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Ketogenic and Calorie-Restricted Diets in Cancer: Molecular Mechanisms, Metabolic Vulnerabilities and Translational Evidence

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Abstract | Cancer is characterized by dynamic metabolic reprogramming that enables malignant cells to sustain proliferation, biosynthesis, redox balance and adaptation to nutrient and treatment stress. This metabolic plasticity has prompted interest in Ketogenic Diets (KDs) and Calorie-Restricted (CR) interventions as potential adjuncts to anticancer therapy. KDs primarily alter carbohydrate availability, ketogenesis and systemic insulin signaling, whereas CR reduces total energy availability and engages cellular energy-sensing pathways. This review synthesizes the biological rationale, molecular mechanisms, preclinical findings and human clinical evidence linking these interventions with cancer metabolism. Particular attention is given to the insulin/IGF-1–PI3K/AKT/mTOR axis, AMP-activated protein kinase, mitochondrial metabolism, oxidative stress, autophagy, ketone-body signaling and tumor–microenvironment interactions. Available evidence indicates that dietary metabolic interventions can modify systemic glucose and other metabolic variables and may influence treatment response in selected experimental models. However, clinical evidence for improvements in tumor control or survival remains limited and heterogeneous. Importantly, metabolic plasticity differs among tumors and nutritional restriction may be harmful in patients with cachexia, sarcopenia, or inadequate intake. The current evidence therefore supports KDs and CR approaches as investigational, biomarker-informed adjuncts rather than replacements for established cancer treatment. Future trials should use standardized dietary protocols, objective measures of adherence and ketosis, metabolic and molecular biomarkers, body-composition assessment and clinically meaningful oncological outcomes.

Key Words Cancer Metabolism, Ketogenic Diet, Calorie Restriction, Metabolic Reprogramming, AMPK, mTOR, Insulin/IGF-1, Tumor Metabolic Plasticity

INTRODUCTION

Review scope and approach. This narrative review focuses on the biological interface between dietary energy/carbohydrate availability and tumor metabolic plasticity. Evidence is considered across mechanistic, preclinical and human clinical literature, with emphasis on molecular pathways, metabolic biomarkers, treatment interactions and nutritional safety. Because ketogenic diets, calorie restriction, fasting and fasting-mimicking diets are metabolically distinct, their evidence is interpreted separately rather than as interchangeable interventions.

Cancer is a heterogeneous group of diseases characterized by uncontrolled proliferation, genomic instability, altered signaling, immune evasion, invasion and metastatic potential. Increasing evidence indicates that metabolic reprogramming is an integral component of malignant transformation rather than merely a secondary consequence of rapid cell growth [1,2]. Cancer cells alter nutrient acquisition and utilization to generate ATP while simultaneously supplying the macromolecular precursors required for DNA, RNA, protein and membrane synthesis [2].

One of the best-known metabolic characteristics of cancer is the Warburg effect. Otto Warburg observed that many tumor cells consume large quantities of glucose and produce lactate even when oxygen is available [3]. This phenomenon is now understood as one component of a much broader metabolic reprogramming process. Importantly, contemporary cancer metabolism research has demonstrated that mitochondria remain functional in many tumors and that cancer cells can use both glycolytic and oxidative pathways depending on genetic, environmental and therapeutic conditions [4,5]. Therefore, the concept that all cancer cells are simply dependent on glycolysis is an oversimplification.

Nevertheless, altered glucose metabolism provides a potential therapeutic opportunity. Many tumors exhibit increased glucose uptake and enhanced expression of glycolytic enzymes, while oncogenic pathways such as PI3K/AKT/mTOR and MYC regulate nutrient acquisition and anabolic metabolism [2,5]. The relationship between glucose, insulin, IGF-1 and growth signaling has consequently stimulated interest in nutritional interventions that modify systemic metabolism.

Ketogenic diets and calorie restriction are two prominent dietary approaches investigated in this context. A ketogenic diet is characterized by severe carbohydrate restriction, relatively high fat intake and adequate protein, producing increased hepatic ketogenesis and circulating ketone bodies. In contrast, calorie restriction involves reducing overall energy intake without necessarily inducing nutritional deficiency. Fasting, intermittent fasting and fasting-mimicking diets represent related but distinct strategies [6,7].

The theoretical attraction of these approaches is based on the possibility that normal cells and malignant cells differ in metabolic flexibility. Normal tissues may adapt to reduced carbohydrate availability by increasing fatty-acid oxidation and ketone-body utilization, whereas selected tumors may be less capable of making the same metabolic transition [8]. However, this metabolic vulnerability is not universal and tumor heterogeneity represents a major limitation to the concept of a universal "cancer diet."

The purpose of this review is to critically evaluate the impact of ketogenic and calorie-restricted diets on cancer metabolism, including their molecular mechanisms, preclinical evidence, clinical findings, potential interaction with cancer treatment, safety concerns and future research requirements.

Cancer Metabolism and the Warburg Effect

Normal cells use multiple metabolic pathways according to tissue requirements, oxygen availability and nutritional conditions. Glucose can undergo glycolysis to generate pyruvate, which may subsequently enter mitochondrial oxidative phosphorylation. Cancer cells frequently increase glucose uptake and glycolytic flux, resulting in substantial lactate production despite oxygen availability [3,4].

The Warburg effect may provide several advantages to rapidly proliferating cells. Although glycolysis produces less ATP per glucose molecule than complete mitochondrial oxidation, high glycolytic flux can rapidly provide energy while simultaneously generating intermediates for biosynthetic pathways. Glycolytic intermediates can contribute to nucleotide, amino-acid and lipid synthesis, while the pentose phosphate pathway generates NADPH and ribose-5-phosphate required for biosynthesis and redox regulation [4,5].

Cancer-associated metabolic reprogramming extends beyond glucose. Tumors can alter glutamine metabolism, fatty-acid synthesis, fatty-acid oxidation, mitochondrial respiration, one-carbon metabolism and amino-acid utilization [2]. Consequently, the metabolic phenotype of an individual tumor depends on its genetic alterations, tissue of origin, microenvironment, oxygenation, nutrient availability and treatment history.

This heterogeneity is important when considering dietary intervention. A glucose-restricted strategy may theoretically affect a highly glycolytic tumor differently from a tumor that relies extensively on oxidative phosphorylation or fatty-acid metabolism.

The emerging view is therefore that cancer metabolism consists of interconnected and adaptable networks rather than one abnormal pathway [2,4] (Table 1).

Table 1: Major Metabolic Alterations in Cancer and Potential Nutritional Implications

Metabolic alteration	Biological significance	Potential nutritional implication
Increased glucose uptake	Supports glycolysis and biosynthesis	Investigates effects of carbohydrate restriction
Increased glycolytic flux	Generates ATP and metabolic intermediates	Provides rationale for metabolic intervention
Lactate production	Alters tumor acidity and microenvironment	May influence immune and stromal interactions
Increased glutamine utilization	Supports TCA cycle and biosynthesis	Demonstrates metabolic heterogeneity
Altered mitochondrial metabolism	Supports adaptation and energy production	Limits simplistic "Warburg-only" models
Increased lipid synthesis	Supports membrane production and signaling	Relevant to lipid metabolism
PI3K/AKT/mTOR activation	Promotes growth and anabolic metabolism	Potentially influenced by insulin/energy availability
AMPK signaling	Senses cellular energy status	Activated under energy stress
Altered redox metabolism	Supports survival under oxidative stress	Potential metabolic vulnerability

Biological Rationale for Ketogenic Diets

A ketogenic diet substantially reduces carbohydrate intake and increases fat availability. Low carbohydrate availability reduces insulin secretion and promotes lipolysis and hepatic ketogenesis. The liver produces ketone bodies, principally β-hydroxybutyrate and acetoacetate, which can be utilized as alternative energy substrates by several normal tissues [6,9].

The proposed anticancer rationale is that normal cells may maintain energy production through fatty-acid oxidation and ketone-body utilization, whereas some malignant cells may have limited metabolic flexibility. Consequently, carbohydrate restriction could theoretically increase metabolic stress in susceptible tumors [8,9].

However, this hypothesis should be interpreted cautiously. Cancer cells are not universally unable to metabolize ketone bodies. Some tumors retain considerable mitochondrial function and can use alternative carbon sources. Contemporary reviews emphasize that the metabolic response to ketogenic diets is highly context-dependent [4,10].

A ketogenic diet may also influence cancer biology through insulin and IGF-1 signaling. Reduced carbohydrate intake can decrease insulin concentrations, potentially reducing downstream signaling through PI3K/AKT/mTOR [10,11]. These pathways regulate proliferation, protein synthesis, cellular survival and metabolism.

Other proposed mechanisms include changes in oxidative stress, mitochondrial metabolism, reactive oxygen species, inflammation, angiogenesis and epigenetic regulation [10,12].

Although these mechanisms are biologically plausible, they should not be equated with proven clinical antitumor activity (Table 2).

Calorie Restriction and Cancer Metabolism

Calorie restriction reduces total energy intake while maintaining adequate nutritional quality. Experimental studies have associated calorie restriction with reduced tumor incidence and altered tumor progression through multiple pathways [13,14].

One important mechanism involves the insulin/IGF-1 axis. Reduced energy intake may decrease insulin and IGF-1 signaling, which can influence PI3K/AKT/mTOR pathways involved in cell growth and survival [13,14]. Calorie restriction can also activate AMPK, an energy sensor that responds to reduced cellular energy availability. AMPK activation can suppress anabolic processes and inhibit mTOR signaling.

The mTOR pathway integrates information concerning nutrients, growth factors and cellular energy. Persistent mTOR activation promotes protein synthesis, cell growth and proliferation. Conversely, reduced nutrient availability can decrease mTOR activity and facilitate autophagy [13,14].

Autophagy is a cellular recycling process that removes damaged organelles and macromolecules. Its role in cancer is complex because it may suppress tumor initiation while also helping established tumors survive metabolic stress [14].

Calorie restriction may additionally influence oxidative stress, mitochondrial function, inflammation, immune responses and cellular stress resistance [6,13] (Table 3).

Ketogenic Diet Versus Calorie Restriction

Ketogenic diets and calorie restriction should not be regarded as interchangeable interventions.

An isocaloric ketogenic diet changes the composition of macronutrients while maintaining energy intake. Calorie restriction decreases total energy intake regardless of macronutrient composition.

This distinction is critical because a patient following a ketogenic diet may spontaneously consume fewer calories. Therefore, an observed reduction in tumor growth or body weight may result from energy restriction rather than ketosis itself (Table 4).

Table 2: Proposed Mechanisms of Ketogenic Diets in Cancer

Mechanism	Potential consequence
Carbohydrate restriction	Reduced dietary glucose availability
Lower insulin	Potential reduction in growth signaling
Altered IGF-1 signaling	Potential modulation of PI3K/AKT/mTOR
Increased ketone bodies	Alternative systemic fuel and signaling molecules
Increased fatty-acid oxidation	Major shift in systemic metabolism
Altered redox state	Potential increase in metabolic stress
Mitochondrial adaptation	May affect metabolically vulnerable tumor cells
Epigenetic effects of β-hydroxybutyrate	Potential changes in gene regulation
Altered inflammatory signaling	Possible tumor-microenvironment effects

Table 3: Potential Effects of Calorie Restriction

Pathway	Potential effect of calorie restriction
Insulin	Reduced circulating insulin
IGF-1	Potential reduction
PI3K/AKT	Potential reduction in growth signaling
mTOR	Potential inhibition
AMPK	Activation during energy stress
Autophagy	Increased under nutrient deprivation
Oxidative stress	May alter cellular stress responses
Inflammation	Potential reduction in selected contexts
Immune function	Context-dependent effects
Tumor proliferation	Potential inhibition in susceptible models

Preclinical Evidence

The majority of mechanistic evidence supporting dietary metabolic interventions originates from cell culture and animal studies.

Preclinical studies have reported that ketogenic diets can slow tumor growth in selected models, particularly when combined with chemotherapy, radiotherapy, antiangiogenic therapy, or other metabolic interventions [10,12]. Proposed explanations include reduced glucose and insulin signaling, increased metabolic stress, altered redox balance and increased susceptibility to oxidative damage.

Similarly, calorie restriction and fasting have demonstrated antitumor effects in several animal models. These interventions may reduce IGF-1 and insulin signaling and alter stress-response pathways [6,13].

Fasting-related strategies have also attracted interest because they may create a temporary metabolic environment in which normal cells become more resistant to stress while tumor cells remain vulnerable. Longo and Mattson described this concept as differential stress resistance [6].

Experimental work has further suggested that fasting-mimicking diets may influence immune-mediated tumor destruction. Di Biase *et al*. reported that fasting-mimicking diet cycles combined with chemotherapy increased cytotoxic CD8+ tumor-infiltrating lymphocytes in experimental models and delayed tumor progression [16].

Similarly, a clinical/translational fasting-mimicking diet study demonstrated changes in metabolic and growth-related biomarkers, supporting further investigation of fasting-related approaches [17].

However, animal models cannot fully reproduce human cancer heterogeneity, nutritional status, treatment schedules, or cachexia. Therefore, positive preclinical findings require confirmation in adequately powered clinical trials.

Clinical Evidence for Ketogenic Diets

Clinical evidence concerning ketogenic diets has expanded considerably, but it remains heterogeneous.

An early systematic review concluded that evidence supporting isocaloric ketogenic diets for cancer treatment was insufficient, particularly because studies were small and varied substantially in design and cancer type [18].

Römer *et al*. subsequently reviewed 39 studies involving 770 patients and found no conclusive evidence that ketogenic diets improved tumor control or overall survival. They also identified important concerns regarding adherence, weight loss, adverse effects and methodological quality [19].

These findings are important because many early reports of ketogenic diets in cancer consisted of case reports, small pilot studies, uncontrolled studies, or highly selected populations. Such studies can demonstrate feasibility and biological effects but cannot establish clinical efficacy.

More recent randomized evidence provides a similarly cautious conclusion. Salido-Bueno *et al*. identified eight randomized controlled trials and found that ketogenic diets significantly reduced glucose but did not significantly improve cholesterol, IGF-1, weight, or quality of life [15].

A more recent systematic review and meta-analysis published in 2025 reported improvements in several metabolic and patient-reported outcomes, including glucose, insulin, fat mass, fatigue and insomnia, although the authors also emphasized differences in intervention characteristics and outcome measures [20].

These apparently different conclusions highlight the importance of distinguishing metabolic effects from oncological outcomes. A diet may improve glucose or insulin without necessarily reducing tumor progression or increasing survival.

Table 4: Comparison of Ketogenic and Calorie-Restricted Diets

Characteristic	Ketogenic diet	Calorie restriction
Primary intervention	Severe carbohydrate restriction	Reduction in total energy
Main metabolic feature	Ketosis	Energy deficit
Ketone production	Usually increased	Variable
Glucose	Usually decreased	May decrease
Insulin	Usually decreased	Often decreased
IGF-1	Variable	Often reduced experimentally
AMPK	May increase	Often activated
mTOR	Potentially suppressed	Potentially suppressed
Main theoretical target	Glucose/ketone metabolism	Nutrient and growth signaling
Main concern	Adherence and nutritional balance	Weight and muscle loss
Current clinical status	Investigational adjunct	Investigational adjunct

Table 5. Summary of Important Evidence

Study/evidence	Main finding	Interpretation
Erickson *et al.* [18]	Insufficient evidence for anticancer efficacy	Early evidence limited
Römer *et al.* [19]	39 studies, 770 patients; no conclusive tumor/survival benefit	Clinical efficacy uncertain
Salido-Bueno *et al.* [15]	Eight RCTs; glucose reduction but no consistent improvement in several outcomes	More RCTs required
Recent 2025 meta-analysis [20]	Improvements in several metabolic and patient-reported outcomes	Promising but heterogeneous
Preclinical studies [10,12]	Tumor inhibition in selected models	Strong biological rationale but limited translation
NCI clinical guidance [21]	KD remains investigational in cancer	Not established as standard treatment

The National Cancer Institute similarly notes that ketogenic diets are being studied in cancer but that their effectiveness for cancer control remains uncertain [21] (Table 5).

Ketogenic Diets and Conventional Cancer Treatment

A major research question is whether ketogenic diets can enhance chemotherapy, radiotherapy, targeted therapy, or immunotherapy.

The rationale is based on the possibility that metabolic stress may make cancer cells more vulnerable to conventional treatment. Reduced insulin/IGF-1 signaling and altered redox metabolism could theoretically increase treatment sensitivity [10,12].

Some preclinical studies have reported enhanced effects when ketogenic diets are combined with chemotherapy or radiation [10,12]. However, these findings are not sufficient to recommend dietary therapy clinically.

The combination of dietary intervention with immunotherapy is also of interest. Cancer cells compete with immune cells for nutrients within the tumor microenvironment. Changes in glucose, fatty acids, ketones and amino acids could theoretically influence both tumor cells and immune-cell function.

This creates a major challenge: a metabolic intervention designed to stress tumor cells must not compromise the nutritional and immune requirements of the patient.

Consequently, dietary intervention should be considered an adjunctive strategy rather than an alternative to established cancer treatment.

Calorie Restriction, Fasting and Fasting-Mimicking Diets

Calorie restriction, intermittent fasting, prolonged fasting and fasting-mimicking diets have overlapping but distinct metabolic effects.

Fasting reduces glucose, insulin and IGF-1 while increasing ketone bodies and activating cellular stress responses [6]. Longo and Mattson described fasting as a metabolic intervention capable of altering oxidative stress, inflammation, energy metabolism and cellular protection [6].

Calorie restriction has also been proposed as a strategy for improving cancer-treatment response. Preclinical evidence suggests that energy restriction may sensitize tumor cells to chemotherapy while enhancing stress resistance in normal cells [13,14].

Fasting-mimicking diets attempt to produce some of the biochemical effects of fasting while allowing limited food intake. Wei *et al*. demonstrated that repeated fasting-mimicking diet cycles influenced metabolic and aging-related biomarkers in humans [17].

Experimental cancer studies have reported encouraging results. Di Biase *et al*. found that fasting-mimicking diet combined with chemotherapy increased tumor-infiltrating cytotoxic T cells and delayed tumor progression in experimental breast cancer and melanoma models [16].

Nevertheless, fasting-related approaches may be inappropriate for patients with significant malnutrition, cachexia, low body mass, uncontrolled diabetes, or other conditions requiring consistent nutritional intake.

Nutritional Risks in Cancer Patients

One of the most important considerations in nutritional oncology is that cancer patients are not metabolically identical to healthy individuals.

Cancer-associated malnutrition can result from inadequate intake, inflammation, altered metabolism, treatment toxicity, gastrointestinal dysfunction and increased energy requirements. Progressive loss of skeletal muscle is associated with reduced physical function and poorer treatment tolerance.

Therefore, a dietary intervention that produces substantial weight loss may be harmful in a patient who is already losing muscle.

Potential complications of overly restrictive diets include:

- Excessive Weight Loss
- Skeletal Muscle Depletion
- Protein Inadequacy
- Micronutrient Deficiency
- Dehydration
- Gastrointestinal symptoms
- Reduced treatment tolerance
- Poor adherence
- Worsening cachexia

The goal of nutritional intervention should therefore be metabolic optimization without compromising nutritional status (Table 6).

Tumor Heterogeneity and Metabolic Flexibility

A central limitation of the ketogenic-diet hypothesis is that cancer is metabolically heterogeneous.

Some tumors display high glycolytic activity, whereas others maintain substantial oxidative phosphorylation. Cancer cells can also adapt their metabolism according to oxygen, nutrient availability, genetic alterations and interactions with stromal cells [2,4].

The tumor microenvironment further complicates this picture. Cancer-associated fibroblasts, endothelial cells, immune cells and malignant cells exchange metabolites and influence each other's metabolic behavior.

Consequently, a universal recommendation that all cancer patients should follow a ketogenic or calorie-restricted diet is not supported by current evidence.

Future nutritional oncology may instead involve metabolic phenotyping. Potential biomarkers could include glucose uptake, lactate production, mitochondrial activity, expression of metabolic enzymes, insulin/IGF-1 signaling, ketone-body utilization and tumor genomic characteristics (Table 7).

Table 6: Potential Benefits and Risks of Metabolic Diets

Potential benefit	Potential concern
Reduced circulating glucose	Excessive weight loss
Reduced insulin	Loss of skeletal muscle
Increased ketone production	Protein inadequacy
Potential metabolic effects	Micronutrient deficiency
Possible treatment sensitization	Dehydration
Potential improvement in selected metabolic markers	Gastrointestinal adverse effects
Possible effects on inflammation	Reduced treatment tolerance
Possible quality-of-life improvement in selected patients	Poor adherence

Table 7: Potential Biomarkers for Precision Nutritional Oncology

Biomarker	Potential relevance
Tumor glucose uptake	Identifies highly glycolytic tumors
GLUT1 expression	Marker of glucose transport
Lactate production	Indicates glycolytic phenotype
Insulin	Reflects systemic metabolic signaling
IGF-1	Growth-related metabolic pathway
β-hydroxybutyrate	Measures ketogenic response
Mitochondrial activity	Indicates oxidative metabolic capacity
AMPK/mTOR signaling	Reflects cellular energy sensing
Tumor genomic profile	May predict metabolic dependencies
Skeletal muscle mass	Assesses nutritional safety

Molecular Mechanisms of Calorie Restriction and Ketosis

The metabolic effects of dietary interventions can be conceptualized as a network rather than a single pathway.

Insulin/IGF-1 Signaling

Reduced carbohydrate or energy availability may lower insulin and IGF-1 signaling. These hormones interact with PI3K/AKT/mTOR pathways that regulate cell proliferation and survival [10,13].

AMPK

AMPK functions as a cellular energy sensor. Energy stress increases AMPK activity, which promotes energy-generating processes while inhibiting some anabolic pathways [13].

mTOR

mTOR integrates nutrient and growth-factor signals. Calorie restriction and fasting can reduce mTOR activity, potentially affecting cellular growth and autophagy [13,14].

Autophagy

Nutrient deprivation can activate autophagy. This may promote cellular recycling and stress adaptation, although the consequences for established tumors can be context-dependent [14].

Oxidative Stress

Cancer cells frequently exist under increased oxidative stress. Dietary metabolic changes may alter reactive oxygen species and antioxidant capacity. In selected tumors, this may contribute to treatment sensitivity [10,12].

Epigenetic Signaling

β-hydroxybutyrate can act not only as a fuel but also as a signaling metabolite. Ketone bodies may influence chromatin regulation and gene expression, adding another potential mechanism through which ketogenic diets affect cellular physiology [10].

Recent Evidence and Emerging Directions

The evidence base is evolving rapidly. A 2024 randomized-trial meta-analysis found that ketogenic diets reduced glucose but did not produce significant improvements in cholesterol, IGF-1, weight, or quality of life [15].

Conversely, a 2025 systematic review and meta-analysis reported broader improvements in metabolic and patient-reported outcomes, including reductions in glucose, insulin, fat mass, fatigue and insomnia [20-26].

These findings do not necessarily conflict. They may reflect differences in study selection, intervention composition, duration, cancer type, control diets and measured outcomes.

A particularly important development is increasing recognition that ketone bodies may act as signaling molecules rather than simply alternative fuels. Research into β-hydroxybutyrate-associated protein modification and metabolic signaling is expanding the mechanistic understanding of ketogenic diets [28-32].

Thus, the next generation of studies should investigate which metabolic changes are causally responsible for clinical benefit, rather than simply determining whether patients achieve ketosis.

Limitations of Current Research

Several methodological problems limit interpretation of the literature.

Small Sample Sizes

Many clinical trials include relatively few participants and are therefore underpowered to detect survival differences.

Heterogeneous Cancers

Breast, prostate, brain, gastrointestinal, lung and other cancers have different metabolic characteristics.

Variable Ketogenic Protocols
Studies differ substantially in carbohydrate content, fat-to-protein ratios, total calories, duration and adherence requirements.

Confounding by Calorie Reduction
Patients following ketogenic diets may unintentionally reduce total energy intake, making it difficult to separate ketosis from calorie restriction.

Variable Adherence
Long-term ketogenic diets can be difficult to maintain.

Inconsistent Outcomes
Studies measure different outcomes, ranging from glucose and ketones to tumor response, progression-free survival and quality of life.

Nutritional Risk
Restrictive diets may be harmful to patients with cancer cachexia or severe malnutrition.

Lack of Long-Term Survival Data
Most studies have relatively short follow-up periods. These limitations have been repeatedly emphasized in systematic reviews of ketogenic diets in cancer [18,19].

Future Research Priorities
Future trials should move beyond the general question of whether ketogenic or calorie-restricted diets "work."

The key questions should be:

- Which patients benefit
- Which tumor types are metabolically susceptible
- Which dietary composition is optimal
- Should the intervention be isocaloric or calorie-restricted
- When should the diet be administered relative to chemotherapy or radiotherapy
- How can muscle mass and nutritional adequacy be preserved

Large randomized controlled trials should therefore incorporate detailed metabolic characterization and standardized nutritional monitoring.

Translational synthesis. The strongest evidence supports biological and metabolic effects rather than a universal anticancer effect. Differences in tumor lineage, oncogenic signaling, mitochondrial capacity, treatment exposure, diet composition, energy intake and nutritional status are likely to determine response. Accordingly, future clinical studies should define the intervention precisely and distinguish effects attributable to ketosis from those attributable to energy restriction (Table 8).

Clinical Implications
Based on current evidence, ketogenic and calorie-restricted diets should not be presented to patients as established cancer treatments.

Table 8: Proposed Design for Future Clinical Trials

Domain	Recommended approach
Population	Clearly defined cancer type and stage
Intervention	Standardized KD or CR protocol
Control	Standard nutritional care
Energy intake	Clearly documented
Protein intake	Adequately maintained
Ketosis	Serial β-hydroxybutyrate measurements
Metabolic markers	Glucose, insulin, IGF-1
Body composition	CT-derived muscle mass or validated assessment
Tumor outcome	Objective response and progression-free survival
Survival	Overall survival
Safety	Malnutrition, sarcopenia, adverse effects
Patient-centered outcomes	Quality of life and physical function
Adherence	Dietary records and biochemical confirmation

Their most defensible role at present is as investigational adjunctive interventions within appropriate clinical or research settings.

Patients interested in these diets should undergo nutritional assessment before implementation. Particular caution is warranted in patients with:

- Cancer-Associated Cachexia
- Significant unintentional weight loss
- Low skeletal muscle mass
- Poor oral intake
- Gastrointestinal dysfunction
- Uncontrolled metabolic disease
- Advanced Disease with High Nutritional Requirements

The National Cancer Institute notes that ketogenic diets are being studied in cancer but that evidence is insufficient to establish their effectiveness for cancer control [21].

Most importantly, dietary interventions should never replace surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapy, endocrine therapy, or other evidence-based cancer treatments.

CONCLUSIONS
Cancer metabolism provides an important conceptual framework for understanding how malignant cells acquire and utilize nutrients. The Warburg effect, altered mitochondrial metabolism, increased glucose utilization, amino-acid dependence, lipid metabolism and nutrient-sensing pathways collectively create potential metabolic vulnerabilities [1–5].

Ketogenic and calorie-restricted diets are attractive because they can alter systemic glucose, insulin, ketone bodies, energy availability, AMPK, mTOR and IGF-1 signaling [6,10,13]. Preclinical evidence provides substantial support for the hypothesis that metabolic interventions can influence tumor growth and treatment response in selected models.

However, clinical evidence remains considerably less conclusive. Randomized evidence indicates that ketogenic diets can reduce glucose, but consistent improvements in tumor progression, survival, weight, IGF-1, cholesterol, or quality of life have not yet been established [15]. Recent meta-analyses suggest

potentially broader metabolic and patient-reported benefits, but substantial heterogeneity remains [20].

Calorie restriction and fasting-mimicking approaches similarly demonstrate promising biological effects, particularly through nutrient-sensing pathways and potential treatment sensitization [6,13,16]. Nevertheless, these interventions must be balanced against the risks of malnutrition, sarcopenia and cachexia.

The future of nutritional oncology is therefore unlikely to involve one universal dietary prescription. Instead, precision metabolic interventions may be developed according to tumor biology, metabolic phenotype, treatment regimen and individual nutritional status.

At present, ketogenic and calorie-restricted diets should be regarded as promising but investigational adjuncts to cancer therapy. Their ultimate clinical value will depend on rigorous randomized trials demonstrating not merely metabolic changes but meaningful improvements in tumor control, treatment tolerance, quality of life and survival.

Author Contributions

All authors contributed to the conception, literature interpretation, drafting, critical revision and approval of the final manuscript.

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