Title
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Permalink
https://escholarship.org/uc/item/4f35f1q5

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Publication Date
2020

DOI
10.1177/2050312120926877

Peer reviewed
A review of nutrition and dietary interventions in oncology

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Abstract
The complex cellular mechanisms and inter-related pathways of cancer proliferation, evasion, and metastasis remain an emerging field of research. Over the last several decades, nutritional research has prominent role in identifying emerging adjuvant therapies in our fight against cancer. Nutritional and dietary interventions are being explored to improve the morbidity and mortality for cancer patients worldwide. In this review, we examine several dietary interventions and their proposed mechanisms against cancer as well as identifying limitations in the currently available literature. This review provides a comprehensive review of the cancer metabolism, dietary interventions used during cancer treatment, anti metabolic drugs, and their impact on nutritional deficiencies along with a critical review of the following diets: caloric restriction, intermittent fasting, ketogenic diet, Mediterranean diet, Japanese diet, and vegan diet.

Keywords
Diet, oncology, caloric restriction, ketogenic diet, intermittent fasting

Date received: 19 February 2020; accepted: 22 April 2020

Introduction to cancer and nutrition
Cancer is the leading cause of death worldwide. In 2018 alone, over 1.7 million people were diagnosed with cancer and over 600,000 deaths have resulted from this disease.1 From 1999 to 2015, the overall incidence of cancer decreased by 2.2% in men and remained stable in women, yet the mortality rate for both has only decreased slightly to 1.8% and 1.4% respectively.2 These modest improvements in outcomes could be attributed to improvements in cancer therapies and detection; however, it is tempting to speculate that greater improvements could be achieved if the therapeutic effects of diet on cancer are considered.

The last decade seems to have witnessed a surge of interest in the role of diet and its effects on cancer metabolism. This interest is at least partly ignited by the rapid increase in the prevalence of obesity in the United States. Between 2015 and 2016, the National Health and Nutrition Examination Survey demonstrated 39.8% of adults and 18.5% of youth were obese.3 A prospective study of over 900,000 adults in the United States, many investigators have sought to investigate the effects of excessive nutritional intake on the outcomes of cancer patients.

In general, cancer therapies target the hypermetabolic state of cancer cells to primarily destroying rapidly dividing tumor cells. However, rapidly dividing normal cells are also affected by anti-neoplastic therapies. As our understanding of tumor proliferation and apoptosis within individual cancers expands, investigators have been making significant strides to create targeted immunotherapies that will eliminate the bystander...
effect seen with traditional chemotherapy such as neutropenia, mucositis, renal failure, and cardiac dysfunction. The first example of immunotherapy was developed by Milstein and Kohler in 1970. Then, in 1997, rituximab, a monoclonal CD20 antibody, became available as a targeted treatment for non-Hodgkin’s lymphoma and has since become a widely utilized therapeutic option for non-Hodgkin’s lymphoma and as a major tool in the treatment of multiple myeloma.19 More recently, immunotherapy has been expanded to include checkpoint inhibitors, which target immune checkpoint molecules on T cells, thus allowing them to kill cancer cells.20,21

Cancer metabolism
Cancer metabolism is an integral component of involuntary weight loss in the setting of disease-associated wasting. It is further and still broadly defined as an inflammatory-associated wasting of protein, particularly skeletal muscle, and loss of energy stores. Cytokines and hormones, such as leptin, insulin, several interleukins, and growth factors, elicited in disease and as principal mediators of inflammation may in effect tilt physiology toward catabolic breakdown of tissue presumably in service of mobilizing critical nutrients for central nervous system and aspects of immune function.20

Cachexia has been shown to be associated with cancer-related mortality; however, no consistently effective therapies have been developed to prevent or hamper its progression.20 Even for patients who are able to eat—apetite suppression or anorexia is a common cachexia symptom—efforts to improved nutrition often offer little respite.21 It is interesting to speculate that underreporting of cachexia as a “contributing cause of death” has perennially affected the primacy placed on research and funding of this enormously pervasive process.

As a special case, cancer-induced cachexia is described as a multifactorial metabolic disorder seen in 50% of cancer patients.22 The exact mechanisms remain unclear, but it is thought that they may be influenced by an increase in energy expenditure, hepatic gluconeogenesis, fat lipolysis, and skeletal muscle proteolysis leading to progressive weight loss throughout therapy.23,24 Further complicating this phenomenon, as noted previously, is that this auto-catabolic process is not reversed by total parental nutrition or supplements.25 It is important to...
note that the relationship between tumor phenotype to host genotype likely results in heterogeneity in the degree of cachexia between individuals with the same malignancy.

Even prior to diagnosis, most cancer patients will experience a significant degree of catabolism leading to both muscle and adipose depletion, in contrast to the predominant wasting of adipose tissue in anorexic patients. This difference may be due to the change in resting energy expenditure (REE), which is defined as the amount of energy expended by a person at rest. A recent meta-analysis of 27 studies comparing 1453 cancer patients to 1145 control patients shows that, on average, the REE of cancer patients was 9.66% higher than that of controls. It is important to note that different malignancies are known to have varying degree of metabolism, and one study found marked REE variation among different cancer groups (p < 0.001). For example, Burkitt’s lymphoma has a doubling time of 24 h, while Hodgkin’s lymphoma has a doubling time of 29 days. Therefore, the specific type of cancer may have large effects on the overall metabolism within the patient.

It was first described in 1927 by Otto Warburg et al. that tumors cells demonstrate an aberrant metabolic pathway that contributes to excessive catabolism. In normal tissues via oxidative phosphorylation, one molecule of glucose is able to produce 36 adenosine triphosphate (ATP) molecules, which are the intracellular energy used to drive cellular processing. Cells also have an alternative pathway known as glycolysis, which utilizes one molecule of glucose to produce just two ATP molecules. In a phenomenon known as the Warburg effect, tumor cells selectively upregulate key regulators of glycolysis, such as hypoxia-induced factor-1α (HIF-1α). HIF-1α drives three main processes: (1) increased expression of glucose transporter-1 (GLUT-1) leading to increased glucose availability for glycolysis; (2) increased pyruvate dehydrogenase kinase production leading to increased conversion of lactate to pyruvate and decreased production of acetyl CoA necessary for the Krebs cycle (produces one ATP and three nicotinamide adenine dinucleotide (NADH)); and (3) increased lactate dehydrogenase production leading to increased conversion of lactate to pyruvate, which serves as the primary substrate for gluconeogenesis in the liver. Increased lactate acid production via glycolysis is also released systemically, where it undergoes gluconeogenesis in an ATP-consumptive process known as the futile lactate–glucose shunt, or Cori cycle. Overall, these processes promote an overall energy deficient state, leading to lipolysis and proteolysis and eventually cachexia. A recent in vivo study with human pancreatic cancer cells in athymic mice reveals that the Warburg effect was present in the complex system of a live animal, thus further supporting these proposed mechanisms of cancer-induced cachexia. After 90 years since the Warburg effect was proposed, it remains unclear if the Warburg effect acts independently or if physiologic interactions in response to the Warburg effect drive cancer-induced cachexia.

Systemic inflammation that occurs during tumor proliferation is thought to contribute to cachexia. Elevation in pro-inflammatory markers, such as C-reactive protein and fibrinogen, has been positively correlated with the degree of muscle wasting in cancer and chronic disease. Cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), contribute to persistent inflammation and increase rates of gluconeogenesis, lipolysis, and proteolysis. TNF-α also stimulates the expression of uncoupling proteins 2 and 3 (UCP2/3) in cachectic skeletal muscle, due to UCP’s mediated proton leakage, and decreases the coupling of respiration to ADP phosphorylation, thereby generating heat instead of ATP from brown fat. In fact, IL-6 levels have been found to be elevated in cachectic patients when compared with patients who maintained their weight during therapy. These mechanisms have been replicated in animal studies, where IL-6 blockade in mice leads to attenuation of protein degradation and TNF-α blockade decreases catabolism in rat models.

The role of neuropeptides in inducing anorexia during a catabolic state is emerging as a major contributing factor to cancer-induced cachexia. There appears to be an imbalance between appetite-stimulating molecules, such as neuropeptide Y (NYP), melanin-concentrating hormone, orexins, endogenous opioids, and cannabinoids compared with appetite suppressant molecules such as serotonin, peptide YY, cholecystokinin, leptin, and insulin. The role of neuropeptide Y is of special consideration as it is produced primarily in the hypothalamus and has a robust feeding stimulatory effect. Overstimulation with NYP leads to obesity in rats, in addition to decreased energy expenditure and reduced brown fat thermogenesis. However, NYP injection into rats with sarcomas showed a reduction in feeding behavior, and a separate study revealed that rats with malignancies demonstrated a reduced release of NYP, suggesting that tumors may induce neurohormonal changes that decrease feeding activity and compound weight loss in cancer patients.

Another hormone of interest is leptin, a protein primarily produced in white and brown adipocytes that is responsible for peripheral signaling to reduce appetite and increase energy expenditure. While decreased food intake normally suppresses leptin production, anorexia has been associated with increased leptin levels in adipose tissue and plasma. Multiple authors have reported low or undetectable circulating leptin levels in cancer patients, suggesting a degree of leptin dysregulation. Elucidating the mechanisms behind neurohormonal dysregulation of leptin may provide insight into further therapeutic options in the future.

**Anti-metabolic drugs and their impact on nutritional deficiencies**

Cancer chemotherapy regimens target rapidly dividing cells by either inhibiting DNA or protein synthesis or restricting essential micronutrients, thus leading to cellular death. Further, studies show that between 30% and 90% of patients have inadequate dietary regimens. Chemotherapy, along with poor nutritional intake during treatment, is a great concern for
patients and physicians. Chemotherapies that affect the nutritional status of patients include anti-metabolites, such as folate, purine, and pyrimidine analogs, in addition to platinum-based drugs. Due to the broad mechanism of action of these drugs, many organ systems are adversely affected.

Methotrexate is an anti-metabolite folate analog that is used in standard therapy protocols for leukemia, lymphoma, and osteosarcoma. Methotrexate leads to cellular death by acting as a dihydrofolate inhibitor, which is responsible for the conversion of dihydrofolate to tetrahydrofolate. Inhibition of tetrahydrofolate formation reduces the availability of one-carbon fragments necessary for the production of purines and the conversion of deoxyuridylate to thymidylate for DNA synthesis and cell reproduction. Although rapidly dividing malignant cells are most affected by inhibition of DNA synthesis, other rapidly proliferating cells are affected as well, such as hematopoietic and epithelial cells, thus leading to myelosuppression and mucositis. Due to these side effects, a leucovorin “rescue” is performed 24 h after methotrexate is administered. Leucovorin is a derivative of tetrahydrofolic acid, which does not require dihydrofolate reductase activity and thus “rescues” the healthy cells by allowing for de novo DNA synthesis to resume. Due to these side effects, a leucovorin “rescue” is performed 24 h after methotrexate is administered. Leucovorin is a derivative of tetrahydrofolic acid, which does not require dihydrofolate reductase activity and thus “rescues” the healthy cells by allowing for de novo DNA synthesis to resume.

5-Fluorouracil (5-FU) is a competitive inhibitor of thymidylate synthase, which blocks thymidine synthesis and inhibits DNA and RNA replication. 5-FU is widely used in colorectal, breast, and head and neck cancers. Interestingly, increased intracellular folate levels increase thymidylate synthase levels, thereby enhancing the inhibitory effects of 5-FU. This interaction between metabolites suggests that optimal nutrition can improve chemotherapy effects in specific cancer groups. Gemcitabine has a similar mechanism of action with 5-FU; however, it is a prodrug that, when phosphorylated, interrupts DNA synthesis and inhibits DNA repair, leading to cellular death. In pancreatic cancer, it has been shown that intravenous omega-3 fatty acids, along with gemcitabine, improve quality of life scores with regard to chemotherapy-induced side effects. The relationship between targeted supplementation and chemotherapy optimization suggests that optimized nutrition and reduction of chemotherapy effects could be dependent on specific treatment regimens.

Platinum-based chemotherapy drugs such as cisplatin, carboplatin, and oxaliplatin are used in the treatment of cancers such as testicular, ovarian, and lung cancer, in addition to osteosarcoma and neuroblastoma. After the platinum-based drug is incorporated into the cell using copper transporters, it binds at the N7 position of guanine, causing cross-linking between adjacent guanine. This leads to failed DNA repair mechanisms and eventually cellular apoptosis. Two studies in patients with solid tumors showed that selenium supplementation, when given during cisplatin therapy, reduced myelosuppression and nephrotoxicity, suggesting that optimal levels of selenium could aid in the toxicity profile related to platinum-based therapies. It was not reported whether mortality or relapse rates were affected by this type of supplementation, and thus, more studies are warranted to elucidate these data (Table 1).

### Dietary approaches

#### Western diet

Environmental and lifestyle factors, including diet, are hypothesized to influence risk of malignancy. In the United States, the vast majority of Americans consume a Western diet, which consists of a high intake of fats, processed meat, dairy, and carbohydrates and low intakes of fiber. This composition has been associated with broadly negative impacts on glycemic load, fatty acid composition, micronutrient and macronutrient composition, sodium intake, and fiber content, all of which have been suggested to contribute to tumorigenesis. Since the diet is a modifiable risk factor

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### Table 1. Chemotherapy and nutritional deficiencies.

| Chemotherapy | Mechanism of chemotherapy | Type of malignancy | Nutritional deficiencies | Nutritional supplementation |
|--------------|---------------------------|--------------------|--------------------------|----------------------------|
| Methotrexate | Antifolate metabolite     | Leukemia           | Folic acid                | Folic acid                 |
| 5-Fluorouracil | Competitive inhibitor of thymidylate synthase | Lymphoma, Osteosarcoma | – | Intravenous omega-3 (with gemcitabine; single-study evidence) |
| Gemcitabine  | Cross-linking between adjacent guanine | Colorectal, Breast, Head and neck, Pancreatic | – | Selenium (with cisplatin) |
| Carboplatin  | Cross-linking between adjacent guanine | Testicular, Ovarian, Lung, Osteosarcoma, Neuroblastoma | – | – |
in many of the diseases we see today, the interaction between how diet may modify cancer risk is an important area of emerging research.

It is postulated that the shift to the Western diet among many countries may be a contributing factor to the apparent increase in chronic diseases, including hypertension, coronary artery disease, hyperlipidemia, and osteoporosis. Over the last few decades, the Western diet has been epidemiologically associated with an increased incidence of many cancers, including prostate cancer, breast cancer, colorectal cancer, among many others. Specifically, one study concluded that a Western diet showed an overall odds ratio of colon cancer risk of 1.88 when compared with individual who consumed higher intakes fruits, vegetables, and grains combined with a lower intake of red/processed meats. Another study found that those who followed a Western diet had an increased risk of prostate cancer, with an odds ratio of 1.34 compared with those who consumed healthier diets of fish, poultry, and whole grains. These large cohort studies suggest that dietary pattern has a substantial impact on risk of developing various malignancies. Despite large samples, hypotheses should be tempered by the clinical reality that there are many antecedent and intervening variables that may confound conclusions.

Nevertheless, specific dietary regimens have gained increased interest as potentially effective adjuvant interventions to traditional cancer therapies. Here, we will discuss some of the more prominent dietary approaches, the evidence behind the respective elements, and the principal limitations.

**CR**

**Introduction.** CR is defined as a reduction in dietary intake by approximately 30%, to improve metabolic profile, without causing malnutrition. It has been postulated to be a potentially powerful dietary intervention that could be integrated into a patient’s cancer therapy due to results showing an increased life span and decreased risk of chronic and age-related diseases, including cancer, type II diabetes, and cardiovascular disease. The mechanism behind CR stems from the concept that excessive adiposity from obesity can increase levels of oxidative stress, inflammation, and growth factors, which all may have promotive effects on tumorigenesis. Thus, the negative net energy resulting from CR may lead to decreased inflammation and growth factor production, thus suppressing the neoplastic activity of the tumor cells. As such, the utility of CR is gaining momentum as a powerful option to improve the efficacy and augment the response of current anti-neoplastic therapies.

**Proposed mechanism.** CR has been shown to exert its effects on tumor progression through altered levels of various growth factors. The most well-studied growth factor is IGF-1, which upregulated by growth hormone and acts with other anabolic hormones to upregulate energy metabolism and proliferation. In murine models, CR has been shown to reduce IGF-1 by about 30%–40% in mice. Conversely, mice with growth hormone deficiency are shown to have low IGF-1 levels associated with delayed incidence of lung adenocarcinoma. Interestingly, in a cohort of Laron dwarfs, who are individuals with an autosomal recessive mutation in the growth hormone receptor and are also IGF-1 deficient, none of the patients with dwarfism had a history of cancer while 9%–24% of family members developed a wide variety of malignancies. In stark contrast, patients with acromegaly, who have chronically elevated IGF-1 levels, have been shown to have an increased risk of colon cancer. Furthering this theory is that infusion of growth hormone or IGF-1 in mice reverses the protective effects of CR against mononuclear cell leukemia development and progression. IGF-1 has a role in the proliferation profile of several malignancies, and CR may be a preventive and/or complementary approach for reducing a known tumor-stimulating growth factor.

IGF-1 is primarily involved in the regulation of two major pathways that coordinate cellular proliferation and growth: Ras/MAPK (mitogen-activated protein kinase) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT). Activation of Ras/MAPK promotes transcription factors involved in cellular growth, while activation of PI3K/AKT decreases apoptosis. CR has been shown to decrease serum levels of IGF-1, thereby causing downregulation of both the Ras/MAPK and PI3K/AKT pathways, which inhibit both tumor growth and development. In addition, CR has been shown to improve insulin sensitivity via downregulation of IGF-1 levels and improve glucose tolerance. Thus, CR may promote insulin sensitivity leading to decreased serum blood glucose and decreased IGF-1 levels, which may mitigate one of the mechanisms driving cancer cell proliferation.

The utility of CR may be further enhanced when complemented with local cytotoxic therapy. Targeting the primary tumor with local radiation, in combination with CR, is hypothesized to alter the molecular profile of the tumor. Indeed, mice receiving an IGF-1R inhibitor, to replicate CR, along with radiation therapy, required a longer period to develop breast cancer metastasis to the lung and had increased overall survival. A report shows that chloroquine, in combination with cell starvation, induces a greater degree of growth arrest and cell death compared with either treatment used in isolation in melanoma, glioma, and fibrosarcoma cells. This synergistic potential of CR is an especially powerful tool that may better the outcomes of patients receiving standard therapies.

Another growth factor associated with obesity is leptin, a hormone produced by white adipose tissue that activates cell proliferation and affects angiogenesis, carcinogenesis, and cytokine production. CR has been shown to decrease leptin release while increasing serum levels of adiponectin, another growth hormone found to improve insulin sensitivity and promote anti-inflammatory and anti-proliferative properties. As stated previously, leptin may have proliferative and angiogenic effects to promote cancer progression. Since CR may
decrease serum leptin levels, this concept has been applied to breast cancers, where it has been shown that leptin may have pro-carcinogenic effects via modulation of signaling pathways responsible for tumor proliferation. Further, a meta-analysis found that elevated leptin levels may play a significant role in the metastasis of breast cancer. Since leptin receptors have been found to be overexpressed in breast tumors compared to normal breast tissue, leptin inhibition has gained attention as a powerful new target in breast cancer therapy. Overall, CR may be utilized as an adjuvant in patients with cancer due to its effects on serum leptin levels.

CR also targets the mechanism of autophagy to inhibit tumor proliferation. Autophagy is a catabolic process of self-eating in response to starvation and stress which in theory could increase tumor cell death, thus inhibiting tumor proliferation. It is utilized by non-cancerous cells to promote the recycling of cellular components required to maintain homeostatic function. Stressors, such as exposure to metals, hypoxia, sepsis, and chemotherapy, induce oxidative damage that may harm organelles, especially mitochondria; thus, autophagy provides the mechanism to degrade defective organelles, remove misfolded proteins, and digest non-critical cellular components as an alternative energy source to repair critical proteins. It has been found that CR may further promote autophagy and assist with maintenance of homeostasis in the exposure to stress. The balance of autophagy is under the influence of the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) axis. IGF-1 has been shown to activate mTOR, which promotes cellular proliferation and inhibits autophagy, while AMPK inhibits mTOR. CR has been shown to activate AMPK, thereby inducing systemic autophagic activity. While the role of autophagy in benign cells is well established, the function of autophagy in cancerous cells is unclear. An upregulation of autophagy in surrounding stromal cells, in the context of decreased autophagy in cancerous cells, has been proposed to be both tumor suppressive and promotive. Conversely, some propose that established cancer cells instead may upregulate autophagy during CR, thus promoting evasion of TNF-α-induced apoptosis and cellular survival. Further research behind the underlying effects on the proliferation pathways is essential to better understand how CR-induced autophagy contributes to tumorigenesis.

Angiogenesis and inflammation have been shown to be related to tumor proliferation, and CR has been shown to modulate these processes to exert anti-neoplastic effects. CR has been shown to decrease expression of plasminogen activator inhibitor 1 (PAI-1) and vascular endothelial growth factor (VEGF) which are cytokines that promote angiogenesis,
thereby allowing for metastatic spread of tumor cells. CR also decreases levels of chronic inflammation by reducing absolute quantity of adipose tissue.99 When adipocytes are present in excess, they risk hypoxia and necrosis from insufficient perfusion.100 Free fatty acids may escape from necrotic tissue and release inflammatory cytokines such as nuclear factor kappa B (NF-kB), a transcription factor that induces gene expression for cellular proliferation and metastasis, or COX-2, which increases production of inflammatory lipid metabolites.101 CR has shown to be a potent inhibitory modulator of tumorigenesis via inhibition of angiogenesis and inflammation.

**Limitations.** It is important to consider the patient’s baseline nutritional status, stage of therapy, and recommendations from the primary oncologist and registered dietician prior to incorporating any dietary intervention. One of the primary concerns with CR is the risk of cachexia. Extreme cachexia has been associated with alterations between the patient’s immune system and metabolic state.73 Since CR requires a decrease in caloric intake, patients who have already experienced significant weight loss due to therapy, vomiting, diarrhea, or anorexia may not be ideal candidates to incorporate CR into their overall treatment plan. In addition, CR may require several months for effects to be observed in patients,102 thus potentially exacerbating further weight loss in patients who may already be significantly underweight and at risk for malnourishment. In addition, some physicians may advise against CR as certain chemotherapy regimens are already associated with patient-driven CR due to nausea and anorexia. As a result, the practicality of CR has been difficult to assess since oncology patients are generally advised to increase food intake to combat therapy-induced weight loss.103 Therefore, other dietary interventions, such as intermittent fasting (IF), fasting-mimicking diets, or ketogenic diets (KDs), which have lower potential for weight loss, have been explored as alternative forms of dietary interventions in cancer therapy.

Due to the concerns surrounding extreme weight loss in at-risk patients, CR mimetics have been proposed as an alternative to provide the beneficial effects of CR without inducing cachexia. CR mimetics are supplements or medications that take advantage of the beneficial effects described during CR without dietary restriction.73 For example, metformin is a common type 2 diabetes medication which activates the AMPK (5’ AMPK) pathway and increases insulin sensitivity in a similar fashion to the proposed CR mechanism described above that has been linked to anti-neoplastic activity.104 Metformin is a relatively safe medication; however, common side effects include hypoglycemia. Another drug of interest is rapamycin, an antibiotic and immunosuppressive drug that inhibits mTOR, which has been shown to delay cancer progression, extend life span, and increase the sensitivity of certain cancers to chemotherapy and radiation therapy.105 Common side effects of rapamycin include hypertriglyceridemia, increased risk of infection, diabetes-like symptoms, and hypertension.106 Given these promising results, a wide variety of CR mimetics are currently under development to affect tumor metabolism and sensitize tumors to standard and emerging cancer therapies.73 Of note, side effect profiles should be considered prior to starting any medications as their risk may vary widely based on the patient’s medical history.

**IF**

**Introduction.** IF has been used as a dietary regimen for acute and chronic diseases worldwide.103 IF is a dietary regimen that includes the complete cessation of caloric intake for a period of time, generally from 16 up to 120 h, followed by a refeeding period. During the refeeding period, a person is not restricted to certain food groups or amount of food they can consume.103 In murine models, IF has been shown to improve the efficacy of chemotherapy regimens used in breast cancer, melanoma, neuroblastoma, pancreatic cancer, and colorectal cancer.107 Interestingly, IF has been shown to protect healthy cells against chemotherapy damage and stress resistance as a “protective effect,” therefore decreasing off-target side effects of standard chemotherapy regimens.107,108 Therefore, the utility of IF has emerged as a possible adjuvant dietary therapy to decrease tumor proliferation and improve therapeutic tolerance.

**Proposed mechanisms.** The primary benefit of IF is based on the physiological mechanisms that occur during starvation. During first 10 h of starvation, the body will utilize consumed food and stored glycogen for energy primarily in the liver. Upon depletion of liver glycogen stores, muscle and adipose tissues are broken down to supply energy through an alternative pathway. Amino acids are produced via breakdown of muscle and fatty acids via breakdown of adipose tissue. Fatty acids can further be broken down into ketone bodies, which can be used as an energy source by most tissues except the brain.108 Clearly, acute periods of starvation induce a drastic change in the metabolic state of the body and has shown to play a role in cancer models.

During fasting, where there is a cessation of caloric intake, normal cells will reallocate energy away from anabolic and regenerative pathways toward maintenance pathways due to resource limitation, which may limit the growth potential of cancerous cells.107 This overall decrease in anabolism is thought to lead to a protective state known as a phenomenon termed differential stress resistance (DSR).110,111 Unfortunately, neoplastic cells are incapable of inhibition of oncogenes, such as Ras/Raf/MAPK, phosphatase and tensin homolog (PTEN), and PI3K, which are the primary drivers of malignant proliferation cellular profiles (Figure 1).107,111 Together, IF may be a mechanism of protecting the healthy cells from transformation into malignant cells and resistance against treatment-related toxicity.

The differential stress response is manifested through several molecular mechanisms. IF has been reported in literature to delay tumor progression and increase effectiveness
of chemotherapy against a variety of cancers, including melanoma, glioma, and breast cancer.\textsuperscript{107} This sensitization of tumor cells to chemotherapy is thought to be related to the decreased circulation of growth factors and changes in plasma levels of nutrients that sensitize cells to toxic therapy.\textsuperscript{112} Specifically, IF has been shown to decrease insulin and growth hormone levels, which lead to decreased IGF-1 levels thus reducing the activation of the Ras/MAPK and PI3K pathways.\textsuperscript{113,114} In addition, IF has been shown to activate AMPK (5' AMPK), which inhibits cellular proliferation and protein synthesis, activates glycolysis and fatty acid oxidation, and induces autophagy.\textsuperscript{115,116} IF has also been shown to increase activation of caspase-3, which is a crucial mediator of programmed cellular death that is selectively upregulated in malignant cells.\textsuperscript{107} IF has multiple molecular mechanisms that appear to have a complex role in cancer metabolism and further studies will be needed to elucidate key pathways.

Murine and human studies have shown that IF may reduce the toxicities from chemotherapy and improve clinical outcomes. Specifically, a case series found that fasting before and after chemotherapy can selectively enhance toxicity of chemotherapy drugs to various malignancies, including the breast, esophagus, and prostate.\textsuperscript{117} One study found that fasting cycles combined with cyclophosphamide reduced breast tumor size to less than half of what was seen with fasting or chemotherapy alone. This same study also saw that combination of low serum glucose with chemotherapy promoted a 20-fold increase in DNA damage in breast and melanoma cancer cells, greater than what was seen with each treatment in isolation.\textsuperscript{107} Another study shows that starvation of mice for 24 h before and after chemotherapy selectively sensitizes cancer cell lines to oxidative stress from doxorubicin and cyclophosphamide.\textsuperscript{108} Thus, multiple studies have shown that there may be a synergistic effect between IF and specific chemotherapies, suggesting that particular cancer types may benefit more from adjuvant dietary interventions such as IF.

Severe side effects from chemotherapy can limit a patient's ability to receive the full course of their treatment regimen; thus, some investigators have sought to study the potential ways that IF could decrease the severity of these side effect profiles. In a murine model, mice that underwent IF for 48–60 h had lower rates of toxicity to etoposide than mice that were allowed to eat ad libitum.\textsuperscript{108,118} In two human cohorts, IF was well tolerated as well and showed significant decrease in chemotherapy-related side effects, such as weakness, fatigue, and nausea,\textsuperscript{117} while another study showed less gastrointestinal (GI) upset from therapy.\textsuperscript{119} Together, these studies suggest that IF may improve side effect profiles, allowing the individual to better tolerate a complete chemotherapy regimen without delays in care or dose reduction, thereby potentially promoting the effectiveness of their therapy.

**Limitations.** The main concern about IF is the potential for significant weight loss. Many cancer patients experience nausea, vomiting, diarrhea, loss of appetite, or depression which can lead to malnutrition in this already at-risk population.\textsuperscript{119} Studies have suggested that IF may need to be extended to at least 24 h and potentially up to 48 h, to see the protective effects described above.\textsuperscript{103} In contrast to an overall reduction in caloric intake which is used in CR, IF has the potential to lead to malnourishment, given the strict caloric limitations.\textsuperscript{73,103} With that in mind, the extended duration of IF may not be possible for some patients for various reasons, including baseline weight and nutritional status prior to diagnosis, particular cancer diagnosis, current chemotherapy regimens being used, and their individual risk for nutritional deficiencies. Therefore, the cost/benefit of IF should be assessed on an individual basis with the treating oncologist, registered dietitian, and patient to determine if IF is safe and feasible. Overall, preliminary results suggest that IF is well tolerated by most patients but the risk of severe weight loss cannot be ignored.

**KD**

**Introduction.** The KD is a high-fat, moderate-protein, and low-carbohydrate diet. Recently, the KD has gained popularity as a method to promote weight loss and reduce risk for various chronic diseases,\textsuperscript{120} including metabolic diseases such as GLUT-1 deficiency and pyruvate dehydrogenase complex deficiency.\textsuperscript{121} Most notably, the KD has been used for over 80 years as an effective adjuvant therapy for children suffering from refractory epilepsy\textsuperscript{122,123} and, more recently, it is being explored with diabetes and cancer.\textsuperscript{124–126}

The foundation of the KD is an emphasis on higher fat consumption with moderate to low protein content and very low carbohydrate intake, with a ratio of fat:carbohydrate and protein around 3:1 or 4:1 in order to drastically decrease circulating glucose, which is thought to be the primary energy source of the rapid dividing malignant cells.\textsuperscript{126} This dramatic shift away from glucose as the primary energy supply to ketosis which is the breakdown of adipose tissue via fatty acid oxidation leading to ketone body formation is known as dietary ketosis.\textsuperscript{127} Ketosis has been hypothesized to inhibit tumor proliferation while still providing sufficient energy for peripheral tissue.\textsuperscript{126,127} Moreover, CR and KD have been found to dramatically decrease tumor cell proliferation through the inhibition of the IGF-1 pathway (Figure 1),\textsuperscript{128,129} however, the degree of weight loss may potentiate cancer-related cachexia.\textsuperscript{103,119} This has led to the KD being explored as an alternative dietary regimen that shifts the metabolic processes away from tumor growth while avoiding CR and prolonged periods of fasting.

**Proposed mechanism.** The proposed effectiveness of the KD relies on the many metabolic differences between normal cells and cancer cells, especially in the metabolism of glucose. As a review, under normal oxygen-rich conditions, glucose is broken down to pyruvate via glycolysis, which is then converted to acetyl CoA. Acetyl CoA enters the mitochondria to initiate the citric acid cycle and the electron transport chain in a process known as oxidative phosphorylation to...
produce energy for the body in the form of adenosine triphosphate or ATP (36 ATP per one glucose molecule). This process is driven by the availability of glucose and is the most efficient mechanism of energy production in the body. Mitochondria with preserved function tightly regulate cellular energy production via these processes, and the majority of ATP is produced through oxidative phosphorylation. This is the primary mechanism by which all cells in our body receive energy for growth and metabolism and cancer cells are no exception. It is has been suggested that tumor cells may have mitochondrial DNA mutations that drive cells to utilize the oxidative phosphorylation pathway, leading to an increase in reactive oxygen species production and oxidative stress as a subsequent by-product of aerobic metabolism.130

In the absence of oxygen, pyruvate is instead converted to lactate for energy production via non-oxidative pathways such as ketosis, which produces far less ATP than oxidative phosphorylation (two ATPs per one glucose molecule). ATP is essential for driving the metabolic machinery in all cells, especially for malignant cells. Since malignant cells require more ATP, it has been postulated that if one can decrease excess glucose intake, then the glycolytic pathways will prevail and essentially “starve” the malignant cells, leading to cellular death. This has led to the idea that a KD may aid in “starving” malignant, thus reducing or preventing cellular proliferation pathways.

Malignant cells are thought to utilize a unique metabolic pattern termed the Warburg effect, where anaerobic glycolysis is preferably utilized instead of oxidative phosphorylation for ATP production, regardless of oxygen status.131 As described above, a diet low in carbohydrates will result in an initial increased rate of glucose metabolism forcing the cells to utilize glycolysis as their primary energy source. This is thought to be beneficial to the patient as malignant cells are rapidly dividing and thus require glucose to more efficiently produce energy to drive their anabolic metabolism. Some studies have shown that glucose uptake and lactate release by tumors is 30- to 43-fold that of non-malignant cells, suggesting that tumor cells will utilize both pathways, including ketosis, to compensate for lack of glucose availability for oxidative phosphorylation (Figure 1).126,132 In addition, to address the lack of glucose, malignant cells rely heavily on the hexose phosphate pathway (HMP shunt),133 which converts glucose 6-phosphate, an intermediate in glycolysis, to the cofactors nicotinamide adenine dinucleotide phosphate (NADPH) and ribose 5-phosphate to detoxify organic peroxides and mitigate oxidative damage.130

The KD seeks to shift the metabolism toward ketosis to limit anabolism, therefore inhibiting growth and proliferation pathways in malignant cells. When glucose is limited, the body is forced to utilize stored adipose tissue instead of glucose for ATP production. After prolonged periods of glucose restriction, the body preferentially enters ketosis where fat is metabolized via fatty acid oxidation to produce ketone bodies including β-hydroxybutyrate, acetone, and acetoacetate. Ketone bodies are then converted to acetyl CoA for use in the citric acid cycle for ATP production.126 This is an important underlying principal in the KD, where glucose availability is limited, creating an environment where non-malignant cells are able to utilize ketones to survive during ketosis, while cancer cells are “starved” of an energy source due to a lack of glucose availability.

Thus, the KD may selectively increase oxidative stress in cancer cells through two mechanisms. First, malignant cells are dependent on glucose metabolism for the production of glucose 6-phosphate, which is converted to detoxifying cofactors via HMP shunt. Without glucose, the source of cofactors to reduce reactive oxygen species is eliminated, thereby inducing oxidative stress in malignant cells.126 Second, forced fatty acid oxidation in the KD provides energy that is primarily utilized by non-malignant cells since cancerous cells are poor metabolizers of ketones. Together, the KD decreases the substrate for the most efficient energy production in the cell via a significant reduction in glucose availability while concurrently promoting oxidative stress in malignant cells by removing the source for detoxifying cofactors.

There are a wide variety of studies that illustrate the possible anti-neoplastic effects of the KD.134,135 A review article evaluated the effects of KD on tumor growth and survival time in animal models. The majority of the papers revealed a beneficial effect seen across a variety of tumor types including prostate, gastric, neuroblastoma, and lung.136 More specifically, in a colon carcinoma murine model, mice fed with a ketogenic formula showed cancer suppression compared with mice fed with regular diets. Interestingly, there was a significant negative correlation between blood ketone concentration and tumor weight. Adverse effects were not noted. The investigators postulated that elevated blood ketone levels may have anti-tumor effects by promoting maintenance of body weight and muscle mass leading to a reduction of inflammation.137 Another mouse model with neuroblastoma xenografts shows a significant decrease in neoplastic growth when exposed to low-dose chemotherapy in combination with a KD diet.138 Despite the evidence of anti-neoplastic activity of the KD in animal models, the data in humans are lacking (Table 1).135

Limitations. Despite the promising effects of the KD, this regimen risks potential side effects including lethargy, nausea, and vomiting, in addition to hypoglycemia.126 These side effects are not universal but could limit one’s ability to adhere to the KD. In addition, the high fat content of KD may not be well tolerated by some individuals, with some studies showing long-term increases in serum total cholesterol along with renal damage.140 In addition, some patients experience progressive bone mineral content loss; however, this is likely multifactorial, given the use of steroids and various chemotherapies, in addition to gender discrepancies, that may contribute to bone loss.141 Although some propose that the KD
can lead to weight loss, more recent data suggest that the KDs may actually prevent cachexia and maintain body weight. Regardless, more studies are needed to further illustrate the utility and adverse effects of the KD (Table 2).

| Dietary intervention | Benefits | Limitations |
|----------------------|----------|-------------|
| Western diet         | None     | Low nutritional density |
|                      |          | Associated with prostate, breast, and colorectal cancer |
| Caloric Restriction  | Reduction in oxidative stress, inflammation, and growth factors (i.e. IGF-1 and Ras/MAPK) | Excessive weight loss |
|                      | Improved insulin sensitivity and glucose tolerance | Risk of cachexia |
|                      | Decreased leptin levels | Risk of malnutrition |
|                      | Promotes autophagy | |
|                      | Decreased angiogenesis | |
| Intermittent fasting | Associated with improved chemotherapy-associated side effects | Excessive weight loss |
|                      | Improved insulin sensitivity and glucose tolerance | Risk of cachexia |
|                      | Decreased growth factors (i.e. IGF-1 and Ras/MAPK) | Risk of malnutrition |
|                      | Decrease anabolic metabolism (termed differential stress resistance) | |
|                      | Increased AMPK | |
| Ketogenic diet       | Increased ketosis | Weight loss |
|                      | Decreased inflammation and growth factors (i.e. IGF-1) | Hypoglycemia, nausea, vomiting, and lethargy |
|                      | Inhibition of tumorigenesis | |
|                      | Utilization of Warburg effect | Increase in serum cholesterol |
|                      | Selective increased oxidative stress in cancer cells | Progressive bone loss |

IGF-1: insulin-like growth factor-1; MAPK: mitogen-activated protein kinase; AMPK: 5’ adenosine monophosphate–activated protein kinase.

**Other dietary regimens under exploration**

**Mediterranean diet**

The Mediterranean diet (MedD) has gained attention as a healthy diet to reduce the risk of cancer. Schwingshackl and Hoffmann provide a comprehensive review on the proposed beneficial effects of the MedD on overall risk of cancer. The MedD is common in countries bordering the Mediterranean Sea. It is defined by a high consumption of plant-based foods, whole grain products, vegetables, fruits, nuts, and legumes along with a regular intake of fish and seafood, while eggs and red/processed meats are limited. Alcohol consumption is moderate, with a preference for red wine, and olive oil serves as a predominant form of fat.

The supposed protective effects of the MedD are not due to any single dietary component but rather the cumulative pattern. Higher fruit and vegetable consumption affects inflammation, redox reactions, and various metabolic processes that may exert anti-cancer effects and promote healthy weight management. Whole grains contain phytic acids and fiber that bind and neutralize carcinogens in the GI tract. Olive oil contains polyphenols, which contribute anti-inflammatory and anti-oxidant effects. The role of dairy products is uncertain and may increase risk of prostate cancer, but calcium and protein in dairy may also illicit anti-neoplastic effects. The MedD reduces intake of red meats, which are pro-inflammatory and pro-oxidative. The benefits of alcohol are controversial since the evidence with moderate consumption and cancer risk is mixed. Evidently, the MedD is a complex diet with numerous components that may exert individual effects on cancer protection and cancer risk.

Overall, there was an observed inverse association between adherence to MedD and cancer mortality. The strongest results were seen in colorectal cancer, with smaller associations seen in cancers of the breast, gastric, liver, gallbladder, head and neck, and prostate. While results are promising, exact interpretation is difficult since there is no clear-cut definition of an MedD since it varies from region to region based on ethnic, cultural, religious, and economic factors. Again, this is because the MedD is not a discrete regimen, but rather a collection of food practices seen in populations that border the Mediterranean Sea. As such, future studies might focus on identifying a more analytically illuminating definition of the MedD that may help delineate its putative beneficial effects.

**Japanese diet**

Individuals from Japan have a lower incidence of various cancers, especially those termed fat-related cancers of the colon, breast, prostate, and ovary. Inhabitants of Okinawa, who historically consume significantly fewer calories than those living on the main islands, have lower death rates from cancer and other chronic conditions compared with Japanese
living in the main lands.\textsuperscript{155} For Japanese individuals who moved from Japan to Hawaii, the incidence of stomach cancer decreased while the rates of breast, colon, and prostate cancer increased in just one generation.\textsuperscript{156} In the last 40 years, the incidence of colon cancer has increased 9.4 times for males and 4.7 times for females as Japanese have adopted a more Western dietary pattern.\textsuperscript{157}

The lower incidence of malignancies is thought to stem from the makeup of the traditional Japanese diet, which is characterized by a low intake of fats and oils, along with a low intake ratio of n-6 polyunsaturated fatty acids (PUFAs) versus n-3 PUFAs.\textsuperscript{154} In addition, other components of the Japanese diet, such as higher intake of vegetables and dietary fiber, may contribute to the lower cancer rates.\textsuperscript{158} Of interest is miso soup, which contains wakame, a vegetable rich in fucoxanthin that may have protective effects against gastric cancer.\textsuperscript{159} Japanese individuals also demonstrate a higher intake of green tea, which is rich in flavonoids and may have anti-oxidant effects.\textsuperscript{160} Soy products contain isoflavones and saponins that may have similar beneficial effects.\textsuperscript{161} Together, these individual components of the Japanese diet are hypothesized to establish the protective roles of this dietary regimen in cancer risk.

A precise characterization of a Japanese diet is difficult to achieve, and just why it is associated with lower incidence of malignancies has been puzzling. Regardless, further studies are warranted to elucidate possible mechanisms behind its apparent protective effects.

**Vegan diet**

A vegetarian diet removes any meat, poultry, and fish from one’s diet. A vegan diet further removes all animal products, including dairy or eggs.\textsuperscript{162} Overall, vegan diets are high in fiber, magnesium, folic acid, iron, and vitamin C and E, and low in overall calories, saturated fats, zinc, calcium, vitamin D, and vitamin B12.\textsuperscript{163} The vegan diet has been associated with a wide variety of health benefits, including lower risk of cardiovascular disease, obesity, and type II diabetes.\textsuperscript{164} Of special interest in this review is the lower risk of cancer in patients who follow a vegan diet.

There are several proposed mechanisms for the protective anti-neoplastic effects of a plant-based diet. The body mass index (BMI) of individuals who follow a vegan diet is much lower;\textsuperscript{165} thus, the risk of obesity-related cancers, such as colorectal, breast, and prostate cancers, is decreased. In addition, vegan diets consist of a higher proportion of fruits and vegetables, which contain phytochemicals and anti-oxidants, in addition to fiber, flavonoids, and vitamin C, which are all proposed to have protective effects against the development of malignancy.\textsuperscript{165–167} Of important consideration is the increased intake of phytochemicals, which are abundant in plants, and the decreased intake of red/processed meats. In animal models and in vitro studies, phytochemicals have been shown to induce apoptosis, arrest cell growth, and decrease angiogenic potential, though beneficial effects have not been shown to be consistent across studies.\textsuperscript{168,169} Red meat has been strongly associated with the development of colorectal cancer,\textsuperscript{170} in addition to malignancies of the esophagus, liver, and lung.\textsuperscript{149} Another characteristic of a vegan diet includes high consumption of legumes, which may decrease risk of prostate cancer.\textsuperscript{171} A differentiating factor between the vegetarian diet and vegan diet is the absence of eggs in the latter, which have been associated with an increased risk of pancreatic cancer.\textsuperscript{172} Evidently, the cumulative effects of the vegan diet, due to food items that are consumed in abundance and food items that are avoided, contribute to the potentially anti-cancer properties of this dietary regimen.

Overall, following a vegan diet appears to provide a variety of health benefits. Although the literature is deficient in clinical trials that assess the relationship between plant-based diets and cancers, data thus far suggest that vegan and vegetarian diets are nonetheless protective against cancer, with a net 10%–12% reduction in overall cancer risk.\textsuperscript{173} As such, further research is warranted to explore the utility of a vegan diet as a lifestyle modification for cancer prevention.

**Conclusion**

Expert nutrition groups have issued clinical guidelines for nutritional treatment of cancer patients. These guidelines state that patients should undergo nutrition screening and assessment and receive early nutrition intervention to improve outcomes. However, it appears that there has been an absence of innovative or clinically meaningful techniques. So, where are we really? With unprecedented sophistication in molecular biology, investigational oncology, and computational power, clinical medicine in general and oncologic nutrition in particular have failed to achieve meaningful progress for patients. A casual survey indicates virtually every major “comprehensive cancer center” has a page on cancer nutrition support. The American Cancer Society’s “Nutrition for People with Cancer” website page declares, “Nutrition is an important part of cancer treatment. Eating the right kinds of foods during and after treatment can help you feel better and stay stronger.” While the internet material is, of course, intended for patients, its quixotic but superficial character speaks volumes. Upon review of the website information and firsthand assessment of clinical reality, it may be reasonably concluded that there is a strong conventional wisdom that the pathology of cancers can result in malnutrition, that cancer treatments often result in malnutrition, and that chronic undernutrition and overnutrition can have an impact on either accelerating or reducing cancer risk or tumor burden (Table 2).

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.
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