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DIETARY INTERVENTIONS IN CANCER

Cancers rewire their metabolism (the Warburg effect) and depend heavily on glucose. By lowering glucose load and supporting mitochondrial function (e.g., low-glycemic/ketogenic approaches), diet can stress cancer cells while better supporting healthy ones.

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Please note: This is a complementary guide on dietary interventions in the treatment of cancer. The full guide, 'Cancer Care: The Role of Repurposed Drugs and Metabolic Interventions in Treating Cancer,' and all scientific references, can be found here: imahealth.org/research/cancer-care

Updated August 28, 2025

Dietary Interventions in Cancer

Traditionally, when a cancer patient asks their oncologist what they should or shouldn't eat, the answer is often, "It does not matter." This response is fundamentally incorrect. All cancer cells, regardless of tissue origin, are metabolically distinct from normal cells. One of their defining features is a heavy dependence on glucose as fuel, even when oxygen is readily available—a metabolic shift known as the Warburg effect, first described by Otto Warburg in 1924. (1,2)

Warburg discovered that, unlike normal cells, which generate energy primarily through oxidative phosphorylation in the mitochondria, cancer cells favor aerobic glycolysis. In this less efficient pathway, glucose is converted to lactate despite adequate oxygen. This reprogramming results in glucose dependence, mitochondrial dysfunction, and acidification of the tumor microenvironment. Cancer cells also resist apoptosis (see below), but depriving them of glucose can trigger cell death.

The conventional theory holds that cancer results from genetic mutations and/or genomic instability, which drive the following six "hallmarks of cancer" described by Hanahan and Weinberg (3):

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death (apoptosis)
4. Enabling replicative immortality
5. Inducing angiogenesis
6. Activating invasion and metastasis

However, this model overlooks a crucial feature found in virtually all cancer types: metabolic reprogramming. Hanahan and Weinberg did not include the Warburg effect—the shift to glucose metabolism through aerobic glycolysis—despite its universality and centrality in tumor biology. (1,2,4)

Conventional thinking also suggests cancer originates from a single mutated cell, forming a unique "cancer genome." A proposed mechanism for this genetic instability is the loss of genomic "caretakers" or "guardians" responsible for sensing and repairing DNA damage. Without these protective systems, genomic instability allows mutations to accumulate, enabling pre-malignant cells to progress through the hallmarks of malignancy.

There is considerable evidence that challenges the primacy of the genetic mutation theory. Dr. Thomas Seyfried provides a compelling argument that cancer is primarily a metabolic rather than a genetic disease. (5,6) He proposes that impaired oxidative phosphorylation and mitochondrial dysfunction are at the root of cancer, and that many of the observed genomic abnormalities are likely secondary to disordered energy production and cellular metabolism.

This theory reframes cancer as a disease of dysfunctional mitochondria, with implications for both prevention and treatment. Seyfried's findings reveal that nearly all cancers share this mitochondrial impairment. (5,6) Still, it is clear that a very complex and bidirectional relationship exists between genetic instability and mitochondrial dysfunction. Furthermore, abnormalities of several stereotypic biochemical pathways—most notably HIF-1 (hypoxia-inducible factor 1), GLUT-1, c-Myc, and hexokinase II—are also frequently dysregulated in aggressive tumors.

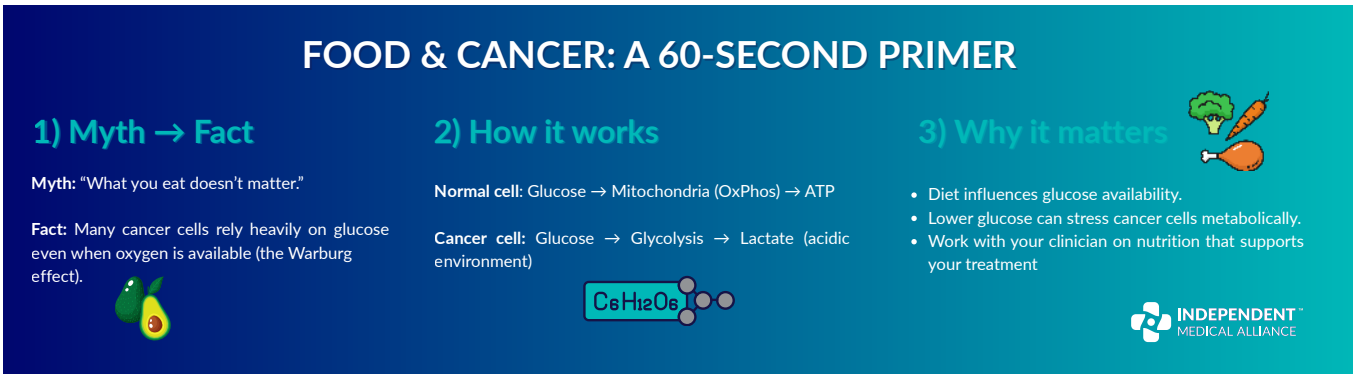
Warburg was awarded the Nobel Prize in Physiology or Medicine in 1931 for his pioneering research on cellular respiration and metabolism. (1,2) He observed that cancer cells are dependent on aerobic glycolysis—breaking down glucose to lactate—even in the presence of oxygen, due to impaired oxidative phosphorylation, in which pyruvate does not enter the Krebs cycle in the mitochondria, and oxygen is not utilized. (1,2) In simple terms, this means cancer feeds on glucose.

Unlike healthy, differentiated cells, which efficiently produce ATP through mitochondrial oxidative phosphorylation, most cancer cells instead rely on aerobic glycolysis—characterized by elevated glucose uptake and increased lactate production, despite the presence of oxygen. (6,7) Warburg proposed that irreversible respiratory damage was the primary cause of cancer and that this metabolic defect initiated the shift to glycolysis. (6) Following his extensive research on tumor metabolism, he concluded, "Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in the normal body cell by fermentation of sugar." (1,2)

This altered metabolic phenotype forms the basis for tumor imaging, which uses radiolabeled glucose analogs and has become a crucial diagnostic tool for cancer detection and management. Genes regulating glycolysis are overexpressed in most cancers. (6) Numerous studies have shown that tumor mitochondria are structurally and functionally abnormal and incapable of generating normal levels of energy. (8-13) There is compelling evidence that mitochondrial dysfunction may also promote genetic instability through the retrograde response (RTG)—a form of mitochondrial stress signaling—that underlies the mutator phenotype of tumor cells. (14-18) This dysfunction can, in turn, induce mutations in tumor suppressor genes and activate oncogenes.

Dietary Caloric Restriction and the Ketogenic Diet

As demonstrated by Dr. Otto Warburg, nearly all cancer cells are dependent on glucose as a metabolic fuel through aerobic glycolysis (1,2), with hyperglycemia being a potent promoter of tumor cell proliferation and associated with poor survival outcomes. (19) Although the mechanisms by which caloric restriction reduces tumorigenesis have not been fully elucidated, they may involve epigenetic changes, altered growth signaling, and modulation of the sirtuin pathway. (20) Caloric restriction affects several of the tumor characteristics identified by Hanahan and Weinberg, including sustained proliferative signaling, evasion of growth suppressors, resistance to apoptosis, replicative immortality, and angiogenesis.

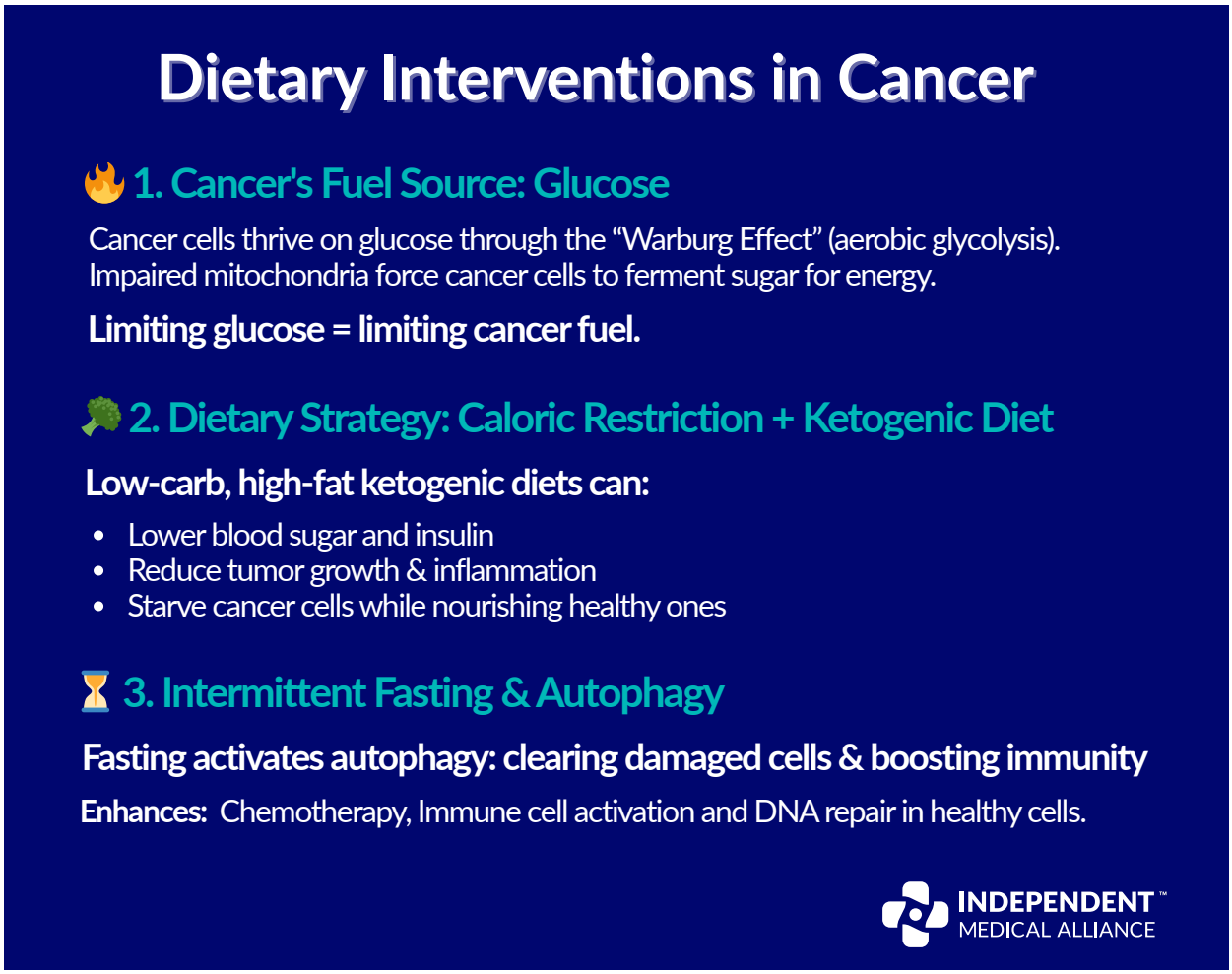


Numerous studies show that dietary energy restriction is a general metabolic therapy that naturally lowers circulating glucose levels and significantly reduces the growth and progression of a wide range of tumor types, including cancers of the breast, brain, colon, pancreas, lung, and prostate. (21-27) An impressive body of evidence indicates that dietary energy restriction can retard the growth rate of many tumors, regardless of the specific genetic defects expressed within the tumor. (21-27) Hyperglycemia with high insulin levels is associated with tumor recurrence. (28, 29) Sugar-sweetened beverages are associated with an increased risk of cancer. (30-32) Both experimental and clinical data suggest that fructose—particularly high-fructose corn syrup—is more carcinogenic than glucose. (33-35)

Insulin resistance contributes significantly to the initiation and progression of cancer. (36) Reversing this resistance is therefore a key therapeutic goal in patients with cancer. Dietary energy restriction specifically targets the IGF-1/PI3K/Akt/HIF-1α signaling pathway, which underlies several cancer hallmarks, including cell proliferation, evasion of apoptosis, and angiogenesis. IGF-1 production is stimulated by growth hormone (GH) and can be inhibited by calorie restriction, suggesting IGF-1 may play a central role in the protective effect of dietary restriction. In this regard, humans with mutations in the GH receptor—known as Laron syndrome—have low serum IGF-1 levels and a remarkably low risk of developing cancer. (20) Glucose reduction not only lowers insulin but also decreases circulating levels of IGF-1, which is necessary for driving tumor cell metabolism and growth. Diabetic patients on insulin or insulin secretagogues were found to have a higher incidence of solid cancers than those on metformin. (37)

Dietary energy restriction targets inflammation and the signaling pathways that promote tumor angiogenesis. Calorie restriction is a simple yet effective strategy to inhibit both tumor angiogenesis and inflammation. It also downregulates numerous genes and metabolic pathways involved in glycolysis. In addition to lowering circulating glucose levels, it increases circulating levels of fatty acids and ketone bodies (β-hydroxybutyrate and acetoacetate). Fats—and especially ketones—can replace glucose as a primary metabolic fuel during periods of calorie restriction. This is a conserved physiological adaptation that evolved to spare protein during starvation. Many tumors, however, have abnormalities in the genes and enzymes necessary for metabolizing ketone bodies for energy. Elevation of ketones is known to suppress both blood glucose and glycolysis, which are major drivers of tumor growth. Transitioning from carbohydrates to ketones as the primary energy source is a simple way to target energy metabolism in glycolysis-dependent tumor cells while enhancing metabolic efficiency in normal cells. Effective ketone and fatty acid metabolism require intact mitochondrial membrane structure and efficient respiration—features that tumor cells often lack. During fasting, ketone bodies are produced in the liver from fatty acids and serve as the primary fuel source for the brain. They bypass the glycolytic pathway in the cytoplasm and are metabolized directly to acetyl-CoA in the mitochondria.

The ketogenic diet is a high-fat, low-carbohydrate diet with adequate protein and calories. It was originally developed in the 1920s as a treatment for intractable epilepsy. (38) The traditional ketogenic diet follows a 4:1 ratio of fat to combined carbohydrate and protein, (38) delivering approximately 90% of calories from fat, 8% from protein, and 2% from carbohydrate. Early ketogenic diets in the 1920s and 1930s were extremely bland and restrictive, making adherence difficult. In recent years, alternative ketogenic protocols have emerged, improving palatability and compliance. (39) Alternatives to the traditional ketogenic diet include a medium-chain triglyceride (MCT)-based ketogenic diet and the Atkins diet. Compared to long-chain triglycerides, MCTs are more rapidly absorbed into the bloodstream and oxidized for energy because they can passively diffuse through membranes. Another characteristic of MCTs is their unique ability to promote the synthesis of ketone bodies in the liver. Thus, adding MCTs to a ketogenic diet allows significantly more carbohydrates to be included. (39)



Therapeutic Effects of Ketosis in Cancer Management

A ketogenic diet has tumor growth-limiting effects, protects healthy cells from damage caused by chemotherapy or radiation, enhances the cytotoxicity of chemotherapeutic agents toward cancer cells, and reduces inflammation. (39) Altered glucose availability and the induction of ketosis influence all the classically defined hallmarks of cancer. (40) Weber et al. demonstrated that ketogenic diets slow melanoma growth in vivo, regardless of tumor genetics and metabolic plasticity. (41) These diets simultaneously affect multiple metabolic pathways, creating an unfavorable environment for melanoma cell proliferation. In glioma models, a ketogenic diet has been shown to reduce angiogenesis, inflammation, peri-tumoral edema, migration, and invasion. (42) Similarly, it alters the hypoxic response and affects the expression of proteins associated with angiogenesis, invasive potential, and vascular permeability in a mouse glioma model. (43) The ketogenic diet may also function as an immune adjuvant, boosting tumor-reactive immune responses in the microenvironment by alleviating immune suppression. (44) A meta-analysis of ketogenic diet use in animal models showed significantly prolonged survival time and reduced tumor weight and tumor volume. (45) The diet was effective across a broad range of cancers and has also been shown to be an effective adjuvant to radiation therapy for malignant glioma. (46)

Ketone bodies have been shown to inhibit histone deacetylase activity and may reduce tumor growth. The ketone body β-hydroxybutyrate functions as an endogenous inhibitor of histone deacetylase, triggering downstream signaling that protects against oxidative stress. (47-50) Calorie restriction, which lowers blood glucose and elevates circulating β-hydroxybutyrate, has been shown to reduce nuclear expression of phosphorylated NF-κB (p65), cytosolic expression of phosphorylated IκB, total IκB, and DNA promoter binding activity of activated NF-κB. (51) NF-κB is a major driver of inflammation in the tumor microenvironment.

The randomized controlled trial by Chi et al. demonstrated that adhering to a caloric-restricted diet for six months may slow the growth of prostate cancer. (52) Men in the control group were instructed to avoid dietary changes, while those in the calorie-restricted group followed a low-carbohydrate diet (<20 grams per day) under dietitian supervision. Elevated serum levels of the ketone body 3-hydroxy-2-methylbutyric acid at both three and six months were associated with significantly longer prostate-specific antigen (PSA) doubling time ($P < 0.0001$), a marker of prostate cancer growth rate.

Similarly, in a post hoc exploratory analysis of the CAPS2 randomized study, PSA doubling time was significantly longer in the low-carbohydrate group compared to the control group (28 vs. 13 months; P = 0.021). (53) These findings support the concept that elevations in ketone bodies are associated with reduced tumor growth.

In a randomized controlled trial (RCT) in women with endometrial or ovarian cancer, a ketogenic diet was associated with significantly improved physical function scores and reduced fatigue. (54) The diet led to selective loss of fat mass, preservation of lean mass, and reduced fasting serum insulin levels. (55)

In another RCT, Khodabakhshi et al. evaluated the feasibility, safety, and benefits of an MCT-based ketogenic diet in patients with locally advanced or metastatic breast cancer who were scheduled to receive chemotherapy. (56) Compared to controls, the intervention group experienced significantly reduced fasting blood glucose, BMI, body weight, and fat percentage (P< 0.001). Overall survival in neoadjuvant patients was higher in the ketogenic group compared to the control (P = 0.04).

A ketogenic diet following completed courses of chemotherapy and radiotherapy was also associated with long-term survival in a patient with metastatic non-small cell lung cancer. (57) Similar long-term survival has been observed in patients with glioblastoma. (57,58) Evidence suggests that therapeutic ketosis can enhance the effectiveness of chemotherapy, radiation, and surgery, improving both progression-free and overall survival. (58) It is also likely that therapeutic ketosis acts synergistically with repurposed anticancer drugs. Therapeutic ketosis, in clinical practice, generally means keeping blood glucose below 90 mg/dL and ketone levels above 2 mmol/L, aiming for a glucose-ketone index (GKI) under 2. (59)

There are no known drugs that can simultaneously target as many tumor-associated signaling pathways as calorie restriction. Thus, dietary energy restriction may serve as a cost-effective adjuvant to traditional chemotherapy and radiation, which tend to be more toxic, expensive, and less precisely targeted. Medium-chain fatty acids found in ketogenic diets are also known to inhibit glutamate receptors directly. (60) In preclinical models, Shukla et al. observed reduced glycolytic flux in tumor cells treated with ketone bodies. These ketones also diminished glutamine uptake, lowered overall ATP content, and induced apoptosis, leading to reduced survival in multiple pancreatic cancer cell lines. (61)

According to Dr. Seyfried:

> *Most human metastatic cancers have multiple characteristics of macrophages. We found that neoplastic cells with macrophage characteristics are heavily dependent on glutamine for growth. We have not yet found any tumor cell that can survive for very long under prolonged restriction of glucose and glutamine. Furthermore, we have not yet found any fatty acid or ketone body that can replace either glucose or glutamine as a growth metabolite. It, therefore, becomes essential to simultaneously restrict both glucose and glutamine while placing the person in nutritional ketosis for successful cancer management. (5)*

These observations are supported by related work on the metabolic and immune characteristics of metastatic cancers. (62,63)

Although dietary energy restriction and anti-glycolytic cancer drugs can be effective against tumors that rely heavily on glycolysis and glucose for growth, they may be less effective against those more dependent on glutamine for energy. Glutamine is a major energy metabolite for many tumor cells, particularly those of hematopoietic or myeloid origin. The green tea polyphenol epigallocatechin gallate (EGCG) targets glutamine metabolism by inhibiting glutamate dehydrogenase activity under low-glucose conditions. (64-69) In addition, compounds such as mebendazole, curcumin, and resveratrol have been shown to inhibit glutaminolysis. (70, 71) Glioblastoma, breast cancer, pancreatic cancer, lung cancer, prostate cancer, and lymphoma have all demonstrated dependence on glutamine as an energy substrate. (70)

A continuous glucose monitor (CGM) is essential for tracking blood glucose levels. Patients should keep detailed records to identify and avoid foods that spike glucose. The target fasting range is 60-80 mg/dL (3.3-4.4 mmol/L), with postprandial (after a meal) glucose remaining under 120 mg/dL (6.6 mmol/L). Ideally, glucose levels should remain flat, with post-meal increases limited to 20 mg/dL.

A blood ketone meter is also recommended to confirm entry into ketosis by measuring β-hydroxybutyrate. Levels below 0.5 mmol/L indicate nonketotic status under normal dietary conditions. Therapeutic ketosis typically requires a blood ketone level above 2 mmol/L, with an optimal range of 3-5 mmol/L. Monitoring changes in both blood glucose and ketones during fasting and physical activity is essential. Therapeutic ketosis is formally defined as a blood glucose level of less than 90 mg/dL, a blood ketone level greater than 2 mmol/L, and a target GKI of less than 2. (59)

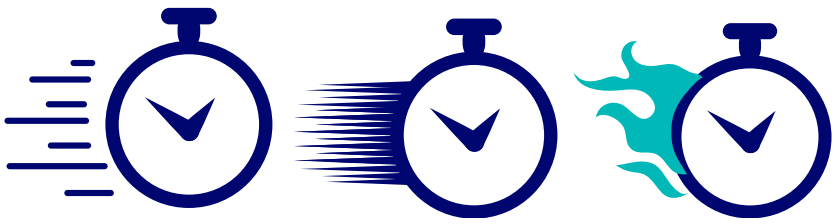
Intermittent Fasting, Autophagy, and Cancer

Fasting has a profound effect on promoting immune system homeostasis, improving mitochondrial health, and increasing stem cell production. (72-76) It stimulates the clearance of damaged mitochondria (mitophagy), misfolded and foreign proteins, and damaged cells (autophagy). Intermittent fasting or time-restricted eating is the single most effective method to activate autophagy. Modulating autophagy for cancer treatment is a promising therapeutic approach currently under intense investigation.

During autophagy, cytoplasmic constituents—including damaged, misfolded, and foreign proteins—are engulfed within double-membrane vesicles called autophagosomes. These autophagosomes then fuse with lysosomes to form autolysosomes, where the contents are degraded and recycled. Autophagy occurs at basal levels under normal physiological conditions and can be upregulated in response to various cellular stressors, including hypoxia, nutrient deprivation, DNA damage, and cytotoxic agents. (77) The molecular machinery regulating autophagy is evolutionarily conserved in higher eukaryotes and governed by specific ATG genes first characterized in yeast. The process of macroautophagy can also lead to cell death—referred to as "autophagic cell death"—due to the accumulation of autophagosomes and autolysosomes in the cytoplasm. Although the relationship between fasting, autophagy, and cancer is still being explored, many researchers propose that intermittent fasting may support the treatment and eradication of tumors and cancer cells. (78)

The metabolic effects of intermittent fasting are numerous and include increased insulin sensitivity; reductions in blood glucose, insulin, and IGF-1; activation of the sirtuin pathway; and stimulation of autophagy. Intermittent fasting is the most effective known strategy to activate autophagy and likely accounts for many of its therapeutic effects, especially in patients with cancer.

Although autophagy could theoretically support cancer cell proliferation, multiple studies have demonstrated that it more often leads to cancer cell death. (79) Many repurposed drugs used in cancer treatment have been shown to enhance tumor cell death by activating the autophagy pathway.



A limited number of rodent and human studies have evaluated the independent effects of intermittent fasting or time-restricted eating in modulating cancer progression. In a postmenopausal breast cancer mouse model driven by a high-fat diet, intermittent fasting markedly inhibited tumor initiation, progression, and metastasis compared with mice fed ad libitum, even without calorie restriction or weight loss. (80) This protective effect was likely mediated, at least in part, by reduced insulin signaling, as systemic insulin infusion via implanted pumps reversed the fasting-induced anticancer benefits. (80) Additional animal models have demonstrated similar benefits of intermittent fasting on cancer progression. (81-83)

Recent in vitro and in vivo studies have shown that intermittent fasting improves the chemotherapeutic response to multiple agents in models of glioma, neuroblastoma, melanoma, fibrosarcoma, breast cancer, colon cancer, pancreatic cancer, hepatocellular cancer, and lung cancer. (77) Fasting appears to enhance chemotherapy effectiveness through several mechanisms, including:

- Enhanced DNA repair in normal cells, but not in malignant cells
- Improved autophagy as a protective mechanism against organelle damage
- Promotion of apoptosis by increasing tumor cell susceptibility to apoptotic stimuli and reducing apoptosis-mediated damage in normal cells
- Reduction of regulatory T cells and enhanced stimulation of CD8+ cytotoxic T cells

Data from small human trials suggest that various intermittent fasting regimens may positively influence risk factors linked to poor breast cancer outcomes, such as impaired glucoregulation, chronic inflammation, obesity, and poor sleep. Experimental animal models and observational human studies support the hypothesis that a prolonged nightly fasting interval, also known as time-restricted eating, may reduce cancer risk and improve outcomes. Marinac et al. investigated whether the duration of nightly fasting predicted recurrence and mortality among women with early-stage breast cancer. (84) The study included 2,413 women without diabetes mellitus, aged 27 to 70 years at diagnosis, who participated in the prospective Women's Healthy Eating and Living study. Fasting duration was estimated from 24-hour dietary recalls collected at baseline, year 1, and year 4. The mean fasting duration was 12.5 ± 1.7 hours per night. In repeated-measures Cox proportional hazards regression models, fasting for fewer than 13 hours per night was associated with a higher risk of breast cancer recurrence compared with fasting for 13 hours or more per night (HR 1.36; 95% CI, 1.05-1.76).

In Conclusion

A carbohydrate-restricted ketogenic diet is recommended for patients with cancer. This approach involves limiting carbohydrate intake to fewer than 25 grams per day and consuming a diet rich in saturated and omega-3 fatty acids. Patients should avoid high-glycemic index foods and all processed foods. (85) Contrary to popular belief, saturated fatty acids are health-supportive, whereas processed omega-6 vegetable oils should be avoided. (86,87) Intermittent fasting and periodic 2- to 3-day water-only fasts may enhance the effectiveness of standard chemotherapy and radiotherapy.

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