important differences in their morphology, metabolism and transcriptional profiles. White adipocytes have few mitochondria, low oxidative rate, and contain an unilocular lipid droplet comprised primarily of triacylglycerol, while brown adipocytes have a high number of mitochondria (hence the darker appearance), high rate of fatty acid and glucose uptake and oxidation, and possess multilocular lipid droplets.[51] Moreover, the secretome of white versus brown adipocytes differs markedly (Figure 3); the former is characterized by secretion of leptin, resistin, PAI-1, inflammatory cytokines, and FFA, while the latter is characterized by secretion of bone morphogenetic proteins, lactate (which induces uncoupling proteins), retinaldehyde, triiodothyonine (T3) and other factors associated with response to cold stress and/or increased energy expenditure.[51] Brown adipocytes also produce adiponectin (but not leptin) and fibroblast growth factor-21, which can be anti-inflammatory and insulin sensitizing.[51] WAT contains a number of stromal cells including pre-adipocytes, vascular cells, fibroblasts and a host of immune cells such as adipose tissue macrophages.[52] Obesity increases WAT mass which drives chronic inflammation through altered adipokine and hormone signaling, generation of crown-like structures, and adipose remodeling and ectopic lipid infiltration to other tissues, as described below. Adipose tissue derived inflammation results in the secretion of a variety of signaling molecules and activation of gene expression programs that facilitate several of the hallmarks of cancer including *sustained proliferative signaling, activation of programs related to invasion and metastasis, induction of angiogenesis, promotion of genome instability, and evasion of immune destruction.*[11]

1. Altered Adipose Secretome: Leptin, an energy-responsive peptide hormone produced by adipocytes, is positively correlated with adiposity. Through signaling to the hypothalamus, leptin decreases hunger cues, food intake and weight gain.[53] Leptin release from adipocytes is stimulated by a variety of factors including insulin, TNFα, glucocorticoids, and estrogen.[53] In obesity, leptin is overproduced by adipocytes, reducing hypothalamic sensitivity to the signal.[54] Circulating leptin binds to receptors in central nervous system and peripheral tissues, regulating processes including energy homeostasis, cytokine production, immune function, and carcinogenesis.[53,55] The leptin receptor OB-R, classified as a class I cytokine receptor, gives leptin the ability to activate signal transducer and activator of transcription (STAT) family transcription factors, resulting in initiation of STAT-induced transcription programs for proliferation, cell growth and survival, migration and differentiation.[56] Deregulation of STATs activity is often observed in cancer.[57]

Adiponectin, another peptide hormone secreted from adipocytes, functions as an energy sensor that promotes energy intake and insulin sensitivity,[58] opposing the functions of leptin. Although the most abundant hormone secreted from the WAT,[59] adiponectin levels are negatively correlated with adiposity and release is stimulated during energy deficit.[60] Adiponectin opposes obesity-associated metabolic alterations through regulating glucose metabolism, increasing insulin sensitivity and fatty acid oxidation, and reducing IGF-1 signaling through activation of AMPK.[61] Adiponectin also attenuates inflammation through inhibition of nuclear factor kappa-light-chain-enhancer of B cells (NF-κB), which reduces expression of proinflammatory cytokines while increasing expression of anti-inflammatory

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cytokines.[62] Due to the anticancer functions of adiponectin, adiponectin agonists are emerging as possible chemotherapeutic agents, particularly for obesity-related cancers.[63] While individually these adipokines have established associations with cancer risk, the leptin to adiponectin ratio is increasingly considered a more sensitive measure in evaluating cancer risk.[64]

Sex hormones, including estrogen, androgens and progestogens, regulate a variety of growth and developmental processes including weight homeostasis.[65] Although the ovaries and testes are the major sites for sex hormone production, adipose tissue can significantly impact synthesis as adipose tissue expresses sex-steroid-metabolizing enzymes, including aromatase, which convert androgens into estrogens.[65] Excess adipose tissue becomes a major site of estrogen production in obesity.[66] In postmenopausal women, BMI is positively correlated with estrone, estradiol, and free estradiol.[67] Elevation of estrogens is also detected in obese men;[68,69] however, testosterone levels are significantly reduced.[70] Circulating estrogens bind to one of two estrogen receptors (ER), ERα or ERβ. Once bound, receptors dimerize and translocate to the nucleus and bind to DNA or other transcription factors, influencing gene expression profiles that regulate growth, proliferation and differentiation.[71] In the context of cancer, the two receptors have differing roles. ERα is mitogenic and an established target in treatment of estrogen receptor-positive breast cancer, while ERβ is suggested to be tumor suppressive.[72] Obesity and postmenopausal status increase risk of ER-positive breast cancers compared with ER-negative breast cancer.[73] Due to the positive association between obesity, circulating estrogen and risk of ER-positive breast cancer, aromatase inhibitors and ER antagonist tamoxifen are effective treatment therapies.[74] In addition to breast cancer,[67,68,75] elevated estrogen levels are associated with increased risk of ovarian[76] and endometrial cancers.[77] In prostate cancer, sex hormone levels are associated with disease progression, not disease risk.[78] Low levels of circulating testosterone correlates with aggressive disease progression.[79] Moreover, sex hormones have been implicated in risk and/or progression of colorectal and lung cancers.[80]

2. Crown-Like Structures: Obesity drives subclinical inflammation in visceral and subcutaneous WAT, characterized by crown-like structures, or rings of activated macrophages surrounding engorged or necrotic adipocytes. This adipocyte-macrophage interaction results in a proinflammatory secretome from both cell types, activating the cellular transcription factor NF-kB, increasing levels of cytokines and other inflammatory factors, and triggering inflammation.[81]

3. Adipose Remodeling and Lipid Infiltration in Other Tissues: During low nutrient availability or increased energy needs, glucagon secretion stimulates lipolysis of adipocytes, releasing FFA into the blood stream.[82] Circulating FFA can then be utilized by peripheral tissues, providing substrate for β-oxidation and serving as intermediates for energy production through TCA cycle and oxidative phosphorylation. Conversely, overnutrition remodels existing adipose tissue, expanding adipocyte number and size, and altering adipokine secretion, FFA flux, and adipocyte death.[83] In response, adipose stromal cells modify their functions to promote clearance of necrotic adipocytes and generation of new adipocytes and vasculature. Chronic overnutrition or obesity-induced tissue remodeling,

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results in sustained, low-grade inflammation and metabolic alterations.[83] As stated above, cancer cells adapt to changing energy needs for proliferation through metabolic reprogramming, increasing anaerobic metabolism and shunting TCA cycle intermediates to synthetic pathways.[10,84] Production of daughter cells demands increased levels of FFA for formation of lipid bilayers, thus excess WAT promotes proliferation of tumor cells through provision of circulating FFA[85,86]

When WAT depots reach capacity, excess lipids are deposited in organs such as the muscle, liver or pancreas, further complicating metabolism.[87] Ectopic lipid intermediates exert lipotoxic effects, impairing cellular organelle functions, releasing inflammatory cytokines, and fostering development of insulin resistance.[88] Consequently, individuals can develop muscle dysfunction and hepatic and pancreatic steatosis, all of which have been positively correlated with insulin resistance and impaired lipid metabolism.[87]

Nonalcoholic fatty liver disease, diagnosed as >5–10% liver fat content by weight in the absence of alcohol use or other liver disease, encompasses a variety of liver diseases including simple steatosis, nonalcoholic steatohepatitis (NASH) and cirrhosis.[89] One of the most common chronic diseases,[90–92] nonalcoholic fatty liver disease is present in 65–85% of obese patients[89,93] with rapidly rising incidence among adults and children.[91,94] Excess lipid accumulation in the liver, induces production of reactive oxygen species, activation of pro-inflammatory programs, and endoplasmic reticular stress, impairing function of cellular organelles and potentially inducing hepatic cell death.[95] Additionally, accumulation of lipids and pro-inflammatory cytokines promotes activation of intracellular kinases, leading to impaired insulin signaling and development of insulin resistance.[96] While simple steatosis is benign, NASH is more detrimental, characterized by liver injury, inflammation and/or fibrosis. NASH can further result in the development of cirrhosis, liver failure, and hepatocellular carcinoma.[97]

Ectopic deposition of adipocytes in the pancreas is hypothesized to be a mechanism behind obesity-associated pancreatic dysfunction.[98,99] Infiltrating fat in the pancreas has been associated with increased BMI, visceral WAT mass, insulin resistance and pancreatic exocrine dysfunction.[98–101] These endocrine alterations further complicate the complex metabolic and inflammatory perturbations characterized in obesity and metabolic syndrome and can trigger the development of pancreatic steatosis, pancreatitis and/or nonalcoholic fatty pancreatic disease, all established risk factors for pancreatic cancer.[100,101]

Induction of Angiogenesis—As adipose tissue depots expand in obesity, the existing vasculature must expand to meet demand. This outgrowth of new blood vessels is termed angiogenesis. Key mediators of this process include VEGF and PAI-1. VEGF, a potent angiogenic factor that is produced by adipocytes and tumor cells, acts on endothelial cells stimulating mitogenic and vascular permeability-enhancing activities.[102] Obesity is associated with increased circulating VEGF, and elevated VEGF correlates with poor prognosis for many obesity-related cancers.[103] PAI-1, another angiogenic factor produced by adipocytes, endothelial cells, and stromal cells in visceral WAT,[104] is frequently elevated in obese subjects. Increased circulating PAI-1 is associated with increased risk of other chronic diseases including CVD, T2DM and a number of cancers.[104] While interaction of

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angiogenic factors with proximal endothelial cells induce formation of local blood vessels, providing a route for oxygen and nutrient delivery and waste removal, these factors can also interact with peripheral tissues, facilitating angiogenesis, and potentially promoting progression at tumor sites. These newly formed blood vessels could provide primary tumor mass with oxygen and nutrients to sustain proliferation and survival as well as a route for metastasis to distant sites. PAI-1 functionally inhibits plasminogen activators, thus regulating extracellular matrix integrity.[105] Extracellular matrix remodeling is a key feature of invasive disease, and integral in the development of metastatic lesions.[106] Due to the antitumorigenic potential of factors that modulate angiogenesis, targeted drugs have been developed. However, caution should be advised in administration of anti-angiogenic treatments in obese patients, as these drugs can induce hypoxia in primary tumors, potentially encouraging metastasis, already a concern in the obese population.[106]

Elevation of these factors may also impact efficacy of treatment regimens, as excess circulating VEGF in obese patients contributes to reduced efficacy of anti-VEGF therapies (e.g. bevacizumab) compared with non-obese ovarian cancer patients.[107]

Emerging Mechanisms Linking Obesity and Cancer—Emerging research suggests other mechanisms including circadian rhythm[108] and the microbiome[109,110] influence the obesity-cancer link. Often referred to as the “body clock,” circadian rhythm regulates multiple physiological processes including secretion of key metabolic hormones leptin, adiponectin and insulin.[111] Circadian rhythm has been linked to metabolic homeostasis, particularly lipogenic and adipogenic pathways, as well as cell cycle regulation. Consequently, disrupted circadian rhythm can lead to metabolic disorders, such as obesity, [112] and increase cancer risk and progression.[108,112] Preclinical models describe circadian rhythm as energy responsive. Consumption of a high fat diet results in disruption of the circadian rhythm, while dietary restriction and fasting can reset the circadian clock and improve metabolic health.[111]

Gut microbiome, or the community of commensal, symbiotic and pathogenic microorganisms that inhabit an individual’s gut, influences a number of chronic diseases including obesity. Obesity changes composition[113] and diversity[114] of the microbiota, shifting towards populations with enhanced ability to harvest dietary energy. These alterations have been linked to elevated systemic inflammation.[115] Broad spectrum antibiotics, which alter microbiota composition, can completely prevent systemic inflammation resultant from high-fat diet feeding.[116] Through this influence on obesity-induced inflammation, microbiota may contribute to the obesity-cancer link. While both of these fields are in their infancy, their existence highlights additional mechanisms that must be delineated to effectively understand and target the obesity-cancer link.

Dietary Interventions Targeting Obesity-Induced Alterations for Primary Cancer Prevention and Therapy

Given the multifaceted role of obesity in promoting a protumorigenic microenvironment that facilitates tumor development and progression, interventions are urgently needed to break the obesity-cancer link. To date, the only weight loss intervention in obese people

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consistently associated with reduced cancer risk is bariatric surgery.[117] In light of the expense and complications inherent in surgical weight loss approaches, current efforts are focusing on reducing adiposity through dietary interventions. To achieve reductions in weight and adiposity these interventions have aimed to 1) promote negative energy balance through reduced energy intake via either calorie restriction (CR) or intermittent fasting (IF) or 2) modulate macronutrient distributions via implementation of low-fat diet (LFD) or a high-fat, ketogenic diet (KD). Preclinical and some clinical studies suggest that these interventions can favorably and inversely modulate cancer risk biomarkers, as discussed below. Modulation of these biomarkers could result in downstream reductions in growth factor signaling, inflammation, and angiogenesis, attenuating cancer risk and progression (Figure 4).

Calorie Restriction—Calorie restriction (CR), defined as reduction of dietary energy intake without malnutrition, is broadly effective dietary intervention that significantly decreases adiposity. Preclinical models demonstrate 30% CR, compared with ad libitum-fed control, ameliorates risk factors and delays onset of cancer through metabolic alterations fostering increased insulin sensitivity and decreased serum glucose, serum triglycerides, growth factor signaling, inflammation, oxidative stress and angiogenesis.[118–122] These metabolic changes translate into significantly decreased cancer incidence in murine models.[123] Due to long latency of cancer in humans, the literature does not have data linking CR directly with cancer incidence in humans. However, randomized control trials implementing long-term 20% CR in overweight human subjects have confirmed reduced adiposity, improved glucose homeostasis, increased adiponectin, and reduced leptin and inflammatory markers TNFα and C-reactive protein.[124,125] Substantial weight loss of >10% may be necessary to consistently observe these benefits.[126–128]

Limited clinical studies exist on CR during cancer treatment. Direct application of CR in cancer patients is complicated by high rates of weight loss associated with cancer cachexia, a condition in which tumor-derived signals degrade muscle and adipose tissue. A recent trial combining CR and physical activity suggests presurgical weight loss is safe and feasible in prostate cancer patients.[129] Moreover, preliminary clinical trials suggest that application of CR in combination with chemotherapy and/or radiation has potential to reduce risk biomarkers and increase responsiveness to treatment.[130,131]

Intermittent Fasting—Preclinical and clinical studies have begun to explore implementation of intermittent fasting (IF), which may be easier for most people to adopt and may have beneficial metabolic effects relative to chronic CR. Human trials most often study one of three IF regimens: alternate day fasting, alternate day energy restriction (~75%) or 2 consecutive days of 65% energy restriction, the latter often referred to as intermittent calorie restriction.[132] Periods of IF stimulate reduced insulin and increased glucagon, resulting in increased lipolysis and fatty acid oxidation to provide alternate substrates for energy production. These metabolic alterations are accompanied by reductions in several cancer-related risk factors including reduced serum glucose, insulin resistance, inflammation, and circulating IGF-1.[133] The impact of IF on angiogenesis in the context of cancer remains unexplored in currently published research. Preclinical studies with IF

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consistently exhibit a cancer preventative effect with reduced rates of tumor growth for multiple cancer types including lymphoma,[134] breast, lung, ovarian, hepatic, and pancreatic.[133,135,136] To our knowledge there is no published data on IF and cancer incidence in human subjects, although there are reports of favorable effects of IF in overweight humans, including improved adipokine ratios and reduced growth factor signaling and inflammatory markers,[136,137] suggesting the reported preclinical anticancer effects of IF may be translatable to humans.

One IF regimen being examined as primary prevention strategy for breast cancer is the 5:2 diet which involves 5 days/week of a healthy diet, such as the Mediterranean diet, with two consecutive days of a low calorie, low carbohydrate diet. The Mediterranean diet is primarily a plant-based diet high in fruits, vegetables, whole grains, legumes and nuts. Compared to North American dietary patterns, the Mediterranean diet has been associated with better control of body weight, reduction of cancer risk biomarkers and decreased cancer incidence.[138–142] The diet results in favorable modulation of inflammation, oxidative stress, and growth factor signaling. Combining a Mediterranean diet with 2 days of a very low calorie, low carbohydrate diet for one month in 24 obese women at high risk for breast cancer induced changes in breast tissue gene expression and metabolites associated with reduced risk of breast cancer.[143]

Regarding the effects of IF on cancer prognosis, a study by Safdie, et al suggests IF during cancer therapy may decrease adverse effects of chemotherapy. Ten cancer patients of varying cancer types (four breast, two prostate, one ovarian, one uterine, one small cell carcinoma of the lung, and one esophageal adenocarcinoma) voluntarily fasted prior to (48–140 hours) or following (5–56 hours) chemotherapy treatment. Compared with non-restricted control subjects, fasting reduced chemotherapy-induced side effects including fatigue, weakness and gastrointestinal side effects while exhibiting the same chemotherapy-induced reduction in tumor volume or biomarkers.[144] Following this ground breaking study, others have implemented IF in small scale clinical trials including de Groot, S., et al., 2015, where short term IF among stage II/III breast cancer patients was well tolerated, reduced signs of hematological toxicity and stimulated faster recovery from DNA damage in normal host peripheral blood mononuclear cells.[145] Limited preclinical findings suggest that IF may selectively protect healthy cells and make cancer cells more vulnerable to chemotherapeutic agents, reducing side-effects and increasing drug efficacy.[133] More research is needed to confirm these findings and identify underlying mechanisms.

Low-fat Diet—Numerous clinical studies have examined the effects of low-fat diet (LFD) interventions on cancer risk. Clinical trials with risk biomarker end points demonstrate that adherence to LFD over a two-year period resulted in normalization of glucose metabolism and reduction in growth factor signaling as well as favorable modulation of adipokine levels.[146] In the Women's Health Initiative clinical trial, nearly 50,000 postmenopausal women were followed for an average of 8.1 years after random assignment to a LFD with high fruit, vegetable, and grain intake or a comparison group. Analyses of this study have indicated that a LFD does not decrease risk of invasive cancer.[147,148] Further separated by cancer type, no decrease in invasive breast,[149] colorectal,[150] endometrial,[147] or melanoma[151] cancer risk was observed, but the diet intervention did decrease ovarian cancer risk.[147] Other

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randomized clinical trials have also demonstrated that LFD intake does not reduce breast cancer risk[152] or adenoma recurrence,[153,154] though a 35% decrease in the odds ratio was observed for "super compliers" in the latter trial.[155]

Researchers have also examined the impact of a LFD on cancer outcomes in several clinical trials, including the Women's Health Initiative trial, which found a reduction in breast cancer mortality in the diet intervention group,[156] but no decrease in total cancer mortality.[148] The Women's Intervention Nutrition Study further demonstrated that LFD significantly increases relapse-free survival in early-stage breast cancer patients, with greater effects seen in subjects with estrogen receptor negative tumors.[157] However, the Women's Healthy Eating and Living trial, which also enrolled early stage breast cancer patients, found no reduction in breast cancer recurrence or mortality with LFD,[158] unless the analysis was limited to subjects without post-treatment hot flashes.[159] Others have examined the effects of short-term low-fat dietary interventions on biomarkers in prostate cancer patients, pre-radical prostatectomy. A low-fat, fish oil-supplemented diet decreased prostate cancer cell proliferation, though fish oil may be the primary mediator of this effect.[160] In support of this hypothesis, proliferation rates were also significantly reduced in men on a flaxseed-supplemented diet, but not in those that followed a LFD without flaxseed.[161]

High-fat, Ketogenic Diet—Ketogenic diet (KD) is a very-low carbohydrate diet with high fat and moderate protein composition. Low carbohydrate consumption reduces available glucose, a cancer cell's preferred energy source, and increases catabolism of proteins and fats to provide gluconeogenic glucose and ketones. With prolonged consumption of KD, glycogen stores reach critical levels and the body is no longer able to oxidize fats to glucose via gluconeogenesis. This results in a shift to increased ketone production and physiological ketosis. Ketosis is not to be confused with ketoacidosis that is seen with diabetes mellitus. In ketosis there is less accumulation of ketones, as they are being used efficiently by the brain and body as an energy source, and individuals do not experience the adverse side effects associated with ketoacidosis.[162] Ketosis from KD has been shown to favorably modulates many cancer risk biomarkers including serum glucose, triglycerides, IGF-1, leptin, adiponectin, inflammatory markers, and angiogenic factors.[163–167] Preclinical studies suggest that KD can attenuate these markers without a reduction in caloric intake; however, weight loss may be needed.[168,169] KD may induce weight loss via several interrelated mechanisms, including: reduced appetite due to high protein intake, which can induce higher satiety, and high ketones, known to modulate appetite-regulating hormones; reduced caloric intake due to satiety; reduced lipogenesis and increased lipolysis; greater metabolic efficiency; and increased metabolic cost of gluconeogenesis and ketogenesis.[162].

Beneficial effects of the ketogenic diet have long been established for epilepsy and T2DM; emerging is its role in primary cancer prevention and adjuvant treatment.[162] Early preclinical studies found KD reduced tumor burden and cachexia in a mouse model of colon cancer.[170] Further preclinical models have confirmed these findings and extended benefits of decreased tumor growth and increased survival to other cancer types including malignant glioma, gastric and prostate cancers.[171] To date results from clinical trials focused on implementation of KD in primary cancer prevention and treatment have been limited, and

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ongoing clinical trials are beginning to address this gap in the literature with KD as adjuvant therapy in glioblastoma, pancreatic, head and neck, lung, and breast cancer patients.[172] It is important to also consider potential adverse effects of KD. Select preclinical studies have found long-term KD to cause dyslipidemia, hepatic steatosis and glucose intolerance.[173] More research is needed to evaluate the safety and efficacy of ketogenic diets as primary cancer prevention and adjuvant treatment interventions.

Summary and Conclusions

A strong link between obesity and cancer risk and/or poor prognosis has been established in the epidemiological and preclinical literature. Several of the Hallmarks of Cancer are impacted by obesity-associated systemic alterations including obesity-associated metabolic reprogramming, dysregulated growth factor signaling, adipose tissue inflammation, and induction of angiogenesis. Establishment of this obesity-cancer link has spurred extensive research focused on implementation of different dietary interventions to attain weight loss, attenuate risk biomarkers, and prevent obesity-associated cancers. Preclinical and early clinical work on putative anticancer dietary interventions, including CR, IF, LFD and KD, are being evaluated, some showing promise in reducing cancer risk. Ongoing clinical trials are also evaluating utilization of these dietary interventions as adjuvant therapy (Table 1). Limited evidence from these trials suggests that CR, IF, and KD may improve response and/or reduce side effects of therapy. Future studies will need to focus on the safety and added benefit, beyond that of current therapies, and consider the potential of the dietary interventions to sensitize patients and improve therapeutic response to lower doses chemotherapy or radiation therapy.

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Abbreviations

AMPK	AMP kinase
BMI	body mass index
BAT	brown adipose tissue
CR	calorie restriction
CVD	cardiovascular disease
ER	estrogen receptor
FFA	free fatty acids
IGF-1	insulin-like growth factor-1

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IL	interleukin
IF	intermittent fasting
KD	ketogenic diet
LFD	low-fat diet
MCP-1	monocyte chemo-attractant protein-1
mTOR	mammalian target of rapamycin
NASH	non-alcoholic steatohepatitis
NFκB	nuclear factor kappa-light-chain-enhancer of B cells
PAI-1	plasminogen activator inhibitor-1
PI3K	phospatidylinositol-3 kinase
PPAR	peroxisome proliferator-activated receptor
STAT	signal transducer and activator of transcription
TCA	tricarboxylic acid
TNF-α	tumor necrosis factor-α
T2DM	type II Diabetes
VEGF	vascular endothelial growth factor
WAT	white adipose tissue

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Research Snapshot

Research Question

What are the mechanisms through which obesity increases cancer risk and progression? Does implementation of dietary interventions attenuate obesity-associated cancer risk factors?

Key Findings

A traditional literature review revealed that obesity-associated metabolic perturbations are emerging as major drivers of obesity-related cancer including alterations in growth factor signaling, inflammation and angiogenesis. Preclinical evidence suggests that dietary interventions such as calorie restriction, intermittent fasting, and ketogenic diet have the potential to reverse some of these obesity-associated alterations; however, more clinical data is needed to confirm translation to human subjects.

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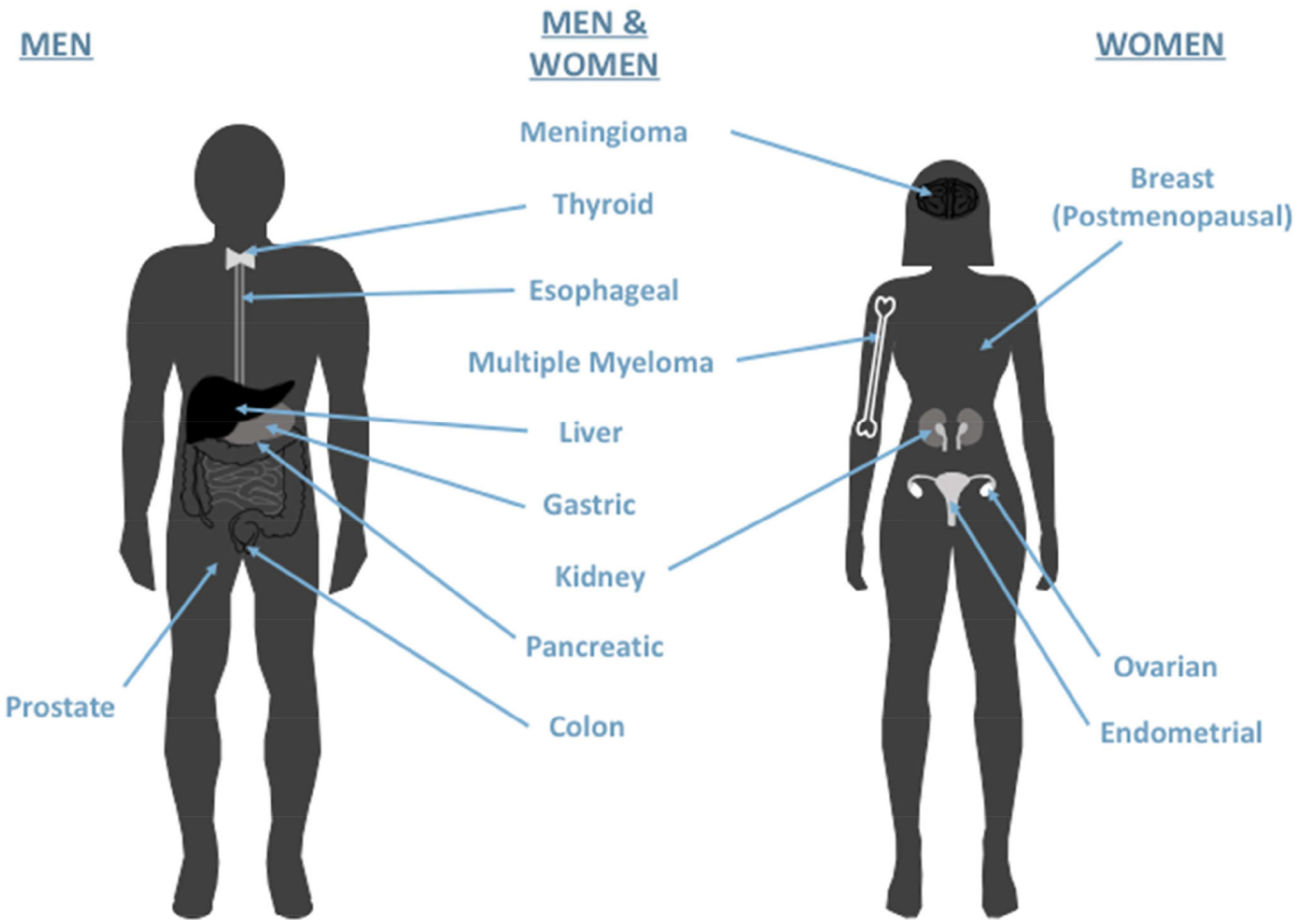

Figure 1.

Obesity is associated with increased risk of developing and dying from the following cancers: breast (in postmenopausal women), ovarian, liver, gallbladder, kidney (renal cell), colon, pancreatic, gastric, esophageal (adenocarcinoma), endometrial, thyroid, multiple myeloma, and meningioma. In addition, obesity is associated with progression (but not incidence) of prostate cancer.

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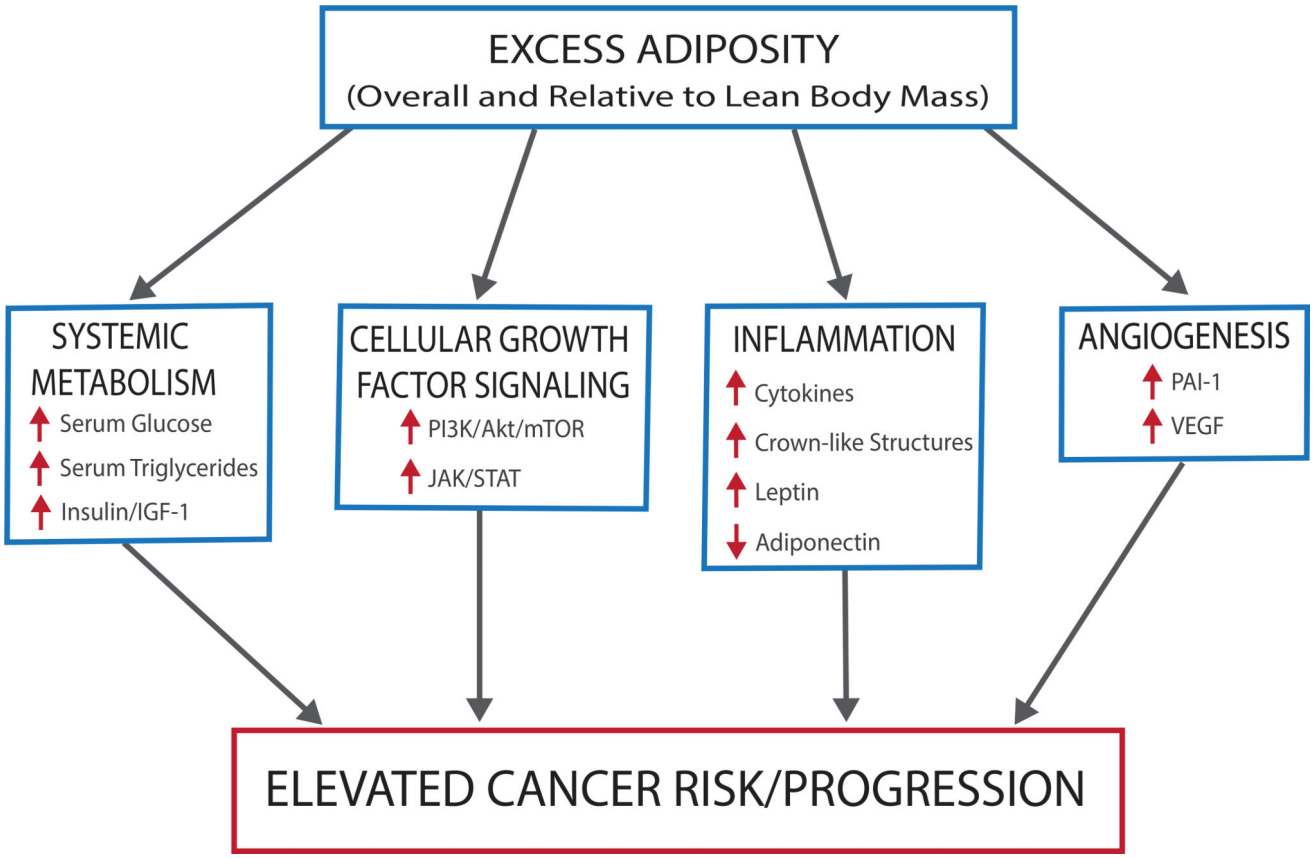

Figure 2.

Expansion of adipose tissue depots characteristic of obesity results in many metabolic disturbances including altered systemic metabolism and increased growth factor, inflammatory and angiogenic signaling. These obesity-associated perturbations foster a microenvironment favorable for tumorigenesis, facilitating many of the hallmarks of cancer and increasing disease risk and progression.

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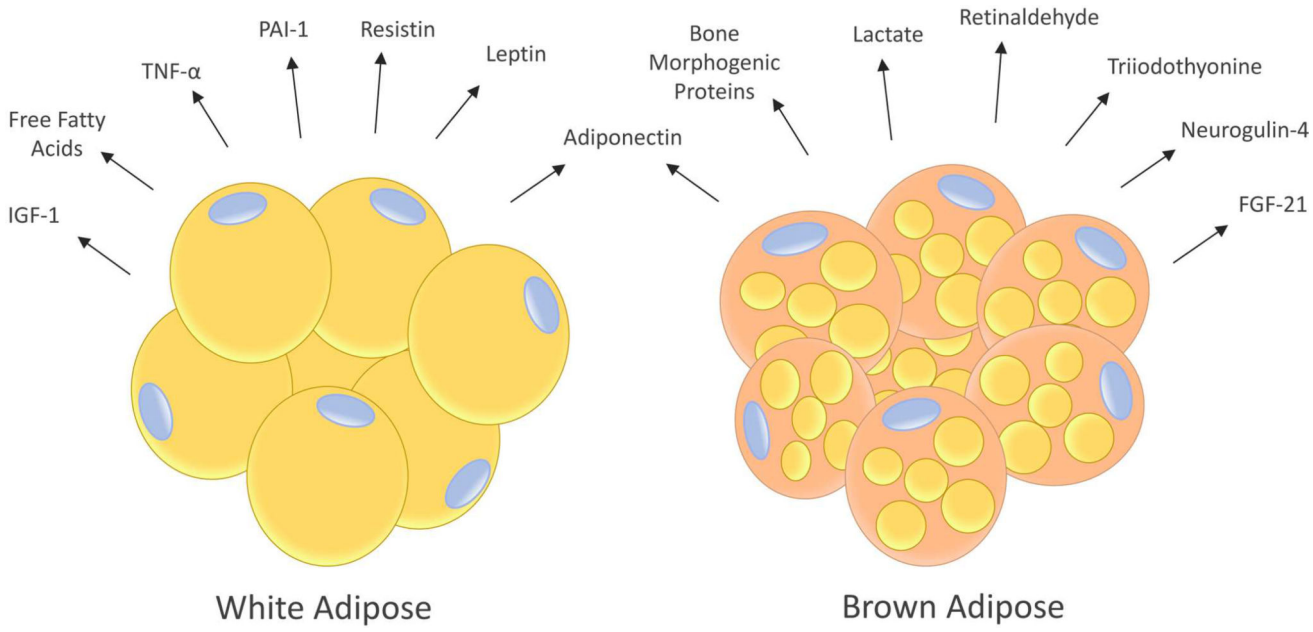

Figure 3.

The human body contains two types of adipocytes: white adipocytes (which have a unilocular lipid droplet) and brown adipocytes (which have many small lipid droplets). When engorged with triglyceride, white adipocytes secrete a number of factors that promote growth factor signaling and inflammation including leptin, resistin, insulin-like growth factor (IGF)-1, free fatty acids, tumor necrosis factor (TNF)-α and interleukin (IL)-6. Additionally, they reduce production of anti-inflammatory adiponectin. Brown adipocytes secrete several factors involved in thermogenesis, decreased inflammation, normalized insulin sensitivity and/or increased energy expenditure such as adiponectin, bone morphogenetic proteins, neuregulin-4, lactate, triiodothyronine (T3), retinaldehyde, and fibroblast growth factor (FGF)-21.

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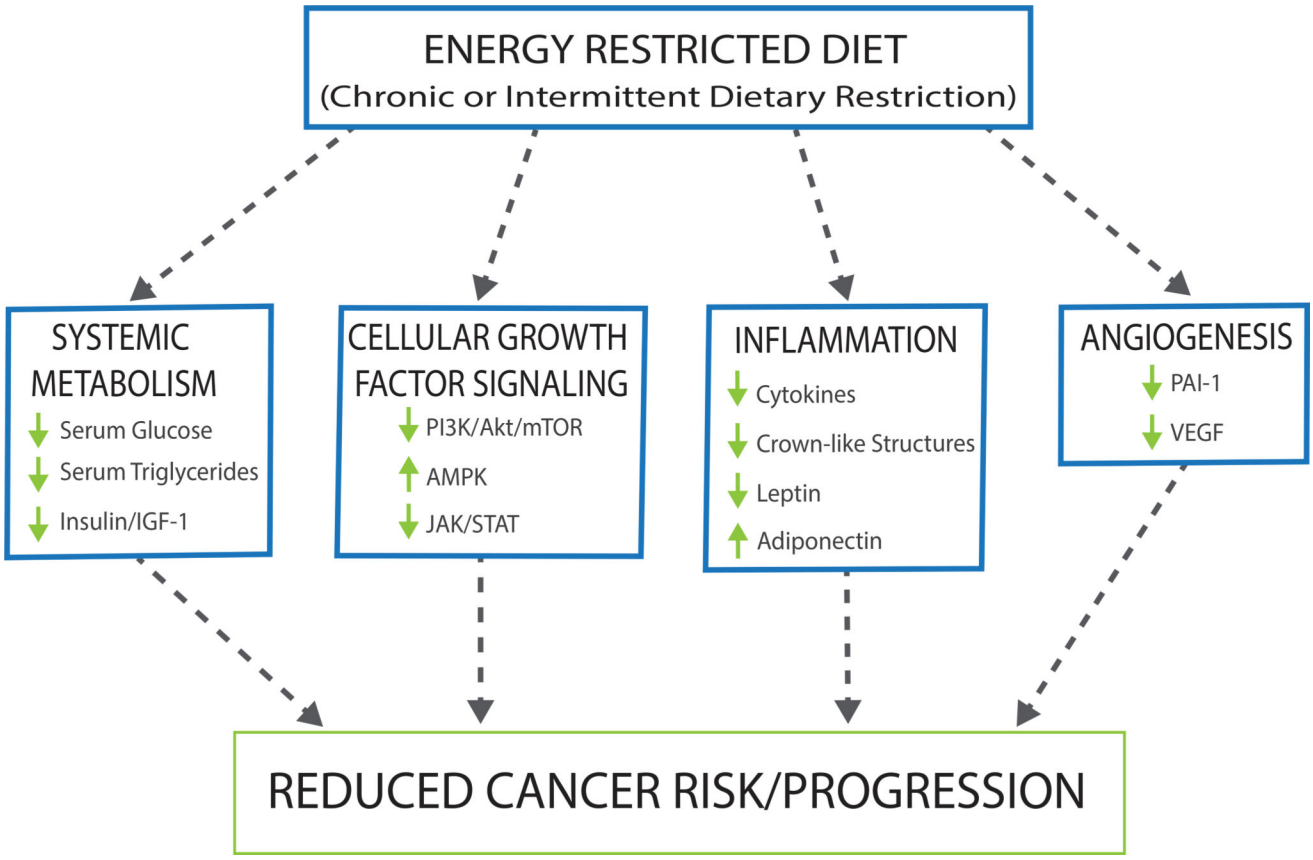

Figure 4.

Reductions in adiposity and weight attained from dietary interventions including caloric restriction (CR), intermittent fasting (IF), low-fat diet (LFD) and ketogenic diet (KD), have been shown to reduce adiposity and inversely modulate many of the same cancer risk biomarkers that are impacted by obesity and excess adiposity. Obesity-associated systemic alterations are reduced through these dietary interventions resulting in decreased circulating glucose, growth factor signaling, inflammation, and angiogenesis, attenuating cancer risk and progression. Metabolic alterations of CR and IF interventions have been associated with reduced cancer risk and progression. KD has not been linked to cancer risk in humans; however, it has been demonstrated that adherence to KD reduces cancer risk and progression in preclinical studies. Evidenced is mixed concerning implementation of a LFD, exhibiting little to no reduction in cancer risk and progression.

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Table 1

	Intervention	Cancer Type (s)	Adjuvant Treatment (s)	Principle Investigator, Institution, Clinical Trials ID	Results/ Anticipated Completion Date
Calorie Restriction	Calorie Restriction	Breast, Endometrial, Prostate	Prior to Cancer Surgery	Nicole Simone, MD Thomas Jefferson University NCT02983279	October 2021
	"Fasting-mimicking Diet" Very Low Calorie, low amino acid	Breast	Chemotherapy	Judith R. Kroep, MD PhD Hanno Pijl, MD PhD Koos JM van der Hoeven, MD PhD Leiden University Medical Center NCT02126449	December 2019
Fasting	Fasting up to 72 hours	All	Gemcitabine Hydrochloride and Cisplatin	Tanya Dorff, MD University of Southern California NCT00936364	July 2018
	Fasting up to 60 hours	Prostate	Chemotherapy	Andreas Michalsen, Prof. Dr.Kurt Miller, Prof. Dr.Ursula Steiner, Dr.Charite University NCT02710721	December 2017
	Fasting up to 48 hours	Breast	Chemotherapy	Hanno Pijl, MD PhD Leiden University Medical Center NCT01304251 (Safdie et al, 2009)	Reduced self-reported side effects
	Fasting up to 72 hours	Ovarian, Breast	Chemotherapy	Andreas Michalsen, Prof. Dr.Charite University NCT01954836	Completed, no reported results
	Fasting during Ramadan	All	Chemotherapy	Ali SM Al-Shanqeeti, MD King Fahad Medical City NCT00757094	Completed, no reported results
Ketogenic Diet	Ketogenic Diet	Glioblastoma	n/a	Pavel Klein, MD Mid-Atlantic Epilepsy and Sleep Center NCT01865162	Completed, no reported results
	Ketogenic Diet	Glioblastoma	n/a	Pavel Klein, MD Mid-Atlantic Epilepsy and Sleep Center NCT02302235	August 2017
	Ketogenic Diet	Glioblastoma	Chemotherapy	Song Lin, MD Beijing Tiantan Hospital NCT02939378	December 2018
	Ketogenic Diet	Glioblastoma	Radiation Therapy, Temozolomide	Adrienne C Scheck, PhD Barrow Neurological Institute NCT02046187	March 2018
	Ketogenic Diet	Glioblastoma	n/a	Michael D Jenkinson, PhD FRCS University of Liverpool NCT03075514	March 2019
	Ketogenic Diet	Glioblastoma	Following Standard Treatment	Johannes Rieger, MD Senckenberg Institute of Neurooncology, University of Frankfurt NCT00575146, (Rieger et al,2014)	Feasible and safe, no significant clinical activity as single agent
	Ketogenic Diet	Glioblastoma	Radiation Therapy, Chemotherapy	Kenneth Schwartz, MD Michigan State University NCT01535911	July 2017

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	Intervention	Cancer Type (s)	Adjuvant Treatment (s)	Principle Investigator, Institution, Clinical Trials ID	Results/ Anticipated Completion Date
	Ketogenic Diet	Glioma	n/a	Nachum Vaisman, Prof.Tel-Aviv Sourasky Medical Center NCT01092247	Completed, no reported results
	Ketogenic Diet	Breast	n/a	Eugene J Fine, MD Albert Einstein College of Medicine, Inc. NCT02744079	September 2020
	Ketogenic Diet	Pancreaticobiliary	n/a	Chang Moo Kang, MD Yonsei University NCT02964806	October 2017
	Ketogenic Diet	Bladder	Prescribed Treatment	Eugene Lee, MD University of Kansas Medical Center NCT02716623	March 2018
	Ketogenic Diet	Colorectal, Prostate, Brain, Breast, Pancreatic, Hepatobiliary, Melanoma, Sarcoma, Lung, Genitourinary	n/a	Jocelyn Tan, MD VA Pittsburgh Health System NCT01716468, (Tan-Shalaby et al, 2016)	Maintained or slightly improved quality of life measures, 10%weight loss resulted in better response
	Ketogenic Diet	Breast, Rectum, Head & Neck	Radiation Therapy	Rainer J Klement, PhD MVZ Leopoldina GmbH NCT02516501	June 2018
Combination	Calorie-restricted, Ketogenic Diet with Intermittent Fasting	Glioblastoma	During Reirradiation	Johannes Rieger, Dr.Joachim P Steinbach, Prof. Johann Wolfgang Goethe University Hospital NCT01754350	October 2017
	Calorie-restriction with Physical Activity	Prostate	Prior to or Post Prostatectomy	Wendy Demark-Wahnefried, PhD, RD University of Alabama at Birmingham NCT01886677	Feasible and safe, no serious adverse events reported.
	Calorie-restriction with Physical Activity	Breast	Prior to Mastectomy/Lumpectomy	Wendy Demark-Wahnefried, PhD, RD University of Alabama at Birmingham NCT02224807	December 2017
	Low-carb Atkins diet, Intermittent Fasting	Glioblastoma	Radiation Therapy and/or Temozolomide	Jaishri O. Blakeley, MD Johns Hopkins University Wake Forest School of Medicine NCT02286167	November2017