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The Role of Diet in Cancer Prevention and Chemotherapy Efficacy

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Abstract

Despite great advances in treatment, cancer remains a leading cause of death worldwide. Diet can greatly impact health, while caloric restriction and fasting have putative benefits for disease prevention and longevity. Strong epidemiological associations exist between obesity and cancer, whereas healthy diets can reduce cancer risk. However, less is known about how diet might impact cancer once it has been diagnosed and particularly how diet can impact cancer treatment. In the present review, we discuss the links between obesity, diet, and cancer. We explore potential mechanisms by which diet can improve cancer outcomes, including through hormonal, metabolic, and immune/inflammatory effects, and present the limited clinical research that has been published in this arena. Though data are sparse, diet intervention may reduce toxicity, improve chemotherapy efficacy, and lower the risk of long-term complications in cancer patients. Thus, it is important that we understand and expand the science of this important but complex adjunctive cancer treatment strategy.

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INTRODUCTION

> Let food be thy medicine and medicine be thy food.
>
> —Hippocrates

Cancer treatment has improved tremendously over the past century. Childhood acute lymphoblastic leukemia (ALL) has changed from a nearly uniformly fatal disease to one with an ~90% cure rate. The 5-year survival rate from all cancers has increased from 49% in 1975–1977 to 70% in 2010–2016 (149), and paradigm-shifting advances are greatly improving treatment outcomes of many cancers, such as chronic myelogenous leukemia, metastatic melanoma, and HER2-positive breast cancer. Despite these advances, cancer remains a most feared diagnosis, driving many to seek out alternative treatments.

We have long known that diet plays an important role in our health. It stands to reason that people would look to diet to provide a sliver of hope for cancer patients. Although the association between obesity and cancer incidence and mortality is well established, the data linking specific nutrients and food items to cancer are sparse. Even more elusive are studies examining how diet can affect the treatment outcome of cancer once it has already been diagnosed.

In the present review, we examine the evidence from preclinical and clinical studies on how diet can affect cancer outcome. Dietary restriction interventions target many of the hormones and pathways affected by obesity; thus, understanding how obesity can worsen cancer treatment may

yield clues as to how diet can help. We discuss the role of diet in cancer incidence and progression but focus primarily on the state of the science evaluating treatment efficacy.

EPIDEMIOLOGY

Cancer Incidence

In 2003, Eugenia Calle and colleagues (24) published a landmark study confirming the strong links between obesity and cancer mortality. In a prospective cohort of more than 900,000 men and women in the United States, the authors found that obesity increased the risk of dying from cancer of the esophagus, colon, liver, gallbladder, pancreas, and kidney in addition to non-Hodgkin's lymphoma and multiple myeloma. They estimated that overweight and obesity were responsible for ~14% of cancer deaths in men and ~20% of cancer deaths in women in the United States. Many studies have confirmed these findings, in the United States and worldwide (136, 137). The World Cancer Research Fund and American Institute of Cancer Research's (WCRF/AICR) Continuous Update Project (181) most recently concluded that there was convincing evidence that body fatness, variably defined by body mass index (BMI), waist circumference, or waist-to-hip ratio, increases the risk of esophageal, pancreatic, liver, colorectal, postmenopausal breast, endometrial, and kidney cancer. They also concluded a probable increased risk of fatness contributing to oropharyngeal, stomach, gallbladder, ovarian, and advanced prostate cancers.

Obesity is defined as a BMI $\geq$30 kg/m^2 ($\geq$95th percentile in youth), and overweight is defined as a BMI $\geq$25 kg/m^2 ($\geq$85th percentile in youth). Although most epidemiological studies examining cancer incidence and mortality have focused on obesity using this anthropomorphic definition, others have examined its physiologic aspects. Metabolic syndrome describes the aggregation of obesity, dyslipidemia, and insulin resistance, which tend to cluster in the obese, particularly those with visceral obesity. In contrast, the term metabolically healthy obese (sometimes colloquially called fat fit) was coined to describe those who are physically obese but show none of the metabolic sequelae. A prospective study of more than 20,000 participants showed that metabolic health was the main contributor to cancer risk, and overweight and obesity per se did not increase the risk of cancer mortality in metabolically healthy individuals (2). Surprisingly, in metabolically unhealthy individuals, overweight and obesity appeared to offer somewhat of a protective effect.

Diabetes has also been associated with risk of cancer incidence and mortality, though heterogeneity can be found in the literature (28, 173). The vast majority of diabetes worldwide is type 2 diabetes, which is caused by a combination of insulin resistance and β-cell failure. Type 2 diabetes is strongly associated with obesity, which likely explains much of this correlation. However, some studies that adjust for BMI report an independent association between diabetes and cancer (8, 190).

Diet itself has been linked to cancer incidence, both in specific dietary components and overall calories. Hursting et al. (68) showed that leukemia incidence worldwide was strongly correlated with caloric intake. In a case-control study, caloric intake (from food frequency questionnaires) more than 20% below that expected from metabolic rate and activity estimates reduced the risk of breast cancer in premenopausal [odds ratio (OR) 0.36, $P < 0.001$], but not postmenopausal, women (95). Levine and colleagues (93) found that high protein intake in people 50–65 years old was associated with a fourfold increased risk of cancer mortality. Red meat intake itself may be linked to breast cancer risk (182). However, meta-analyses have failed to identify a negative impact of high-protein intake on prostate, ovarian, colorectal, or renal cell cancer (86, 92, 103, 126).

The American Cancer Society and the WCRF/AICR have published dietary guidelines to prevent cancer (81, 181). Both sets of guidelines promote maintaining a healthy weight, being

physically active, consuming fruits and vegetables, and limiting red meat and alcohol consumption. The WCRF/AICR guidelines further recommend decreasing intake of energy-dense foods and salt and support breastfeeding. A recent meta-analysis including 10 large prospective cohorts showed that high adherence to either of these dietary guidelines was associated with a lower risk of cancer overall and specifically a lower risk of breast, colorectal, and endometrial cancer, compared with subjects with the lowest adherence (81). As avoiding obesity is an inherent part of these guidelines, these studies do not clearly determine whether diet per se can modulate the risk of developing cancer.

Although obesity increases the incidence of many cancers, emerging evidence shows that weight loss can modulate this risk. Self-reported weight loss in postmenopausal women enrolled in the Women's Health Initiative was associated with an ~29% decreased risk of endometrial cancer (97). Bariatric surgery has been associated with a reduction in cancer incidence: A recent meta-analysis confirmed that bariatric surgery reduced the risk of cancer in morbidly obese people, although the authors also cautioned regarding the significant heterogeneity existing between studies (26).

Cancer Outcome

Most of the association between obesity and cancer mortality is based on the higher risk of being diagnosed with cancer. Evidence has also been found that obese patients, once diagnosed with cancer, have a poorer outcome than nonobese patients. Poorer outcome and increased mortality have been observed in obese patients following diagnosis of breast (31), colon (160), prostate (4), pancreatic (189), ovarian (186), and hematologic (124) cancers. Although many reports support this conclusion, a recent systematic review concluded that few studies were designed to examine this relationship and so warned caution in interpreting these results (128). Interestingly, obesity is associated with an improved outcome in patients with metastatic melanoma treated with targeted therapy or immunotherapy (109); no significant effect was observed in patients treated with chemotherapy. Thus, obesity generally increases one's risk of both developing cancer and not surviving after diagnosis for most, but not all, cancers.

POTENTIAL MECHANISMS LINKING OBESITY TO CANCER OUTCOME

Obesity is not a simple phenotype but is associated with a number of physical, genetic, physiological, socioeconomic, and behavioral variables, many of which could contribute to these associations with cancer. Animal models provide evidence that the observed associations between obesity and cancer in humans are likely based in biology and are not exclusively behavioral, environmental, or genetic. Obesity increases the rate of cancer development and growth in most preclinical models of genetic cancer predisposition (57, 66, 191), carcinogen exposure (66, 157, 195), and cancer implantation (42, 184, 192). However, fewer studies have looked at how obesity can impair cancer treatment in preclinical models (12, 49, 71). Uncovering the biologic mechanisms linking obesity to cancer may provide some clues for reversing these links.

Pharmacokinetics

One clear dilemma that oncologists face when treating obese patients is how much chemotherapy to use. Obesity can affect both the volume of distribution and the clearance of chemotherapies, yet few studies evaluate pharmacokinetics (PK) of drugs in obese subjects. We have recently shown

that adipocytes metabolize and inactivate the chemotherapy drug daunorubicin (153), which could especially impair treatment in patients with excess adipose tissue. The dosing of some drugs, such as vincristine, is arbitrarily capped, which could disproportionately affect obese patients. Clinicians may be reticent to prescribe large doses of chemotherapies by actual body weight, particularly in obese patients who may already be at higher risk of toxicities. Despite the paucity of data, the American Society of Clinical Oncology developed guidelines stating that chemotherapy should be dosed in obese adult patients on the basis of actual weight (59).

Inflammation

Inflammation has long been known as a driver of cancer incidence and, indeed, is considered a hallmark of cancer (63). Obesity itself is a state of subclinical inflammation. Though the mechanisms driving this state are not fully understood, they are likely driven in part by adipose tissue inflammation. A number of immune cells, including macrophages, B and T lymphocytes, natural killer (NK) cells, and natural killer T (NKT) cells, normally infiltrate adipose tissue. As obesity develops, these immune cells accumulate and take on proinflammatory states. Macrophages increase expression of tumor necrosis factor α (TNFα) and other proinflammatory cytokines (sometimes simplistically referred to as an M1 state). They tend to accumulate around necrotic adipocytes, sometimes forming a crown-like structure. T lymphocyte numbers increase, particularly $CD8^+$ T cells, along with B cells, mast cells, and NKT cells (6). The interaction between these immune cells and the obese adipocytes contributes to local and systemic increases in a number of proinflammatory cytokines, including TNFα, interleukin 6 (IL-6), IL-1β, and plasminogen activator inhibitor-1 (13). At the same time, levels of the anti-inflammatory signal adiponectin are lower in the obese. Together, this inflammatory milieu could contribute to increased carcinogenesis and/or impaired anticancer immunity.

In addition to systemic signals, local adipose tissue inflammation may promote the incidence of some cancers as well as contribute to their aggressiveness and treatment resistance. Adipose tissue macrophages and crown-like structures in breast adipose tissue have been linked to breast cancer (114). Expansion of breast and colon cancer into adjacent adipose tissue is associated with local adipose tissue inflammation (83, 197) and potentially a poorer outcome (83). Whether this is a response to the tumor expansion or a precursor to it is not clear, but interactions between the inflamed adipose tissue and tumor cells clearly can promote further infiltration and treatment resistance.

Hormones

Estrogens have long been known to increase cancer risk, particularly that of estrogen-sensitive tissues, such as breast and endometrium. Adipose tissue is a major source of estrogen, which it converts from circulating androgens via high expression of the aromatase enzyme; thus, obesity is associated with increased circulating estrogen concentrations. Interestingly, obesity is associated with a lower risk of premenopausal breast cancer and a higher risk of postmenopausal breast cancer. This finding could potentially be explained by the fact that estrogen levels after menopause are more significantly elevated in obese individuals than before menopause, when ovarian secretion dominates systemic levels.

Obesity is strongly associated with insulin resistance, which leads to compensatory hyperinsulinemia. Insulin resistance primarily impacts the glucoregulatory effects of insulin, whereas its growth-promoting effects on protein synthesis and cell proliferation are relatively spared and therefore enhanced in the hyperinsulinemic state. Insulin receptor signaling involves several

pathways implicated in cancer, including phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), and extracellular signal-regulated kinase (ERK). Activation of these pathways can increase proliferation, prevent apoptosis, and often be associated with chemotherapy resistance. In addition, insulin inhibits the synthesis of sex hormone–binding globulin, leading to an increased proportion of free, active estrogen in circulation. Insulin also increases the production of insulin-like growth factor 1 (IGF-1). Thus, insulin likely contributes to increased cancer incidence and poorer prognosis in obese individuals through a number of direct and indirect mechanisms.

IGF-1 is considered a major link between obesity and cancer. As its name implies, IGF-1 has similar effects on cells as insulin, stimulating PI3K/AKT and MAPK pathways. Although total IGF-1 concentrations can be low or normal in obese patients, the free, active form of the hormone is generally elevated. IGF-1 has been shown to increase proliferation rates and cause chemotherapy resistance in a number of cancers (62, 94). People with Laron syndrome have extremely low IGF-1 levels and are protected from cancer (88), as are animal models of low IGF-1 (131, 135).

Leptin is secreted by adipocytes in proportion to obesity and whole-body adiposity (32). Despite this strong correlation with obesity, epidemiological studies have not found consistent links between leptin and cancer incidence (61, 187). The leptin receptor signals through Jak/Stat and indirectly increases PI3K, mammalian target of rapamycin (mTOR), and AKT signaling, all of which could contribute to cancer cell progression. However, the data addressing this issue are mixed. Leptin receptor expression has been associated with improved outcome in leukemia (82, 96). However, leptin signaling, particularly through the Notch pathway, may be important for cancer stem cells, and blocking this pathway appears to improve outcome in in vivo models of pancreatic (64) and breast (177) cancer.

Adiponectin circulates at very high concentrations in blood, in inverse proportion to adiposity, and has overall positive effects on metabolism and inflammation. Adiponectin signals through the AMPK pathway, which can promote apoptosis in cancer cells (90), decrease angiogenesis, and limit tumor growth in animal models (see 33). Thus, the lower circulating adiponectin level seen in obesity likely plays a permissive role in tumorigenesis and cancer treatment resistance.

Metabolic Fuels

Obesity is simplistically a disorder of increased nutrient availability and thus is associated with a surfeit of stored and circulating fuels. As the metabolic syndrome develops into frank diabetes, systemic levels of glucose, triglycerides, and some amino acids increase. The three branched chain amino acids (BCAA), valine, leucine, and isoleucine, play an integral role in obesity and the metabolic syndrome. As cancer cells have increased metabolic demands and altered metabolism, increased availability of some of these fuels possibly contributes to the risk and outcome of cancer in obesity.

Microbiome

Over the past two decades, we have become more aware of how the microbiome affects nearly all aspects of our health. In particular, our microbiome can have large effects on our immunity and metabolome, both locally and systemically. Microbiota in the gut can produce butyrate, which has beneficial effects to reduce inflammation, as well as secondary bile acids, which can be carcinogenic (122); the balance of these types of beneficial and detrimental pathways can contribute to cancer risk. Obesity is associated with predictable changes in the intestinal microbiome, namely increased representation by Firmicutes and lower prevalence of *Bacteroides*, though this oversimplification does not do justice to the vast and complex literature on this topic (see 106 for a recent review).

Some evidence has been found that these microbiome changes are causal or at least reinforcing for the development or persistence of the obese state. With respect to cancer, evidence links the obesity-associated microbiome and colorectal (122) and liver (188) cancers, though the data are not yet conclusive (58). The microbiome likely represents an important link between obesity and cancer, but the complexity of both obesity and the microbiome makes teasing apart these effects difficult.

Covariates

In addition to these mechanistic links, a host of covariates undoubtedly contribute to the observed associations between obesity and cancer. It is not unreasonable to hypothesize that there may be genetic polymorphisms that can predispose to both obesity and cancer. Although few specific polymorphisms can explain a significant portion of obesity, *FTO* gene polymorphisms are fairly common, and the ~16% of people who are homozygous for the risk allele have a 1.67 OR of adult obesity (54). Recently, *FTO* polymorphisms have been linked to increased cancer risk, particularly leukemias and glioblastomas (38). A number of other genetic polymorphisms likely contribute to obesity and may also directly or indirectly increase the risk of cancer.

Given the higher prevalence of obesity in people of lower socioeconomic status (SES) and ethnic and racial minorities, considering the influence of these factors on cancer incidence and mortality is important. Lower SES plays a clear role in contributing to cancer mortality, such that poverty has been called a carcinogen (179). Lower SES can contribute to increased cancer risk and worse cancer outcome in a number of ways, including less access to preventive medicine and screening, increased risk behaviors, later presentation of disease, and barriers to optimal treatment (179).

Race and ethnicity can also predispose to both obesity and cancer incidence/poor outcome, some of which is mediated by lower SES. Hispanics in the United States are at a much higher risk of obesity and type 2 diabetes. Overall, Hispanics tend to have a lower incidence of most cancers compared with non-Hispanic whites. However, stomach, gallbladder, liver, and cervical cancers are striking exceptions, with much higher incidence in Hispanics (110). The incidence of childhood ALL has been increasing over the past decade, which has been attributed to an increased prevalence in older Hispanic children (9). This association is compounded by the fact that Hispanic children have a worse survival from hematologic malignancies (77). The mechanisms behind these associations are as yet unknown but could be mediated in part by dietary differences, predilection for obesity and insulin resistance, genetic polymorphisms, SES, or other cultural behavioral differences. Because the Hispanic ethnicity encompasses a wide range of people who appear to have differing susceptibilities to obesity, diabetes, and cancer, studies to tease apart these associations should consider and account for this variability.

Blacks males in the United States are at a higher risk of developing cancer and have a higher cancer mortality rate than non-Hispanic whites (156). Black women have a lower risk of breast cancer incidence, but when diagnosed, they are more likely to have more aggressive forms and worse outcomes (117). Although much of this discrepancy appears to be from presentation at a more advanced stage of disease, disparate access to quality health care, and higher health burden from other illnesses, even after adjusting for these factors, there appears to be a modest cancer-specific survival difference (7). More work is needed to tease out the cultural, genetic, and SES differences to identify potential mechanisms behind these associations.

Finally, a number of behaviors could contribute to the relationships between obesity and cancer. Obese individuals may be more likely to be heavy drinkers (147), consume more red meat (142), live near large roadways exposing them to air pollution (107), and eat less fiber (161) and foods containing antioxidants (67). Obese patients appear to be less likely to be screened for some cancers

(11, 150), for a variety of reasons including physicians' discomfort in performing screening exams (52). This could result in obese patients presenting with cancer at a later stage.

Specific Cancers

In addition to the systemic and overarching influences described above, obesity has specific effects on many organs that can predispose them to cancer development and/or limit cancer treatment. Lipid accumulation in the liver, or nonalcoholic fatty liver disease (NAFLD), is common in obesity, particularly in the Hispanic population. NAFLD can progress to steatohepatitis (NASH), as an increasing degree of liver inflammation develops. The increased risk of NAFLD and NASH likely explains the strong association between obesity and hepatocellular carcinoma (HCC): Obese men were ~4.5 times more likely to die from liver cancer than controls (24). Given the higher prevalence of both obesity and obesity-related liver disease in Hispanics, that Hispanic ethnicity is associated with an increased risk of developing HCC is not surprising.

Esophageal carcinoma is known to be related to chronic gastroesophageal reflux. Reflux of the acidic stomach contents can cause irritation and inflammation in the inferior esophagus, eventually leading to metaplasia and premalignant changes, termed Barrett's esophagus. Obese individuals are at a higher risk of suffering from reflux (OR 1.73), Barrett's esophagus (OR 1.24), and esophageal adenocarcinoma (OR 2.45) (see 139). These associations are likely primarily due to increased abdominal pressure, though confounding effects of specific dietary components have not been ruled out.

Obese individuals are approximately twice as likely to die from pancreatic cancer compared with lean individuals (24). Because mortality from pancreatic cancer is so high, this association is undoubtedly driven by increased incidence, though BMI at diagnosis also predicts survival (189). Obesity is a strong risk factor for pancreatitis, mediated in part by increased prevalence of diabetes, gallstones, and hypertriglyceridemia (78), and pancreatitis is itself a major risk factor for pancreatic cancer. However, chronic pancreatitis accounts for only a small percentage of pancreatic cancer patients (45), and so obesity must have additional effects independent of pancreatitis.

Cancer Metabolism

To understand how diet can affect cancer treatment and prognosis, first understanding some of the unique aspects of cancer metabolism is important. In 1925, Otto Warburg (178) observed that cancerous tumors take up more glucose than other tissues and metabolize it without relying on oxidative phosphorylation, termed the Warburg effect. Although aerobic glycolysis does not provide as much ATP as oxidative phosphorylation, it is believed to better support cancer cell metabolism for a number of reasons. First, tumors can grow rapidly, sometimes outpacing their blood supply, leading to a relatively hypoxic environment. Second, the metabolic machinery needed to perform glycolysis is much less extensive than oxidative phosphorylation, being independent of mitochondria. Third, carbon atoms from glucose can be used to synthesize amino acids, nucleic acids, and other metabolic intermediates in a process of anapleurosis.

Our understanding of the Warburg effect has significantly evolved over the last century. Many cancer cells have been shown to have high respiratory rates, arguing against their reliance on aerobic metabolism (183). The Lisanti group (129) demonstrated that cancer cells induce stromal cells in their microenvironment to shift to anaerobic metabolism, inducing them to release lactate and pyruvate, which are used by the cancer cells for oxidative metabolism. This reverse Warburg effect could result in overall increased glucose uptake and aerobic metabolism in a tumor, mostly due to the stromal cells.

In addition to increased glucose utilization, cancer cells often exhibit a dependence on free fatty acids (FFA). FFA provide the acyl chains of phospholipids, the primary component of cell and organelle lipid bilayer membranes. As a dividing cell duplicates its plasma membranes with every division, a large investment in FFA is required for a cancer cell to proliferate. FFA synthesis is energetically expensive, utilizing 14 NADPH and 7 ATP to synthesize 1 molecule of palmitate. Increased de novo FFA synthesis and exogenous FFA uptake have both been associated with cancer aggressiveness and survival (84, 118, 123, 146). Conversely, FFA can provide a large amount of energy and are often abundant in tumor microenvironments, particularly those in proximity to adipocytes. Thus, cancer cells in adipocyte-rich environments have been shown to rely heavily on FFA oxidation (119, 166).

Adipocytes can also be a source of amino acids. We have shown that adipocyte release of glutamine and asparagine can particularly interfere with ALL treatment with L-asparaginase (49). Glutamine is also extremely important for other cancer cells, where it contributes to the synthesis of nucleotides, amino acids, and tricarboxylic acid (TCA) cycle intermediates (194). Cancer cells use BCAA for protein synthesis and energy metabolism and often overexpress branched chain aminotransferase enzymes needed for BCAA metabolism (5). Thus, cancer cells exhibit unique metabolic needs that may be met in obese, adipose-rich environments.

WEIGHT CHANGES DURING CANCER TREATMENT

During the development of cancer, and over the course of its treatment, the body can exhibit dramatic changes in weight and composition. Many cancers are associated with cachexia, which encompasses weight loss disproportionately and affects lean body mass. Cachexia is generally attributed to inflammatory cytokines associated with cancer burden, such as TNFα, IL-6, and IL-1α; however, anorexia can be exacerbated by pain, depression, and nausea associated with the diagnosis of cancer and its treatments. Weight loss associated with cachexia is generally considered a poor prognostic sign. Cancer cachexia could be a marker of a more aggressive or advanced cancer or of a more toxic response to treatment. Alternatively (or additionally), the unhealthy weight loss associated with cachexia could somehow impair cancer treatment outcome.

Conversely, significant weight gain can occur over the course of some cancers. Cancers that are treated with high doses of glucocorticoids, particularly hematologic cancers, are associated with an increase in adiposity due to the adipogenic effects of these agents. We showed that BMI was not an accurate measure of obesity in adolescents during treatment for high-risk ALL: Over the first month of treatment, subjects gained ~1.5 kg of body fat and lost ~6 kg of lean mass, resulting in a substantially higher body fat percentage (125). Thus, weight and BMI were not helpful in distinguishing these changes in body fat, such that even those who lost weight generally developed sarcopenic obesity. This risk for excess adiposity and obesity persists throughout treatment for ALL; indeed, childhood cancer survivors are at more than a fourfold risk of metabolic syndromes (51), including obesity, hypertension, dyslipidemia, and insulin resistance (121).

The bone marrow environment also undergoes drastic changes during chemotherapy treatment. Most chemotherapeutic agents are toxic to hematopoietic cells, leading to a drastic reduction in marrow space filled by hematopoietic cells. Much of this space becomes occupied by adipocytes through unclear mechanisms. Steroid treatments used in some cancers exacerbate this, and the bone marrow in the iliac crest and long bones can be transformed predominantly into fat tissue. These fat cells may play a role in supporting hematologic and other cancers that reside in or metastasize to the marrow.

DIET INTERVENTIONS

Given the associations between obesity and poor cancer outcomes, the observation that cancer cells are excessive users of metabolic fuels, such as glucose, amino acids, and fats, and the strong desire of patients, families, and practitioners to offer further hope, it is not surprising that dietary intervention has been a popular topic of discussion in the cancer treatment world. If proven beneficial to therapeutic efficacy, dietary interventions could lead to improved outcomes with little or no additional toxicity. Indeed, some data show that diet interventions could potentially reduce chemotherapy side effects. Unfortunately, the vast majority of the discourse has been based on opinion and anecdotal evidence, and a paucity of scientifically validated diet interventions can be offered to cancer patients. We summarize below the preclinical and clinical evidence related to the most common diet interventions proposed for cancer patients.

Fasting

Fasting has been touted for its health benefits for decades. Epidemiological studies show improved life span and reduced incidence of cancer and cardiovascular disease in people who practice intermittent fasting for religious or personal reasons. Fasting has been tested in several preclinical models of cancer initiation/progression, with mixed results. Generally, studies have used intermittent fasting, which describes one or more fasting sessions that last for 24 or more hours. A meta-analysis evaluating the literature between 1994 and 2014 identified eight preclinical studies of intermittent fasting and cancer, five of which identified a benefit of intermittent fasting and three of which did not (99). Studies that have looked at the impact of fasting on the growth of implanted cancer cells in mice have found beneficial effects in some models (15, 23, 91, 96, 104, 145, 164) but not in others (21, 36, 85, 91, 96, 134, 168), and some studies have found beneficial effects on one cancer but not another (91, 96), indicating that fasting could potentially have cancer-specific effects. Approximately two-thirds of these cancer models using immunocompetent mice identified beneficial effects of fasting (9 out of 14), whereas only one-half using immunocompromised models concluded a positive effect (4 out of 8). This variability might imply that the beneficial effects of fasting on cancer progression/treatment efficacy require an intact immune system. Indeed, fasting has been shown to prevent and reduce autoimmunity (29). One study showed that fasting reduced the accumulation of tumor-associated macrophages (TAMs), consistent with an immune system–mediated benefit (164). A few studies have examined the effects of fasting on spontaneous tumor onset/progression of cancer in either genetic or carcinogenic models of cancer, with most identifying a beneficial effect of fasting on tumor incidence (14, 48, 140, 170).

Whether fasting can improve cancer treatment outcome has also been tested in several preclinical studies (**Table 1**). Most studies found synergistic effects of fasting on anticancer therapy, including radiation and chemotherapies, though there were several exceptions to this. In addition to cancer progression and treatment efficacy, fasting may play a role in the reduction of treatment toxicities. Fasting has been shown to protect mice from toxicity induced by etoposide (134), irinotecan (75), doxorubicin (20), and abdominal radiation (36).

Few clinical studies have tested fasting on therapeutic outcome. A case series by Safdie et al. (144) demonstrated that complete fasting, starting 36–140 hours before and continuing through 8–56 hours after chemotherapy, is feasible in adult patients with solid tumors. These were complete fasts, with the exception of water and sometimes vitamins, and were associated with subjective reduction in chemotherapy side effects and no clear evidence of impaired chemotherapy efficacy. Short-term fasting was tested in a randomized study of 13 patients receiving neoadjuvant treatment for breast cancer. Fasting for 24 hours before and after chemotherapy was well-tolerated in the 7 patients randomized to fast, and subjects exhibited higher red cell and white cell counts

Table 1 Preclinical studies examining the role of fasting on cancer outcome

Cancer (cell line)	Animal model	Route	Fasting scheme	Effect of fasting alone	Effect of fasting with treatment	Reference
Immunocompetent						
Breast (67NR and 4T1)	14-week-old BALB/c	Orthotopic	ADF	Slowed tumor growth	Synergy with irradiation	145
Breast (4T1)	12-week-old BALB/c female	SQ	Two 48- to 60-hour fasting cycles	Slowed tumor growth	Synergy with cyclophosphamide	91
Breast (4T1)	12-week-old BALB/c female	IV	One 48-hour fast	NA	Synergy with cyclophosphamide to prolong survival	91
Colorectal (CT26)	6-week-old female BALB/c	SQ	Two 48-hour fasting cycles	Slowed tumor growth	Synergy with oxaliplatin	15
Melanoma (B16)	12-week-old C57BL/6 male and female	SQ	Two 48- to 60-hour fasting cycles	Slowed tumor growth	Synergy with doxorubicin	91
Melanoma (B16)	12-week-old C57BL/6 male and female	IV	One 48-hour fast	No sustained benefit	Synergy with doxorubicin to prolong survival	91
Neuroblastoma (NXS2)	6- to 7-week-old female A/J	IV	One 48-hour fast	No benefit	Less treatment toxicity of one high dose of etoposide, but more rapid tumor progression	134
Neuroblastoma (NXS2)	6-week-old female A/J	IV	Two 48-hour fasting cycles	NA	Synergy with doxorubicin to prolong survival	91
Neuroblastoma (Neuro 2A)	6-week-old female A/J	IV	One 48-hour fast	NA	Synergy with doxorubicin and cisplatin cocktail to prolong survival	91
Pancreatic (KPC)	9-week-old male and female C57BL/6J	Orthotopic	One 24-hour fast	No benefit	Synergy with irradiation	36
Immunocompromised						
Breast (MDA-MB-231)	5- to 7-week-old nude mice	SQ	Four 48-hour fasting cycles	No sustained benefit	No apparent synergy with doxorubicin	91
Breast (H3122)	6- to 8-week-old athymic BALB/c mice	SQ	Three 48-hour fasting cycles	Slowed tumor growth	Synergy with crizotinib (tyrosine kinase inhibitor)	23
Colorectal (HCT116)	6- to 8-week-old athymic BALB/c mice	SQ	Three 48-hour fasting cycles	Slowed tumor growth	Synergy with regorafenib (tyrosine kinase inhibitor)	23
Glioma (GL26)	7-week-old nude mice	SQ	One 48- to 60-hour fasting cycle	Slowed tumor growth	Synergy with doxorubicin	91
Ovarian (OVCAR3)	5- to 7-week-old nude mice	SQ	Two 48-hour fasting cycles	No sustained benefit	No apparent synergy with doxorubicin	91

Abbreviations: ADF, alternate day feeding; IV, intravenous; NA, not assessed; SQ, subcutaneous.

after chemotherapy compared with the nonfasted groups (35). Further confirming the feasibility of fasting in cancer patients, Dorff et al. (43) prescribed escalating doses of fasting in consecutive subgroups, increasing from 24 hours before treatment to 48 hours before and 24 hours after treatment. Twenty subjects with a variety of cancers being treated with platinum-based therapies were enrolled. Of these, 13 were considered compliant with the intervention, consuming <200 kcal/day. Fasting-related symptoms were generally mild, and no grade 3 or 4 fasting-related toxicities were reported. In another study, 34 patients being treated for breast or ovarian cancer were randomized in a crossover design to receive short-term fasting during the first or second half of their planned chemotherapies, versus an ad libitum (AL) diet during the other half. Fasting lasted 60 hours total (36 hours before and 24 hours after chemotherapy) and showed some efficacy in improving quality of life and reducing fatigue, though effect on chemotherapy efficacy was not evaluated (10).

Calorie Restriction

Although periods of complete fasting are likely to induce the most drastic metabolic shifts, this might not be feasible or acceptable to all patients, and so alternative approaches have been explored. Caloric restriction may provide some of the same benefits as fasting through similar mechanisms. Caloric restriction can also be imposed for longer periods of time, thus conceivably providing more sustained benefits. Many preclinical studies have evaluated the effects of caloric restriction on cancer initiation and progression, again with a high degree of variability between cancer models, diet interventions, and outcomes evaluated. A majority of studies limit calories by reduction of carbohydrates, though some include protein limitation or proportional limitation of all nutrients. When diet is imposed as a chronic condition, animals are generally provided 60–85% of what an AL control would consume. Intermittent strategies involve more severe caloric restriction, generally 50–67% of AL for 1- to 3-week discrete periods. These restriction periods alternate with periods of either full AL consumption or consumption matched to an AL group (to prevent compensatory overeating during nonfasting periods). Thus, it can be difficult to compare studies that use different calorie restriction regimens.

Despite the variability in regimens, convincing evidence has been found that calorie restriction can delay cancer in spontaneous and carcinogenesis models (14, 17–19, 25, 30, 39, 41, 44, 47, 50, 56, 60, 69, 70, 72, 73, 87, 89, 101, 102, 111–113, 132, 141, 154, 163, 165, 169, 171, 176, 185) as well as in transplants in syngeneic (22, 37, 46, 65, 120, 130, 151, 152, 175) and xenograft models (55, 74, 89, 100). Only a minority of studies found no effect or a negative effect of caloric restriction (16, 20, 76, 85, 108, 127, 167, 172). A handful of studies have tested whether calorie restriction can improve treatment efficacy (**Table 2**). Our group showed that switching mice from a high-fat to a low-fat diet improved the treatment efficacy of vincristine against syngeneic B-cell ALL; however, we observed no synergy with dexamethasone or L-asparaginase (174).

Carbohydrate Restriction/Ketogenic Diet

Using a ketogenic diet as an alternative to fasting and caloric restriction has generated great interest. A ketogenic diet could be better tolerated in some patients, and it has a long safety record as a treatment for epilepsy. A recent meta-analysis identified 12 studies that tested unrestricted ketogenic diet against standard diet in murine cancer models and concluded an overall growth delay with the ketogenic diet (80). A few studies have evaluated a ketogenic diet during anticancer treatment, reporting synergy in most cases with irradiation, metformin, and chemotherapy (**Table 3**).

A recent systematic review identified six articles describing clinical intervention with a ketogenic diet in pediatric or adult patients with glioma, together including 39 subjects, along with 12

Table 2 Preclinical studies examining the role of caloric restriction on cancer outcome

Cancer (cell line)	Animal model	Route	Diet scheme	Effect of diet alone	Effect of diet with treatment	Reference(s)
B-ALL (8093)	C57BL/6J	Retro-orbital	Switch from 60% to 10% fat diet	No benefit	Improved efficacy of vincristine, but no effect on dexamethasone or L-asparaginase	174
Breast (4T1)	8- to 14-week-old BALB/c	Orthotopic	70% of AL	Slowed tumor growth	Synergy with irradiation, cisplatin, and docetaxol	145, 158, 159
Breast (4T1)	12- to 15-week-old BALB/c mice	SQ	50% of AL	NA	No synergy with cisplatin	20

Abbreviations: AL, ad libitum; NA, not assessed; SQ, subcutaneous.

ongoing trials (105). Although none of the published studies were randomized controlled trials, the results showed that a ketogenic diet could be well-tolerated with few adverse effects and may confer some benefit to overall and progression-free survival; however, the case-series studies were designed without comparisons with control groups, which preclude more definitive conclusions.

Other Diet Interventions

A number of diets that do not fit into the above categories may provide beneficial effects on cancer risk and outcome. Strict adherence to a Mediterranean diet has been associated with reduced all-cause cancer mortality as well as mortality from breast, colorectal, head and neck, gastric, prostate, liver, respiratory, and pancreatic cancers (148). Olive oil, a major component of the Mediterranean diet, contains high concentrations of monounsaturated fatty acids, antioxidants, and other potentially beneficial components. People in the highest category of olive oil consumption exhibited a lower odds of overall cancer as well as breast and gastrointestinal cancers (133). Protein restriction can reduce the growth of human xenograft breast and prostate cancer (53), though low animal protein intake was not associated with cancer mortality in prospective cohorts (162). A meta-analysis including 96 cohort and cross-sectional studies concluded that vegetarian and vegan diets reduced the incidence of cancer by ~8% and ~15%, respectively (40). Further, higher intake of vegetable versus animal fats after diagnosis of prostate cancer was associated with an improved survival (138). In a meta-analysis, increased soy intake was associated with a decreased risk of breast mortality and recurrence (155). Numerous studies have evaluated specific dietary components for anticancer effects in vitro and preclinical models (for example, 48, 111). However, to our knowledge, no studies have examined whether any of these diets or dietary components can improve chemotherapy treatment outcomes.

MECHANISMS

The above diets induce a host of metabolic effects, many of which can be beneficial for a patient during cancer treatment. With caloric restriction and fasting, systemic levels of glucose and some lipids and amino acids decrease, limiting the available fuel for cancer cells to grow and divide. Ketogenic diets could exert additional anticancer effects through toxicity of ketones themselves. Indeed, ketogenic diet efficacy may be reversed in tumors that express high levels of ketone-metabolizing enzymes (193).

Table 3 Preclinical trials of ketogenic diets on cancer outcome

Cancer (cell line)	Animal models	Route	Diet scheme	Effect of diet alone	Effect of diet with treatment	Reference(s)
Breast (4T1)	BALB/C	SQ	70% of AL of diet containing 2% CHO and 93.4% fat calories	Reduced tumor growth	Enhanced antitumor effect of metformin	196
Glioma (GL261 cells)	Male albino C57BL/6	Orthotopic	AL 3% CHO and 72% fat calories	Prolonged survival	Synergy with irradiation	1, 98
Glioma (GL261)	Female albino C57BL/6	Orthotopic	AL 3% CHO and 72% fat calories	Prolonged survival	Synergistic with whole brain irradiation	1, 180
Lung (NCI-H292 and A549 cells)	Female athymic-*nu/nu* mice	SQ	AL 1.6% CHO and 90% fat calories	No effect of KD alone on tumor volume or survival	Enhanced tumor response and survival with irradiation and/or carboplatin	3
Medulloblastoma (cells from above mice)	NOD/SCID	SQ	AL 6:1, 3.2% CHO and 75.1% fat paste	No effect on tumor growth	No effect on SMO inhibitor GDC-0449 antitumor activity	34
Neuroblastoma [SK-N-BE(2) and SH-SY5Y cells]	Female CD1-nu	SQ	AL or 2/3 AL KD with 8% CHO and 78% fat calories	CR KD slowed tumor growth and prolonged survival of both tumors; AL KD only slowed tumor growth and prolonged survival for SK-N-BE(2) tumors	Both diets slowed growth of KH-SY5Y tumors but not SK-N-BE(2) tumors during cyclophos-phamide treatment	115, 116

Abbreviations: AL, ad libitum; CHO, carbohydrates; CR, caloric restriction; KD, ketogenic diet; SMO, smoothened gene, a component of the sonic hedgehog pathway; SQ, subcutaneous.

A primary hypothesis on how fasting, and potentially caloric restriction, works is termed differential stress (134). Upon fasting, levels of many anabolic hormones drop, including insulin, IGF-1, and leptin. Combined with reduced metabolic fuel availability, these changes reduce anabolic signaling in noncancerous cells, leading to increased mTOR and decreased AKT. These signals slow cell growth and proliferation and can induce autophagy, all of which would tend to make healthy cells less susceptible to chemotherapies—particularly those that target dividing cells. Conversely, one of the hallmarks of cancer cells is growth and proliferation independent of local and systemic signals; thus, fasting may not alter proliferation rates of these cells, which would therefore retain susceptibility to chemotherapy. In addition, the decrease in availability of fuels, including glucose, lipids, and amino acids, can have additional detrimental effects on cancer cells, which may not

exhibit the same metabolic flexibility of host cells. Thus, rapid proliferation in the face of fuel deprivation may induce oxidative stress, increasing the likelihood of DNA replication errors and catastrophic mitotic events. Together, these effects should widen the therapeutic window between host and cancer cells and allow a more targeted killing of cancer by chemotherapy.

Hormonal changes induced by diet interventions can have additional effects as well. Some cancer cells are sensitive to growth-promoting hormones such as insulin and IGF-1 and may become more sensitive to chemotherapy once these signals are reduced by dietary intervention. This effect was demonstrated by Dunn et al. (47), who showed that replacement of IGF-1 reversed the survival benefit observed during dietary restriction. Alternatively, caloric restriction and fasting cause adiponectin levels to rise, which could theoretically promote apoptosis in cancer cells. Other hormonal effects might be more complicated. Lu et al. (96) elegantly showed that leukemia cells in obese mice were resistant to leptin but, upon fasting, would increase expression of leptin receptors, leading to leukemia cell differentiation and improved mouse survival.

Dietary interventions likely have multiple effects on the host environment that can impact cancer progression and sensitivity to treatment. An energy-restricted diet can reduce inflammatory monocyte populations in overweight and obese adults within 16 weeks (79). A ketogenic diet was shown to enhance antitumor immunity, increasing tumor infiltration by $CD4^+$ T cells, but without increasing T-regulatory cell number (98). Importantly, the beneficial effects of the diet were reversed with $CD8^+$ T cell depletion. Diet interventions have major effects on the microbiome, which can in turn alter inflammation, the systemic metabolome, and even potentially chemotherapy metabolism (143). Dietary restriction can reduce vascularization, potentially limiting tumor oxygen and nutrient access (169). These and other beneficial effects of diet intervention could potentially provide additive benefits to cancer treatment.

WHICH IS THE BEST DIET?

Although much can be learned about obesity, diet, and cancer outcomes from preclinical studies, it is important to keep in mind that mice are not humans. The most common mouse model of obesity, the diet-induced obese C57BL/6 mouse, becomes obese on a diet consisting of 45% or 60% of calories from fat. This is in contradistinction to humans, whose obesity is thought to be more related to excess carbohydrates. Few studies have tested multiple diets in a head-to-head fashion, and even in those, the winning diet may be better simply due to specifics of the models chosen. For example, caloric restriction at 60% of AL showed a better survival benefit in p53 heterozygous mice than fasting one day per week (14). But what if they had tested fasting two days per week, or every other day? A 60-hour fast was more effective than 50% caloric restriction in protecting mice from doxorubicin toxicity (20), but what if it was less effective in synergizing with its anticancer activity? Or with the activity of a different chemotherapy? Making fair diet comparisons in these types of studies is difficult if not impossible, because matching caloric intake does not necessarily match tolerability. Further, diets may act differently in different cancer models, varying by cancer type, stage, mutations, species, treatment regimen, etc. A recent meta-analysis compared the efficacy of chronic versus intermittent caloric restriction and found that intermittent calorie restriction was more effective in reducing the incidence of cancer in genetically engineered models, whereas chronic calorie restriction was better for carcinogen models (27). Translating these results into clinical recommendations is difficult.

A systematic review and meta-analysis including many of the above studies compared the efficacy of caloric restriction, ketogenic diet, and intermittent fasting on cancer initiation, progression, and metastasis (99); the authors concluded that caloric restriction and ketogenic diet were highly effective, whereas the data on intermittent fasting were not yet conclusive. Given the paucity of

data examining dietary intervention during cancer treatment, particularly in patients, more work will need to be done to test which interventions have the best efficacy against specific cancers.

CONCLUSIONS

Our diet clearly has a major impact on our cancer risk. The preclinical literature strongly supports the potential of diet intervention to improve cancer treatment outcomes. However, determining which dietary strategy is best is not possible at this point, and diet efficacies will likely vary based on patient, cancer types, and treatment regimen. Clinicians who care for overweight and obese patients know that sometimes the best diet is the one that the patient is willing and able to adhere to, and so a degree of personalization may be needed when instituting these strategies in the clinic. Unfortunately, this approach requires flexibility, ancillary support staff, and an understanding that a lifestyle intervention may have efficacy on par with cytotoxic agents.

Although translating these findings from mice to patients is not straightforward, it is imperative that we continue to explore this avenue. Diet intervention has the potential to improve cancer outcome without introducing additional toxicities and long-term complications. Indeed, most evidence indicates that diet intervention reduces toxicity and thereby facilitates more effective chemotherapy. Integrating this shift in paradigm into oncology will require more clinical trials and time.

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