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

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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);

tumor necrosis factor-α (TNF-α); type II Diabetes (T2DM); vascular endothelial growth factor (VEGF); white adipose tissue (WAT)

50 **Introduction**

51 Over the past half century in the United States the prevalence of obesity, defined as body
52 mass index (BMI) of 30 kg/m^2 or greater, has tripled. Today nearly 40% of adults and
53 20% of children in the United States are obese[1]. Worldwide, more than 600 million adults
54 are obese and 2.1 billion are overweight[2]. Obesity increases risk of several chronic
55 diseases and comorbidities including type II diabetes (T2DM), cardiovascular disease
56 (CVD), hypertension, chronic inflammation and, as discussed in this review, many types
57 of cancer[3].

58

59 As illustrated in Figure 1, and based on the recent report from the International Agency
60 for Research on Cancer, risk of 13 distinct cancer types is increased with excess body
61 fatness[4]. These obesity-associated cancers include breast (in postmenopausal women),
62 ovarian, liver, gallbladder, kidney, colon, pancreatic, gastric, esophageal, endometrial,
63 thyroid, multiple myeloma, and meningioma[4]. Overall, an estimated 13% of incident
64 cases worldwide, and approximately 20% of incident cases in Europe and North America,
65 are attributable to obesity[5]. Aside from higher risk of developing cancer, obese
66 individuals are more likely to have reduced response to anticancer therapies[6], and obesity
67 is implicated in approximately 20% of all cancer-related mortalities[7]. This includes
68 prostate cancer, for which obesity increases progression but not incidence[8]. Here, we
69 discuss (with a focus on developing mechanism-based intervention strategies) many ways
70 in which obesity can influence normal epithelial tissue homeostasis and cancer
71 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

95 metabolic reprogramming, inflammation, and genome instability (including epigenetic
96 changes) represent the "hallmarks of hallmarks" and underlie many of the other essential
97 aberrations of cancer. In the case of cancer-associated metabolic reprogramming, cancer
98 cells often preferentially metabolize glucose through glycolysis rather than oxidative
99 phosphorylation (even under normoxic conditions) to generate substrate for cell
100 division[10-12]. Thus, citric acid cycle intermediates not utilized for ATP production are
101 shuttled out of the mitochondria providing precursors for nucleotide, amino acid and lipid
102 synthesis pathways for the dividing cell[12]. In this way, cancer cells readily take up and
103 metabolize glucose to provide substrate for daughter cell production, with glucose
104 transporters and glycolytic enzymes being elevated in most cancers[13].
105
106 **Metabolic Syndrome and Systemic Metabolic Perturbations**
107 Interactions between cellular energetics in cancer cells and systemic metabolic changes
108 associated with obesity are emerging as critical drivers of obesity-related cancer.
109 Intrinsically linked with obesity and associated with alterations in several cancer-related
110 host factors is metabolic syndrome, characterized by insulin resistance, hyperglycemia,
111 hypertension and dyslipidemia. In both obesity and metabolic syndrome, alterations occur
112 in circulating levels of insulin and insulin-like growth factor (IGF)-1; adipokines (e.g.
113 leptin, adiponectin, resistin, and monocyte chemotactic protein (MCP)-1); inflammatory
114 factors (e.g. interleukins (IL)-6, 10, and 17, interferon-γ and tumor necrosis factor (TNF)-
115 α); several chemokines; lipid mediators such as prostaglandin E2; and vascular-
116 associated factors (e.g. vascular endothelial growth factor (VEGF) and plasminogen
117 activator inhibitor (PAI)-1)[14-16]. Each of these factors has a putative role in development

118 and progression of cancer, as well as a number of other chronic diseases[14,16] including
119 CVD and T2DM, and will be explored in more detail below.
120
121 **Insulin, IGF-1 and Growth Factor Signaling**
122 In response to elevated blood glucose level, pancreatic β-cells release insulin, a peptide
123 hormone that stimulates peripheral uptake of glucose, glucose metabolism, and energy
124 storage pathways. As depicted in Figure 2, obesity and metabolic syndrome are
125 characterized by hyperglycemia and associated aberrations in insulin signaling, growth
126 factor signaling, and glucose metabolism[17]. One growth factor implicated in cancer risk
127 and progression is IGF-1. Produced primarily following growth hormone stimulation in
128 the liver, IGF-1 functions as a regulator of growth and development processes[18]. IGF
129 binding proteins bind to IGF-1 in circulation and limit its bioavailability to bind to IGF-1
130 receptor and induce downstream signaling to promote growth and/or survival[19].
131 Hyperglycemia and hyperinsulinemia, hallmarks of metabolic syndrome, increase IGF-1
132 production and bioavailability. Hyperglycemia suppresses IGF-1 binding protein
133 synthesis and hyperinsulinemia promotes expression of growth hormone receptor and
134 subsequent IGF-1 synthesis[17]. Growth and survival functions of IGF-1 give it the
135 potential to impact many hallmarks of cancer, including suppression of apoptosis and
136 promotion of cell cycle progression, angiogenesis and metastatic potential[20]. As a result,
137 elevated IGF-1 is established as a risk factor for many types of cancer[19].
138
139 IGF-1 receptor and insulin receptor stimulate the same downstream activation of
140 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

210 estrogens is also detected in obese men[44,46]; however, testosterone levels are significantly
211 reduced[47]. Alteration of sex hormones can result in several biological disorders including
212 hypertension, menstrual disturbances, erectile dysfunction, gynecomastia, hirsutism, and
213 increased adiposity[44]. Moreover, sex hormones have been implicated in risk and/or
214 progression of multiple cancer types[48]. In prostate cancer, sex hormone levels are
215 associated with disease progression, not disease risk[49]. Low levels of circulating
216 testosterone correlates with aggressive disease progression[50]. Elevated estrogen levels are
217 associated with increased risk of breast[44,45,51], ovarian[52], and endometrial cancers[53].
218
219 Menopausal status can also modulate sex hormone secretion and signaling in women.
220 Prior to menopause, ovaries are the main site of estrogen production, whereas after
221 menopause, peripheral sites including adipose tissue, are the main source of estrogen
222 production. In postmenopausal, obese women adipose tissue serves as the main site of
223 estrogen synthesis[45]. Once released, circulating estrogens bind to one of two estrogen
224 receptors (ER), ERα or ERβ. Once bound, receptors dimerize and translocate to the
225 nucleus where they bind to DNA or other transcription factors, influencing gene
226 expression profiles that regulate growth, proliferation and differentiation[54]. In the context
227 of cancer, the two receptors have differing roles. ERα is mitogenic and an established
228 target in treatment of estrogen receptor-positive breast cancer, while ERβ is suggested to
229 be tumor suppressive[55]. Obesity and postmenopausal status increases risk of ER-positive
230 breast cancers compared with ER-negative breast cancer[56]. Due to the positive
231 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

278 detrimental, characterized by liver injury, inflammation and/or fibrosis. NASH can
279 further result in the development of cirrhosis, liver failure, and hepatocellular
280 carcinoma[72].
281
282 Deposition of adipocytes in the pancreas appears to occur early in obesity-associated
283 pancreatic dysfunction, altering secretion and signaling of endocrine factors including
284 insulin. Infiltrating fat in the pancreas has been associated with increased visceral WAT
285 mass and insulin resistance[73,74]. These endocrine alterations further complicate the
286 complex metabolic and inflammatory perturbations characterized in obesity and
287 metabolic syndrome and can trigger the development of pancreatic steatosis, pancreatitis
288 and/or nonalcoholic fatty pancreatic disease, established risk factors for pancreatic
289 cancer[73,74].
290
291 **Angiogenesis**
292 As adipose tissue depots expand in obesity, the existing vasculature must expand to meet
293 demand. This outgrowth of new blood vessels is termed angiogenesis. Key mediators of
294 this process include VEGF and PAI-1. VEGF, is a potent angiogenic factor that is
295 produced by adipocytes and tumor cells. VEGF acts on endothelial cells stimulating
296 mitogenic and vascular permeability-enhancing activities[75]. Obesity is associated with
297 increased circulating VEGF, and elevated VEGF correlates with poor prognosis for many
298 obesity-related cancers[76]. PAI-1 is another angiogenic factor, produced by adipocytes,
299 endothelial cells, and stromal cells in visceral WAT[77], that is frequently elevated in obese
300 subjects. Increased circulating PAI-1 is associated with increased risk of other chronic

301 diseases including CVD, T2DM and a number of cancers[77]. While interaction of
302 angiogenic factors with proximal endothelial cells induce formation of local blood
303 vessels, providing a route for oxygen and nutrient delivery and waste removal, these
304 factors can also interact with peripheral tissues, facilitating angiogenesis, and potentially
305 promoting progression at tumor sites. These newly formed blood vessels would
306 potentially provide primary tumor mass with oxygen and nutrients to sustain proliferation
307 and survival as well as a route for metastasis to distant sites. PAI-1 functionally inhibits
308 plasminogen activators, thus regulating extracellular matrix integrity[78]. Extracellular
309 matrix remodeling is a key feature of invasive disease, and integral in the development of
310 metastatic lesions[79]. Due to the antitumorigenic potential of factors that modulate
311 angiogenesis, targeted drugs have been developed. However, caution should be advised
312 in administration of anti-angiogenic treatments in obese patients, as these drugs can
313 induce hypoxia in primary tumors, potentially encouraging metastasis, already a concern
314 in the obese population[79]. Elevation of these factors may also impact efficacy of
315 treatment regimens, as excess circulating VEGF in obese patients contributes to reduced
316 efficacy of anti-VEGF therapies (e.g. bevacizumab) compared with non-obese ovarian
317 cancer patients[80].
318
319 **Dietary Interventions Targeting Obesity for Cancer Prevention and Treatment**
320 Given the multifaceted role of obesity in promoting a protumorigenic microenvironment
321 that facilitates tumor development and progression, interventions are urgently needed to
322 break the obesity-cancer link. To date, the only weight loss intervention in obese people
323 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

370 currently published research. Preclinical studies with IF consistently exhibit a cancer
371 preventative effect with reduced rates of tumor growth for multiple cancer types[95-97]. To
372 our knowledge there is no published data on IF and cancer incidence in human subjects,
373 although there are reports of favorable effects of IF in overweight human, including
374 improved adipokine ratios and reduced inflammation[96,98], suggesting the reported
375 preclinical anticancer effects of IF may be translatable to humans.
376
377 One IF regimen being examined as a breast cancer prevention strategy is called the 5:2
378 diet and involves 5 days/week of a healthy diet, such as the Mediterranean diet, with two
379 consecutive days of a low calorie, low carbohydrate diet. The Mediterranean diet is
380 primarily a plant-based diet high in fruits, vegetables, whole grains, legumes and nuts.
381 Compared to North American dietary patterns, the Mediterranean diet has been
382 associated with better control of body weight, reduction of cancer risk biomarkers and
383 decreased cancer incidence[99-103]. The diet results in favorable modulation of
384 inflammation, oxidative stress, and growth factor signaling. Combining a Mediterranean
385 diet with 2 days of a very low calorie, low carbohydrate diet for one month in 24 obese
386 women at high risk for breast cancer induced changes in breast tissue gene expression
387 and metabolites associated with reduced risk of breast cancer[104].
388
389 Regarding the effects of IF on cancer prognosis, a study by Safdie, et al suggests IF
390 during cancer therapy may decrease adverse effects of chemotherapy. Ten cancer patients
391 (various cancer types) voluntarily fasted prior to (48-140 hours) or following (5-56 hours)
392 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[105]. 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[106]. 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[95]. More research is needed to confirm these findings and identify underlying mechanisms.

3. Physical Activity

Engaging in physical activity (PA), alone or in combination with reduced dietary energy intake, can be another effective method in generating a negative energy balance, reducing weight and adiposity. A published systematic review of the literature on PA in cancer survivors revealed that PA produced favorable modulation of insulin/IGF-1 pathways and inflammation[107]. Limited evidence from preclinical studies suggest that PA may also reduce the level of intratumoral mTOR activation, VEGF expression and angiogenesis[108,109]. Intervention studies suggest that reduction in these risk biomarkers associated with PA may be reliant on significant weight loss[110-112]. Furthermore, the amount of exercise can influence effectiveness of PA. For example, in one study PA did not significantly reduce inflammatory markers unless participants achieved 120 minutes

416 per week, just short of the American Cancer Society's recommendation of 150
417 minutes[113]. Epidemiological and cohort studies confirm an anticancer potential and
418 demonstrate a 20-30% reduction in cancer risk with substantial PA for multiple cancer
419 types including breast, colon and endometrial[114].
420
421 PA is also safe and beneficial during cancer therapy for multiple cancer types[115-117]. Not
422 only can PA improve body composition, it can also reduce unwanted side effects of
423 treatment and improve physical functioning and quality of life parameters. A randomized
424 control trial in stage II breast cancer patients found that 10 weeks of interval-based,
425 aerobic exercise reduced chemotherapy-induced nausea and increased individual
426 functional capacity[118,119]. Courneya, et al. findings suggest that PA may increase
427 chemotherapy completion rate without causing adverse events such as lymphedema in
428 breast cancer patients[120]. Benefits are further exhibited in elderly patients with exercise
429 during treatment improving memory and self-reported health and reducing fatigue[121].
430 Studies on exercise during treatment suggest that higher-intensity exercise provides more
431 benefit than low-intensity exercise[122].
432
433 Despite the observed positive benefits of PA, important questions remain regarding
434 intensity and amount of physical activity that must be performed to fully reap the
435 benefits. Based on current knowledge, the American Cancer Society advises 150 minutes
436 of moderate or 75 minutes of vigorous per week for cancer prevention and
437 survivorship[123].
438

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
498 **References**

499 1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in
500 the distribution of body mass index among US adults, 1999-2010. *JAMA.*
501 2012;307(5):491-497.
502 2. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence
503 of overweight and obesity in children and adults during 1980-2013: a
504 systematic analysis for the Global Burden of Disease Study 2013. *Lancet.*
505 2014;384(9945):766-781.
506 3. Khaodhiar L, McCowen KC, Blackburn GL. Obesity and its comorbid conditions.
507 *Clinical cornerstone.* 1999;2(3):17-31.

508 4. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body Fatness and Cancer--
509 Viewpoint of the IARC Working Group. *N Engl J Med.* 2016;375(8):794-798.
510 5. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to
511 high body-mass index in 2012: a population-based study. *The Lancet Oncology.*
512 2014.
513 6. Lashinger LM, Rossi EL, Hursting SD. Obesity and resistance to cancer
514 chemotherapy: interacting roles of inflammation and metabolic dysregulation.
515 *Clinical pharmacology and therapeutics.* 2014;96(4):458-463.
516 7. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and
517 mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J*
518 *Med.* 2003;348(17):1625-1638.
519 8. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the
520 evidence. *European urology.* 2013;63(5):800-809.
521 9. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000;100(1):57-70.
522 10. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.*
523 2011;144(5):646-674.
524 11. Chen X, Qian Y, Wu S. The Warburg effect: evolving interpretations of an
525 established concept. *Free Radic Biol Med.* 2015;79:253-263.
526 12. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even
527 warburg did not anticipate. *Cancer cell.* 2012;21(3):297-308.
528 13. Ganapathy-Kanniappan S, Geschwind JF. Tumor glycolysis as a target for
529 cancer therapy: progress and prospects. *Mol Cancer.* 2013;12:152.

530 14. Hursting SD, Berger NA. Energy balance, host-related factors, and cancer
531 progression. *J Clin Oncol.* 2010;28(26):4058-4065.
532 15. Hursting SD, Smith SM, Lashinger LM, Harvey AE, Perkins SN. Calories and
533 carcinogenesis: lessons learned from 30 years of calorie restriction research.
534 *Carcinogenesis.* 2010;31(1):83-89.
535 16. Bonomini F, Rodella LF, Rezzani R. Metabolic syndrome, aging and
536 involvement of oxidative stress. *Aging and disease.* 2015;6(2):109-120.
537 17. Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic
538 syndrome and cancer. *International journal of biological sciences.*
539 2011;7(7):1003-1015.
540 18. Agrogiannis GD, Sifakis S, Patsouris ES, Konstantinidou AE. Insulin-like growth
541 factors in embryonic and fetal growth and skeletal development (Review).
542 *Molecular medicine reports.* 2014;10(2):579-584.
543 19. Pollak M. The insulin and insulin-like growth factor receptor family in
544 neoplasia: an update. *Nat Rev Cancer.* 2012;12(3):159-169.
545 20. Brahmkhatri VP, Prasanna C, Atreya HS. Insulin-like growth factor system in
546 cancer: novel targeted therapies. *BioMed research international.*
547 2015;2015:538019.
548 21. Wong KK, Engelman JA, Cantley LC. Targeting the PI3K signaling pathway in
549 cancer. *Current opinion in genetics & development.* 2010;20(1):87-90.
550 22. Memmott RM, Dennis PA. Akt-dependent and -independent mechanisms of
551 mTOR regulation in cancer. *Cellular signalling.* 2009;21(5):656-664.

552 23. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that
553 maintains energy homeostasis. *Nature reviews Molecular cell biology.*
554 2012;13(4):251-262.
555 24. Populo H, Lopes JM, Soares P. The mTOR signalling pathway in human cancer.
556 *International journal of molecular sciences.* 2012;13(2):1886-1918.
557 25. Cifarelli V, Lashinger LM, Devlin KL, et al. Metformin and Rapamycin Reduce
558 Pancreatic Cancer Growth in Obese Prediabetic Mice by Distinct MicroRNA-
559 Regulated Mechanisms. *Diabetes.* 2015.
560 26. Athar M, Kopelovich L. Rapamycin and mTORC1 inhibition in the mouse: skin
561 cancer prevention. *Cancer Prev Res (Phila).* 2011;4(7):957-961.
562 27. Nogueira LM, Dunlap SM, Ford NA, Hursting SD. Calorie restriction and
563 rapamycin inhibit MMTV-Wnt-1 mammary tumor growth in a mouse model of
564 postmenopausal obesity. *Endocr Relat Cancer.* 2012;19(1):57-68.
565 28. Tomimoto A, Endo H, Sugiyama M, et al. Metformin suppresses intestinal polyp
566 growth in ApcMin/+ mice. *Cancer science.* 2008;99(11):2136-2141.
567 29. Chaudhary SC, Kurundkar D, Elmets CA, Kopelovich L, Athar M. Metformin, an
568 antidiabetic agent reduces growth of cutaneous squamous cell carcinoma by
569 targeting mTOR signaling pathway. *Photochemistry and photobiology.*
570 2012;88(5):1149-1156.
571 30. De Angel RE, Conti CJ, Wheatley KE, et al. The enhancing effects of obesity on
572 mammary tumor growth and Akt/mTOR pathway activation persist after
573 weight loss and are reversed by RAD001. *Mol Carcinog.* 2013;52(6):446-458.

574 31. Checkley LA, Rho O, Moore T, Hursting S, DiGiovanni J. Rapamycin is a potent
575 inhibitor of skin tumor promotion by 12-O-tetradecanoylphorbol-13-acetate.
576 *Cancer Prev Res (Phila).* 2011;4(7):1011-1020.
577 32. Saely CH, Geiger K, Drexel H. Brown versus white adipose tissue: a mini-
578 review. *Gerontology.* 2012;58(1):15-23.
579 33. Eto H, Suga H, Matsumoto D, et al. Characterization of structure and cellular
580 components of aspirated and excised adipose tissue. *Plastic and reconstructive*
581 *surgery.* 2009;124(4):1087-1097.
582 34. Gautron L, Elmquist JK. Sixteen years and counting: an update on leptin in
583 energy balance. *J Clin Invest.* 2011;121(6):2087-2093.
584 35. Friedman JM, Mantzoros CS. 20 years of leptin: from the discovery of the leptin
585 gene to leptin in our therapeutic armamentarium. *Metabolism.* 2015;64(1):1-
586 4.
587 36. Park HK, Ahima RS. Leptin signaling. *F1000Prime Rep.* 2014;6:73.
588 37. Mullen M, Gonzalez-Perez RR. Leptin-Induced JAK/STAT Signaling and Cancer
589 Growth. *Vaccines (Basel).* 2016;4(3).
590 38. Yu H, Lee H, Herrmann A, Buettner R, Jove R. Revisiting STAT3 signalling in
591 cancer: new and unexpected biological functions. *Nat Rev Cancer.*
592 2014;14(11):736-746.
593 39. Vaiopoulos AG, Marinou K, Christodoulides C, Koutsilieris M. The role of
594 adiponectin in human vascular physiology. *International journal of cardiology.*
595 2012;155(2):188-193.

596 40. Fantuzzi G. Adiponectin in inflammatory and immune-mediated diseases.
597 *Cytokine.* 2013;64(1):1-10.
598 41. Otvos L, Jr., Haspinger E, La Russa F, et al. Design and development of a
599 peptide-based adiponectin receptor agonist for cancer treatment. *BMC*
600 *biotechnology.* 2011;11:90.
601 42. Ollberding NJ, Kim Y, Shvetsov YB, et al. Prediagnostic leptin, adiponectin, C-
602 reactive protein, and the risk of postmenopausal breast cancer. *Cancer Prev*
603 *Res (Phila).* 2013;6(3):188-195.
604 43. Brown LM, Gent L, Davis K, Clegg DJ. Metabolic impact of sex hormones on
605 obesity. *Brain Res.* 2010;1350:77-85.
606 44. Kirschner MA, Schneider G, Ertel NH, Worton E. Obesity, androgens, estrogens,
607 and cancer risk. *Cancer Res.* 1982;42(8 Suppl):3281s-3285s.
608 45. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the
609 estrogen connection. *Endocrinology.* 2009;150(6):2537-2542.
610 46. Meyer MR, Clegg DJ, Prossnitz ER, Barton M. Obesity, insulin resistance and
611 diabetes: sex differences and role of oestrogen receptors. *Acta Physiol (Oxf).*
612 2011;203(1):259-269.
613 47. Allan CA, McLachlan RI. Androgens and obesity. *Current opinion in*
614 *endocrinology, diabetes, and obesity.* 2010;17(3):224-232.
615 48. Folkerd EJ, Dowsett M. Influence of sex hormones on cancer progression. *J Clin*
616 *Oncol.* 2010;28(26):4038-4044.
617 49. Endogenous H, Prostate Cancer Collaborative G, Roddam AW, Allen NE,
618 Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a

619 collaborative analysis of 18 prospective studies. *J Natl Cancer Inst.*
620 2008;100(3):170-183.
621 50. Schnoeller T, Jentzmik F, Rinnab L, et al. Circulating free testosterone is an
622 independent predictor of advanced disease in patients with clinically localized
623 prostate cancer. *World J Urol.* 2013;31(2):253-259.
624 51. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk.
625 *Epidemiologic reviews.* 1993;15(1):48-65.
626 52. Ho SM. Estrogen, progesterone and epithelial ovarian cancer. *Reproductive*
627 *biology and endocrinology : RB&E.* 2003;1:73.
628 53. Rizner TL. Estrogen biosynthesis, phase I and phase II metabolism, and action
629 in endometrial cancer. *Molecular and cellular endocrinology.* 2013;381(1-
630 2):124-139.
631 54. Heldring N, Pike A, Andersson S, et al. Estrogen receptors: how do they signal
632 and what are their targets. *Physiological reviews.* 2007;87(3):905-931.
633 55. Huang B, Warner M, Gustafsson JA. Estrogen receptors in breast
634 carcinogenesis and endocrine therapy. *Molecular and cellular endocrinology.*
635 2014.
636 56. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP,
637 Sherman ME. Etiology of hormone receptor-defined breast cancer: a
638 systematic review of the literature. *Cancer Epidemiol Biomarkers Prev.*
639 2004;13(10):1558-1568.
640 57. Goodwin PJ. Obesity and endocrine therapy: host factors and breast cancer
641 outcome. *Breast.* 2013;22 Suppl 2:S44-47.

642 58. Subbaramaiah K, Howe LR, Bhardwaj P, et al. Obesity is associated with
643 inflammation and elevated aromatase expression in the mouse mammary
644 gland. *Cancer Prev Res (Phila).* 2011;4(3):329-346.
645 59. Duncan RE, Ahmadian M, Jaworski K, Sarkadi-Nagy E, Sul HS. Regulation of
646 lipolysis in adipocytes. *Annual review of nutrition.* 2007;27:79-101.
647 60. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose Tissue Remodeling: Its Role
648 in Energy Metabolism and Metabolic Disorders. *Front Endocrinol (Lausanne).*
649 2016;7:30.
650 61. Balaban S, Lee LS, Schreuder M, Hoy AJ. Obesity and Cancer Progression: Is
651 There a Role of Fatty Acid Metabolism? *BioMed research international.*
652 2015;2015:274585.
653 62. Henry SL, Bensley JG, Wood-Bradley RJ, Cullen-McEwen LA, Bertram JF,
654 Armitage JA. White adipocytes: more than just fat depots. *The international*
655 *journal of biochemistry & cell biology.* 2012;44(3):435-440.
656 63. Suganami T, Tanaka M, Ogawa Y. Adipose tissue inflammation and ectopic lipid
657 accumulation. *Endocrine journal.* 2012;59(10):849-857.
658 64. Geisler CE, Renquist BJ. Hepatic lipid accumulation: cause and consequence of
659 dysregulated glucoregulatory hormones. *J Endocrinol.* 2017.
660 65. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis
661 in an urban population in the United States: impact of ethnicity. *Hepatology.*
662 2004;40(6):1387-1395.
663 66. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic
664 fatty liver disease. *Dig Dis.* 2010;28(1):155-161.

665 67. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver
666 disease and risk for hepatocellular cancer, based on systematic review. *Clinical*
667 *gastroenterology and hepatology : the official clinical practice journal of the*
668 *American Gastroenterological Association.* 2012;10(12):1342-1359 e1342.
669 68. Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Jarvinen H, Svegliati-Baroni
670 G. From the metabolic syndrome to NAFLD or vice versa? *Digestive and liver*
671 *disease : official journal of the Italian Society of Gastroenterology and the Italian*
672 *Association for the Study of the Liver.* 2010;42(5):320-330.
673 69. Berardis S, Sokal E. Pediatric non-alcoholic fatty liver disease: an increasing
674 public health issue. *European journal of pediatrics.* 2014;173(2):131-139.
675 70. Tolman KG, Dalpiaz AS. Treatment of non-alcoholic fatty liver disease.
676 *Therapeutics and clinical risk management.* 2007;3(6):1153-1163.
677 71. Farese RV, Jr., Zechner R, Newgard CB, Walther TC. The problem of
678 establishing relationships between hepatic steatosis and hepatic insulin
679 resistance. *Cell metabolism.* 2012;15(5):570-573.
680 72. Hui JM, Kench JG, Chitturi S, et al. Long-term outcomes of cirrhosis in
681 nonalcoholic steatohepatitis compared with hepatitis C. *Hepatology.*
682 2003;38(2):420-427.
683 73. Smits MM, van Geenen EJ. The clinical significance of pancreatic steatosis.
684 *Nature reviews Gastroenterology & hepatology.* 2011;8(3):169-177.
685 74. van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder
686 CJ. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas
687 disease. *Pancreas.* 2010;39(8):1185-1190.

688 75. Byrne AM, Bouchier-Hayes DJ, Harmey JH. Angiogenic and cell survival
689 functions of vascular endothelial growth factor (VEGF). *Journal of cellular and*
690 *molecular medicine.* 2005;9(4):777-794.
691 76. Cottam D, Fisher B, Ziemba A, et al. Tumor growth factor expression in obesity
692 and changes in expression with weight loss: another cause of increased
693 virulence and incidence of cancer in obesity. *Surgery for obesity and related*
694 *diseases : official journal of the American Society for Bariatric Surgery.*
695 2010;6(5):538-541.
696 77. Iwaki T, Urano T, Umemura K. PAI-1, progress in understanding the clinical
697 problem and its aetiology. *British journal of haematology.* 2012;157(3):291-
698 298.
699 78. Bauman KA, Wettlaufer SH, Okunishi K, et al. The antifibrotic effects of
700 plasminogen activation occur via prostaglandin E2 synthesis in humans and
701 mice. *J Clin Invest.* 2010;120(6):1950-1960.
702 79. Malik R, Lelkes PI, Cukierman E. Biomechanical and biochemical remodeling
703 of stromal extracellular matrix in cancer. *Trends in biotechnology.*
704 2015;33(4):230-236.
705 80. Slaughter KN, Thai T, Penaroza S, et al. Measurements of adiposity as clinical
706 biomarkers for first-line bevacizumab-based chemotherapy in epithelial
707 ovarian cancer. *Gynecologic oncology.* 2014;133(1):11-15.
708 81. Casagrande DS, Rosa DD, Umpierre D, Sarmento RA, Rodrigues CG, Schaan BD.
709 Incidence of cancer following bariatric surgery: systematic review and meta-
710 analysis. *Obes Surg.* 2014;24(9):1499-1509.

711 82. Hursting SD, Dunlap SM, Ford NA, Hursting MJ, Lashinger LM. Calorie
712 restriction and cancer prevention: a mechanistic perspective. *Cancer Metab.*
713 2013;1(1):10.
714 83. Longo VD, Fontana L. Calorie restriction and cancer prevention: metabolic and
715 molecular mechanisms. *Trends Pharmacol Sci.* 2010;31(2):89-98.
716 84. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health
717 and survival in rhesus monkeys from the NIA study. *Nature.*
718 2012;489(7415):318-321.
719 85. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease
720 onset and mortality in rhesus monkeys. *Science.* 2009;325(5937):201-204.
721 86. Lv M, Zhu X, Wang H, Wang F, Guan W. Roles of caloric restriction, ketogenic
722 diet and intermittent fasting during initiation, progression and metastasis of
723 cancer in animal models: a systematic review and meta-analysis. *PLoS One.*
724 2014;9(12):e115147.
725 87. Weiss EP, Racette SB, Villareal DT, et al. Improvements in glucose tolerance
726 and insulin action induced by increasing energy expenditure or decreasing
727 energy intake: a randomized controlled trial. *Am J Clin Nutr.* 2006;84(5):1033-
728 1042.
729 88. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: An
730 update. *Ageing Res Rev.* 2016.
731 89. Fabian CJ, Kimler BF, Donnelly JE, et al. Favorable modulation of benign breast
732 tissue and serum risk biomarkers is associated with > 10 % weight loss in
733 postmenopausal women. *Breast Cancer Res Treat.* 2013;142(1):119-132.

734 90. Byers T, Sedjo RL. Does intentional weight loss reduce cancer risk? *Diabetes*
735 *Obes Metab.* 2011;13(12):1063-1072.
736 91. Fontana L, Villareal DT, Das SK, et al. Effects of 2-year calorie restriction on
737 circulating levels of IGF-1, IGF-binding proteins and cortisol in nonobese men
738 and women: a randomized clinical trial. *Aging Cell.* 2016;15(1):22-27.
739 92. Saleh AD, Simone BA, Palazzo J, et al. Caloric restriction augments radiation
740 efficacy in breast cancer. *Cell Cycle.* 2013;12(12):1955-1963.
741 93. Brandhorst S, Longo VD. Fasting and Caloric Restriction in Cancer Prevention
742 and Treatment. *Recent Results Cancer Res.* 2016;207:241-266.
743 94. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and
744 disease processes. *Ageing Res Rev.* 2016.
745 95. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical
746 applications. *Cell metabolism.* 2014;19(2):181-192.
747 96. Harvie MN, Howell T. Could Intermittent Energy Restriction and Intermittent
748 Fasting Reduce Rates of Cancer in Obese, Overweight, and Normal-Weight
749 Subjects? A Summary of Evidence. *Adv Nutr.* 2016;7(4):690-705.
750 97. Harvie M, Howell A. Energy restriction and the prevention of breast cancer.
751 *Proc Nutr Soc.* 2012;71(2):263-275.
752 98. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or
753 continuous energy restriction on weight loss and metabolic disease risk
754 markers: a randomized trial in young overweight women. *Int J Obes (Lond).*
755 2011;35(5):714-727.

756 99. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean
757 diet and health status: meta-analysis. *BMJ.* 2008;337:a1344.
758 100. Brown T, Avenell A, Edmunds LD, et al. Systematic review of long-term lifestyle
759 interventions to prevent weight gain and morbidity in adults. *Obes Rev.*
760 2009;10(6):627-638.
761 101. Romaguera D, Norat T, Mouw T, et al. Adherence to the Mediterranean diet is
762 associated with lower abdominal adiposity in European men and women. *J*
763 *Nutr.* 2009;139(9):1728-1737.
764 102. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of
765 cancer: an updated systematic review and meta-analysis of observational
766 studies. *Cancer Med.* 2015;4(12):1933-1947.
767 103. de Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N.
768 Mediterranean dietary pattern in a randomized trial: prolonged survival and
769 possible reduced cancer rate. *Arch Intern Med.* 1998;158(11):1181-1187.
770 104. Harvie MN, Sims AH, Pegington M, et al. Intermittent energy restriction
771 induces changes in breast gene expression and systemic metabolism. *Breast*
772 *Cancer Res.* 2016;18(1):57.
773 105. Safdie FM, Dorff T, Quinn D, et al. Fasting and cancer treatment in humans: A
774 case series report. *Aging (Albany NY).* 2009;1(12):988-1007.
775 106. de Groot S, Vreeswijk MP, Welters MJ, et al. The effects of short-term fasting
776 on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer
777 patients: a randomized pilot study. *BMC Cancer.* 2015;15:652.

778 107. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A,
779 Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer
780 survivors: a systematic review. *J Natl Cancer Inst.* 2012;104(11):815-840.
781 108. Shalamzari SA, Agha-Alinejad H, Alizadeh S, et al. The effect of exercise training
782 on the level of tissue IL-6 and vascular endothelial growth factor in breast
783 cancer bearing mice. *Iran J Basic Med Sci.* 2014;17(4):231-258.
784 109. Jiang W, Zhu Z, Thompson HJ. Effects of physical activity and restricted energy
785 intake on chemically induced mammary carcinogenesis. *Cancer Prev Res*
786 *(Phila).* 2009;2(4):338-344.
787 110. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB. Leisure-time
788 physical activity and reduced plasma levels of obesity-related inflammatory
789 markers. *Obes Res.* 2003;11(9):1055-1064.
790 111. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes
791 on vascular inflammatory markers in obese women: a randomized trial. *JAMA.*
792 2003;289(14):1799-1804.
793 112. Imayama I, Ulrich CM, Alfano CM, et al. Effects of a caloric restriction weight
794 loss diet and exercise on inflammatory biomarkers in overweight/obese
795 postmenopausal women: a randomized controlled trial. *Cancer Res.*
796 2012;72(9):2314-2326.
797 113. Jones SB, Thomas GA, Hesselsweet SD, Alvarez-Reeves M, Yu H, Irwin ML.
798 Effect of exercise on markers of inflammation in breast cancer survivors: the
799 Yale exercise and survivorship study. *Cancer Prev Res (Phila).* 2013;6(2):109-
800 118.

801 114. Kruk J, Czerniak U. Physical activity and its relation to cancer risk: updating
802 the evidence. *Asian Pac J Cancer Prev.* 2013;14(7):3993-4003.
803 115. Courneya KS, Sellar CM, Stevinson C, et al. Randomized controlled trial of the
804 effects of aerobic exercise on physical functioning and quality of life in
805 lymphoma patients. *J Clin Oncol.* 2009;27(27):4605-4612.
806 116. Nilsen TS, Raastad T, Skovlund E, et al. Effects of strength training on body
807 composition, physical functioning, and quality of life in prostate cancer
808 patients during androgen deprivation therapy. *Acta Oncol.* 2015;54(10):1805-
809 1813.
810 117. Schulz SV, Laszlo R, Otto S, et al. Feasibility and effects of a combined adjuvant
811 high-intensity interval/strength training in breast cancer patients: a single-
812 center pilot study. *Disabil Rehabil.* 2017:1-8.
813 118. Winningham ML, MacVicar MG. The effect of aerobic exercise on patient
814 reports of nausea. *Oncol Nurs Forum.* 1988;15(4):447-450.
815 119. MacVicar MG, Winningham ML, Nickel JL. Effects of aerobic interval training
816 on cancer patients' functional capacity. *Nurs Res.* 1989;38(6):348-351.
817 120. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance
818 exercise in breast cancer patients receiving adjuvant chemotherapy: a
819 multicenter randomized controlled trial. *J Clin Oncol.* 2007;25(28):4396-4404.
820 121. Sprod LK, Mohile SG, Demark-Wahnefried W, et al. Exercise and Cancer
821 Treatment Symptoms in 408 Newly Diagnosed Older Cancer Patients. *J Geriatr*
822 *Oncol.* 2012;3(2):90-97.

823 122. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O.
824 Exercise interventions on health-related quality of life for people with cancer
825 during active treatment. *Clin Otolaryngol.* 2012;37(5):390-392.
826 123. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society Guidelines on
827 nutrition and physical activity for cancer prevention: reducing the risk of
828 cancer with healthy food choices and physical activity. *CA Cancer J Clin.*
829 2012;62(1):30-67.
830 124. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: a review of the
831 therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr.*
832 2013;67(8):789-796.
833 125. Fu SP, Li SN, Wang JF, et al. BHBA suppresses LPS-induced inflammation in BV-
834 2 cells by inhibiting NF-kappaB activation. *Mediators Inflamm.*
835 2014;2014:983401.
836 126. Goldberg EL, Asher JL, Molony RD, et al. beta-Hydroxybutyrate Deactivates
837 Neutrophil NLRP3 Inflammasome to Relieve Gout Flares. *Cell Rep.*
838 2017;18(9):2077-2087.
839 127. Merra G, Gratteri S, De Lorenzo A, et al. Effects of very-low-calorie diet on body
840 composition, metabolic state, and genes expression: a randomized double-
841 blind placebo-controlled trial. *Eur Rev Med Pharmacol Sci.* 2017;21(2):329-
842 345.
843 128. Woolf EC, Curley KL, Liu Q, et al. The Ketogenic Diet Alters the Hypoxic
844 Response and Affects Expression of Proteins Associated with Angiogenesis,

845 Invasive Potential and Vascular Permeability in a Mouse Glioma Model. *PLoS*
846 *One.* 2015;10(6):e0130357.
847 129. Nandivada P, Fell GL, Pan AH, et al. Eucaloric Ketogenic Diet Reduces
848 Hypoglycemia and Inflammation in Mice with Endotoxemia. *Lipids.*
849 2016;51(6):703-714.
850 130. Badman MK, Kennedy AR, Adams AC, Pissios P, Maratos-Flier E. A very low
851 carbohydrate ketogenic diet improves glucose tolerance in ob/ob mice
852 independently of weight loss. *Am J Physiol Endocrinol Metab.*
853 2009;297(5):E1197-1204.
854 131. Tisdale MJ, Brennan RA, Fearon KC. Reduction of weight loss and tumour size
855 in a cachexia model by a high fat diet. *Br J Cancer.* 1987;56(1):39-43.
856 132. Allen BG, Bhatia SK, Anderson CM, et al. Ketogenic diets as an adjuvant cancer
857 therapy: History and potential mechanism. *Redox Biol.* 2014;2:963-970.
858 133. Branco AF, Ferreira A, Simoes RF, et al. Ketogenic diets: from cancer to
859 mitochondrial diseases and beyond. *Eur J Clin Invest.* 2016;46(3):285-298.
860 134. Wakefield AP, House JD, Ogborn MR, Weiler HA, Aukema HM. A diet with 35%
861 of energy from protein leads to kidney damage in female Sprague-Dawley rats.
862 *Br J Nutr.* 2011;106(5):656-663.
863 135. Ellenbroek JH, van Dijck L, Tons HA, et al. Long-term ketogenic diet causes
864 glucose intolerance and reduced beta- and alpha-cell mass but no weight loss
865 in mice. *Am J Physiol Endocrinol Metab.* 2014;306(5):E552-558.
866

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

890 droplets). When engorged with triglyceride, white adipocytes secrete a number of factors
891 that promote growth factor signaling and inflammation including leptin, resistin, insulin-
892 like growth factor (IGF)-1, free fatty acids, tumor necrosis factor (TNF)-α and
893 interleukin (IL)-6. Additionally, they reduce production of anti-inflammatory
894 adiponectin. Brown adipocytes secrete several factors involved in thermogenesis,
895 decreased inflammation, normalized insulin sensitivity and/or increased energy
896 expenditure such as adiponectin, bone morphogenetic proteins, neuregulin-4, lactate,
897 triiodothyronine (T3), retinaldehyde, and fibroblast growth factor (FGF)-21.
898
899 Figure 4: In obesity, as adipocytes accumulate triglycerides, their secretomes shift
900 towards the production of pro-inflammatory and/or insulin resistant molecules, including
901 numerous cytokines, adipokines (e.g. leptin and resistin), and free fatty acids.
902 Engorged/necrotic adipocytes attract macrophages and other immune cells that further
903 contribute to the pro-inflammatory environment. The altered secretome resulting from
904 macrophage-adipocyte interactions modulates several enzymes associated with increased
905 inflammation-related lipid mediators (such as prostaglandins and leukotrienes) and
906 hormones (such as aromatase, which converts androgens to estrogens).
907
908 Figure 5: Dietary and lifestyle interventions of caloric restriction (CR), intermittent
909 fasting (IF), physical activity (PA) and adherence to a ketogenic diet (KD), have been
910 shown to reduce adiposity and favorably modulate many of the same cancer risk
911 biomarkers that are impacted by obesity including: insulin, IGF-1, leptin, adiponectin,
912 cytokines, angiogenic factors, and crown-like structures. These metabolic alterations

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