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

Smith, L. A., O'Flanagan, C. H., Bowers, L. W., Allott, E. H., & Hursting, S. D. (2018). Translating Mechanism-Based Strategies to Break the Obesity-Cancer Link: A Narrative Review. *Journal of the Academy of Nutrition and Dietetics*, *118*(4), 652-667. https://doi.org/10.1016/j.jand.2017.08.112

Published in:
Journal of the Academy of Nutrition and Dietetics

Document Version:
Peer reviewed version

Hungering for New Mechanism-Based Strategies to Break the Obesity-Cancer Link: A Narrative Review

Research Snapshot

Research Question: What are the mechanisms through which obesity increases cancer risk and progression? Does implementation of dietary or lifestyle 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, ketogenic diet and physical activity have the potential to reverse some of these obesity-associated alterations; however, more clinical data is needed to confirm translation to human subjects.

Abstract

The prevalence of obesity, an established risk factor for many cancers, has increased dramatically over the past 50 years in the United States and many other countries. 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 prevention and treatment of obesity-related cancers. We now know that obesity can impact each of the well-established hallmarks of cancer, but obesity-associated perturbations in systemic metabolism and inflammation, and the interactions of these perturbations with cancer cell energetics, are emerging as the primary drivers of obesity-associated cancer development and progression. Several obesity-related host factors, including components of the adipose secretome and structural components of the tumor microenvironment, are extrinsic to, and interact with, the intrinsic molecular characteristics of cancer cells (including cancer stem cells). Each will be considered in the context of potential preventive and therapeutic strategies to reduce the burden of obesity-related cancers. This review will focus on current knowledge of the mechanisms behind the obesity-cancer link as well as relevant dietary and lifestyle interventions that are being implemented in preclinical and clinical trials, with the ultimate goal of reducing incidence and progression of obesity-related cancers.

Abbreviations : AMP kinase (AMPK); body mass index (BMI); brown adipose tissue (BAT); calorie restriction (CR); cardiovascular disease (CVD); estrogen receptor (ER); free fatty acids (FFA); insulin-like growth factor-1 (IGF-1); interleukin (IL); intermittent fasting (IF); ketogenic diet (KD); monocyte chemo-attractant protein-1 (MCP-1); mammalian target of rapamycin (mTOR); non-alcoholic steatohepatitis (NASH); nuclear factor kappa-light-chain-enhancer of B cells (NFκB); plasminogen activator inhibitor-1 (PAI-1); phospatidylinositol-3 kinase (PI3K); peroxisome proliferator-activated receptor (PPAR); physical activity (PA); signal transducer and activator of transcription (STAT);

47 tumor necrosis factor-α (TNF-α); type II Diabetes (T2DM); vascular endothelial growth

48 factor (VEGF); white adipose tissue (WAT)

49

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. Today nearly 40% of adults and 20% of children in the United States are obese[1]. Worldwide, more than 600 million adults are obese and 2.1 billion are overweight[2]. 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[4]. These obesity-associated cancers include 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) many ways in which obesity can influence normal epithelial tissue homeostasis and cancer development and/or progression, including metabolic perturbations involving hormonal,

growth factor and inflammatory alterations, as well as interactions with the microenvironment.

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 cancer prevention and treatment. Searches were completed using PubMed and Google Scholar. A variety of key words were searched including obesity, metabolic syndrome, cancer prevention, cancer treatment, calorie restriction, intermittent fasting, ketogenic diet, and physical activity.

Obesity Impacts Each Hallmark 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" first published in 2000[9] and updated in their 2011 "Hallmarks of Cancer: the Next Generation"[10]. These essential aberrations of cancer cells, include sustaining proliferative signaling, increased chronic inflammation, evading growth suppressors, resisting cell death, displaying genome instability, enabling replicative immortality, inducing angiogenesis, and activating processes related to invasion and metastasis. Conceptual progress in the decade between these two articles led to identification of additional hallmarks, including reprogramming of energy metabolism, evading immune destruction, and creation of the tumor microenvironment through recruitment of various non-cancerous cells. Emerging evidence supports the concept that

metabolic reprogramming, inflammation, and genome instability (including epigenetic changes) represent the "hallmarks of hallmarks" and underlie many of the other essential aberrations of cancer. In the case of cancer-associated metabolic reprogramming, cancer cells often preferentially metabolize glucose through glycolysis rather than oxidative phosphorylation (even under normoxic conditions) to generate substrate for cell division[10-12]. Thus, citric acid cycle intermediates not utilized for ATP production are shuttled out of the mitochondria providing precursors for nucleotide, amino acid and lipid synthesis pathways for the dividing cell[12]. In this way, cancer cells readily take up and metabolize glucose to provide substrate for daughter cell production, with glucose transporters and glycolytic enzymes being elevated in most cancers[13].

Metabolic Syndrome and Systemic Metabolic Perturbations

Interactions between cellular energetics in cancer cells and systemic metabolic changes associated with obesity are emerging as critical drivers of obesity-related cancer. Intrinsically linked with obesity and associated with alterations in several cancer-related host factors is metabolic syndrome, characterized by insulin resistance, hyperglycemia, hypertension and dyslipidemia. In both obesity and metabolic syndrome, alterations occur in circulating levels of insulin and insulin-like growth factor (IGF)-1; adipokines (e.g. leptin, adiponectin, resistin, and monocyte chemotactic protein (MCP)-1); inflammatory factors (e.g. interleukins (IL)-6, 10, and 17, interferon-γ and tumor necrosis factor (TNF)-α); several chemokines; lipid mediators such as prostaglandin E2; and vascular-associated factors (e.g. vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor (PAI)-1)[14-16]. Each of these factors has a putative role in development

and progression of cancer, as well as a number of other chronic diseases[14,16] including CVD and T2DM, and will be explored in more detail below.

Insulin, IGF-1 and Growth Factor Signaling

In response to elevated blood glucose level, pancreatic β-cells release insulin, a peptide hormone that stimulates peripheral uptake of glucose, glucose metabolism, and energy storage pathways. As depicted in Figure 2, obesity and metabolic syndrome are characterized by hyperglycemia and associated aberrations in insulin signaling, growth factor signaling, and glucose metabolism[17]. One growth factor implicated in cancer risk and progression is IGF-1. Produced primarily following growth hormone stimulation in the liver, IGF-1 functions as a regulator of growth and development processes[18]. IGF binding proteins bind to IGF-1 in circulation and limit its bioavailability to bind to IGF-1 receptor and induce downstream signaling to promote growth and/or survival[19]. 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[17]. Growth and survival functions of IGF-1 give it the potential to impact many hallmarks of cancer, including suppression of apoptosis and promotion of cell cycle progression, angiogenesis and metastatic potential[20]. As a result, elevated IGF-1 is established as a risk factor for many types of cancer[19].

IGF-1 receptor and insulin receptor stimulate the same downstream activation of phosphoinositide 3-kinase (PI3K)/Akt pathway (Figure 2), a pathway frequently altered

141 in epithelial cancers[21]. In response to these growth factors and nutrient availability,
142 PI3K/Akt produces lipid messengers that initiate the Akt signaling cascade[21], activating
143 downstream mammalian target of rapamycin (mTOR) [22]. When activated mTOR initiates
144 downstream signaling that promotes cell growth, proliferation and survival. In response
145 to low nutrient conditions AMP-activated kinase (AMPK), another energy responsive
146 pathway, inhibits mTOR activation and downstream signaling[23]. Oncogenic signals or
147 loss of tumor suppressors can activate mTOR and contribute to the hallmarks of cancer,
148 promoting proliferation, survival, angiogenesis, and metastasis[24]. In preclinical models,
149 blocking mTOR signaling with drugs such as rapamycin (mTOR inhibitor)[25-27] and
150 metformin (AMPK activator)[25,28,29], block tumor-enhancing effects associated with the
151 obese phenotype[30]. Interestingly, rapamycin has exhibited anti-inflammatory attributes,
152 attenuating inflammation as well as tumor promotion, suggesting crosstalk between
153 mTOR-related growth and survival signals and inflammatory signals[31].
154
155 **Chronic Inflammation: The Role of Adipose Tissue**
156 Mammals, including humans, have 2 major fat depots: subcutaneous and visceral (intra-
157 abdominal). These adipose depots contain white adipose tissue (WAT) that stores energy
158 in the form of triacylglycerol and brown adipose tissue (BAT) that dissipates energy by
159 burning fatty acids to generate heat. WAT and BAT have important differences in their
160 morphology, metabolism and transcriptional profiles. White adipocytes have few
161 mitochondria, low oxidative rate, and contain a unilocular lipid droplet comprised
162 primarily of triacylglycerol, while brown adipocytes have a high number of mitochondria
163 (hence the darker appearance), high rate of fatty acid and glucose uptake and oxidation,

and possess multilocular lipid droplets[32]. 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 free fatty acids (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[32]. Brown adipocytes also produce adiponectin (but not leptin) and fibroblast growth factor-21, which can be anti-inflammatory and insulin sensitizing[32]. WAT also contains a number of stromal cells including pre-adipocytes, vascular cells, fibroblasts and a host of immune cells such as adipose tissue macrophages[33]. Increased WAT mass in obesity drives chronic inflammation in at least 3 ways, depicted in Figure 4 and summarized below:

1. *Altered Adipose Secretome*

Leptin is an energy-sensing peptide hormone produced by adipocytes. Leptin levels, positively correlated with adiposity, function as an energy sensor through signaling to the hypothalamus, decreasing hunger cues, food intake and weight gain. Leptin release from adipocytes is stimulated by a variety of factors including insulin, TNFα, glucocorticoids, and estrogen[34]. In obesity, leptin is overproduced by adipocytes, reducing hypothalamic sensitivity to the signal[35]. Circulating leptin binds to various receptors in central nervous system and peripheral tissues, regulating processes including energy homeostasis, cytokine production, immune function, and carcinogenesis[34,36]. 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

187 initiation of STAT-induced transcription programs for proliferation, cell growth and
188 survival, migration and differentiation[37]. Deregulation of STATs activity is often
189 observed in cancer[38].
190
191 Adiponectin, another peptide hormone secreted from adipocytes, functions as an energy
192 sensor that promotes hunger and energy intake, opposing the functions of leptin.
193 Although the most abundant hormone secreted from the WAT, adiponectin levels are
194 negatively correlated with adiposity and release is stimulated during energy deficit.
195 Adiponectin opposes obesity-associated metabolic alterations through regulating glucose
196 metabolism, increasing insulin sensitivity and fatty acid oxidation, and reducing IGF-1
197 signaling through activation of AMPK, inhibitor of downstream mTOR[39]. Adiponectin
198 also attenuates inflammation through inhibition of nuclear factor kappa-light-chain-
199 enhancer of B cells (NF-κB), which reduces expression of proinflammatory cytokines
200 while increasing expression of anti-inflammatory cytokines[40]. Due to the anticancer
201 functions of adiponectin, adiponectin agonists are emerging as possible chemotherapeutic
202 agents, particularly for obesity-related cancers[41]. While associations between each of
203 these adipokines and cancer risk are established, the leptin to adiponectin ratio is
204 increasingly considered a more sensitive measure in evaluating cancer risk[42].
205
206 Sex hormones, including estrogen, androgens and progestogens, regulate a variety of
207 growth and developmental processes including weight homeostasis[43]. Long established is
208 the association between sex hormone levels and obesity[44]. In postmenopausal women,
209 BMI is positively correlated with estrone, estradiol, and free estradiol[45]. Elevation of

estrogens is also detected in obese men[44,46]; however, testosterone levels are significantly reduced[47]. Alteration of sex hormones can result in several biological disorders including hypertension, menstrual disturbances, erectile dysfunction, gynecomastia, hirsutism, and increased adiposity[44]. Moreover, sex hormones have been implicated in risk and/or progression of multiple cancer types[48]. In prostate cancer, sex hormone levels are associated with disease progression, not disease risk[49]. Low levels of circulating testosterone correlates with aggressive disease progression[50]. Elevated estrogen levels are associated with increased risk of breast[44,45,51], ovarian[52], and endometrial cancers[53].

Menopausal status can also modulate sex hormone secretion and signaling in women. Prior to menopause, ovaries are the main site of estrogen production, whereas after menopause, peripheral sites including adipose tissue, are the main source of estrogen production. In postmenopausal, obese women adipose tissue serves as the main site of estrogen synthesis[45]. Once released, circulating estrogens bind to one of two estrogen receptors (ER), ERα or ERβ. Once bound, receptors dimerize and translocate to the nucleus where they bind to DNA or other transcription factors, influencing gene expression profiles that regulate growth, proliferation and differentiation[54]. 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[55]. Obesity and postmenopausal status increases risk of ER-positive breast cancers compared with ER-negative breast cancer[56]. Due to the positive association between obesity, circulating estrogen and risk of ER-positive breast cancer,

aromatase inhibitors and ER antagonist, including tamoxifen, have been investigated for their effectiveness as adjuvant therapy[57].

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 (Figure 4). 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[58].

3. Adipose Remodeling and Lipid Infiltration in Other Tissues

During conditions of low nutrient availability or increased energy needs, glucagon secretion stimulates lipolysis of adipocytes, releasing FFA into the blood stream[59]. Circulating FFA can then be utilized by peripheral tissues, providing substrate for β-oxidation and serving as intermediates for energy production through the citric acid cycle and oxidative phosphorylation. Overnutrition remodels existing adipose tissue, expanding adipocyte number and size, and altering adipokine secretion, FFA flux, and adipocyte death[60]. In response, adipose stromal cells modify their functions to promote clearance of necrotic adipocytes and generation of new adipocytes and vasculature. Tissue remodeling in chronic overnutrition or obesity, results in sustained, low-grade inflammation and metabolic alterations[60]. As stated above, cancer cells adapt to changing energy needs for proliferation through metabolic reprogramming, increasing anaerobic metabolism and

255 shunting citric acid cycle intermediates to synthetic pathways[10,12]. Production of daughter
256 cells demands increased levels of FFA for formation of lipid bilayers, thus excess WAT
257 promotes proliferation of tumor cells through provision of circulating FFA[61].
258
259 Chronic overnutrition can lead to lipid accumulation beyond capacity of adipose depots,
260 leading to deposition of lipids in peripheral tissues including muscle, liver and pancreatic
261 tissue[62]. Ectopic lipid intermediates exert lipotoxic effects, impairing cellular organelle
262 functions, releasing inflammatory cytokines, and fostering development of insulin
263 resistance[63]. Consequently, individuals can develop muscle dysfunction and hepatic and
264 pancreatic steatosis, all of which have been positively correlated with insulin resistance
265 and impaired lipid metabolism[62].
266
267 Nonalcoholic fatty liver disease, diagnosed as >5-10% liver fat content by weight in the
268 absence of alcohol use or other liver disease, encompasses a variety of liver diseases
269 including simple steatosis, nonalcoholic steatohepatitis (NASH) and cirrhosis[64]. One of
270 the most common chronic diseases[65-67], Nonalcoholic fatty liver disease is present in 65-
271 85% of obese patients[64,68] with rapidly rising incidence among adults and children[66,69].
272 Excess accumulation of lipids in the liver, exerts lipotoxic effects including production of
273 reactive oxygen species, activation of pro-inflammatory programs, and endoplasmic
274 reticular stress, impairing function of cellular organelles and potentially inducing hepatic
275 cell death[70]. Additionally, accumulation of lipids and pro-inflammatory cytokines
276 promotes activation of intracellular kinases, leading to impaired insulin signaling and
277 development of insulin resistance[71]. 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[72].

Deposition of adipocytes in the pancreas appears to occur early in obesity-associated pancreatic dysfunction, altering secretion and signaling of endocrine factors including insulin. Infiltrating fat in the pancreas has been associated with increased visceral WAT mass and insulin resistance[73,74]. 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, established risk factors for pancreatic cancer[73,74].

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, is a potent angiogenic factor that is produced by adipocytes and tumor cells. VEGF acts on endothelial cells stimulating mitogenic and vascular permeability-enhancing activities[75]. Obesity is associated with increased circulating VEGF, and elevated VEGF correlates with poor prognosis for many obesity-related cancers[76]. PAI-1 is another angiogenic factor, produced by adipocytes, endothelial cells, and stromal cells in visceral WAT[77], that 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[77]. While interaction of 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 would potentially 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[78]. Extracellular matrix remodeling is a key feature of invasive disease, and integral in the development of metastatic lesions[79]. 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[79]. 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[80].

Dietary Interventions Targeting Obesity for Cancer Prevention and Treatment

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 consistently associated with reduced cancer risk is bariatric surgery[81]. In light of the

expense and complications inherent in surgical weight loss approaches, current efforts are focusing on reducing adiposity through lifestyle and dietary interventions. To achieve reductions in weight and adiposity these interventions have aimed to 1) promote negative energy balance through either reduced energy intake via calorie restriction (CR) or intermittent fasting (IF) or through increased energy expenditure via physical activity (PA) or 2) implementation of ketogenic diet (KD) a dietary pattern associated with weight loss and reduced cancer progression. Preclinical and some clinical studies suggest that these interventions can favorably and inversely modulate cancer risk biomarkers including insulin, IGF-1, leptin, adiponectin, cytokines, angiogenic factors, and crown-like structures compared to the obese state. Modulation of these biomarkers could result in downstream reductions in growth factor signaling, inflammation, and angiogenesis, attenuating cancer risk and progression (Figure 5).

1. 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, growth factor signaling, inflammation, oxidative stress and angiogenesis[82-85]. These metabolic changes translate into significantly decreased cancer incidence in murine models[86]. 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 has confirmed reduced adiposity, improved glucose homeostasis, increased adiponectin, and reduced leptin and inflammatory markers TNFα and C-reactive protein[87,88]. Substantial weight loss of >10% may be necessary to consistently gain these benefits[89-91].

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. Emerging findings from preliminary clinical trials suggest that application of CR as an adjuvant therapy in combination with chemotherapy and/or radiation has potential to increase responsiveness to treatment[92,93].

2. 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[94]. 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 lower insulin resistance, inflammation, and circulating IGF-1[95]. The impact of IF on angiogenesis in the context of cancer remains unexplored in

currently published research. Preclinical studies with IF consistently exhibit a cancer preventative effect with reduced rates of tumor growth for multiple cancer types[95-97]. 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 human, including improved adipokine ratios and reduced inflammation[96,98], suggesting the reported preclinical anticancer effects of IF may be translatable to humans.

One IF regimen being examined as a breast cancer prevention strategy is called the 5:2 diet and 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[99-103]. 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[104].

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 (various cancer types) voluntarily fasted prior to (48-140 hours) or following (5-56 hours) chemotherapy treatment. Compared with non-restricted control subjects, fasting reduced

393 chemotherapy-induced side effects including fatigue, weakness and gastrointestinal side
394 effects while exhibiting the same chemotherapy-induced reduction in tumor volume or
395 biomarkers[105]. Following this ground breaking study, others have implemented IF in
396 small scale clinical trials including de Groot, S., et al., 2015, where short term IF among
397 stage II/III breast cancer patients was well tolerated, reduced signs of hematological
398 toxicity and stimulated faster recovery from DNA damage in normal host peripheral
399 blood mononuclear cells[106]. Limited preclinical findings suggest that IF may selectively
400 protect healthy cells and make cancer cells more vulnerable to chemotherapeutic agents,
401 reducing side-effects and increasing drug efficacy[95]. More research is needed to confirm
402 these findings and identify underlying mechanisms.
403
404
405 *3. Physical Activity*
406 Engaging in physical activity (PA), alone or in combination with reduced dietary energy
407 intake, can be another effective method in generating a negative energy balance, reducing
408 weight and adiposity. A published systematic review of the literature on PA in cancer
409 survivors revealed that PA produced favorable modulation of insulin/IGF-1 pathways and
410 inflammation[107]. Limited evidence from preclinical studies suggest that PA may also
411 reduce the level of intratumoral mTOR activation, VEGF expression and
412 angiogenesis[108,109]. Intervention studies suggest that reduction in these risk biomarkers
413 associated with PA may be reliant on significant weight loss[110-112]. Furthermore, the
414 amount of exercise can influence effectiveness of PA. For example, in one study PA did
415 not significantly reduce inflammatory markers unless participants achieved 120 minutes

per week, just short of the American Cancer Society's recommendation of 150 minutes[113]. Epidemiological and cohort studies confirm an anticancer potential and demonstrate a 20-30% reduction in cancer risk with substantial PA for multiple cancer types including breast, colon and endometrial[114].

PA is also safe and beneficial during cancer therapy for multiple cancer types[115-117]. Not only can PA improve body composition, it can also reduce unwanted side effects of treatment and improve physical functioning and quality of life parameters. A randomized control trial in stage II breast cancer patients found that 10 weeks of interval-based, aerobic exercise reduced chemotherapy-induced nausea and increased individual functional capacity[118,119]. Courneya, et al. findings suggest that PA may increase chemotherapy completion rate without causing adverse events such as lymphedema in breast cancer patients[120]. Benefits are further exhibited in elderly patients with exercise during treatment improving memory and self-reported health and reducing fatigue[121]. Studies on exercise during treatment suggest that higher-intensity exercise provides more benefit than low-intensity exercise[122].

Despite the observed positive benefits of PA, important questions remain regarding intensity and amount of physical activity that must be performed to fully reap the benefits. Based on current knowledge, the American Cancer Society advises 150 minutes of moderate or 75 minutes of vigorous per week for cancer prevention and survivorship[123].

4. 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 adverse side effects associated with ketoacidosis[124]. Ketosis from KD favorably modulates many cancer risk biomarkers including IGF-1, leptin, adiponectin, inflammatory markers, and angiogenic factors (Figure 5)[125-128]. Preclinical studies suggest that KD can attenuate these markers without a reduction in caloric intake; however, weight loss may be needed[129,130]. 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 the satiety; reduced lipogenesis and increased lipolysis; greater metabolic efficiency; and increased metabolic cost of gluconeogenesis and ketogenesis[124].

Beneficial effects of the ketogenic diet have long been established for epilepsy and T2DM; emerging is its role in cancer prevention and treatment[124]. Early preclinical studies found KD reduced tumor burden and cachexia in a mouse model of colon

462 cancer[131]. Further preclinical models have confirmed these findings and extended benefits
463 of decreased tumor growth and increased survival to other cancer types including
464 malignant glioma, gastric and prostate cancers[132]. To date results from clinical trials
465 focused on implementation of KD in cancer prevention and treatment have been limited,
466 and ongoing clinical trials are addressing this gap in the literature with multiple cancer
467 types[133].
468
469 It is important to also consider potential adverse effects of KD. Reduction of
470 carbohydrate in KD is replaced with increased protein and fat. High protein intake has
471 been linked to kidney damage[134], although this is not widely accepted with other
472 preclinical, human, and meta-analysis studies finding no evidence of renal damage with
473 high protein intake[124]. Additionally, select preclinical studies have found long-term KD
474 to cause dyslipidemia, hepatic steatosis and glucose intolerance[135]. More research is
475 needed to evaluate the safety and efficacy of ketogenic diets as cancer prevention and
476 treatment interventions.
477
478 **Summary and Conclusions**
479 A strong link between obesity and cancer risk has been established in the epidemiological
480 and preclinical literature. Obesity is associated with several systemic metabolic
481 perturbations that are correlated with increased cancer risk and/or poor prognosis,
482 including dysregulation of insulin and growth factor signaling, adipokine signaling,
483 inflammation, and angiogenesis. Establishment of this obesity-cancer link has spurred
484 research focused on a variety of lifestyle and dietary interventions to promote a negative

485 energy balance, attain weight loss, attenuate risk biomarkers, and prevent obesity-
486 associated cancers. Preclinical and early clinical work on these putative anticancer dietary
487 and lifestyle interventions, including CR, PA, IF, and KD, are also being evaluated, some
488 showing promise in reducing cancer risk. Additionally, the literature suggests that these
489 interventions may improve response to chemotherapy for multiple cancer types. While
490 many clinical studies have evaluated the safety and efficacy of PA as adjuvant therapy
491 and suggest it is safe for patients, there are few clinical trials that evaluate the utilization
492 of dietary interventions such as CR, IF, and KD as adjuvant therapy (Table 1). Future
493 studies will need to focus on the safety and added benefit to current therapies, and should
494 also consider the potential of the dietary interventions to sensitize patients and facilitate
495 the use of lower doses of chemotherapy or radiation therapy to improve therapeutic
496 response.
497
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867 **Figure Legends**

868 Figure 1: Obesity is associated with increased risk of developing and dying from the
869 following cancers: breast (in postmenopausal women), ovarian, liver, gallbladder, kidney
870 (renal cell), colon, pancreatic, gastric, esophageal (adenocarcinoma), endometrial,
871 thyroid, multiple myeloma, and meningioma[4]. In addition, obesity is associated with
872 progression (but not incidence) of prostate cancer[8].

873

874 Figure 2: Obesity and metabolic syndrome result in many metabolic disturbances
875 including elevations in circulating insulin, adipokines (e.g. leptin-to-adiponectin ratio),
876 cytokines, angiogenic factors (PAI-1 and VEGF), as well as increased prevalence of
877 adipose tissue crown-like structures, a marker of adipose inflammation. These factors can
878 activate receptor tyrosine kinase signaling through the PI3 kinase (PI3K)/Akt/mammalian
879 target of rapamycin (mTOR) pathway. An increase in steady state signaling through this
880 pathway can drive increases in cellular proliferation and protein translation, and reinforce
881 cancer-associated metabolic reprogramming. Activation of NF-κB by proinflammatory
882 cytokines, induces translocation to the nucleus and upregulates expression of genes
883 involved in survival proliferation, inflammation and immune regulation. Together,
884 obesity-associated elevation of growth factor signaling and inflammation and reduction
885 of vascular integrity fosters a microenvironment favorable for tumorigenesis, increasing
886 cancer risk and progression.

887

888 Figure 3: The human body contains two types of adipocytes: white adipocytes (which
889 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.

Figure 4: In obesity, as adipocytes accumulate triglycerides, their secretomes shift towards the production of pro-inflammatory and/or insulin resistant molecules, including numerous cytokines, adipokines (e.g. leptin and resistin), and free fatty acids. Engorged/necrotic adipocytes attract macrophages and other immune cells that further contribute to the pro-inflammatory environment. The altered secretome resulting from macrophage-adipocyte interactions modulates several enzymes associated with increased inflammation-related lipid mediators (such as prostaglandins and leukotrienes) and hormones (such as aromatase, which converts androgens to estrogens).

Figure 5: Dietary and lifestyle interventions of caloric restriction (CR), intermittent fasting (IF), physical activity (PA) and adherence to a ketogenic diet (KD), have been shown to reduce adiposity and favorably modulate many of the same cancer risk biomarkers that are impacted by obesity including: insulin, IGF-1, leptin, adiponectin, cytokines, angiogenic factors, and crown-like structures. These metabolic alterations

could result in downstream reductions in growth factor signaling, inflammation, and angiogenesis and attenuate cancer risk and progression. Metabolic alterations with CR, IF and PA interventions have been associated with reduced cancer risk and progression. While KD has not been linked to cancer risk, it has been demonstrated that adherence to KD reduces cancer risk and progression in preclinical studies. a) Insufficient evidence exist to conclude the impact of PA and IF on PAI-1 and VEGF expression. b) Current literature does not exist examining the impact of KD on crown-like structures.