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

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1 **Hungering for New Mechanism-Based Strategies to Break the Obesity-Cancer Link:**

2 **A Narrative Review**

3

4 **Research Snapshot**

5 Research Question: What are the mechanisms through which obesity increases cancer
6 risk and progression? Does implementation of dietary or lifestyle interventions attenuate
7 obesity-associated cancer risk factors?

8

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

16

17 **Abstract**

18 The prevalence of obesity, an established risk factor for many cancers, has increased
19 dramatically over the past 50 years in the United States and many other countries.
20 Relative to normoweight cancer patients, obese cancer patients often have poorer
21 prognoses, resistance to chemotherapies, and are more likely to develop distant
22 metastases. Recent progress on elucidating the mechanisms underlying the obesity-cancer
23 connection suggests that obesity exerts pleomorphic effects on pathways related to tumor

24 development and progression, and thus there are multiple opportunities for prevention
25 and treatment of obesity-related cancers. We now know that obesity can impact each of
26 the well-established hallmarks of cancer, but obesity-associated perturbations in systemic
27 metabolism and inflammation, and the interactions of these perturbations with cancer cell
28 energetics, are emerging as the primary drivers of obesity-associated cancer development
29 and progression. Several obesity-related host factors, including components of the
30 adipose secretome and structural components of the tumor microenvironment, are
31 extrinsic to, and interact with, the intrinsic molecular characteristics of cancer cells
32 (including cancer stem cells). Each will be considered in the context of potential
33 preventive and therapeutic strategies to reduce the burden of obesity-related cancers.
34 This review will focus on current knowledge of the mechanisms behind the obesity-
35 cancer link as well as relevant dietary and lifestyle interventions that are being
36 implemented in preclinical and clinical trials, with the ultimate goal of reducing
37 incidence and progression of obesity-related cancers.

38

39 **Abbreviations** : AMP kinase (AMPK); body mass index (BMI); brown adipose tissue
40 (BAT); calorie restriction (CR); cardiovascular disease (CVD); estrogen receptor (ER);
41 free fatty acids (FFA); insulin-like growth factor-1 (IGF-1); interleukin (IL); intermittent
42 fasting (IF); ketogenic diet (KD); monocyte chemo-attractant protein-1 (MCP-1);
43 mammalian target of rapamycin (mTOR); non-alcoholic steatohepatitis (NASH); nuclear
44 factor kappa-light-chain-enhancer of B cells (NFκB); plasminogen activator inhibitor-1
45 (PAI-1); phosphatidylinositol-3 kinase (PI3K); peroxisome proliferator-activated receptor
46 (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

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/m² or greater, has tripled. Today nearly 40% of adults and
53 20% of children in the United States are obese¹. Worldwide, more than 600 million adults
54 are obese and 2.1 billion are overweight². 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 cancer³.

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 fatness⁴. These obesity-associated cancers include breast (in postmenopausal women),
62 ovarian, liver, gallbladder, kidney, colon, pancreatic, gastric, esophageal, endometrial,
63 thyroid, multiple myeloma, and meningioma⁴. Overall, an estimated 13% of incident
64 cases worldwide, and approximately 20% of incident cases in Europe and North America,
65 are attributable to obesity⁵. Aside from higher risk of developing cancer, obese
66 individuals are more likely to have reduced response to anticancer therapies⁶, and obesity
67 is implicated in approximately 20% of all cancer-related mortalities⁷. This includes
68 prostate cancer, for which obesity increases progression but not incidence⁸. 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,

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

74

75 **Methods**

76 A traditional literature review was performed to describe the multiple mechanisms
77 underlying the obesity-cancer link, as well as dietary interventions targeting those
78 mechanisms for cancer prevention and treatment. Searches were completed using
79 PubMed and Google Scholar. A variety of key words were searched including obesity,
80 metabolic syndrome, cancer prevention, cancer treatment, calorie restriction, intermittent
81 fasting, ketogenic diet, and physical activity.

82

83 **Obesity Impacts Each Hallmark of Cancer**

84 Hanahan and Weinberg identified essential biological capabilities acquired by all cancer
85 cells during the multistep development of tumors in their classic article titled “The
86 Hallmarks of Cancer” first published in 2000⁹ and updated in their 2011 “Hallmarks of
87 Cancer: the Next Generation”¹⁰. These essential aberrations of cancer cells, include
88 sustaining proliferative signaling, increased chronic inflammation, evading growth
89 suppressors, resisting cell death, displaying genome instability, enabling replicative
90 immortality, inducing angiogenesis, and activating processes related to invasion and
91 metastasis. Conceptual progress in the decade between these two articles led to
92 identification of additional hallmarks, including reprogramming of energy metabolism,
93 evading immune destruction, and creation of the tumor microenvironment through
94 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 division¹⁰⁻¹². 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 cell¹². 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 cancers¹³.

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 chemoattractant 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 metabolism¹⁷. 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 processes¹⁸. 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 survival¹⁹.
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 synthesis¹⁷. 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 potential²⁰. As a result,
137 elevated IGF-1 is established as a risk factor for many types of cancer¹⁹.

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 cancers²¹. In response to these growth factors and nutrient availability,
142 PI3K/Akt produces lipid messengers that initiate the Akt signaling cascade²¹, 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 signaling²³. Oncogenic signals or
147 loss of tumor suppressors can activate mTOR and contribute to the hallmarks of cancer,
148 promoting proliferation, survival, angiogenesis, and metastasis²⁴. 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 phenotype³⁰. 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 signals³¹.

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,

164 and possess multilocular lipid droplets³². Moreover, the secretome of white versus brown
165 adipocytes differs markedly (Figure 3); the former is characterized by secretion of leptin,
166 resistin, PAI-1, inflammatory cytokines, and free fatty acids (FFA), while the latter is
167 characterized by secretion of bone morphogenetic proteins, lactate (which induces
168 uncoupling proteins), retinaldehyde, triiodothyronine (T3) and other factors associated
169 with response to cold stress and/or increased energy expenditure³². Brown adipocytes
170 also produce adiponectin (but not leptin) and fibroblast growth factor-21, which can be
171 anti-inflammatory and insulin sensitizing³². WAT also contains a number of stromal cells
172 including pre-adipocytes, vascular cells, fibroblasts and a host of immune cells such as
173 adipose tissue macrophages³³. Increased WAT mass in obesity drives chronic
174 inflammation in at least 3 ways, depicted in Figure 4 and summarized below:

175

176 1. *Altered Adipose Secretome*

177 Leptin is an energy-sensing peptide hormone produced by adipocytes. Leptin levels,
178 positively correlated with adiposity, function as an energy sensor through signaling to the
179 hypothalamus, decreasing hunger cues, food intake and weight gain. Leptin release from
180 adipocytes is stimulated by a variety of factors including insulin, TNF α , glucocorticoids,
181 and estrogen³⁴. In obesity, leptin is overproduced by adipocytes, reducing hypothalamic
182 sensitivity to the signal³⁵. Circulating leptin binds to various receptors in central nervous
183 system and peripheral tissues, regulating processes including energy homeostasis,
184 cytokine production, immune function, and carcinogenesis^{34,36}. The leptin receptor OB-R,
185 classified as a class I cytokine receptor, gives leptin the ability to activate signal
186 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 differentiation³⁷. Deregulation of STATs activity is often
189 observed in cancer³⁸.

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 mTOR³⁹. Adiponectin
198 also attenuates inflammation through inhibition of nuclear factor kappa-light-chain-
199 enhancer of B cells (NF- κ B), which reduces expression of proinflammatory cytokines
200 while increasing expression of anti-inflammatory cytokines⁴⁰. Due to the anticancer
201 functions of adiponectin, adiponectin agonists are emerging as possible chemotherapeutic
202 agents, particularly for obesity-related cancers⁴¹. 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 risk⁴².

205

206 Sex hormones, including estrogen, androgens and progestogens, regulate a variety of
207 growth and developmental processes including weight homeostasis⁴³. Long established is
208 the association between sex hormone levels and obesity⁴⁴. In postmenopausal women,
209 BMI is positively correlated with estrone, estradiol, and free estradiol⁴⁵. Elevation of

210 estrogens is also detected in obese men^{44,46}; however, testosterone levels are significantly
211 reduced⁴⁷. Alteration of sex hormones can result in several biological disorders including
212 hypertension, menstrual disturbances, erectile dysfunction, gynecomastia, hirsutism, and
213 increased adiposity⁴⁴. Moreover, sex hormones have been implicated in risk and/or
214 progression of multiple cancer types⁴⁸. In prostate cancer, sex hormone levels are
215 associated with disease progression, not disease risk⁴⁹. Low levels of circulating
216 testosterone correlates with aggressive disease progression⁵⁰. Elevated estrogen levels are
217 associated with increased risk of breast^{44,45,51}, ovarian⁵², and endometrial cancers⁵³.

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 synthesis⁴⁵. Once released, circulating estrogens bind to one of two estrogen
224 receptors (ER), ER α or ER β . 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 differentiation⁵⁴. In the context
227 of cancer, the two receptors have differing roles. ER α is mitogenic and an established
228 target in treatment of estrogen receptor-positive breast cancer, while ER β is suggested to
229 be tumor suppressive⁵⁵. Obesity and postmenopausal status increases risk of ER-positive
230 breast cancers compared with ER-negative breast cancer⁵⁶. Due to the positive
231 association between obesity, circulating estrogen and risk of ER-positive breast cancer,

232 aromatase inhibitors and ER antagonist, including tamoxifen, have been investigated for
233 their effectiveness as adjuvant therapy⁵⁷.

234

235 *2. Crown-Like Structures*

236 Obesity drives subclinical inflammation in visceral and subcutaneous WAT,
237 characterized by crown-like structures, or rings of activated macrophages surrounding
238 engorged or necrotic adipocytes (Figure 4). This adipocyte-macrophage interaction
239 results in a proinflammatory secretome from both cell types, activating the cellular
240 transcription factor NF- κ B, increasing levels of cytokines and other inflammatory factors,
241 and triggering inflammation⁵⁸.

242

243 *3. Adipose Remodeling and Lipid Infiltration in Other Tissues*

244 During conditions of low nutrient availability or increased energy needs, glucagon
245 secretion stimulates lipolysis of adipocytes, releasing FFA into the blood stream⁵⁹.
246 Circulating FFA can then be utilized by peripheral tissues, providing substrate for β -
247 oxidation and serving as intermediates for energy production through the citric acid cycle
248 and oxidative phosphorylation. Overnutrition remodels existing adipose tissue, expanding
249 adipocyte number and size, and altering adipokine secretion, FFA flux, and adipocyte
250 death⁶⁰. In response, adipose stromal cells modify their functions to promote clearance of
251 necrotic adipocytes and generation of new adipocytes and vasculature. Tissue remodeling
252 in chronic overnutrition or obesity, results in sustained, low-grade inflammation and
253 metabolic alterations⁶⁰. As stated above, cancer cells adapt to changing energy needs for
254 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 FFA⁶¹.

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 tissue⁶². Ectopic lipid intermediates exert lipotoxic effects, impairing cellular organelle
262 functions, releasing inflammatory cytokines, and fostering development of insulin
263 resistance⁶³. 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 metabolism⁶².

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 cirrhosis⁶⁴. One of
270 the most common chronic diseases⁶⁵⁻⁶⁷, 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 death⁷⁰. Additionally, accumulation of lipids and pro-inflammatory cytokines
276 promotes activation of intracellular kinases, leading to impaired insulin signaling and
277 development of insulin resistance⁷¹. 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 carcinoma⁷².

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 activities⁷⁵. Obesity is associated with
297 increased circulating VEGF, and elevated VEGF correlates with poor prognosis for many
298 obesity-related cancers⁷⁶. PAI-1 is another angiogenic factor, produced by adipocytes,
299 endothelial cells, and stromal cells in visceral WAT⁷⁷, 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 cancers⁷⁷. 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 integrity⁷⁸. Extracellular
309 matrix remodeling is a key feature of invasive disease, and integral in the development of
310 metastatic lesions⁷⁹. 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 population⁷⁹. 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 patients⁸⁰.

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 surgery⁸¹. In light of the

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

336

337 *1. Calorie Restriction*

338 Calorie restriction (CR), defined as reduction of dietary energy intake without
339 malnutrition, is broadly effective dietary intervention that significantly decreases
340 adiposity. Preclinical models demonstrate 30% CR, compared with ad libitum-fed
341 control, ameliorates risk factors and delays onset of cancer through metabolic alterations
342 fostering increased insulin sensitivity and decreased serum glucose, growth factor
343 signaling, inflammation, oxidative stress and angiogenesis⁸²⁻⁸⁵. These metabolic changes
344 translate into significantly decreased cancer incidence in murine models⁸⁶. Due to long
345 latency of cancer in humans, the literature does not have data linking CR directly with
346 cancer incidence in humans. However, randomized control trials implementing long-term

347 20% CR in overweight human subjects has confirmed reduced adiposity, improved
348 glucose homeostasis, increased adiponectin, and reduced leptin and inflammatory
349 markers TNF α and C-reactive protein^{87,88}. Substantial weight loss of >10% may be
350 necessary to consistently gain these benefits⁸⁹⁻⁹¹.

351

352 Limited clinical studies exist on CR during cancer treatment. Direct application of CR in
353 cancer patients is complicated by high rates of weight loss associated with cancer
354 cachexia, a condition in which tumor-derived signals degrade muscle and adipose tissue.
355 Emerging findings from preliminary clinical trials suggest that application of CR as an
356 adjuvant therapy in combination with chemotherapy and/or radiation has potential to
357 increase responsiveness to treatment^{92,93}.

358

359 *2. Intermittent Fasting*

360 Preclinical and clinical studies have begun to explore implementation of intermittent
361 fasting (IF), which may be easier for most people to adopt and may have beneficial
362 metabolic effects relative to chronic CR. Human trials most often study one of three IF
363 regimens: alternate day fasting, alternate day energy restriction (~75%) or 2 consecutive
364 days of 65% energy restriction, the latter often referred to as intermittent calorie
365 restriction⁹⁴. Periods of IF stimulate reduced insulin and increased glucagon, resulting in
366 increased lipolysis and fatty acid oxidation to provide alternate substrates for energy
367 production. These metabolic alterations are accompanied by reductions in several cancer-
368 related risk factors including lower insulin resistance, inflammation, and circulating IGF-
369 1⁹⁵. 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 types⁹⁵⁻⁹⁷. 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 incidence⁹⁹⁻¹⁰³. 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 cancer¹⁰⁴.

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

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 biomarkers¹⁰⁵. 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 cells¹⁰⁶. 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 efficacy⁹⁵. 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 inflammation¹⁰⁷. 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 loss¹¹⁰⁻¹¹². 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

416 per week, just short of the American Cancer Society's recommendation of 150
417 minutes¹¹³. 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 endometrial¹¹⁴.

420

421 PA is also safe and beneficial during cancer therapy for multiple cancer types¹¹⁵⁻¹¹⁷. 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 patients¹²⁰. Benefits are further exhibited in elderly patients with exercise
429 during treatment improving memory and self-reported health and reducing fatigue¹²¹.

430 Studies on exercise during treatment suggest that higher-intensity exercise provides more
431 benefit than low-intensity exercise¹²².

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 survivorship¹²³.

438

439 *4. Ketogenic Diet*

440 Ketogenic diet (KD) is a very-low carbohydrate diet with high fat and moderate protein
441 composition. Low carbohydrate consumption reduces available glucose, a cancer cell's
442 preferred energy source, and increases catabolism of proteins and fats to provide
443 gluconeogenic glucose and ketones. With prolonged consumption of KD, glycogen stores
444 reach critical levels and the body is no longer able to oxidize fats to glucose via
445 gluconeogenesis. This results in a shift to increased ketone production and physiological
446 ketosis. Ketosis is not to be confused with ketoacidosis that is seen with diabetes mellitus.
447 In ketosis there is less accumulation of ketones, as they are being used efficiently by the
448 brain and body as an energy source, and individuals do not experience adverse side
449 effects associated with ketoacidosis¹²⁴. Ketosis from KD favorably modulates many
450 cancer risk biomarkers including IGF-1, leptin, adiponectin, inflammatory markers, and
451 angiogenic factors (Figure 5)¹²⁵⁻¹²⁸. Preclinical studies suggest that KD can attenuate
452 these markers without a reduction in caloric intake; however, weight loss may be
453 needed^{129,130}. KD may induce weight loss via several interrelated mechanisms, including:
454 reduced appetite due to high protein intake, which can induce higher satiety, and high
455 ketones, known to modulate appetite-regulating hormones; reduced caloric intake due to
456 the satiety; reduced lipogenesis and increased lipolysis; greater metabolic efficiency; and
457 increased metabolic cost of gluconeogenesis and ketogenesis¹²⁴.

458

459 Beneficial effects of the ketogenic diet have long been established for epilepsy and
460 T2DM; emerging is its role in cancer prevention and treatment¹²⁴. Early preclinical
461 studies found KD reduced tumor burden and cachexia in a mouse model of colon

462 cancer¹³¹. 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 cancers¹³². 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 types¹³³.

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 damage¹³⁴, 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 intake¹²⁴. Additionally, select preclinical studies have found long-term KD
474 to cause dyslipidemia, hepatic steatosis and glucose intolerance¹³⁵. 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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864 glucose intolerance and reduced beta- and alpha-cell mass but no weight loss
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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 meningioma⁴. In addition, obesity is associated with
872 progression (but not incidence) of prostate cancer⁸.

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- κ B 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.