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Review

Diet and Endocrine Mechanisms Linking Obesity to Cancer

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Abstract

Obesity increases the risk of several cancers through endocrine, metabolic, and inflammatory alterations. Diet influences these processes by shaping energy balance, adipose tissue function, insulin signaling, and interactions between the gut and peripheral organs. This narrative review examines how adipose tissue dysfunction supports tumor development and how nutritional interventions, physical activity, and incretin-based therapies may modify the underlying pathways. Particular attention is given to the insulin–insulin-like growth factor (IGF) axis, adipokines, nutrient sensing, and the context-dependent actions of muscle-derived interleukin-6. Evidence from human dietary studies does not establish a universal advantage of continuous restriction over intermittent regimens, and findings from animal tumor models require separate interpretation. Structured exercise has improved disease-free survival in a randomized trial after adjuvant chemotherapy for resected colon cancer. Incretin-based therapies produce substantial weight loss and selected cardiovascular benefits, whereas their effects on cancer incidence, recurrence, and survival remain incompletely established. Observational associations and experimental antitumor mechanisms should therefore inform prospective research rather than treatment claims. An integrated approach to obesity in oncology should address metabolic health while preserving nutritional adequacy, muscle mass, and treatment tolerance.

Keywords: obesity; cancer; diet; endocrine signaling; insulin resistance; physical activity; GLP-1 receptor agonists

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1. Introduction

Obesity is a modifiable contributor to cancer risk and a disorder of endocrine and metabolic regulation. Dietary patterns and physical inactivity can promote excess adiposity, while the resulting changes in adipose tissue, insulin signaling, and inflammatory mediators may create conditions that favor tumor development [1,2]. The International Agency for Research on Cancer (IARC) evaluation identified sufficient evidence linking excess body fat to cancers at 13 sites, including colorectal, pancreatic, hepatic, renal, endometrial, ovarian, thyroid, gastric cardia, gallbladder, and postmenopausal breast cancers, esophageal adenocarcinoma, meningioma, and multiple myeloma [3]. However, these associations are not uniform across tumors or patient populations. In breast cancer, menopausal status and receptor phenotype modify the relationship with adiposity; findings for individual subtypes should not be generalized to all breast cancers [4–6].

Diet is relevant to this relationship because it influences both energy intake and the endocrine environment in which adipose tissue, skeletal muscle, liver, and tumors interact. This narrative review follows the sequence from diet-associated metabolic stress to endocrine dysfunction and cancer biology, and then considers nutritional, exercise, and incretin-based interventions. The clinical purpose of these interventions differs across settings: primary prevention in individuals without cancer, metabolic and supportive care during cancer treatment, and efforts to influence recurrence or survival after treatment. These objectives should not be conflated, particularly because intentional weight loss may be inappropriate in patients with inadequate intake, malnutrition, sarcopenia, or cancer cachexia. Therefore mechanistic plausibility, biomarker changes, observational associations, and randomized clinical outcomes are considered separately.

Existing reviews have described obesity-associated inflammation, insulin resistance, adipokine signaling, and cancer risk. The distinctive focus of this review is to integrate these mechanisms within an endocrine and clinical framework that follows the pathway from diet-associated metabolic stress and adipose tissue dysfunction to tumor biology and intervention strategies. This approach also addresses an important translational limitation: mechanistic plausibility, biomarker improvement, and weight loss should not be equated with reduced cancer incidence, recurrence or mortality. Throughout the review, evidence from experimental models, observational studies, and randomized clinical trials was considered separately to identify where causal inference is justified, where findings remain conflicting, and which questions require prospective oncology-specific investigation.

2. Materials and Methods

This narrative review was informed by searches of PubMed/MEDLINE and Scopus, with the main literature search completed on 30 June 2026. Searches addressed obesity and cancer, with particular attention to diet, endocrine signaling, insulin resistance, adipokines, inflammation, physical activity, nutrient sensing, and incretin-based therapies. Publications were selected for their relevance to these topics, with selection and interpretation guided by the collective scientific and clinical experience of the coauthors. The synthesis included clinical trials, observational studies, systematic reviews, clinical guidelines, and mechanistic investigations. Preclinical findings, observational associations, and randomized clinical outcomes were interpreted separately. During manuscript revision, targeted verification of cited studies and consideration of additional publications were undertaken to clarify specific mechanistic and clinical questions.

3. Adipose Tissue Dysfunction and Endocrine Signaling in Obesity

Sustained energy intake above expenditure promotes adipose tissue expansion. When vascular adaptation does not meet tissue demand, adipocyte hypertrophy can be accompanied by hypoxia, cellular stress, cell death, immune infiltration, and fibrosis [7,8]. Damage-associated molecular patterns activate innate immune receptors, including Toll-like receptors, and NF-κB signaling primes inflammatory gene expression [9]. Extracellular ATP acting through P2X7 can provide an additional signal for NOD-like receptor protein 3 (NLRP3) inflammasome activation. Serum amyloid A has also been experimentally linked to this pathway [10,11]. Inflammasome activation promotes caspase-1-dependent maturation of interleukin-1β (IL-1β) and interleukin-18 (IL-18) and can engage gasdermin-mediated inflammatory cell death. These responses help connect adipose tissue injury to sustained metabolic inflammation (Figure 1).

Lipid excess can activate innate inflammatory pathways through several mechanisms. Cholesterol crystals, upon phagocytosis by macrophages, cause lysosomal rupture and activate the NLRP3 inflammasome [12,13]. Saturated fatty acids have been linked to impaired

AMP-activated protein kinase (AMPK) signaling, mitochondrial stress, and inflammasome activation [14]. However, these pathways are not interchangeable: macrophage-specific ceramide synthesis is dispensable for inflammasome-driven inflammation and insulin resistance in one obesity model [15]. Tumor necrosis factor-α (TNF-α) can also increase adipocyte lipolysis by altering the regulation of lipid-droplet proteins and lipases [16]. The resulting release of fatty acids can sustain metabolic stress in adipose tissue and other organs.

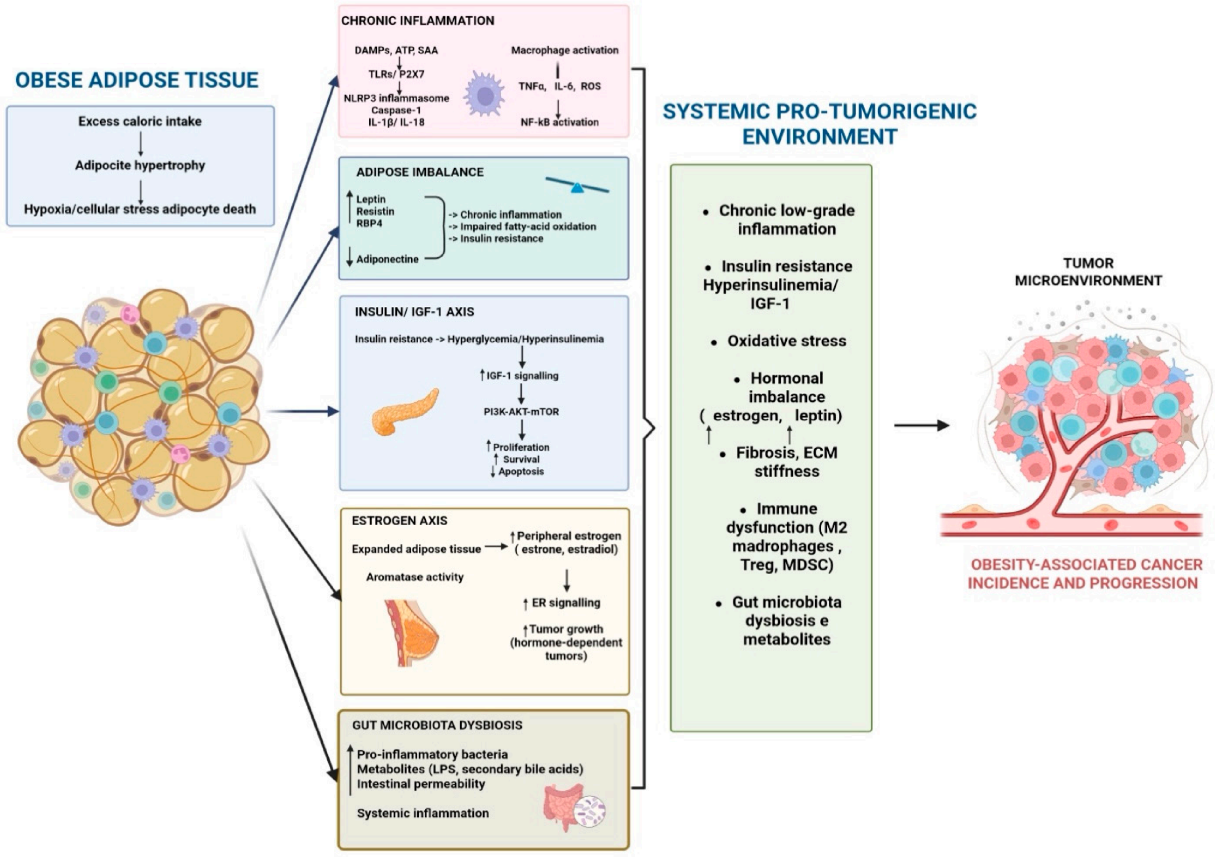


Figure 1. Endocrine and inflammatory pathways connecting adipose tissue dysfunction with cancer biology. Adipose tissue expansion can be accompanied by hypoxia, altered adipokine secretion, insulin resistance, inflammatory signaling, extracellular matrix remodeling, and changes in gut microbial functions. These pathways may influence tumor initiation and progression in a tissue-dependent manner. Increased insulin–IGF pathway activity does not imply a uniform increase in circulating IGF-1, and the effects of estrogen signaling depend on cancer subtype and menopausal status. The diagram is a conceptual synthesis rather than evidence that every pathway operates in all patients. Upward (↑) and downward (↓) arrows adjacent to labels indicate increases and decreases, respectively, in the indicated levels, activities, or processes. Connecting arrows depict proposed relationships between pathways. Created in BioRender. shani, S. (2026) https://BioRender.com/xx2mlxh.

Ectopic lipid accumulation in the liver and skeletal muscle can impair insulin action through partially distinct lipid-signaling mechanisms. Diacylglycerols can activate novel protein kinase C isoforms, including protein kinase C epsilon (PKCε) in the liver and protein kinase C theta (PKCθ) in skeletal muscle, thereby disrupting proximal insulin-receptor signaling and reducing insulin-stimulated glucose metabolism. Ceramides act through different mechanisms and can inhibit Akt signaling, for example, through the activation of protein phosphatase 2A or atypical PKCζ, thereby reducing downstream metabolic responses to insulin. Although both lipid species have been associated with insulin resistance, their effects depend on tissue distribution, lipid species, subcellular localization, and the ex-

perimental or clinical context. Impaired muscle insulin signaling reduces insulin-stimulated glucose uptake, whereas hepatic insulin resistance weakens the suppression of glucose production [17]. Compensatory hyperinsulinemia can therefore coexist with hyperglycemia and increased lipid availability, providing a mechanistic connection between dysfunctional adipose tissue and altered growth-factor signaling.

Adipose tissue expansion also changes endocrine output. Retinol-Binding Protein-4 (RBP4) and resistin can contribute to inflammatory activation and impaired insulin signaling in experimental models [18,19]. Reduced levels of adiponectin suppress the pathways responsible for promoting fatty acid oxidation, maintaining metabolic balance, and exerting anti-inflammatory and cardioprotective effects [20,21]. Hyperleptinemia in obesity can coexist with impaired central leptin responsiveness, while hypothalamic inflammation may further disturb appetite regulation [22]. Peripheral leptin signaling should be considered separately. In tumor-bearing mouse models, leptin signaling contributed to increased PD-1 expression and impaired CD8+ T-cell function [23]. These immune effects should be distinguished from central leptin resistance and should not be assumed to occur uniformly across patients with obesity.

Dietary effects on these pathways extend beyond total energy intake and involve food structure, nutrient composition, and lipid metabolism. An inpatient randomized trial found greater energy intake and weight gain during an ultra-processed dietary intervention than during an unprocessed one [24]. Associations between food processing, circulating fatty acids, and estimated desaturase activity have also been reported, resulting in a marked imbalance characterized by elevated levels of omega-6 polyunsaturated fatty acids at the expense of omega-3 fatty acids [25–27]. These findings do not establish that seed oils or dietary linoleic acid cause obesity-related inflammation. Lipid mediators derived from polyunsaturated fatty acids participate in both inflammatory signaling and its resolution. Omega-6 fatty acids are metabolized into arachidonic acid, which acts as a precursor for pro-inflammatory mediators, such as series 2 prostaglandins and series 4 leukotrienes. Specialized pro-resolving mediators derived from omega-3 fatty acids, such as resolvins, protectins, and maresins, regulate processes such as efferocytosis and tissue repair [28]. The relevant question is how dietary exposure and metabolic dysfunction alter this balance in a particular tissue, rather than whether all omega-6-derived signaling pathways are harmful.

Diet can also affect endocrine and immune function through the gut microbiota. Changes in microbial metabolism, epithelial barrier integrity, and exposure to microbial products may contribute to inflammatory signaling, while bile-acid metabolism links microbial activity to host metabolic pathways [29,30]. These interactions involve community function as well as taxonomic composition and vary with diet and host physiology. Short-chain fatty acids likewise have context-dependent effects on epithelial, immune, and metabolic responses. The contribution of diet–microbiota interactions to an individual cancer therefore requires evidence beyond the presence of dysbiosis.

4. Endocrine and Immune Pathways Connecting Obesity to Cancer

Inflammation, altered hormone signaling, and tissue remodeling provide complementary routes through which obesity may affect carcinogenesis. Persistent inflammatory signaling and oxidative stress can influence genomic stability and the selection of proliferative cell states [31]. Estrogen signaling is relevant to hormone-sensitive breast and IGF-receptor pathways, regulating growth and survival [32–34]. Microbial metabolites may contribute in selected settings [35]. Adipose fibrosis and extracellular matrix stiffness can further alter the local environment in which malignant cells grow [36,37]. These mechanisms help explain risk associations, but do not establish that weight loss after diagnosis reverses every tumor-promoting process.

Lipid availability can also reshape the antitumor immune response. Excessive uptake and accumulation of specific lipids can impair mitochondrial function and cytotoxic T-cell activity, although fatty acid oxidation itself is not uniformly detrimental [38]. Experimental studies have linked palmitate-induced mitochondrial damage to reduced histone acetylation and impaired CD8+ T-cell antitumor responses [39]. Studies on T-cell lipid metabolism have further described the interactions among nutrient exposure, stress responses, and exhaustion-associated programs. Lipotoxicity triggers the inositol-requiring enzyme 1 alpha (IRE1a)- X-box binding protein 1 (XBP1) pathway in lymphocytes, leading to increased expression of inhibitory receptors such as programmed cell death protein 1 (PD-1), which suppresses their cytotoxic activity and links nutrient-induced stress to T-cell exhaustion programs [40,41]. These observations support a mechanistic connection between systemic metabolic dysfunction and the tumor immune environment without establishing a uniform immune phenotype in all patients with obesity.

Obesity can therefore influence cancer biology by interacting with endocrine, inflammatory, and metabolic pathways. This provides a rationale for addressing obesity in prevention and cancer care. The clinical objectives must nevertheless be defined for each setting: reducing long-term metabolic risk, preserving function during treatment, and improving tumor outcomes are related but separate aims.

A major unresolved question is the relative contribution of these pathways in individual tumors and patients. Hyperinsulinemia, altered estrogen signaling, adipokine imbalance, chronic inflammation, lipid-mediated immune dysfunction, fibrosis, and microbiota-related effects may coexist, but their importance is likely shaped by tumor site, molecular subtype, menopausal status, adipose distribution, diabetes status, and treatment exposure. Consequently, obesity should not be treated as a biologically uniform exposure. Future studies should combine longitudinal metabolic phenotyping, body composition assessment, tumor molecular profiling, and immune characterization to determine which obesity-related mechanisms are dominant in specific clinical settings and which are modifiable after cancer diagnosis.

5. Lifestyle and Pharmacological Interventions

Dietary changes, physical activity, and anti-obesity medication can address different components of metabolic dysfunction, but their clinical application depends on the treatment setting. In people without cancer, weight management may contribute to reducing long-term metabolic risk and potentially cancer risk. In patients with cancer, nutritional and exercise interventions may instead aim to preserve functional capacity, metabolic control, muscle mass, treatment tolerance, and quality of life. Interventions intended to reduce recurrence or improve survival require direct evidence from trials in the relevant cancer population. A favorable effect on body weight alone is not evidence of improved cancer outcomes. In oncology, decisions about intentional weight loss should consider disease stage, treatment, food intake, muscle mass, inflammatory burden, and the risks of malnutrition or sarcopenia [41,42].

5.1. Dietary Interventions and Nutrient Sensing

For adults with obesity who are nutritionally stable and suitable for intentional weight loss, a sustainable energy deficit should be individualized rather than being defined by a universal calorie threshold. This approach is principally relevant to obesity management and long-term metabolic risk reduction; it should not be applied indiscriminately to patients with active cancer, treatment-related symptoms, involuntary weight loss, or established nutritional risk. Energy restriction should be avoided or approached with caution in patients with reduced food intake, unintentional weight loss, malnutrition, sarcopenia, or cachexia [42,43].

Energy restriction reduces body mass and produces adaptive changes in expenditure, appetite, and endocrine regulation [44]. A 16-week controlled-feeding trial reported that systemic inflammatory markers decreased after intermittent fasting was introduced and weight loss occurred, but not during an initial phase focused on Mediterranean diet quality alone. These findings suggest that negative energy balance and weight loss, rather than dietary patterns alone, were the principal drivers of the observed anti-inflammatory response [45].Trials of time-restricted eating and alternate-day fasting have shown that metabolic and body composition responses depend on the protocol and population studied [46–48]. Prolonged fasting is a distinct intervention, and findings from short physiological studies should not be considered as proof of long-term effectiveness or safety in cancer care [49,50]. During anticancer treatment, adequate energy and protein intake requires particular attention because reduced intake and treatment-related toxicities can contribute to weight loss, loss of lean mass, sarcopenia, impaired physical function, and reduced tolerance of therapy [43]. Dietary intervention should be guided by the clinical objective and the patient's nutritional condition. In people without cancer, or in cancer survivors with stable disease and adequate nutritional status, dietary approaches that reduce excess adiposity and improve insulin resistance, cardiometabolic risk, and chronic inflammation may contribute to long-term risk reduction [51,52]. These preventive and metabolic objectives differ from nutritional care during active cancer treatment. Patients with established malignancy may experience reduced food intake because of anorexia, nausea, mucositis, dysphagia, gastrointestinal dysfunction, pain, or treatment-related toxicities [43,53]. In this context, indiscriminate caloric restriction may worsen inadequate energy and protein intake, accelerate the loss of skeletal muscle, and increase the risk of sarcopenia or malnutrition [43,53]. Nutritional management should therefore prioritize adequate energy and protein intake, preservation of lean mass and physical function, symptom control, and the ability to complete anticancer treatment [43,53]. Intentional weight loss should be considered only after individualized assessment of disease stage, treatment intent, body composition, weight trajectory, metabolic comorbidities, and nutritional risk [43,54].

The insulin–IGF axis illustrates why endocrine responses to dietary restriction should be evaluated in humans rather than inferred from rodent models. In the two-year CALERIE trial in non-obese adults, calorie restriction increased insulin-like growth factor binding protein-1 (IGFBP-1) and reduced the IGF-1-to-IGFBP-1 ratio, but did not significantly lower circulating IGF-1 relative to the ad libitum control group [55]. Prolonged fasting is a distinct nutritional exposure that engages growth hormone (GH)-dependent adaptations to energy deficit, including effects on fuel mobilization and neuroendocrine regulation [56]. These responses should not be assumed to occur during moderate calorie restriction. Interpretation of the GH–IGF axis therefore requires attention to the duration and severity of restriction, nutrient intake, and the tissue or experimental context.

At the cellular level, energy stress can activate AMPK and influence mTOR, unc-51 like autophagy activating kinase 1 (ULK1), and autophagy [57]. Autophagy participates in adipocyte homeostasis and inflammatory regulation, whereas AMPK-dependent changes in NAD+ metabolism can engage SIRT1 histone deacetylase [58,59]. Amino-acid availability provides another link between diet and cellular adaptation. Amino acid deficiency activates general control nonderepressible 2 (GCN2) and the integrated stress response, increasing activating transcription factor 4 (ATF4)-dependent transcriptional programs involved in amino acid transport, redox regulation, autophagy, and proteostasis [60,61]. In some experimental settings, ATF4 signaling can interact with nuclear factor erythroid 2-related factor 2 (NRF2)-associated antioxidant responses and limit oxidative stress [62]. However, the consequences of GCN2–ATF4–NRF2 activation are not uniformly anti-inflammatory. They depend on the cell type, the duration and severity of nutrient deprivation, the local

metabolic environment, and the presence of malignancy or chronic inflammation. In some contexts, stress-adaptation programs may reduce oxidative or inflammatory signaling; in others, they may promote survival of metabolically stressed immune or tumor cells [60,61]. These mechanisms therefore provide a framework for interpreting nutrient sensing but do not justify generalized protein or amino-acid restriction, particularly in patients with compromised nutritional status or reduced muscle mass.

These pathways provide a mechanistic basis for nutritional interventions, but their effects on cancer are context-dependent; although cellular stress responses may support normal tissue maintenance, they can also promote the survival of established tumors. Their direction and clinical relevance vary by cell type and disease state; therefore, protein restriction is not recommended for patients with compromised nutritional status or reduced muscle mass.

The biological consequences of AMPK, mTOR, and NRF2 signaling also vary across stages of carcinogenesis and among tumor types. During tumor initiation, chronic hyperinsulinemia, IGF signaling, inflammation, and oxidative stress may promote proliferation, survival, and genomic instability in susceptible tissues [63,64]. However, in established tumors, nutrient and oxidative stress responses may have divergent effects. AMPK-mediated suppression of anabolic signaling and mTOR activity may constrain proliferation in some contexts, whereas AMPK activation, autophagy, and antioxidant programs may also help metabolically stressed cancer cells maintain energy balance and survive nutrient limitation or anticancer treatment [65–68]. Similarly, NRF2-dependent antioxidant signaling may limit oxidative injury in normal tissues and during early carcinogenesis, but persistent NRF2 activation in malignant cells can support redox homeostasis, metabolic adaptation, and resistance to treatment [69,70]. These considerations are particularly relevant in metabolically heterogeneous tumors, including colorectal, breast, liver, and pancreatic cancers, in which nutrient availability, oncogenic alterations, stromal interactions, and treatment exposure can shape pathway activity [65,71,72]. Therefore, modulation of nutrient-sensing pathways through dietary interventions should not be assumed to exert uniform antitumor effects across cancer types or disease stages [72].

Dietary restriction can alter lipid metabolism, but the effects are not uniform across experimental systems. In the mouse models studied by Lien et al., calorie restriction inhibited tumor growth, whereas a ketogenic diet did not, despite both diets lowering glycemia. Differences in responses were linked to reduced desaturase activity, which restricts the production of monounsaturated lipids crucial for the synthesis of the cytoplasmic membrane [73]. Human weight-loss studies and adipose tissue analyses have also reported changes in fatty acid profiles and related pathways [74,75]. Moderate calorie restriction reduced inflammatory markers without impairing measured cell-mediated immunity in non-obese adults [76]. This result supports an effect on systemic inflammation in the studied population, but not an established antitumor benefit in patients receiving cancer treatment.

Continuous energy restriction and intermittent fasting should be compared with attention to total energy deficit, adherence, nutritional adequacy, and body composition. Clinical trials do not establish a uniform advantage of intermittent fasting over continuous restriction across protocols and populations [46–48,77,78]. Observational associations between weight cycling and adverse muscle or adiposity measures concern repeated weight loss and regain and should be distinguished from the effects of prescribed fasting interventions [79]. In a three-week trial in lean, healthy adults, alternate-day fasting produced less fat loss than matched daily energy restriction; this finding does not establish the long-term consequences attributed to weight cycling [48]. A separate preclinical finding concerns post-fast refeeding. In mice, refeeding activated mTORC1 and polyamine metabolism, and conditional loss of Apc in intestinal stem cells during this phase increased tumor formation [80]. This result identifies an interaction

between nutritional timing and oncogenic susceptibility in a specific experimental model; it does not demonstrate that intermittent fasting causes cancer in humans.

Preclinical oncology studies also require careful comparison. In the murine models studied by Pomatto-Watson et al., daily calorie restriction suppressed tumor growth more effectively than fasting cycles [81]. In an obese mouse model of acute lymphoblastic leukemia, switching from a high-fat diet to a normocaloric low-fat diet enhanced vincristine efficacy and improved leukemia-free survival compared with fasting-mimicking diet cycles [82,83]. Weight loss can improve the condition of obese mice and enhance their responsiveness to anticancer therapies. However, in some obese tumor models, caloric restriction protocols, such as fasting cycles, may reduce weight but offer fewer antitumor benefits than a normocaloric diet. These findings suggest that, in obese mouse models, a normocaloric diet providing the macro- and micronutrients necessary for optimal cellular and immune function may enhance the efficacy of antitumor therapy better than fasting regimens that limit nutrient availability. These findings indicate that dietary context, including baseline adiposity, macronutrient composition, energy intake, tumor model, and concurrent therapy, can modify antitumor responses in experimental systems. They do not establish that normocaloric diets or fasting regimens improve cancer outcomes in patients.

To date, differences in tumor models, background diets, and treatments have prevented the direct clinical ranking of these regimens. Evidence for dietary interventions as cancer treatments in humans remains limited [84]. In individuals without cancer, dietary strategies may reasonably target obesity, insulin resistance, and long-term metabolic risk when nutritionally appropriate. In contrast, for patients with established malignancy—particularly those receiving systemic treatment or experiencing involuntary weight loss—obesity can coexist with malnutrition or low muscle mass. In these settings, nutritional assessment, adequate energy and protein intake, preservation of lean mass, and maintenance of treatment tolerance should take priority over indiscriminate calorie restriction [42,43,85].

The available evidence does not support a universal ranking of calorie restriction, intermittent fasting, ketogenic diets, or other dietary strategies for cancer prevention and treatment. Apparent differences among interventions may reflect variations in total energy deficit, protein intake, baseline adiposity, tumor model, background diet, adherence, and preservation of lean mass, rather than a unique effect of meal timing or macronutrient composition. In particular, favorable findings in rodents cannot establish safety or efficacy in patients receiving anticancer therapy, in whom treatment-related toxicities, reduced intake, sarcopenia, and malnutrition may alter the risk–benefit balance. Randomized trials should therefore compare dietary interventions at matched energy deficits and assess body composition, treatment tolerance, recurrence, and survival rather than body weight alone.

5.2. Endocrine and Immune Effects of Physical Activity

Physical activity complements dietary management by improving fitness, supporting the maintenance of lean body mass, and contributing to weight maintenance. The magnitude of weight loss and maintenance response varies with intervention and patient characteristics [86,87]. Its endocrine and functional effects are relevant even when changes in the scale are modest.

The inflammatory consequences of obesity also intersect with autoimmune and immune-mediated disease. Selected autoimmune rheumatic diseases are associated with increased risks of particular malignancies, and cancer or its treatment can provoke rheumatic manifestations [88,89]. This overlap is relevant here because it highlights the clinical context in which an exercise intervention is prescribed. It does not mean that obesity-related inflammation, autoimmunity, and cancer share a single causal pathway or respond identically to immune modulation.

Physical inactivity and sedentary behavior are common concerns in autoimmune rheumatic disease, and physical activity can contribute to functional and disease management [90,91]. In oncology, the proposed immune effects of exercise must be evaluated separately from the other benefits. Exercise-associated epigenetic changes offer additional mechanistic hypotheses, but evidence of pathway modulation alone does not demonstrate prevention of cancer or modification of its clinical course [92].

Skeletal muscle provides a direct endocrine connection between physical activity and the metabolic pathways discussed above. During contraction, it releases signals, including interleukin-6 (IL-6), whose acute effects depend on their timing, concentration, target tissue, and receptor context. This offers a focused way to integrate immunomodulation into obesity care while keeping biological mechanisms separate from demonstrated cancer outcomes. Exercise increases energy demand and stimulates neuroendocrine responses that mobilize fuels. Catecholamine signaling promotes adipocyte lipolysis through the coordinated regulation of adipose triglyceride lipase and hormone-sensitive lipase, making fatty acids available to working muscles [93–95]. Re-esterification and triacylglycerol cycling contribute to the regulation of lipid flux and energy expenditure [96]. These processes link muscle activity to adipose tissue function, without implying that all liberated fatty acids are immediately oxidized.

Muscle IL-6 production and release respond to contraction and metabolic demand. Muscle contraction raises cytoplasmic calcium, activating calcineurin, which dephosphorylates nuclear factor of activated T cells (NFAT) to enable its nuclear entry and stimulate IL-6 transcription [97]. Concurrently, glycogen depletion and a higher AMP/ATP ratio activate AMPK, an energy sensor that promotes IL-6 production to maintain metabolic balance during exercise [98]. A β2-adrenergic agonist increased the muscle IL-6 response to resistance exercise in humans, by increasing cAMP production and protein kinase A (PKA) activity [99]. Lactate-dependent protease activity has also been implicated in IL-6 release during exercise [100]. During exercise, lactate enters muscle cells via monocarboxylate transporter 1/4 (MCT1/4), lowering pH and activating G protein–coupled receptors to stimulate cyclic adenosine monophosphate (cAMP) -PKA and IL-6 secretion, while also inhibiting histone deacetylase (HDAC) to enhance IL-6 transcription [101].

IL-6 signals through membrane-bound IL-6 receptor (mIL-6R) and gp130 in classic signaling, or through soluble IL-6 receptor (sIL-6R) and gp130 in trans-signaling. Neither signaling mode is intrinsically protective or harmful. Their effects depend on the cellular source and duration of IL-6 exposure, receptor expression and availability, target tissue, coexisting metabolic stress, and the broader inflammatory environment [102,103]. Acute muscle-derived IL-6 release during exercise should therefore be distinguished from persistent IL-6 elevation in chronic inflammatory diseases and cancer. This distinction does not imply that classic signaling is uniformly beneficial or that trans-signaling is uniformly detrimental.

Human experimental studies support the acute anti-inflammatory and metabolic components of the exercise-associated IL-6 response. In healthy volunteers, exercise-induced IL-6 synthesis and release were accompanied by increased circulating IL-1 receptor antagonist and IL-10, and exercise or IL-6 administration attenuated the TNF-α response to experimental endotoxemia [104,105]. Acute IL-6 administration did not impair muscle glucose uptake or whole-body glucose disposal in healthy volunteers [106]. Training studies also associate regular physical activity with changes in inflammatory markers [107,108]. In adults with abdominal obesity, IL-6 receptor blockade prevented the reduction in visceral adipose tissue observed during a 12-week exercise intervention [109]. These findings support a physiological role for IL-6 signaling in some exercise-associated adaptations but do not establish that IL-6 is the sole mediator of exercise benefits or that modulation of IL-6 signaling improves clinical cancer outcomes (Figure 2).

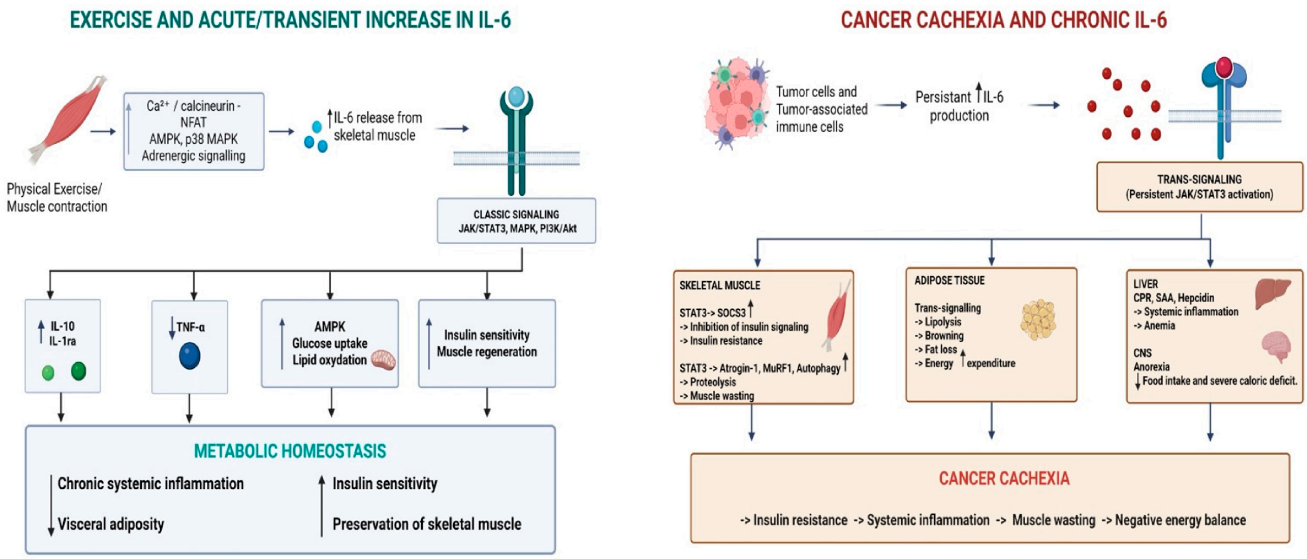


Figure 2. Context-dependent IL-6 signaling during exercise and cancer-associated wasting. Acute IL-6 release during exercise can participate in metabolic adaptation and anti-inflammatory responses, including induction of IL-10 and IL-1 receptor antagonist. Persistent IL-6 signaling can contribute to inflammatory and catabolic processes in cancer. Classic and trans-signaling may coexist, and their effects cannot be assigned exclusively to exercise or cachexia. The depicted pathways are a simplified model; cancer cachexia is multifactorial, and exercise is not established as a means of reversing every pathway shown. Upward (↑) and downward (↓) arrows adjacent to labels indicate increases and decreases, respectively, in the indicated levels, activities, or processes. Connecting arrows depict proposed relationships between pathways. Created in BioRender. shani, S. (2026) https://BioRender.com/xx2mlxh.

In cancer-associated wasting, persistent inflammatory signaling promotes tissue catabolism. IL-6 binds the soluble receptor sIL-6R—produced by a disintegrin and metalloproteinase 17 (ADAM17) cleavage or alternative splicing of mIL-6R—to form a complex with gp130 that activates trans-signaling and the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway in cells lacking IL-6R. The activation of STAT3 contributes to tissue wasting and insulin resistance by inhibiting insulin receptors through suppressor of cytokine signaling 3 (SOCS3). In hepatocytes, phosphorylated STAT3 stimulates the synthesis of C-reactive protein (CRP), serum amyloid A (SAA), and hepcidin, leading to inflammation, hypoferremia, and anemia associated with chronic disease [110]. In muscle, STAT3 activates the ubiquitin-proteasome system (Atrogin-1, MuRF1) and autophagy, accelerating contractile protein breakdown and muscle atrophy. IL6-sIL6R pathway activation promotes lipid breakdown, adipose tissue browning, and increased resting energy expenditure. Experimental inhibition of STAT3 has preserved muscle mass in a cancer-cachexia model, and adipose tissue browning has been linked to increased energy expenditure in another model [111,112]. These findings support mechanistic roles for inflammatory pathways, but cachexia also involves additional tumor-derived factors, reduced intake, and altered metabolism. Exercise must therefore be adapted to functional capacity and nutritional status rather than prescribed at high intensity as a general treatment for cachexia [43].

The strongest clinical evidence should be described within its specific population. In CHALLENGE, 889 patients with resected stage III or high-risk stage II colon cancer who had completed adjuvant chemotherapy were assigned to a three-year structured exercise program or health-education materials. Exercise improved disease-free survival, a composite of recurrence, a new primary cancer, or death, with a hazard ratio of 0.72 (95% CI, 0.55–0.94). Five-year disease-free survival was 80.3% versus 73.9%. Overall survival findings also favored exercise (hazard ratio, 0.63; 95% CI, 0.43–0.94), with eight-year survival of 90.3%

versus 83.2% [113]. Its findings apply to the postoperative setting studied and do not identify a single exercise modality or molecular mediator responsible for the benefit. Cohort-based syntheses and prospective survivor studies provide additional associations between activity and lower mortality, but remain susceptible to confounding and reverse causation [114,115] (Table 1). Although IL-6-related mechanisms may contribute to metabolic and immune adaptations to exercise, the survival benefit observed in CHALLENGE cannot be attributed to a single cytokine pathway or exercise-induced molecular mechanism.

The clinical implication is to incorporate appropriately tailored physical activity into cancer care while monitoring symptoms, functions, nutritional status, and treatment-related limitations. In primary prevention, physical activity supports weight management and cardiometabolic health. During cancer treatment, its principal aims may include maintaining physical function, muscle mass, and quality of life, rather than maximizing weight loss. In the postoperative colon-cancer population studied in the CHALLENGE trial, structured exercise improved disease-free and overall survival outcomes; however, this result should not be generalized to all tumor types, treatment settings, or exercise regimens [113]. Improved fitness, metabolic health, and preservation of muscle remain clinically important outcomes, whereas an oncologic survival benefit should be claimed only in populations supported by outcome trials.

Exercise provides one of the strongest opportunities to translate metabolic interventions into cancer care; however, the biological mediators of its clinical effects remain incompletely defined. Acute changes in IL-6, catecholamines, substrate use, and immune-cell trafficking are biologically plausible but cannot alone explain improved oncologic outcomes. The CHALLENGE trial provides outcome evidence in a defined postoperative colon-cancer population, whereas evidence for other tumor types, disease stages, treatment settings, and exercise prescriptions remains less certain. Future trials should determine the minimum effective dose and modality of exercise, identify patients who are most likely to benefit, and evaluate whether improvements in fitness, muscle mass, insulin sensitivity, or immune function mediate recurrence and survival outcomes.

5.3. Incretin Therapies and the Limits of Oncologic Evidence

Incretins are nutrient-responsive gut hormones that connect food intake to pancreatic and systemic metabolism. GLP-1 receptor activation reduces appetite through central pathways and slows gastric emptying, whereas glucose-dependent insulinotropic polypeptide (GIP) has distinct actions that should not be assumed to reproduce every GLP-1 effect [116–118]. Both hormones enhance glucose-dependent insulin secretion, while GLP-1 can suppress glucagon secretion in a glucose-dependent manner [119,120]. Receptor-mediated cAMP signaling engages protein kinase A (PKA) and exchange protein directly activated by cAMP 2 (EPAC2), facilitating insulin granule exocytosis [120,121]. Pharmacological agonists exploit these pathways at exposures and durations that differ from physiological hormone release.

GIP also participates in postprandial adipose tissue metabolism. Experimental and human physiological studies have described effects on lipoprotein lipase expression, adipose tissue blood flow, and glucose uptake [122–124]. These observations provide a rationale for studying adipose nutrient handling, but do not establish that GIP alone consistently reduces ectopic fat, inflammation, or fibrosis. The weight-loss effects of dual GIP/GLP-1 agonism must be assessed from trials of the combined intervention.

Incretin-based treatments include GLP-1 receptor agonists, dual or triple receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. These classes differ in terms of receptor targets, pharmacological exposure, and effects on body weight.

Semaglutide, liraglutide, and dulaglutide activate GLP-1 receptors. Tirzepatide combines GIP and GLP-1 receptor agonism; other dual agonists combine GLP-1 and glucagon

receptor activity. Retatrutide targets GIP, GLP-1, and glucagon receptors [125]. DPP-4 inhibitors, including sitagliptin, saxagliptin, and linagliptin, reduce degradation of endogenous incretins [126]. DPP-4 inhibition is generally weight-neutral and should not be grouped with anti-obesity agonists as an equivalent weight-loss strategy [127–133].

Weight-loss estimates are specific to the drug, dose, population, treatment duration, and estimand. In STEP 1, in adults without diabetes, semaglutide 2.4 mg weekly produced a mean weight change of −14.9% at 68 weeks, compared with −2.4% with placebo [134]. In SURMOUNT-1, also in adults without diabetes, the corresponding changes at 72 weeks were −20.9% with tirzepatide 15 mg weekly and −3.1% with placebo [135]. SURPASS-5 addressed tirzepatide in people with type 2 diabetes receiving insulin glargine, and should not be used to infer the same effect in all people with obesity [136]. In the phase 2 retatrutide trial, mean weight change at 48 weeks reached −24.2% at 12 mg versus −2.1% with placebo [137]. These are separate trials, not a head-to-head ranking of receptor classes, and they do not demonstrate anticancer efficacy.

Cardiovascular and metabolic outcomes require endpoint-specific interpretations. SELECT enrolled adults with overweight or obesity, established cardiovascular disease, and no diabetes; semaglutide reduced major adverse cardiovascular events relative to placebo (hazard ratio, 0.80) [138]. SCALE reported an 8.0% mean weight reduction with liraglutide 3.0 mg at 56 weeks compared with 2.6% with placebo [139]. In SYNCHRONIZE-1, the primary treatment-regimen estimand showed weight changes at 76 weeks of −13.0% with survodutide at 6.0 mg and −5.4% with placebo [140]. These findings establish clinically meaningful weight-loss effects in the studied populations, and SELECT establishes cardiovascular benefits in its specific population. However, these trials were not designed to assess cancer incidence, recurrence, progression, or survival rates. Weight reduction and cardiovascular benefits therefore do not establish anticancer efficacy and should not be interpreted as evidence that incretin therapies prevent cancer or improve oncological outcomes (Table 1).

Table 1. Selected clinical studies of dietary, exercise, and incretin-based interventions.

Study	Design and Comparison	Principal Finding	Interpretation
A. Dietary interventions			
Liu 2022 [46]	RCT in adults with obesity; time-restricted eating plus calorie restriction versus restriction alone.	No significant additional weight-loss benefit at 12 months.	Metabolic trial; no cancer efficacy endpoint.
TREAT 2020 [47]	RCT in adults with overweight or obesity; 16:8 eating window versus consistent meal timing.	No clear superiority in terms of weight or major metabolic outcomes.	Protocol-specific results; monitor body composition.
Templeman 2021 [48]	RCT in lean adults; alternate-day fasting versus matched daily energy restriction.	Fasting was not consistently superior for weight loss or metabolic health.	Lean population; no direct oncology inference.
CALERIE 2016 [55]	Two-year RCT in non-obese adults; calorie restriction versus ad libitum intake.	IGFBP-1 increased; IGF-1 did not significantly decrease.	Endocrine biomarkers; no demonstrated cancer benefit.
HELENA 2018 [78]	RCT in adults with overweight or obesity; 5:2 versus continuous restriction.	Comparable weight and metabolic outcomes at 50 weeks of treatment.	Does not support general superiority of either schedule.

Table 1. *Cont.*

Study	Design and Comparison	Principal Finding	Interpretation
B. Exercise interventions			
CHALLENGE 2025 [113]	RCT after resection and adjuvant chemotherapy for stage III or high-risk stage II colon cancer.	Three-year exercise program: disease-free survival HR 0.72 (95% CI, 0.55–0.94); 5-year estimates 80.3% versus 73.9%.	Randomized oncologic outcome; applies to the studied setting.
Ungvari 2025 [114]	Systematic review and meta-analysis of cohort evidence on activity after cancer diagnosis.	Higher activity levels were associated with lower mortality rates.	Predominantly observational; confounding factors remained.
Rees-Punia 2026 [115]	Prospective cohort analysis of physical activity among cancer survivors.	Higher activity levels were associated with lower mortality rates.	Observational study; does not establish treatment causality.
C. Pharmacological interventions			
STEP 1 2021 [134]	RCT without diabetes; semaglutide 2.4 mg weekly versus placebo, with lifestyle intervention.	Mean weight change at 68 weeks: −14.9% versus −2.4%, respectively.	Obesity efficacy; no established cancer-outcome benefit.
SURMOUNT-1 2022 [135]	RCT without diabetes; tirzepatide versus placebo.	At 15 mg weekly, the mean weight change at 72 weeks was: −20.9% versus −3.1%.	Drug- and dose-specific obesity results.
SURPASS-5 2022 [136]	RCT in type 2 diabetes; tirzepatide versus placebo added to insulin glargine.	Improved glycemic control and reduced body weight.	Insulin-treated diabetes population; no cancer efficacy endpoint.
Retatrutide 2023 [137]	Phase 2 RCT in overweight or obese patients without diabetes; triple agonist versus placebo.	At 12 mg, mean weight change at 48 weeks: −24.2% vs. −2.1%.	Phase 2 obesity evidence; distinct from later TRIUMPH reports.
SELECT 2023 [138]	RCT with established cardiovascular disease and overweight or obesity, without diabetes.	Semaglutide 2.4 mg versus placebo: major cardiovascular events HR 0.80 (95% CI, 0.72–0.90).	Cardiovascular benefits; not an oncology efficacy trial.

RCT, randomized controlled trial; HR, hazard ratio; CI, confidence interval. Effect estimates refer to the indicated population, dose, duration, and analyses. Cross-trial percentages are not direct comparisons of the results. Cancer outcomes have not been established in metabolic trials.

Observational oncology studies on incretin-based therapies are hypothesis-generating and require cautious interpretation. An ASCO 2026 conference abstract compared GLP-1 receptor agonists with DPP-4 inhibitors in matched cohorts with stage I–III solid tumors and reported lower hazards of metastatic progression in selected cancers [141]. A retrospective breast-cancer study reported associations between GLP-1 receptor agonist use and lower mortality and recurrence hazards in comparisons with nonuse or insulin/metformin. However, comparisons with sodium-glucose cotransporter-2 (SGLT2) inhibitors were sensitive to the analytical approach: associations were not statistically significant in the matched analyses without further adjustment or in the 12-month landmark analyses, whereas adjusted Cox models yielded favorable associations [142].

These associations may be influenced by confounding by indication because patients prescribed GLP-1-based therapies can differ from non-users or users of alternative therapies with respect to obesity severity, diabetes duration and control, comorbidities, cancer stage, treatment access, and health-related behaviors. Comparator selection is particularly important because DPP-4 inhibitors, SGLT2 inhibitors, insulin, and non-use represent distinct

clinical exposure groups. Exposure classification and timing can also introduce bias when prescriptions, treatment duration, adherence, treatment discontinuation, or post-diagnosis initiation are incompletely captured. In addition, immortal-time bias may occur if patients must survive long enough after cancer diagnosis to receive or be classified as being exposed to incretin-based therapy. Residual confounding, reverse causation, and incomplete ascertainment of clinical and lifestyle variables further limit causal inference. Consequently, these studies cannot establish a direct antitumor effect or support the prescription of GLP-1 receptor agonists, dual agonists, or triple agonists as cancer treatments.

Randomized evidence provides a complementary perspective on cancer incidence. A systematic review and meta-analysis of 48 placebo-controlled trials involving 94,245 participants suggested little or no effect of GLP-1 receptor agonists and dual agonists on thyroid, pancreatic, breast, and kidney cancer risk, with moderate certainty of evidence; estimates for other cancer sites were less certain [143]. However, the included trials were not designed to evaluate cancer outcomes and had limited follow-up. These findings therefore do not establish long-term cancer prevention effects or efficacy against established malignancy.

Experimental studies offer candidate mechanisms for further investigation. Exendin-4 affects AMPK–Akt–mTOR signaling and autophagy in ovarian cancer cell lines [144], with additional work reporting reduced growth and increased apoptosis [145]. Exenatide inhibits hepatocarcinogenesis through the cAMP–PKA–EGFR–STAT3 pathway in experimental models [146]. Tirzepatide has also altered glucose metabolism and tumor development in a preclinical colon cancer study [147]. Additional work in papillary thyroid carcinoma and colorectal cancer models suggests effects on macrophage biology and epithelial–mesenchymal transition [148,149]. These findings depend on the model, receptor context, and experimental exposure. Clinical synergy with immune checkpoint inhibitors remains to be established. Randomized oncology trials are needed to separate the effects mediated by weight loss and metabolic improvement from any direct tumor or immune action. Prospective trials with prespecified cancer incidence, recurrence, progression, survival, body composition, and treatment tolerance outcomes are required to determine whether metabolic improvement or pharmacological incretin signaling modifies cancer outcomes.

In patients with cancer, GLP-1-based therapy should be considered only for established metabolic indications and with assessment of nutritional intake, weight trajectory, muscle status, gastrointestinal tolerability, concomitant medication, and oncological treatment context; its use should not be based on an assumed anti-cancer benefit. ESPEN advises against energy restriction in patients with or at risk of malnutrition [43]. The US label for semaglutide contraindicates its use in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 [150].

The principal knowledge gap is whether incretin-based therapies modify cancer outcomes beyond their established effects on body weight and glycemic control (GC). Observational comparisons are vulnerable to confounding by indication, differences in metabolic disease severity, treatment timing, comparator selection, and survivorship-related biases. In addition, preclinical reports of direct effects on tumor or immune pathways cannot be assumed to occur at clinically relevant drug exposures in heterogeneous human cancer. Prospective studies are needed to evaluate cancer incidence, recurrence, survival, treatment tolerance, body composition, and nutritional outcomes in patients receiving incretin-based therapies. These studies should also distinguish intentional fat loss from concurrent loss of lean mass, particularly in patients receiving active anticancer treatment.

6. Conclusions

Diet-associated adipose tissue dysfunction offers a coherent endocrine framework for understanding the relationship between obesity and cancer. Insulin signaling, adipokines,

nutrient sensing, inflammation, and muscle-derived signals connect energy balance with the tissues in which tumors arise and progress. These pathways also identify potential intervention targets, but the strength of clinical evidence differs across approaches. Dietary management can improve metabolic health, and exercise has demonstrated oncologic benefits in the specific setting studied by CHALLENGE. However, evidence that a specific dietary restriction strategy improves tumor control, recurrence, or survival remains insufficient, and findings from animal models should not be generalized to patients with cancer. Incretin-based therapies are effective treatments for selected metabolic indications, while their proposed effects on cancer outcomes require prospective confirmation.

The choice and combination of these approaches should reflect the clinical objectives and the patient's metabolic, oncological, nutritional, and functional status. In primary prevention, sustainable weight management may reduce metabolic risk and contribute to lowering the risk of obesity-associated cancers. During active cancer treatment, dietary and exercise interventions should prioritize adequate energy and protein intake, preservation of muscle mass and function, symptom management, and treatment tolerance, particularly in individuals at risk of malnutrition or sarcopenia. In survivorship and postoperative settings, intentional weight loss or structured exercise may be considered when nutritional status is stable, but effects on recurrence and survival should be inferred only from trials conducted in the relevant population. Future studies should measure cancer incidence, recurrence, survival, treatment tolerance, endocrine biomarkers, nutritional status, and body composition to determine which interventions improve clinically meaningful outcomes, for whom, and under which conditions.

The central contribution of this review is to position obesity-associated cancer biology within a continuum extending from diet-associated metabolic stress and adipose tissue dysfunction to endocrine, inflammatory, immune, and tumor-specific consequences. This framework highlights that no single pathway or intervention is likely to be uniformly applicable across cancers or patient populations. Important uncertainties remain regarding the reversibility of obesity-related tumor-promoting processes, the optimal dietary and exercise strategies during and after treatment, and the oncologic implications of incretin-based therapies. Future oncology-specific trials should integrate clinical outcomes with longitudinal measures of body composition, metabolic function, nutritional status, and tumor and immune biomarkers to identify the interventions that improve cancer outcomes, for whom, and through which mechanisms.

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