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GLP-1 Receptor Agonists and Cancer Risk in Obesity Treatment

Lorne J. Hofseth¹  | E. Angela Murphy²  | Mary C. Playdon³  | Liza Makowski⁴  | Anna R. Ibele⁵  |
Ciaran M. Fairman⁶  | James R. Hebert⁷ 

¹Department of Drug Discovery and Biomedical Sciences, College of Pharmacy, University of South Carolina, Columbia, South Carolina, USA | ²Department of Pathology, Microbiology & Immunology, School of Medicine, University of South Carolina, Columbia, South Carolina, USA | ³Department of Nutrition & Integrative Physiology, University of Utah; Cancer Control and Population Sciences, Huntsman Cancer Institute, Salt Lake City, Utah, USA | ⁴Department of Molecular Medicine and Therapeutics, Pelotonia Research Center, The Ohio State University, Wexner Medical Center, Columbus, Ohio, USA | ⁵Department of General Surgery, University of Utah, Salt Lake City, Utah, USA | ⁶Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina, USA | ⁷Cancer Prevention and Control Program and Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina, USA

Correspondence: James R. Hebert (jhebert@sc.edu)

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ABSTRACT

Obesity is a well-established risk factor for numerous cancers, with body habitus, especially central adiposity, contributing to increased cancer incidence and worse prognosis. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially developed to treat Type 2 diabetes, have rapidly gained prominence as powerful anti-obesity agents due to their ability to induce significant weight loss and potential to improve metabolic health. These medications act by reducing appetite, enhancing insulin sensitivity, lowering systemic inflammation, and preferentially targeting fat mass for reduction. This review explores the growing body of evidence linking GLP-1 RA therapy to potential changes in cancer risk among individuals with obesity. To date, data suggest that GLP-1 RAs do not increase overall cancer risk and may reduce the risk of certain obesity-related cancers, likely by interrupting obesity-driven metabolic dysregulation. Still, questions remain about the beneficial effects of weight loss and the sustainability of health benefits if weight is regained after stopping treatment. We examine how GLP-1 RAs' anti-inflammatory and metabolic effects might mediate reductions in cancer risk, review emerging data regarding both protective signals and specific safety concerns (e.g., increased risk of medullary thyroid carcinoma), and emphasize the critical role of combining pharmacotherapy with lifestyle interventions to maintain muscle mass and long-term weight loss. Ultimately, given the strong link between obesity and cancer, GLP-1 RAs represent a promising new class of agents that may not only help to manage obesity but also serve as effective chemopreventive tools against obesity-associated cancers.

1 | Introduction

The global rise in obesity is linked to a parallel increase in obesity-associated cancers [1]. Epidemiologic studies attribute about 20% of all malignancies to excess body weight [2, 3], and obesity has been demonstrated to independently worsen cancer outcomes [4]. The mechanistic underpinnings of these

associations are complex and multifactorial (Figure 1). For instance, adipose tissue in obesity becomes a source of chronic inflammation and dysregulated adipokine secretion (e.g., elevated leptin, reduced adiponectin, and altered cytokines) that creates a pro-tumorigenic milieu [5]. Furthermore, obesity-related metabolic dysfunctions (insulin resistance, hyperinsulinemia, and altered IGF-1 signaling) are implicated in cancer

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development and progression [6]. Weight loss, therefore, is a foundational strategy for reducing cancer risk in individuals with obesity. Indeed, intentional weight reduction has been associated with lower cancer incidence; for example, bariatric surgery (which induces substantial weight loss) reduces the risk of obesity-related cancers by 33% (over 50% for hepatocellular, endometrial, and pancreatic cancers) [7–10] as well as cancers overall [11]. Yet, a proportion of people receiving bariatric surgery fail to experience substantial weight loss or metabolic benefits. Moreover, sustained weight loss through lifestyle modification alone is often challenging, and many people do not maintain sufficient weight reduction to impact long-term cancer risk.

While glucagon-like peptide-1 receptor agonists (GLP-1 RAs) do not impart the same degree of weight loss as that accomplished with bariatric surgery, they have transformed obesity treatment by helping people achieve levels of weight loss superior to those of any other medical therapy to date [12]. These agents not only promote substantial and sustained weight reduction but also improve glycemic control and cardiovascular risk factors [13, 14]. GLP-1 RAs mimic the natural incretin hormone GLP-1, resulting in appetite suppression, delayed gastric emptying, enhanced satiety, and improved insulin sensitivity. In clinical use, GLP-1 RAs such as terzepatide and semaglutide typically produce a 10%–15% reduction in body weight for the majority of people [12, 15–22] (Table 1).

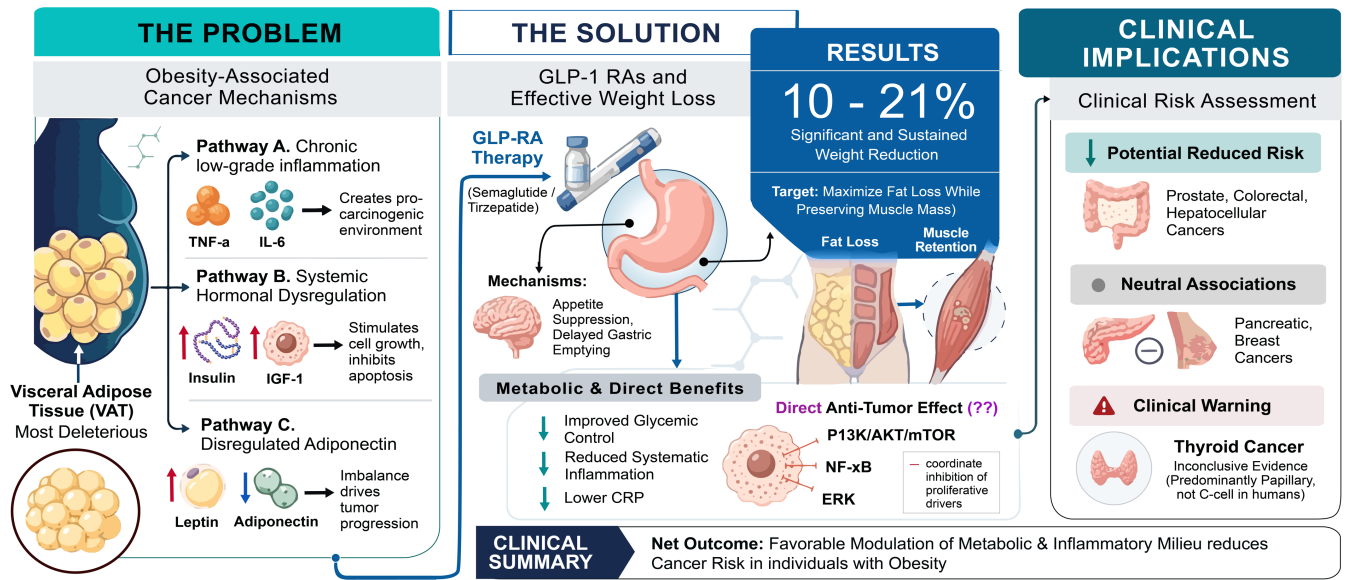


FIGURE 1 | Obesity-associated mechanisms of cancer development and the potential benefits of GLP-1RAs. Obesity promotes cancer through chronic inflammation, hormonal dysregulation, and adipokine imbalance. GLP-1RAs produce significant and sustained weight loss while improving glycemic control and reducing systemic inflammation. Emerging evidence also suggests potential direct antitumor effects through modulation of key signaling pathways. Current clinical data indicate reduced risk for several obesity-related cancers, neutral associations with others, and ongoing investigation into thyroid cancer risk. Overall, GLP-1RAs may help lower cancer risk by improving the metabolic and inflammatory environment associated with obesity.

TABLE 1 | FDA-approved GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists used for obesity and/or Type 2 diabetes, their manufacturers, and representative average percentage weight loss reported in clinical trials.

Drug	Manufacturer	Average % Wt. loss	References
Exenatide (Byetta; Bydureon BCise)	AstraZeneca	~2%–4%	[15–18]
Liraglutide (Saxenda; Victoza)	Novo Nordisk	~5%–9%	[19, 20]
Dulaglutide (Trulicity)	Eli Lilly	~3%–5%	[23, 24]
Tirzepatide (Zepbound; Mounjaro)	Eli Lilly	~15%–21%	[21, 22, 25–29]
Semaglutide (Wegovy; Ozempic; Rybelsus)	Novo Nordisk	~10%–15%	[13, 29–32]
Lixisenatide (Adlyxin)	Sanofi	~1%–3%	[33]

TABLE 2 | Emerging anti-obesity therapies in clinical development, and representative weight-loss outcomes reported in clinical trials.

Drug	Mechanism	Company/status	Weight loss	References
Retatrutide Glucagon	GLP-1/GIP/	Eli Lilly/Investigational	17%/36 weeks	[35, 36]
Amycretin	GLP-1/Amylin	Novo Nordisk/Phase 2/3	24%/36 weeks	[34, 37]
CagriSema	GLP-1/Amylin	Novo Nordisk/Phase 3	16%/32 weeks	[38]
Orforglipron	GLP-1	Eli Lilly/Phase 3	7%–11%/72 weeks	[39–41]

Additional promising and potentially more efficacious incretin-based therapies include Retatrutide, Amycretin, CagriSema, and Orforglipron. Tirzepatide (marketed as *Mounjaro* for Type 2 diabetes and *Zepbound* FDA-approved for obesity), a dual GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) agonist, is emerging as an effective weight loss therapy, with $\approx 20\%$ weight loss being reported over 40 weeks [34]. Promising GLP-1 agonists still in development include (Table 2) retatrutide, a triple agonist targeting GLP-1, GIP, and glucagon receptors, associated with weight loss of up to 24% over 36 weeks in clinical trials [35, 42]. Amycretin, a dual GLP-1 and amylin receptor agonist, has demonstrated substantial weight loss of up to $\sim 22\%$ in early-phase clinical trials over 36 weeks, suggesting efficacy that may exceed that of currently approved GLP-1 receptor agonists, although confirmation in large, long-term studies is needed [43]. CagriSema, a fixed-dose combination of semaglutide and the amylin analog cagrilintide, has demonstrated approximately 15%–17% weight loss over 32 weeks in Phase 2 trials, exceeding the efficacy of either agent alone [44]. Orforglipron, the first oral, nonpeptide GLP-1 receptor agonist, has demonstrated dose-dependent weight loss of up to $\sim 15\%$ over 36 weeks in Phase 2 trials, offering a convenient pill-based alternative to injectable incretin therapies [39]. More recently, in the Phase 3 ATTAIN-2 trial in individuals with obesity and Type 2 diabetes, once-daily orforglipron produced significant, placebo-adjusted weight reductions of up to $\sim 9.6\%$ at 72 weeks, along with improvements in glycemic and cardiometabolic parameters, with a safety profile consistent with GLP-1 RA drugs [40]. These emerging therapies represent a significant advance in obesity pharmacotherapy, with the potential to surpass earlier agents such as liraglutide and semaglutide in both efficacy and patient convenience.

A critical consideration in interpreting the efficacy and safety of incretin-based therapies is the substantial heterogeneity across agents with respect to receptor potency, pharmacokinetics, dosing regimens, and resultant biological effects. GLP-1 RAs are not a uniform class; rather, they encompass short-acting agents (e.g., exenatide, lixisenatide) with modest weight loss effects; intermediate agents (e.g., liraglutide) requiring higher daily dosing to achieve clinically meaningful weight loss; and long-acting, highly potent analogs (e.g., semaglutide) engineered for sustained receptor activation. Similarly, newer multi-agonists such as tirzepatide and retatrutide exhibit clear dose-dependent effects, with higher doses driving substantially greater weight loss but also potentially amplifying pharmacodynamic consequences. As such, aggregating outcomes across trials without accounting for differences in dose, duration, and molecular design may obscure meaningful distinctions in both efficacy and risk. Importantly, agents with

greater potency and prolonged exposure may exert differential effects on proliferative signaling pathways, raising unresolved questions regarding long-term safety, including cancer risk. For example, earlier GLP-1 RAs such as albiglutide demonstrated minimal weight loss in cardiovascular outcome trials [45], underscoring that not all agents confer comparable metabolic benefits. Therefore, both efficacy and safety (particularly in the context of chronic use for obesity) must be interpreted in a drug-specific and dose-dependent manner, with careful attention to pharmacologic properties, rather than considering them as producing a homogeneous class effect.

Beyond weight loss, GLP-1 receptor agonists improve multiple aspects of metabolic health, including lowering fasting glucose and insulin levels, improving insulin sensitivity and lipid profiles, reducing systemic inflammation, modulating the gut microbiome and gut-brain axis, and restoring hormonal regulation of appetite and glucose homeostasis [46] all of which could theoretically modulate cancer risk. Given the strong link between obesity and cancer, there is intense interest in whether GLP-1 RA-induced weight loss and metabolic changes translate into reduced cancer incidence. At the same time, safety concerns are raised about potential associations between GLP-1 RAs and certain malignancies (notably thyroid and pancreatic cancers) based on early animal studies and case reports [4]. This has prompted extensive research to clarify the net effect of GLP-1 RAs on cancer risk.

In this review, we discuss the impact of obesity on cancer risk and how GLP-1 RAs may alter the metabolic and inflammatory milieu to reduce cancer risk in individuals with obesity. We then summarize emerging evidence from clinical trials and population-based studies on cancer risk in people receiving GLP-1 RAs, highlighting patterns of cancer risk reduction as well as any indication of risk elevation. We also address the critical issues of lean body mass (LBM) loss and weight regain associated with GLP-1 RA therapy, as these factors influence long-term health outcomes. Finally, we emphasize the need for integrated lifestyle interventions alongside pharmacotherapy to ensure sustainable weight management and maximal health benefits, and we conclude with perspectives on the overall impact of GLP-1 RAs in cancer prevention and outline priorities for future research.

2 | Obesity, Body Composition, and Cancer Risk

Excess adiposity is a significant risk factor for cancer development. Increased body mass index (BMI) shows a linear

positive correlation with the risk of many site-specific tumors [47]. Key biological mechanisms link obesity to carcinogenesis: chronic low-grade inflammation, hormonal changes, and altered adipokine levels create a pro-carcinogenic environment [48]. During obesity, expanding adipose tissue stores secrete abnormally high levels of pro-inflammatory cytokines (such as TNF- α and IL-6) and adipokines such as leptin, while beneficial adiponectin levels decline [49]. Elevated leptin in obesity can promote cancer cell proliferation, invasion, and angiogenesis, and it impairs apoptosis and immune surveillance, whereas adiponectin has anti-proliferative, pro-apoptotic effects [49]. This imbalance drives tumor progression. Obesity is also associated with hyperinsulinemia and increased bioavailability of insulin-like growth factor-1 (IGF-1), which can stimulate cell growth and inhibit apoptosis in various tissues [50, 51]. Insulin resistance and high circulating glucose further contribute to a metabolic environment conducive to cancer cell survival [52]. Epidemiologic data link Type 2 diabetes and poor glycemic control with elevated cancer risk and mortality [53], underscoring the interplay between metabolic health and oncogenesis.

2.1 | Body Fat Distribution and Cancer Risk

The relationship between adipose tissue distribution and carcinogenesis is heterogeneous. Visceral adipose tissue (VAT, the fat surrounding internal organs, which typically consists of white adipose tissue) appears more deleterious than subcutaneous fat [5, 54]. VAT is metabolically active and secretes pro-inflammatory cytokines, adipokines, and growth factors that can promote tumor development. Epidemiologic studies have found that higher visceral fat (often measured by waist circumference, waist: hip ratio, bioelectrical impedance, or imaging) is associated with a greater cancer risk independent of BMI [55]. A large study conducted using UK Biobank data ($n = 461,665$; median 12-year follow-up) published in 2024 showed that visceral adipose tissue estimated from anthropometric measures and validated against MRI body composition accounted for a higher proportion of risk in the population than overall obesity, with population-attributable risks for high VAT of 9.0% in men and 11.6% in women, compared with 5.0% and 8.2%, respectively, for high BMI [56]. By contrast, subcutaneous fat appears less metabolically inflammatory than visceral fat and generally shows weaker or null associations with metabolic risk, consistent with depot-specific adipose biology [57]. This implies that two individuals with the same BMI can have different cancer risk depending on adipose tissue distribution. Whether reducing visceral adiposity lowers cancer incidence remains untested, but VAT is a biologically plausible and modifiable target for cancer prevention. GLP-1 receptor agonists preferentially reduce VAT, making this pharmacotherapy an attractive potential obesity related cancer prevention therapy candidate [54].

3 | Sarcopenic Obesity and Low Muscle Mass

Skeletal muscle is a metabolic organ and its mass shapes the same insulin- and inflammation-related pathways that link adiposity to cancer risk. It is the predominant site of

insulin-mediated glucose disposal in the postprandial state [58], and it acts as an endocrine organ, releasing contraction-induced myokines such as IL-6 that regulate glucose uptake, fat oxidation, and systemic inflammation [59]. Through these functions, greater relative muscle mass is associated with lower insulin resistance and a reduced likelihood of prediabetes. Sarcopenic obesity refers to the phenotype of having both excess fat and low muscle mass (sarcopenia). This combination may compound cancer risk and worsen outcomes [60–62]. Individuals with sarcopenic obesity often exhibit worse metabolic profiles (insulin resistance and chronic inflammation) than people with obesity who have more muscle [63]. Research has shown [64] that sarcopenic obesity is associated with higher frailty, treatment complications, and shorter survival in several cancers. For example, in a recent cohort of 6790 people with cancer, it was reported that those with sarcopenic obesity had a 50% higher risk of mortality compared with people without sarcopenia (hazard ratio ~ 1.5) [65]. The presence of too little muscle may also blunt the benefits of weight loss. Muscle helps regulate blood sugar and inflammation; therefore, a person living with obesity who has very low muscle mass may not experience as much risk reduction from losing weight if that weight loss also comes with further muscle wasting [66–68]. These observations underscore that improving body composition (by decreasing fat mass while preserving or increasing LBM, especially skeletal muscle) is an optimal strategy to lower cancer risk [67]. Simply focusing on scale weight or BMI is not enough; the nature of weight loss (i.e., fat vs. muscle) and the specific type of fat loss (i.e., visceral vs. subcutaneous) impacts the extent of cancer risk reduction [69, 70].

Because chronic hyperinsulinemia and insulin resistance are among the principal mediators linking adiposity to carcinogenesis [51, 71], muscle mass plausibly lowers cancer risk indirectly by improving cancer-related pathways. Consistent with this, higher leisure-time physical activity, which builds and preserves muscle, is associated with a lower risk of 13 of 26 cancer types across pooled cohorts totaling 1.44 million adults, with most associations independent of body size [72]. Direct evidence that muscle mass itself is associated with cancer incidence is more limited and site-specific: in the UK Biobank, sarcopenia and its correlates (low grip strength and low muscle-mass index) were associated with a higher incidence of predominantly gastrointestinal cancers that was observed more strongly among men, and these associations persisted after adjustment for BMI [73]. Epidemiologic evidence for muscle as an independent cancer risk factor remains scarce. A substantial fraction of the GLP-1-induced weight lost is lean mass [13], reinforcing the importance of considering therapeutic effects on overall body composition. The prior evidence linking sarcopenic obesity and behaviors that support the preservation or increase in lean muscle mass in cancer etiology provides a rationale for pairing GLP-1 RA therapy with physical activity/resistance exercise and adequate protein intake to preserve lean mass in concert with VAT reduction, rather than focusing solely on scale weight or BMI as clinical targets for cancer risk reduction. However, clinical studies testing combined lifestyle and GLP-1 RA therapy for effects on cancer relevant mechanisms are lacking.

4 | Weight Loss Benefits for Cancer Prevention: Lifestyle and Bariatric Surgery

Observational evidence indicates that weight loss lowers the risk of obesity-related cancers, although randomized controlled trials confirming this relationship are limited. In a large cohort of postmenopausal women participating in the Women's Health Initiative, those who intentionally lost $\geq 5\%$ of their body weight had approximately a 12% reduction in the risk of developing obesity-associated cancers compared with women with stable weight [74]. Notably, weight loss was associated with significantly lower rates of obesity-related cancers including breast cancer, even after accounting for whether the weight loss was intentional or not. Abdominal fat loss (reduction in waist circumference) showed similar benefits. In the largest pooled analysis to date of prospective data from 180,885 women in 10 cohorts, sustained weight loss was associated with progressively lower breast cancer risk in women aged 50 years and older [75]. Only one randomized, controlled trial, the Look AHEAD study, found a 16% lower incidence of obesity-related cancer in the intensive-lifestyle arm, directionally consistent with the observational data but not statistically significant, as the trial was underpowered for cancer endpoints [76]. These observational findings align with the biology that reducing excess adipose tissue (especially VAT) lowers levels of pro-carcinogenic factors such as insulin, estrogen, and inflammatory cytokines [77].

Studies of cancer risk following bariatric surgery provide the clearest evidence that substantial weight loss lowers cancer incidence. Bariatric surgery typically achieves large, durable weight reduction of 20%–30% of body weight. In the SPLENDID matched-cohort study of 30,318 adults, bariatric surgery was associated with a 32% lower incidence of obesity-associated cancer and 48% lower cancer-related mortality, with the strongest individual-site reduction for endometrial cancer (hazard ratio = 0.47) [11, 78]. The prospective Swedish Obese Subjects study, with roughly 20 kg of sustained weight loss, similarly found a 33% lower overall cancer incidence in women (42% lower risk) but not men [7], and a large multisite cohort showed similar results [9]. In a 2023 systematic review of 32 studies, bariatric surgery was associated with roughly a 38% reduction in overall cancer incidence and about a 41% reduction in obesity-related cancer incidence (relative risk ~0.59) [10]. Significant risk reductions were observed for many obesity-linked cancers. For example, people, post-surgery, had a 50%–60% lower risk of endometrial, ovarian, and breast cancers on average. Bariatric surgery was also associated with a 50% reduction in cancer mortality in these analyses [10]. These improvements are likely mediated by the metabolic and endocrine changes accompanying sustained weight loss, including reductions in chronic systemic inflammation, improved insulin sensitivity with lower circulating insulin and IGF-1 levels, and favorable changes in adipokine signaling, characterized by decreased leptin and increased adiponectin. Together, these alterations create a less pro-tumorigenic systemic environment [79].

Not all weight loss is equal in terms of health benefits. Losing fat mass is the goal, but where the loss occurs (i.e., visceral vs. subcutaneous) and whether the adipose tissue lost is brown

or white are also important determinants of metabolic health and disease risk [80]. Visceral adipose tissue is metabolically active and contributes disproportionately to chronic low-grade inflammation, insulin resistance, and the production of pro-inflammatory adipokines that promote obesity-associated diseases, including cancer. In contrast, subcutaneous adipose tissue, particularly in the gluteofemoral region, is generally considered metabolically protective because it serves as a relatively safe reservoir for lipid storage and is associated with improved insulin sensitivity and lower cardiometabolic risk [81, 82]. Brown adipose tissue, unlike white adipose tissue, dissipates energy through nonshivering thermogenesis and contributes to improved glucose and lipid metabolism, making preservation or activation of brown fat a potentially beneficial therapeutic target [83]. Consequently, weight-loss strategies that preferentially reduce visceral white adipose tissue while preserving metabolically beneficial tissues are likely to confer greater health benefits than equivalent reductions in body weight alone. Losing LBM (muscle and bone) is almost always detrimental. Calorie restriction without exercise can lead to significant muscle loss, especially in older adults [84]. For example, in older adults with obesity, diet-induced weight loss alone can exacerbate sarcopenia and frailty, whereas combining weight loss with resistance exercise helps preserve lean mass and improves functional capacity [85]. This principle emphasizes that effective obesity interventions should maximize fat loss while minimizing muscle loss. Maintaining muscle through exercise and adequate protein intake during weight loss is, therefore, essential because it ensures that the weight reduction translates into better metabolic health and cancer risk reduction, rather than introducing new risks associated with sarcopenia.

5 | Weight Loss, Metabolic, and Anti-Inflammatory Effects of GLP-1 Receptor Agonists

GLP-1 RAs promote weight loss and improve metabolic health, both of which may favorably influence cancer risk. Pharmacologically, these agents bind to GLP-1 receptors in the pancreas and brain, mimicking the actions of endogenous GLP-1. Activation of central GLP-1 receptors, particularly within the hypothalamus, suppresses appetite and promotes earlier satiety, resulting in reduced caloric intake. In peripheral tissues, GLP-1 RAs enhance glucose-dependent insulin secretion, suppress glucagon release, and delay gastric emptying, leading to improved glycemic control and reduced energy intake [86, 87]. In individuals with obesity, with or without Type 2 diabetes, these combined effects often produce substantial and sustained weight loss. GLP-1 RAs also improve insulin sensitivity and reduce hyperglycemia and hyperinsulinemia, metabolic abnormalities that have been implicated in tumor growth and cancer progression [13, 52]. Although originally developed to lower HbA1c in people with Type 2 diabetes, GLP-1 receptor agonists have also been associated with improved cancer-related survival in this population [88].

The weight-loss effects of GLP-1 RAs are notable. Over months of therapy, people typically experience progressive weight loss predominantly through a reduction in fat mass and lean body

mass [13]. GLP-1 RAs produce sustained weight reduction that is maintained for as long as the medication is continued, with substantial weight regain after discontinuation [89]. Alongside weight loss, GLP-1 RAs help remodel adipose tissue and improve adipose function [90]. Weight reduction with GLP-1 RAs is accompanied by decreased secretion of pro-inflammatory adipokines and cytokines from adipose tissue, as total fat mass (especially visceral fat) shrinks [91]. People receiving GLP-1 RAs often show lower levels of C-reactive protein and other inflammatory markers [92], reflecting a systemic anti-inflammatory effect. By reducing obesity-induced inflammation, GLP-1 RAs may directly counter one of the key drivers of obesity-related cancer risk. GLP-1 RAs may, therefore, contribute to lower cancer risk in part by dampening chronic inflammation and improving the immune-metabolic environment [48, 93]. In addition, GLP-1 RAs exert favorable changes in lipid metabolism and blood pressure, contributing to overall metabolic health. Improved metabolic profiles (lower insulin, glucose, triglycerides, and blood pressure) can remove or reduce growth stimuli for cancer cells. Preclinical research also suggests that GLP-1 RAs might have direct anti-tumor effects independent of weight loss, including effects on tumor growth, migration, intracellular signaling, and antitumor immune responses [94, 95]; however, GLP-1 receptor (GLP-1R) expression is generally low in most human tumors, reducing the likelihood that direct receptor-mediated effects are the predominant mechanism at the population level [96].

5.1 | Mechanistic Insights

GLP-1Rs are expressed in multiple organs and cell types in humans and model species [97, 98]. In the pancreas, GLP1R is abundant on β -cells and present (though typically lower) on δ -cells. Very few α -cells express GLP1R. In the gastrointestinal tract, GLP1R is highest in duodenal Brunner's glands and is found on gastric mucosal cells and enteric neurons. Notably, primates show GLP1R on stomach parietal cells [98], whereas in mice GLP1R is localized to gastric mucous neck cells [99]. Enteric (myenteric) neurons throughout the gut express GLP1R in both species [98, 99]. In the brain, GLP1R is present in regions governing metabolism and appetite: abundant in the hind-brain/area postrema and hypothalamus (arcuate, PVN, VMH) [100, 101]. In the cardiovascular system, GLP1R is found on sinoatrial node myocytes and atrial cardiomyocytes (murine GLP1R is limited to atria [100]), and low-level GLP1R mRNA is detectable in human ventricular tissue [101]. Vascular smooth muscle cells (arterioles in kidney, lung, etc.) also express GLP1R [98]. Other sites include kidney arterioles, lung vasculature (SMCs), thyroid C-cells (mediating calcitonin release), and joint chondrocytes [102]. GLP1R can be induced in activated immune cells (T cells) and is reported in epicardial fat [103].

Independent of weight loss, the activation of GLP-1R in experimental models has been shown to inhibit cancer cell proliferation, induce apoptosis, and suppress migration and invasion via multiple signaling pathways [104]. In some tumor models, GLP-1R agonists activate cAMP/PKA and/or AMPK signaling, with downstream inhibition of pro-survival pathways including PI3K/AKT/mTOR and ERK-MAPK signaling [105, 106]. For example, liraglutide (a GLP-1RA) inhibits colorectal cancer

cell proliferation, migration, and invasion by blocking the PI3K/AKT/mTOR cascade [107]. Similarly, GLP-1R stimulation has been shown to increase cAMP levels that inhibit AKT and ERK1/2 activity and induce apoptosis in tumor cells [108]. These effects include cell-cycle arrest (via downregulation of cyclin D1/A2) and activation of pro-apoptotic kinases (such as p38 MAPK), and autophagy. In endometrial cancer cells, GLP-1RA treatment activates AMPK, inhibits mTOR signaling, and promotes apoptosis [108]. Concurrently, GLP-1R signaling can restrain NF- κ B activity: for instance, GLP-1RA treatment of breast cancer cells suppresses NF- κ B and activates cAMP/CREB, thereby increasing apoptosis and slowing proliferation [108]. Thus, GLP-1RAs coordinately inhibit proliferative drivers (PI3K/AKT, ERK) and pro-survival pathways (NF- κ B) while engaging cell-death and cell-cycle checkpoint pathways. GLP-1R signaling is not uniformly anti-proliferative. In tissues that express the receptor, activation can promote growth: in murine intestine, GLP-1R agonists increase mucosal proliferation and polyp number and size through an Fgf7-dependent mechanism, and GLP-1R stimulation drives C-cell proliferation in the rodent thyroid. These tissue-specific pro-proliferative effects, together with low GLP-1R expression in most human tumors, indicate that direct action may be context-dependent.

GLP-1RAs also remodel the tumor microenvironment and host metabolism; independent of anti-obesogenic effects. GLP-1R signaling has been reported in several immune cell populations, including macrophages, monocytes, and lymphocytes. In macrophage models, GLP-1/GLP-1R signaling can promote an anti-inflammatory, M2-like phenotype while reducing M1-associated inflammatory mediators, including TNF- α and IL-6. Mechanistically, these effects have been linked to cAMP-PKA signaling, AMPK activation, and suppression of inflammatory pathways such as JNK/STAT3 and NF- κ B [93, 109]. The result is improved CD8⁺ T-cell metabolic fitness and memory formation, and reduced T-cell exhaustion [102, 110]. Moreover, GLP-1R agonists create a host metabolic milieu that is unfriendly to tumorigenesis: they lower insulin and IGF-1 levels, reduce obesity and ectopic fat, and decrease systemic inflammation [111]. By improving glycemic control and insulin sensitivity, GLP-1RAs diminish growth signals that often fuel cancer. In preclinical models, these combined effects, such as direct blockade of oncogenic pathways (PI3K/AKT/mTOR, NF- κ B, and ERK) and a healthier metabolic/inflammatory state translate to reduced angiogenesis, invasion (lower MMPs, EMT markers), and tumor progression.

In summary, by producing weight and visceral fat loss, GLP-1 RAs lower insulin, IGF-1, and systemic inflammation and reprogram immune cells toward a less inflammatory state, thereby reducing the metabolic drivers of obesity-associated cancer. In preclinical models, GLP-1R activation in tumors drives cAMP/PKA-dependent inhibition of AKT and ERK, activation of AMPK/p38 and autophagy, and induction of cell-cycle arrest and apoptosis. It also inhibits NF- κ B and related cytokine signaling. At the same time, GLP-1RAs reprogram immune cells to a less inflammatory state and improve host metabolism. These pleiotropic, pathway-specific mechanisms support a net anti-tumor effect of GLP-1R agonists, particularly against obesity-driven cancers.

6 | Human Evidence for GLP-1 RA Use and Cancer Risk

Table S1 summarizes the current evidence on the association between GLP-1RAs and cancer risk. The highest-quality evidence derives from randomized controlled trials. These investigations provide critical insights into the safety profile of GLP-1RAs in people with Type 2 diabetes and obesity, with a focus on overall and specific cancer risks.

The LEADER randomized controlled trial, which enrolled 9340 people with Type 2 diabetes at high cardiovascular risk, found no significant increase in overall malignant neoplasm risk with liraglutide compared with placebo over a median follow-up of 3.8 years (HR 1.06, 95% CI 0.90–1.25) [112]. Notably, however, liraglutide was associated with a significant reduction in prostate cancer risk (HR 0.54; 95% CI: 0.34–0.88) [112]. The LEADER trial's strengths lie in its large sample size, randomized design, and robust statistical reporting. However, the short follow-up period, potential limitations in subgroup analyses, and lack of mechanistic insights weaken its ability to definitively conclude long-term cancer risk or explain the prostate cancer finding. The trial was not designed to evaluate site-specific neoplasm risk, and the low event rate for specific cancer types makes inference regarding site-specific cancer risk underpowered. Larger studies with longer follow-up and broader populations are needed to confirm and expand on these results.

Two large-scale TriNetX US Collaborative Network database (2013–2023) studies provide real-world evidence. In a study of over 1.1 million adults, reported that semaglutide conferred broad cancer protection, particularly for gastrointestinal, breast, skin, genitourinary, and prostate cancers [113, 114]. Liraglutide showed mixed outcomes, with possible increased risks for thyroid, breast, respiratory, hematologic, and mesothelial cancers, while dulaglutide showed modest protective effects, especially for GI and skin cancers [113]. These estimates were not corrected for multiple comparisons across numerous cancer types and agents, are susceptible to confounding by indication and differential surveillance, and imply within-class differences that are biologically implausible for agents sharing a common mechanism of action. Wang et al.'s TriNetX retrospective cohort study of 1,651,452 people with Type 2 diabetes reported that GLP-1 receptor agonist use was associated with significantly lower risks of several obesity-associated cancers compared with insulin, including pancreatic cancer (HR 0.41, 95% CI 0.33–0.50), colorectal cancer (HR 0.54, 95% CI 0.46–0.64), and kidney cancer (HR 0.76, 95% CI 0.64–0.91); however, these apparent protective associations were not observed when GLP-1RAs were compared with metformin; kidney cancer risk was higher in the GLP-1RA group versus metformin (HR 1.54, 95% CI 1.27–1.87) [114]. Because insulin is mitogenic, the insulin comparison may reflect risk attributable to the comparator rather than benefit conferred by GLP-1 RAs, and the absence of any reduction versus metformin supports this interpretation. The observational nature of these electronic medical record-based studies, potential confounding, and limited follow-up periods necessitate caution in interpreting results. The mixed outcomes for liraglutide in the first study and the lack of unique benefits compared with metformin in the second highlight the need

for randomized controlled trials with longer follow-up to confirm these findings and elucidate mechanisms.

Two multinational real-world cohort studies specifically examined thyroid cancer risk (papillary/follicular types). One across six countries incorporating ~2.6 million people with T2D found no increased risk with GLP-1RAs (HR 0.81; 95% CI: 0.59–1.12) compared with DPP-4 inhibitors [115]. A Scandinavian registry study of 437,077 people likewise showed no elevated thyroid cancer risk (HR 0.93; 95% CI: 0.66–1.31) across several GLP-1RAs, further supporting their neutral effect on thyroid cancer [116]. Both multinational cohort studies provide robust real-world evidence supporting the neutral effect of GLP-1RAs on thyroid cancer risk in people with T2D, with HRs of 0.81 and 0.93 indicating no significant increase compared with DPP-4 inhibitors or an unspecified control. Strengths include large sample sizes, real-world data, and consistent findings, but weaknesses such as observational designs, unspecified follow-up periods, and wide confidence intervals limit causal inference and precision. Future studies with longer follow-up, drug-specific analyses, and randomized designs are needed to further confirm the thyroid safety of GLP-1RAs.

7 | Meta-Analysis and Systematic Review Evidence

Across tens of thousands of people with obesity or T2D in randomized, controlled trials and millions of participants in observational studies, GLP-1RAs show cancer-type-specific effects, with neutral to protective associations for most cancers, but uncertainty remains around thyroid cancer risk and long-term effects (as these drugs have been in widespread use for only a few years, while cancers have decades-long latency). The most rigorous synthesis, a 2026 meta-analysis of 48 randomized trials (~94,245 participants), found no significant association between GLP-1 RAs and any of 13 obesity-related cancers, including thyroid cancer (OR 1.37; 95% CI 0.82–2.31), although follow-up was short for detecting long-latency cancer risk outcomes [117].

Thyroid cancer risk is the most debated. Several meta-analyses report increased odds with GLP-1RAs. For instance, Tang and Zhang [118] found ORs up to 2.70; Silverii and Monami [119] reported a moderate increase (OR 1.52); and Hu and Song [120] suggested a modest elevation (RR 1.30). However, other analyses such as Cao et al. [121] and Pasternak et al. [116] found no statistically significant increase, leaving this risk inconclusive. Importantly, when specified, the thyroid tumors reported in human GLP-1RA studies are predominantly papillary (follicular-cell-derived) rather than C-cell (medullary) in origin, contrasting with rodent models that show C-cell hyperplasia. The increased thyroid cancer risk reported in some meta-analyses may arise from biological mechanisms (C-cell stimulation in susceptible individuals), detection bias due to increased screening (particularly identifying small papillary microcarcinomas), and methodological limitations (confounding, small event rates, and comparator choice). However, conflicting findings (no risk in Cao et al. [121] and Pasternak et al. [116]) suggest that risk estimation remains inconclusive, likely due to

study heterogeneity and human-specific differences from rodent models. In contrast, prostate cancer consistently shows reduced risk with GLP-1RA use. Multiple meta-analyses [122–124] report relative risk reductions ranging from 27% to 47%, indicating a robust protective association. For colorectal cancer, findings are more nuanced. Bushi et al. [125] reported significant reductions when GLP-1RAs were compared to insulin, thiazolidinediones, and Sodium-Glucose Cotransporter 2 inhibitors. However, no advantage was seen versus metformin or dipeptidyl peptidase-4 inhibitors. Sun and Liu [126] noted a potential increase in colorectal cancer risk based on Mendelian randomization, but the accompanying RCT meta-analysis was neutral. Similarly, GLP-1RAs were not associated with a higher GI cancer risk [127] or esophageal cancer [128].

Pancreatic cancer risk appears neutral overall, with no credible evidence of increased risk across large-scale reviews [121, 129]. Importantly, GLP-1RAs may lower hepatocellular carcinoma risk, especially among people with cirrhosis. Pasta et al. [130] and Shabil et al. [131] both showed significant reductions (HRs as low as 0.41), although comparisons with metformin remain inconclusive. Finally, no significant association with breast cancer was found across multiple trials [132, 133], supporting the safety of GLP-1RAs in hormone-sensitive cancers beyond prostate. Kidney cancer risk was higher among individuals taking GLP-1 RAs than with metformin in one large cohort [114, 134], which was supported by findings from an obesity cohort (Dai) and in pooled analyses of data from clinical trials [117], warranting further research.

In summary, observational data suggest possible risk reductions with GLP-1RA use for prostate and hepatocellular cancer and a comparator-dependent reduction for colorectal cancer, though these observations have not been confirmed in randomized trials. Associations of GLP-1 RA use with risk of breast, gastrointestinal, and pancreatic cancer are largely null, with a type-specific increased risk for thyroid cancer, though the evidence remains inconsistent.

8 | LBM Loss and Weight Regain: Implications for Cancer Risk

One concern associated with GLP-1 RA-mediated weight loss is the composition of the weight lost. Ideally, weight reduction should primarily come from white adipose tissue rather than brown adipose tissue or LBM, especially skeletal muscle. While GLP-1 RAs do preferentially reduce fat mass, studies have shown that some loss of LBM accompanies the fat loss. Approximately 25%–40% of total weight lost during GLP-1RA-based or incretin-mimetic pharmacotherapy may derive from lean/fat-free mass rather than fat mass, although DXA-defined lean mass includes skeletal muscle as well as nonmuscle fat-free tissues and water [135]. In the STEP-1 semaglutide 2.4 mg DXA substudy, semaglutide reduced total fat mass by 19.3% and total lean body mass by 9.7%; reanalysis of these body-composition data estimated that 6.92 kg of the 17.32 kg mean weight loss was lean mass, or approximately 40% of total weight lost [136].

Weight loss induced by GLP-1 receptor agonists includes reductions in both fat mass and LBM, as occurs with virtually all effective weight-loss interventions. Early studies with liraglutide reported that lean body mass accounted for as much as approximately 60% of total weight lost in some cohorts [137], although subsequent studies have demonstrated substantial variability, with lean mass typically representing approximately 15%–40% of total weight loss depending on the population studied, duration of treatment, and methods used to assess body composition [137]. Recent reviews further emphasize that changes in lean body mass should be interpreted cautiously because lean body mass encompasses skeletal muscle as well as water, connective tissue, and organ mass, and does not directly measure functional skeletal muscle. Consequently, reductions in lean body mass do not necessarily indicate proportional losses in muscle strength or quality. The phenomenon is not unique to GLP-1 receptor agonists; calorie restriction and bariatric surgery similarly result in concurrent losses of fat and lean tissue during weight reduction [138, 139]. Nevertheless, because GLP-1 receptor agonists can produce substantial weight loss over relatively short periods, preservation of skeletal muscle through adequate dietary protein intake and resistance exercise remains an important clinical objective [137, 140]. Skeletal muscle plays a central role in maintaining resting energy expenditure, physical function, and metabolic health. Excessive loss of muscle during weight reduction may contribute to declines in strength, functional capacity, and resting metabolic rate, potentially increasing susceptibility to weight regain and frailty, particularly in older adults [137, 140]. Accordingly, current clinical recommendations emphasize combining GLP-1 receptor agonist therapy with structured exercise and nutritional strategies to maximize fat loss while preserving lean tissue and physical function [137, 140].

Another practical issue is weight regain after discontinuation of GLP-1 RAs. Withdrawal trials show that when GLP-1 RA-based therapy is stopped, people regain a substantial portion of the lost weight, often trending back toward baseline over months to a year, with partial reversal of cardiometabolic benefits [141, 142]. In the STEP1 trial extension, participants who discontinued semaglutide regained about two thirds of their prior weight loss within 1 year [141]. A randomized trial extension similarly found that weight regain is common after cessation of GLP-1 RA treatment unless people transitioned to an alternative maintenance strategy such as continued exercise [143]. This rebound reflects the loss of pharmacologic appetite suppression and metabolic effects, leading to increases in hunger and energy intake. Discontinuation rates are also common in clinical practice; in a cohort of 125,474 adults, 64.8% of those without Type 2 diabetes discontinued within 1 year, although a substantial fraction subsequently reinitiated therapy, often prompted by weight regain [144]. Following discontinuation, individuals may regain up to two-thirds of the weight they initially lost [145]. In addition, there is evidence that the weight-loss response to long-term GLP-1 RA therapy plateaus over time, likely due to adaptive metabolic and appetite-regulating mechanisms, which may necessitate dose escalation or adjunctive behavioral and nutritional interventions [146]. Prolonged semaglutide use has also been associated with weight-loss plateaus and subsequent weight regain after discontinuation [13, 141].

From a cancer prevention perspective, weight regain may negate the protective metabolic benefits achieved during weight loss. For example, an individual who loses 15% of body weight but subsequently regains that weight may also lose any associated reduction in obesity-related cancer risk [74, 141]. Indeed, repeated cycles of intentional weight loss followed by regain may further complicate cancer prevention, because weight cycling can attenuate the metabolic benefits of sustained weight loss and has been associated with increased risk for some obesity-related cancers, particularly endometrial cancer. However, the epidemiologic evidence is mixed, and large prospective cohorts do not consistently show increased overall cancer risk; therefore, the strongest conclusion is that durable weight-loss maintenance, rather than repeated loss-regain cycles, is likely to be most relevant for long-term cancer-risk reduction [147, 148]. Although in pre-clinical studies where retatrutide was discontinued after weight loss and weight rebounded, protection against cancer progression persisted, suggesting that some benefit of weight loss with GLP-1 RA may be preserved [149]. In summary, while GLP-1 RAs are highly effective for inducing weight loss, their long-term benefit depends on maintaining that loss. This requires attention to preserving LBM and implementing strategies to prevent rebound weight gain because both are essential for overall health and durable cancer risk reduction. Lifestyle interventions remain central to achieving these goals.

9 | Integrating Lifestyle Interventions With GLP-1 RA Therapy

GLP-1 RAs are most effective when used as an adjunct to, not a replacement for, lifestyle modification. Lifestyle interventions (particularly nutrition and exercise) remain the foundation of healthy weight management and are critical for maintaining weight loss and muscle mass during GLP-1 RA treatment [150]. People should engage in a comprehensive weight-loss program that combines pharmacotherapy with diet, physical activity, and behavioral strategies.

9.1 | Dietary Management

A high-protein, nutritionally balanced diet helps ensure that weight loss comes predominantly from fat stores rather than muscle by providing the amino acids needed to preserve lean tissue during a calorie deficit [151, 152]. Some GLP-1 RA studies and case series have emphasized adequate protein intake and resistance training during treatment, with reports suggesting better preservation of lean mass among participants consuming higher protein diets [153]. Additionally, moderating the pace of weight loss (i.e., achieving a steady, moderate rate) may reduce lean mass loss compared with very rapid weight loss, as faster rates of weight reduction are consistently associated with greater proportional losses of fat-free mass [84]. Dietitians often work with people receiving GLP-1 RAs to craft meal plans that create a modest caloric deficit while emphasizing protein adequacy and nutrient density, thereby complementing the medication's appetite-lowering effects while helping preserve lean mass and nutritional status [154]. Optimizing the balance of macronutrients (protein, fats, and carbohydrates) and micronutrients is crucial for metabolic health. Diets high in refined

carbohydrates, saturated fats, and ultra-processed foods can promote systemic inflammation, whereas dietary patterns rich in fiber, unsaturated fats, vitamins, minerals, and phytochemicals are generally associated with lower inflammatory burden and improved cardiometabolic health [155]. However, calorie restriction often leads to reduced intake of vitamins, minerals, and phytochemicals, necessitating careful dietary planning to maintain adequate levels of these essential nutrients [156, 157].

9.2 | Physical Activity

Regular physical activity, particularly resistance training, is strongly recommended for people undergoing weight loss with GLP-1 receptor agonists. Resistance training (e.g., weightlifting or body-weight exercises) provides a key anabolic stimulus that helps preserve or increase muscle mass counteracting the well-documented loss of fat-free mass that accompanies weight reduction. Evidence from weight-loss interventions consistently shows that incorporating resistance exercise attenuates lean mass loss compared to diet-induced weight loss alone, supporting its role as a critical adjunct to pharmacologic therapy [84, 158, 159]. Exercise also improves insulin sensitivity and cardiovascular fitness, compounding the metabolic benefits of GLP-1 RA therapy [160]. Even moderate resistance exercise a few times per week has been shown to attenuate loss of fat-free mass during dieting [84]. Cardiovascular exercise helps increase energy expenditure and can aid in additional fat loss and weight maintenance. Importantly, establishing an exercise routine while on pharmacotherapy also sets the stage for keeping the weight off after stopping the medication. People who adopt regular exercise and healthy eating habits are more likely to sustain their weight loss, whereas those relying solely on medication often regain weight if the drug is discontinued [141, 161]. Clinicians thus counsel that GLP-1 RAs “do the heavy lifting” to jump-start weight loss, but people need to “pick up the weights” (literally and figuratively) to preserve muscle and maintain success.

9.3 | Behavioral Support

Behavioral strategies, including structured weight-loss programs, dietary counseling, cognitive behavioral therapy, motivational interviewing, and mindfulness-based interventions, can enhance adherence to GLP-1RA therapy by addressing emotional eating, dietary lapses, self-monitoring, and motivation [162]. These interventions provide people with practical skills and coping strategies that facilitate the long-term adoption and maintenance of healthful eating and physical activity behaviors, thereby improving treatment persistence and reducing the likelihood of weight regain after initial weight loss [163, 164]. While GLP-1RAs produce substantial physiological reductions in appetite, body weight, and adverse metabolic parameters, behavioral support complements these effects by targeting the psychological, cognitive, and environmental factors that influence sustained behavior change. Emerging evidence suggests that people receiving GLP-1RA therapy in conjunction with structured behavioral support achieve better long-term adherence and maintenance of weight loss than those receiving pharmacotherapy alone, even when differences in short-term weight

loss are modest [165, 166]. This integrated approach may also promote preservation of lean body mass through reinforcement of healthy dietary patterns and regular physical activity while further reducing obesity-associated cancer risk. Accordingly, combining GLP-1RA therapy with evidence-based behavioral interventions represents a comprehensive strategy for achieving durable obesity management and maximizing long-term clinical benefit.

10 | Conclusion and Future Directions

By suppressing appetite and enhancing satiety, GLP-1RAs drive dramatic visceral fat loss, better insulin sensitivity, lower blood pressure and reduced systemic inflammation (all factors that can interrupt pathways of obesity-driven cancer). Preclinical and clinical evidence now suggests GLP-1RA-induced weight loss may translate into lower incidence of several obesity-related malignancies. The balance of data remains reassuring in most settings. Initial concerns about pancreatic cancer have not been borne out, and overall cancer incidence appears no higher on GLP-1 therapy. Some uncertainties persist (e.g., thyroid cancers need longer-term study). However, on balance, a favorable cancer prevention profile is emerging for GLP-1RA use among people with obesity. However, dietitians and clinicians have observed that when GLP-1 RAs are used beyond strict guidelines or without nutritional supervision, people can end up effectively starving themselves [145, 167]. In some cases, GLP-1 therapy produces such extreme appetite suppression that metabolism can mirror that of an anorexic state. Studies find many GLP-1 agnostic users quickly become deficient in vitamin D, iron, B-vitamins, and other nutrients [167]. In the short term, caloric deficit can cause fatigue, dizziness, nausea or other GI upset, electrolyte imbalances, and orthostatic hypotension. Without resistance exercise and adequate protein intake, this pattern raises concern for sarcopenia and functional decline rather than preservation of metabolically healthy body composition [13, 168].

It is well known that chronically inadequate nutrition can undermine many aspects of health. Rapid, unbalanced weight loss without supervision may increase the risk of bone loss and fracture vulnerability, especially in older or frail people, and may contribute to persistent sarcopenia, reduced functional capacity, and lower metabolic rate. Inadequate protein and micronutrient intake may also compromise immune function and contribute to cognitive and functional decline, particularly in older adults or individuals with preexisting frailty [84, 169]. Thus, the goal must be sustainable health improvement, not the creation of new nutritional deficits. Moving forward, GLP-1RA therapy is best integrated into a comprehensive clinical care plan. Weight-loss medications work best when combined with diet, exercise, and behavioral support, and this is doubly true for preserving muscle and nutrient status. Future research and clinical guidelines must, therefore, expand beyond just cancer outcomes. Investigators should monitor body composition, nutrient levels, and functional health in long-term GLP-1RA users, to ensure benefits (e.g., reduced cancer risk) are not offset by collateral harm. In practice, every GLP-1RA prescription should come with nutrition counseling: e.g., smaller protein-rich meals, vitamin supplementation, and resistance training are now

recommended to protect bone and muscle during therapy and specific prescriptions for physical activity. Finally, because so many people are now receiving GLP-1 RA therapy for weight management, there are excellent opportunities for creating cohorts of individuals that can be followed over time. It will be important to do so given the fact that cancer latency tends to be very long (e.g., decades) while widespread use of these drugs outside of prescriptions for individuals with Type 2 diabetes has been occurring for only several years.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. T. K. Lam, P. Daschner, N. Ishibe, et al., "Metabolic Dysregulation and Cancer Risk Program (MeDOC): A Transdisciplinary Approach to Obesity-Associated Cancers," *Journal of the National Cancer Institute* 10 (2024): 1555–1561, <https://doi.org/10.1093/jnci/djae134>.
2. C. Li, C. Lin, X. Cai, F. Lv, W. Yang, and L. Ji, "Weight Loss, Obesity Medication, and Risk of Obesity-Associated Cancer: A Meta-Analysis of Randomized Controlled Trials," *Obesity (Silver Spring, Md)* 34 (2025): 16–24, <https://doi.org/10.1002/oby.70054>.
3. F. Safizadeh, M. Mandic, M. Hoffmeister, and H. Brenner, "Reevaluating the Fraction of Cancer Attributable to Excess Weight: Overcoming the Hidden Impact of Prediagnostic Weight Loss," *European Journal of Epidemiology* 9 (2024): 991–1003, <https://doi.org/10.1007/s10654-024-01146-0>.
4. S. Shen, K. A. Brown, A. K. Green, and N. M. Iyengar, "Obesity and Cancer: A Translational Science Review," *JAMA* 15 (2026): 1341–1350, <https://doi.org/10.1001/jama.2026.1114>.
5. L. Crudele, E. Piccinin, and A. Moschetta, "Visceral Adiposity and Cancer: Role in Pathogenesis and Prognosis," *Nutrients* 13, no. 6 (2021): e2101, <https://doi.org/10.3390/nu13062101>.
6. E. Jacobo-Tovar, A. Medel-Sánchez, C. Durán-Castillo, and R. Guardado-Mendoza, "Insulin Resistance in Cancer Risk and Prognosis," *Seminars in Cancer Biology* 114 (2025): 73–87, <https://doi.org/10.1016/j.semcancer.2025.06.006>.

7. L. Sjöström, A. Gummesson, C. D. Sjöström, et al., "Effects of Bariatric Surgery on Cancer Incidence in Obese Patients in Sweden (Swedish Obese Subjects Study): A Prospective, Controlled Intervention Trial," *Lancet Oncology* 7, no. 9 (2009): 653–662, [https://doi.org/10.1016/s1470-2045\(09\)70159-7](https://doi.org/10.1016/s1470-2045(09)70159-7).
8. Y. W. Sagy, N. Ramot, E. Battat, et al., "Glucagon-Like Peptide-1 Receptor Agonists Compared With Bariatric Metabolic Surgery and the Risk of Obesity-Related Cancer: An Observational, Retrospective Cohort Study," *EClinicalMedicine* 83 (2025): 103213, <https://doi.org/10.1016/j.eclinm.2025.103213>.
9. D. P. Schauer, H. S. Feigelson, C. Koebnick, et al., "Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort," *Annals of Surgery* 1 (2019): 95–101, <https://doi.org/10.1097/sla.0000000000002525>.
10. R. B. Wilson, D. Lathigara, and D. Kaushal, "Systematic Review and Meta-Analysis of the Impact of Bariatric Surgery on Future Cancer Risk," *International Journal of Molecular Sciences* 7 (2023), <https://doi.org/10.3390/ijms24076192>.
11. A. Aminian, R. Wilson, A. Al-Kurd, et al., "Association of Bariatric Surgery With Cancer Risk and Mortality in Adults With Obesity," *JAMA* 24 (2022): 2423–2433, <https://doi.org/10.1001/jama.2022.9009>.
12. S. S. Raza, Z. Zakir, A. Hashmat, S. K. Awan, and G. Varrassi, "Medical Management of Obesity: A Comprehensive Review of Food and Drug Administration (FDA)-Approved and Investigational Therapies," *Cureus* 11 (2025): e96739, <https://doi.org/10.7759/cureus.96739>.
13. J. P. H. Wilding, R. L. Batterham, S. Calanna, et al., "Once-Weekly Semaglutide in Adults With Overweight or Obesity," *New England Journal of Medicine* 11 (2021): 989–1002, <https://doi.org/10.1056/NEJMoa2032183>.
14. A. M. Lincoff, K. Brown-Frandsen, H. M. Colhoun, et al., "Semaglutide and Cardiovascular Outcomes in Obesity Without Diabetes," *New England Journal of Medicine* 24 (2023): 2221–2232, <https://doi.org/10.1056/NEJMoa2307563>.
15. J. B. Buse, D. J. Drucker, K. L. Taylor, et al., "DURATION-1: Exenatide Once Weekly Produces Sustained Glycemic Control and Weight Loss Over 52 Weeks," *Diabetes Care* 6 (2010): 1255–1261, <https://doi.org/10.2337/dc09-1914>.
16. R. M. Bergenstal, C. Wysham, L. Macconell, et al., "Efficacy and Safety of Exenatide Once Weekly Versus Sitagliptin or Pioglitazone as an Adjunct to Metformin for Treatment of Type 2 Diabetes (DURATION-2): A Randomised Trial," *Lancet* 9739, no. 10 (2010): 431–439, [https://doi.org/10.1016/s0140-6736\(10\)60590-9](https://doi.org/10.1016/s0140-6736(10)60590-9).
17. R. A. DeFronzo, R. E. Ratner, J. Han, D. D. Kim, M. S. Fineman, and A. D. Baron, "Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type 2 Diabetes," *Diabetes Care* 5 (2005): 1092–1100, <https://doi.org/10.2337/diacare.28.5.1092>.
18. B. Gallwitz, J. Guzman, F. Dotta, et al., "Exenatide Twice Daily Versus Glimepiride for Prevention of Glycaemic Deterioration in Patients With Type 2 Diabetes With Metformin Failure (EUREXA): An Open-Label, Randomised Controlled Trial," *Lancet* 9833, no. 12 (2012): 2270–2278, [https://doi.org/10.1016/s0140-6736\(12\)60479-6](https://doi.org/10.1016/s0140-6736(12)60479-6).
19. H. F. Lofton, G. Maranga, R. Hold, et al., "A Randomized, Double-Blind, Placebo-Controlled Trial of Weight Loss Using Liraglutide 3.0 mg for Weight Recurrence After Roux-en-Y Gastric Bypass," *Surgery for Obesity and Related Diseases* 2 (2025): 135–145, <https://doi.org/10.1016/j.soard.2024.08.037>.
20. E. Sani, G. D. D. Prato, M. G. Zenti, A. Bordugo, M. Trombetta, and E. Bonora, "Effects of Semaglutide on Glycemic Control and Weight Loss in a Patient With Prader-Willi Syndrome: A Case Report," *Endocrine, Metabolic & Immune Disorders Drug Targets* 10 (2022): 1053–1057, <https://doi.org/10.2174/1871530322666220509225637>.
21. J. Rosenstock, J. P. Frias, H. W. Rodbard, et al., "Tirzepatide vs Insulin Lispro Added to Basal Insulin in Type 2 Diabetes: The SURPASS-6 Randomized Clinical Trial," *JAMA* 17 (2023): 1631–1640, <https://doi.org/10.1001/jama.2023.20294>.
22. P. Zeitler, R. J. Galindo, M. J. Davies, et al., "Early-Onset Type 2 Diabetes and Tirzepatide Treatment: A Post Hoc Analysis From the SURPASS Clinical Trial Program," *Diabetes Care* 6 (2024): 1056–1064, <https://doi.org/10.2337/dc23-2356>.
23. E. Bonora, J. P. Frias, F. J. Tinahones, et al., "Effect of Dulaglutide 3.0 and 4.5 mg on Weight in Patients With Type 2 Diabetes: Exploratory Analyses of AWARD-11," *Diabetes, Obesity & Metabolism* 10 (2021): 2242–2250, <https://doi.org/10.1111/dom.14465>.
24. J. P. Frias, E. Bonora, L. Nevárez Ruiz, et al., "Efficacy and Safety of Dulaglutide 3.0 and 4.5 mg in Patients Aged Younger Than 65 and 65 Years or Older: Post Hoc Analysis of the AWARD-11 Trial," *Diabetes, Obesity & Metabolism* 10 (2021): 2279–2288, <https://doi.org/10.1111/dom.14469>.
25. A. L. Birkenfeld, M. Bergman, and N. Stefan, "Tirzepatide for Obesity Treatment and Diabetes Prevention," *New England Journal of Medicine* 24 (2025): 2491–2492, <https://doi.org/10.1056/NEJMc2504728>.
26. L. J. Aronne, D. B. Horn, C. W. le Roux, et al., "Tirzepatide as Compared With Semaglutide for the Treatment of Obesity," *New England Journal of Medicine* 1 (2025): 26–36, <https://doi.org/10.1056/NEJMoa2416394>.
27. A. M. Jastreboff, C. W. le Roux, A. Stefanski, et al., "Tirzepatide for Obesity Treatment and Diabetes Prevention," *New England Journal of Medicine* 10 (2025): 958–971, <https://doi.org/10.1056/NEJMoa2410819>.
28. A. M. Jastreboff, L. J. Aronne, N. N. Ahmad, et al., "Tirzepatide Once Weekly for the Treatment of Obesity," *New England Journal of Medicine* 3 (2022): 205–216, <https://doi.org/10.1056/NEJMoa2206038>.
29. E. R. Hankosky, X. He, R. Malik, et al., "Tirzepatide 10 and 15 mg Versus Semaglutide 2.4 mg in People With Obesity or Overweight With Type 2 Diabetes: An Indirect Treatment Comparison," *Diabetes, Obesity & Metabolism* 7 (2025): 3757–3765, <https://doi.org/10.1111/dom.16401>.
30. D. H. Ryan, I. Lingvay, J. Deanfield, et al., "Long-Term Weight Loss Effects of Semaglutide in Obesity Without Diabetes in the SELECT Trial," *Nature Medicine* 7 (2024): 2049–2057, <https://doi.org/10.1038/s41591-024-02996-7>.
31. W. T. Garvey, R. L. Batterham, M. Bhatta, et al., "Two-Year Effects of Semaglutide in Adults With Overweight or Obesity: The STEP 5 Trial," *Nature Medicine* 10 (2022): 2083–2084, <https://doi.org/10.1038/s41591-022-02026-4>.
32. M. Kellerer, M. S. Kaltoft, J. Lawson, et al., "Effect of Once-Weekly Semaglutide Versus Thrice-Daily Insulin Aspart, Both as Add-On to Metformin and Optimized Insulin Glargine Treatment in Participants With Type 2 Diabetes (SUSTAIN 11): A Randomized, Open-Label, Multinational, Phase 3b Trial," *Diabetes, Obesity & Metabolism* 9 (2022): 1788–1799, <https://doi.org/10.1111/dom.14765>.
33. L. Sheng, M. Deng, X. Li, et al., "The Effect of Subcutaneous Lixisenatide on Weight Loss in Patients With Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis of Randomized Controlled Trials," *Diabetes Research and Clinical Practice* 210 (2024): 111617, <https://doi.org/10.1016/j.diabres.2024.111617>.
34. J. P. Patel, D. Hardaswani, J. Patel, et al., "Comparative Effectiveness of Semaglutide, Liraglutide, Orlistat, and Phentermine for Weight Loss in Obese Individuals: A Systematic Review," *Cureus* 3 (2025): e80321, <https://doi.org/10.7759/cureus.80321>.
35. J. Rosenstock, J. Frias, A. M. Jastreboff, et al., "Retatrutide, a GIP, GLP-1 and Glucagon Receptor Agonist, for People With Type 2 Diabetes: A Randomised, Double-Blind, Placebo and Active-Controlled, Parallel-Group, Phase 2 Trial Conducted in the USA," *Lancet* 6736, no. 23 (2023): 529–544, [https://doi.org/10.1016/s0140-6736\(23\)01053-x](https://doi.org/10.1016/s0140-6736(23)01053-x).

36. A. Abdrabou Abouelmagd, A. M. Abdelrehim, M. N. Bashir, et al., "Efficacy and Safety of Retatrutide, a Novel GLP-1, GIP, and Glucagon Receptor Agonist for Obesity Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *Proceedings (Baylor University Medical Center)* 3 (2025): 291–303, <https://doi.org/10.1080/08998280.2025.2456441>.
37. L. Fu, R. Ding, G. Xu, J. Hu, and P. Yang, "Amycretin in Obesity: Mechanisms, Clinical Efficacy, and Future Perspectives," *Metabolism* 179 (2026): 156594, <https://doi.org/10.1016/j.metabol.2026.156594>.
38. A. F. Gadelmawla, N. Hammad, K. Atta, et al., "CagriSema Versus Semaglutide Monotherapy or Placebo for Obesity: A Systematic Review and Meta-Analysis of Randomized Controlled Trials With GRADE Assessment," *American Journal of Cardiology* 267 (2026): 28–37, <https://doi.org/10.1016/j.amjcard.2026.02.030>.
39. S. Wharton, L. J. Aronne, A. Stefanski, et al., "Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment," *New England Journal of Medicine* 18 (2025): 1796–1806, <https://doi.org/10.1056/NEJMoa2511774>.
40. D. B. Horn, D. H. Ryan, S. G. Kis, et al., "Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, for the Treatment of Obesity in People With Type 2 Diabetes (ATTAIN-2): A Phase 3, Double-Blind, Randomised, Multicentre, Placebo-Controlled Trial," *Lancet* 6736, no. 25 (2026): 2927–2944, [https://doi.org/10.1016/s0140-6736\(25\)02165-8](https://doi.org/10.1016/s0140-6736(25)02165-8).
41. J. Rosenstock, S. Hsia, L. Nevarez Ruiz, et al., "Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes," *New England Journal of Medicine* 11 (2025): 1065–1076, <https://doi.org/10.1056/NEJMoa2505669>.
42. E. Harris, "Triple-Hormone Combination Retatrutide Induces 24% Body Weight Loss," *JAMA* 4 (2023): 306, <https://doi.org/10.1001/jama.2023.12055>.
43. K. Dahl, S. Toubro, S. Dey, et al., "Amycretin, a Novel, Unimolecular GLP-1 and Amylin Receptor Agonist Administered Subcutaneously: Results From a Phase 1b/2a Randomised Controlled Study," *Lancet* 6736, no. 25 (2025): 149–162, [https://doi.org/10.1016/s0140-6736\(25\)01185-7](https://doi.org/10.1016/s0140-6736(25)01185-7).
44. D. C. W. Lau, L. Erichsen, A. M. Francisco, et al., "Once-Weekly Cagrilintide for Weight Management in People With Overweight and Obesity: A Multicentre, Randomised, Double-Blind, Placebo-Controlled and Active-Controlled, Dose-Finding Phase 2 Trial," *Lancet* 398, no. 10317 (2021): 2160–2172, [https://doi.org/10.1016/s0140-6736\(21\)01751-7](https://doi.org/10.1016/s0140-6736(21)01751-7).
45. A. F. Hernandez, J. B. Green, S. Janmohamed, et al., "Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes): A Double-Blind, Randomised Placebo-Controlled Trial," *Lancet* 392, no. 10157 (2018): 1519–1529, [https://doi.org/10.1016/s0140-6736\(18\)32261-x](https://doi.org/10.1016/s0140-6736(18)32261-x).
46. S. Ansari, B. Khoo, and T. Tan, "Targeting the Incretin System in Obesity and Type 2 Diabetes Mellitus," *Nature Reviews. Endocrinology* 8 (2024): 447–459, <https://doi.org/10.1038/s41574-024-00979-9>.
47. E. Fontvieille, V. Viallon, M. Recalde, et al., "Body Mass Index and Cancer Risk Among Adults With and Without Cardiometabolic Diseases: Evidence From the EPIC and UK Biobank Prospective Cohort Studies," *BMC Medicine* 1 (2023): 418, <https://doi.org/10.1186/s12916-023-03114-z>.
48. N. M. Iyengar, A. Gucalp, A. J. Dannenberg, and C. A. Hudis, "Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation," *Journal of Clinical Oncology* 35 (2016): 4270–4276, <https://doi.org/10.1200/jco.2016.67.4283>.
49. N. Ouchi, J. L. Parker, J. J. Lugus, and K. Walsh, "Adipokines in Inflammation and Metabolic Disease," *Nature Reviews. Immunology* 2 (2011): 85–97, <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=21252989>, <http://www.tdnet.com/uscm/Resolver?SID=OVID:Ovid+MEDLINE%28R%29+%3C2007+to+September+Week+2+2011%3E&genre=article&id=pmid:21252989&id=doi:&issn=1474-1733&volume=11&issue=2&spage=85&pages=85-97&date=2011&title=Nature+Reviews.+Immunology&atitle=Adipokines+in+inflammation+and+metabolic+disease.&aualast=Ouchi&pid=%3Cauthor%3EOuchi+N%3C%2FAuthor%3E%3CAN%3E21252989%3C%2FAN%3E>.
50. M. Pollak, "Insulin and Insulin-Like Growth Factor Signalling in Neoplasia," *Nature Reviews. Cancer* 12 (2008): 915–928, <https://doi.org/10.1038/nrc2536>.
51. E. Giovannucci, D. M. Harlan, M. C. Archer, et al., "Diabetes and Cancer: A Consensus Report," *Diabetes Care* 7 (2010): 1674–1685, <https://doi.org/10.2337/dc10-0666>.
52. E. J. Gallagher and D. LeRoith, "Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality," *Physiological Reviews* 3 (2015): 727–748, <https://doi.org/10.1152/physrev.00030.2014>.
53. S. Ling, K. Brown, J. K. Miksza, et al., "Association of Type 2 Diabetes With Cancer: A Meta-Analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People," *Diabetes Care* 9 (2020): 2313–2322, <https://doi.org/10.2337/dc20-0204>.
54. T. Hropot, R. Herman, A. Janez, L. Lezaic, and M. Jensterle, "Brown Adipose Tissue: A New Potential Target for Glucagon-Like Peptide 1 Receptor Agonists in the Treatment of Obesity," *International Journal of Molecular Sciences* 10 (2023), <https://doi.org/10.3390/ijms24108592>.
55. K. I. Avgerinos, N. Spyrou, C. S. Mantzoros, and M. Dalamaga, "Obesity and Cancer Risk: Emerging Biological Mechanisms and Perspectives," *Metabolism* 92 (2019): 121–135, <https://doi.org/10.1016/j.metabol.2018.11.001>.
56. Y. Lu, Y. C. Zhao, K. Liu, et al., "A Validated Estimate of Visceral Adipose Tissue Volume in Relation to Cancer Risk," *Journal of the National Cancer Institute* 12 (2024): 1942–1951, <https://doi.org/10.1093/jnci/djae193>.
57. S. Agrawal, M. D. R. Klarqvist, N. Diamant, et al., "BMI-Adjusted Adipose Tissue Volumes Exhibit Depot-Specific and Divergent Associations With Cardiometabolic Diseases," *Nature Communications* 1 (2023): 266, <https://doi.org/10.1038/s41467-022-35704-5>.
58. R. A. DeFronzo and D. Tripathy, "Skeletal Muscle Insulin Resistance Is the Primary Defect in Type 2 Diabetes," *Diabetes Care Suppl* 2 (2009): S157–S163, <https://doi.org/10.2337/dc09-S302>.
59. B. K. Pedersen and M. A. Febbraio, "Muscle as an Endocrine Organ: Focus on Muscle-Derived Interleukin-6," *Physiological Reviews* 4 (2008): 1379–1406, <https://doi.org/10.1152/physrev.90100.2007>.
60. C. E. Orsso, M. Montes-Ibarra, M. Findlay, et al., "Mapping Ongoing Nutrition Intervention Trials in Muscle, Sarcopenia, and Cachexia: A Scoping Review of Future Research," *Journal of Cachexia, Sarcopenia and Muscle* 3 (2022): 1442–1459, <https://doi.org/10.1002/jcsm.12954>.
61. L. Chen, J. Ming, T. Chen, et al., "Association Between Dietary Inflammatory Index Score and Muscle Mass and Strength in Older Adults: A Study From National Health and Nutrition Examination Survey (NHANES) 1999–2002," *European Journal of Nutrition* 8 (2022): 4077–4089, <https://doi.org/10.1007/s00394-022-02941-9>.
62. J. Bauer, J. E. Morley, A. Schols, et al., "Sarcopenia: A Time for Action. An SCWD Position Paper," *Journal of Cachexia, Sarcopenia and Muscle* 5 (2019): 956–961, <https://doi.org/10.1002/jcsm.12483>.
63. P. Srikanthan and A. S. Karlamangla, "Relative Muscle Mass Is Inversely Associated With Insulin Resistance and Prediabetes. Findings From the Third National Health and Nutrition Examination Survey," *Journal of Clinical Endocrinology and Metabolism* 9 (2011): 2898–2903, <https://doi.org/10.1210/jc.2011-0435>.
64. K. Silay and H. Selvi Ozturun, "Sarcopenic Obesity Is Linked to Worse Clinical Outcomes Than Sarcopenia or Obesity Alone in Hospitalized Older Adults," *BMC Geriatrics* 1 (2025): 443, <https://doi.org/10.1186/s12877-025-06105-2>.

65. C. Liu, T. Liu, L. Deng, et al., "Sarcopenic Obesity and Outcomes for Patients With Cancer," *JAMA Network Open* 6 (2024): e2417115, <https://doi.org/10.1001/jamanetworkopen.2024.17115>.
66. C. Chrysoshoou, M. Kouvari, G. Lazaros, et al., "Predicted Skeletal Muscle Mass and 4-Year Cardiovascular Disease Incidence in Middle-Aged and Elderly Participants of IKARIA Prospective Epidemiological Study: The Mediating Effect of Sex and Cardiometabolic Factors," *Nutrients* 11 (2020), <https://doi.org/10.3390/nu12113293>.
67. A. Kohlgruber and L. Lynch, "Adipose Tissue Inflammation in the Pathogenesis of Type 2 Diabetes," *Current Diabetes Reports* 11 (2015): 92, <https://doi.org/10.1007/s11892-015-0670-x>.
68. J. C. McNelis and J. M. Olefsky, "Macrophages, Immunity, and Metabolic Disease," *Immunity* 1 (2014): 36–48, <https://doi.org/10.1016/j.immuni.2014.05.010>.
69. G. C. Kabat, M. Y. Kim, M. Stefanick, et al., "Metabolic Obesity Phenotypes and Risk of Colorectal Cancer in Postmenopausal Women," *International Journal of Cancer* 3 (2018): 543–551, <https://doi.org/10.1002/ijc.31345>.
70. B. A. Stoll, "Western Nutrition and the Insulin Resistance Syndrome: A Link to Breast Cancer," *European Journal of Clinical Nutrition* 2 (1999): 83–87, <https://doi.org/10.1038/sj.ejcn.1600700>.
71. E. E. Calle and R. Kaaks, "Overweight, Obesity and Cancer: Epidemiological Evidence and Proposed Mechanisms," *Nature Reviews. Cancer* 8 (2004): 579–591, <https://doi.org/10.1038/nrc1408>.
72. S. C. Moore, I. M. Lee, E. Weiderpass, et al., "Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults," *JAMA Internal Medicine* 6 (2016): 816–825, <https://doi.org/10.1001/jamainternmed.2016.1548>.
73. P. Filis, C. K. Papagiannopoulos, G. Markozannes, et al., "Associations of Sarcopenia, Sarcopenia Components and Sarcopenic Obesity With Cancer Incidence: A Prospective Cohort Study of 414,094 Participants in UK Biobank," *International Journal of Cancer* 7 (2025): 1316–1332, <https://doi.org/10.1002/ijc.35480>.
74. J. Luo, M. Hendryx, J. E. Manson, et al., "Intentional Weight Loss and Obesity-Related Cancer Risk," *JNCI Cancer Spectrum* 4 (2019): pkz054, <https://doi.org/10.1093/jncics/pkz054>.
75. L. R. Teras, A. V. Patel, M. Wang, et al., "Sustained Weight Loss and Risk of Breast Cancer in Women 50 Years and Older: A Pooled Analysis of Prospective Data," *Journal of the National Cancer Institute* 9 (2020): 929–937, <https://doi.org/10.1093/jnci/djz226>.
76. H. C. Yeh, J. P. Bantle, M. Cassidy-Begay, et al., "Intensive Weight Loss Intervention and Cancer Risk in Adults With Type 2 Diabetes: Analysis of the Look AHEAD Randomized Clinical Trial," *Obesity (Silver Spring, Md)* 9 (2020): 1678–1686, <https://doi.org/10.1002/oby.22936>.
77. N. M. Iyengar, C. A. Hudis, and A. J. Dannenberg, "Obesity and Cancer: Local and Systemic Mechanisms," *Annual Review of Medicine* 66 (2015): 297–309, <https://doi.org/10.1146/annurev-med-050913-022228>.
78. P. W. Lim, C. H. Stucky, N. Wasif, et al., "Bariatric Surgery and Longitudinal Cancer Risk: A Review," *JAMA Surgery* 3 (2024): 331–338, <https://doi.org/10.1001/jamasurg.2023.5809>.
79. F. Lunger, P. Aeschbacher, P. C. Nett, and G. Peros, "The Impact of Bariatric and Metabolic Surgery on Cancer Development," *Frontiers in Surgery* 9 (2022): 918272, <https://doi.org/10.3389/fsurg.2022.918272>.
80. Y. A. Kononova, T. P. Tuchina, and A. Y. Babenko, "Brown and Beige Adipose Tissue: One or Different Targets for Treatment of Obesity and Obesity-Related Metabolic Disorders?," *International Journal of Molecular Sciences* 24 (2024), <https://doi.org/10.3390/ijms252413295>.
81. M. M. Ibrahim, "Subcutaneous and Visceral Adipose Tissue: Structural and Functional Differences," *Obesity Reviews* 1 (2010): 11–18, <https://doi.org/10.1111/j.1467-789X.2009.00623.x>.
82. J. P. Després, "Body Fat Distribution and Risk of Cardiovascular Disease: An Update," *Circulation* 10 (2012): 1301–1313, <https://doi.org/10.1161/circulationaha.111.067264>.
83. A. M. Cypess and C. R. Kahn, "Brown Fat as a Therapy for Obesity and Diabetes," *Current Opinion in Endocrinology, Diabetes, and Obesity* 2 (2010): 143–149, <https://doi.org/10.1097/MED.0b013e328337a81f>.
84. E. M. Weinheimer, L. P. Sands, and W. W. Campbell, "A Systematic Review of the Separate and Combined Effects of Energy Restriction and Exercise on Fat-Free Mass in Middle-Aged and Older Adults: Implications for Sarcopenic Obesity," *Nutrition Reviews* 7 (2010): 375–388, <https://doi.org/10.1111/j.1753-4887.2010.00298.x>.
85. D. T. Villareal, L. Aguirre, A. B. Gurney, et al., "Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults," *New England Journal of Medicine* 20 (2017): 1943–1955, <https://doi.org/10.1056/NEJMoa1616338>.
86. D. J. Drucker, "Mechanisms of Action and Therapeutic Application of Glucagon-Like Peptide-1," *Cell Metabolism* 4 (2018): 740–756, <https://doi.org/10.1016/j.cmet.2018.03.001>.
87. M. A. Nauck and J. J. Meier, "Management of Endocrine Disease: Are All GLP-1 Agonists Equal in the Treatment of Type 2 Diabetes?," *European Journal of Endocrinology* 6 (2019): R211–R0566, <https://doi.org/10.1530/eje-19-0566>.
88. A. E. Henney, M. Heague, D. R. Riley, et al., "Synergistic Associations of Metformin and GLP-1 Receptor Agonist Use With Adiposity-Related Cancer Incidence in People Living With Type 2 Diabetes," *Diabetes, Obesity & Metabolism* 2 (2026): 946–959, <https://doi.org/10.1111/dom.70267>.
89. D. Rubino, N. Abrahamsson, M. Davies, et al., "Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial," *JAMA* 14 (2021): 1414–1425, <https://doi.org/10.1001/jama.2021.3224>.
90. S. S. Wilbon and M. G. Kolonin, "GLP1 Receptor Agonists-Effects Beyond Obesity and Diabetes," *Cells* 1 (2023), <https://doi.org/10.3390/cells13010065>.
91. N. Sattar and D. K. McGuire, "Pathways to Cardiorenal Complications in Type 2 Diabetes Mellitus: A Need to Rethink," *Circulation* 1 (2018): 7–9, <https://doi.org/10.1161/circulationaha.118.035083>.
92. M. N. Kosiborod, M. C. Petrie, B. A. Borlaug, et al., "Semaglutide in Patients With Obesity-Related Heart Failure and Type 2 Diabetes," *New England Journal of Medicine* 15 (2024): 1394–1407, <https://doi.org/10.1056/NEJMoa2313917>.
93. S. H. Alharbi, "Anti-Inflammatory Role of Glucagon-Like Peptide 1 Receptor Agonists and Its Clinical Implications," *Therapeutic Advances in Endocrinology and Metabolism* 15 (2024): 20420188231222367, <https://doi.org/10.1177/20420188231222367>.
94. I. Stanisavljevic, S. Pavlovic, B. Simovic Markovic, et al., "Semaglutide Decelerates the Growth and Progression of Breast Cancer by Enhancing the Acquired Antitumor Immunity," *Biomedicine & Pharmacotherapy* 181 (2024): 117668, <https://doi.org/10.1016/j.biopha.2024.117668>.
95. R. Trakoonsenathong, W. Kunprom, C. Aphivatanasiri, et al., "Liraglutide Exhibits Potential Anti-Tumor Effects on the Progression of Intrahepatic Cholangiocarcinoma, In Vitro and In Vivo," *Scientific Reports* 1 (2024): 13726, <https://doi.org/10.1038/s41598-024-64774-2>.
96. E. Valencia-Rincón, R. Rai, V. Chandra, and E. A. Wellberg, "GLP-1 Receptor Agonists and Cancer: Current Clinical Evidence and Translational Opportunities for Preclinical Research," *Journal of Clinical Investigation* 21 (2025), <https://doi.org/10.1172/jci194743>.
97. A. H. Shilleh, K. Vilorio, J. Broichhagen, J. E. Campbell, and D. J. Hodson, "GLP1R and GIPR Expression and Signaling in Pancreatic Alpha Cells, Beta Cells and Delta Cells," *Peptides* 175 (2024): 171179, <https://doi.org/10.1016/j.peptides.2024.171179>.

98. C. Pyke, R. S. Heller, R. K. Kirk, et al., "GLP-1 Receptor Localization in Monkey and Human Tissue: Novel Distribution Revealed With Extensively Validated Monoclonal Antibody," *Endocrinology* 4 (2014): 1280–1290, <https://doi.org/10.1210/en.2013-1934>.
99. K. V. Grunddal, E. P. Jensen, C. Ørskov, et al., "Expression Profile of the GLP-1 Receptor in the Gastrointestinal Tract and Pancreas in Adult Female Mice," *Endocrinology* 1 (2022), <https://doi.org/10.1210/endo/bqab216>.
100. P. Richards, H. E. Parker, A. E. Adriaenssens, et al., "Identification and Characterization of GLP-1 Receptor-Expressing Cells Using a New Transgenic Mouse Model," *Diabetes* 4 (2014): 1224–1233, <https://doi.org/10.2337/db13-1440>.
101. L. L. Baggio, B. Yusta, E. E. Mulvihill, et al., "GLP-1 Receptor Expression Within the Human Heart," *Endocrinology* 4 (2018): 1570–1584, <https://doi.org/10.1210/en.2018-00004>.
102. Z. Zheng, Y. Zong, Y. Ma, et al., "Glucagon-Like Peptide-1 Receptor: Mechanisms and Advances in Therapy," *Signal Transduction and Targeted Therapy* 1 (2024): 234, <https://doi.org/10.1038/s41392-024-01931-z>.
103. G. Iacobellis, "Letter to the Editor: "GLP-1 Receptor Expression Within the Human Heart,"" *Endocrinology* 5 (2018): 1964–1965, <https://doi.org/10.1210/en.2018-00196>.
104. A. Lin, Y. Ding, Z. Li, et al., "Glucagon-Like Peptide 1 Receptor Agonists and Cancer Risk: Advancing Precision Medicine Through Mechanistic Understanding and Clinical Evidence," *Biomarker Research* 1 (2025): 50, <https://doi.org/10.1186/s40364-025-00765-3>.
105. J. A. Koehler, L. L. Baggio, B. Yusta, et al., "GLP-1R Agonists Promote Normal and Neoplastic Intestinal Growth Through Mechanisms Requiring Fgf7," *Cell Metabolism* 3 (2015): 379–391, <https://doi.org/10.1016/j.cmet.2015.02.005>.
106. R. M. Badi, E. F. Khaleel, M. H. El-Bidawy, H. H. Satti, and D. G. Mostafa, "Exendin-4 Induces Cytotoxic Autophagy in Two Ovarian Cancer Cell Lines Through Inhibition of Mtorc1 Mediated by Activation of AMPK and Suppression of Akt," *Folia Biologica (Praha)* 5-6 (2020): 186–203, <https://doi.org/10.14712/fb2020066050186>.
107. G. Tong, T. Peng, Y. Chen, et al., "Effects of GLP-1 Receptor Agonists on Biological Behavior of Colorectal Cancer Cells by Regulating PI3K/AKT/mTOR Signaling Pathway," *Frontiers in Pharmacology* 13 (2022): 901559, <https://doi.org/10.3389/fphar.2022.901559>.
108. L. Ji, X. He, X. Min, et al., "Glucagon-Like Peptide-1 Receptor Agonists in Neoplastic Diseases," *Frontiers in Endocrinology* 15 (2024): e1465881, <https://doi.org/10.3389/fendo.2024.1465881>.
109. S. Wan and H. Sun, "Glucagon-Like Peptide-1 Modulates RAW264.7 Macrophage Polarization by Interfering With the JNK/STAT3 Signaling Pathway," *Experimental and Therapeutic Medicine* 5 (2019): 3573–3579, <https://doi.org/10.3892/etm.2019.7347>.
110. C. Frey, "GLP-1 Receptor Agonists and Immune Checkpoint Inhibitor Therapy: A Narrative Review on Mechanistic and Clinical Evidence," *Future Oncology* 10 (2026): 1221–1231, <https://doi.org/10.1080/14796694.2026.2654735>.
111. S. S. Ibrahim, R. S. Ibrahim, B. Arabi, A. Brockmueller, M. Shakibaei, and D. Büsnelberg, "The Effect of GLP-1R Agonists on the Medical Triad of Obesity, Diabetes, and Cancer," *Cancer Metastasis Reviews* 4 (2024): 1297–1314, <https://doi.org/10.1007/s10555-024-10192-9>.
112. M. A. Nauck, T. J. Jensen, C. Rosenkilde, S. Calanna, and J. B. Buse, "Neoplasms Reported With Liraglutide or Placebo in People With Type 2 Diabetes: Results From the LEADER Randomized Trial," *Diabetes Care* 8 (2018): 1663–1671, <https://doi.org/10.2337/dc17-1825>.
113. S. Levy, A. Attia, R. M. Elshazli, et al., "Differential Effects of GLP-1 Receptor Agonists on Cancer Risk in Obesity: A Nationwide Analysis of 1.1 Million Patients," *Cancers* 1 (2024), <https://doi.org/10.3390/cancers17010078>.
114. L. Wang, R. Xu, D. C. Kaelber, and N. A. Berger, "Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes," *JAMA Network Open* 7 (2024): e2421305, <https://doi.org/10.1001/jamanetworkopen.2024.21305>.
115. S. M. Baxter, L. C. Lund, J. H. Andersen, et al., "Glucagon-Like Peptide 1 Receptor Agonists and Risk of Thyroid Cancer: An International Multisite Cohort Study," *Thyroid* 1 (2025): 69–78, <https://doi.org/10.1089/thy.2024.0387>.
116. B. Pasternak, V. Wintzell, A. Hviid, et al., "Glucagon-Like Peptide 1 Receptor Agonist Use and Risk of Thyroid Cancer: Scandinavian Cohort Study," *BMJ* 385 (2024): e078225, <https://doi.org/10.1136/bmj-2023-078225>.
117. A. Ko, Y. C. Chang, F. Bahar, et al., "Risk for Cancer With Glucagon-Like Peptide-1 Receptor Agonists and Dual Agonists: A Systematic Review and Meta-Analysis," *Annals of Internal Medicine* 2 (2026): 216–229, <https://doi.org/10.7326/annals-25-02237>.
118. H. Tang, B. Zhang, Y. Lu, et al., "Assessing the Benefit-Risk Profile of Newer Glucose-Lowering Drugs: A Systematic Review and Network Meta-Analysis of Randomized Outcome Trials," *Diabetes, Obesity & Metabolism* 3 (2025): 1444–1455, <https://doi.org/10.1111/dom.16147>.
119. G. A. Silverii, M. Monami, M. Gallo, et al., "Glucagon-Like Peptide-1 Receptor Agonists and Risk of Thyroid Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *Diabetes, Obesity & Metabolism* 3 (2024): 891–900, <https://doi.org/10.1111/dom.15382>.
120. W. Hu, R. Song, R. Cheng, et al., "Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: A Meta-Analysis of Randomized Controlled Trials," *Front Endocrinol (Lausanne)*. (2022): 927859, <https://doi.org/10.3389/fendo.2022.927859>.
121. C. Cao, S. Yang, and Z. Zhou, "GLP-1 Receptor Agonists and Risk of Cancer in Type 2 Diabetes: An Updated Meta-Analysis of Randomized Controlled Trials," *Endocrine* 2 (2019): 157–165, <https://doi.org/10.1007/s12020-019-02055-z>.
122. N. Sharma, M. N. Khatib, A. K. Balaraman, et al., "Effect of GLP-1 Receptor Agonists on Prostate Cancer Risk Reduction: A Systematic Review and Meta-Analysis," *International Urology and Nephrology* 4 (2025): 1039–1049, <https://doi.org/10.1007/s11255-024-04266-4>.
123. Y. Lin, G. Xu, L. Li, J. Xiang, and L. Zhai, "Incretin-Based Drugs Decrease the Incidence of Prostate Cancer in Type 2 Diabetics: A Pooling-Up Analysis," *Medicine (Baltimore)* 20 (2024): e38018, <https://doi.org/10.1097/md.00000000000038018>.
124. H. Cui, Y. Wang, S. Yang, et al., "Antidiabetic Medications and the Risk of Prostate Cancer in Patients With Diabetes Mellitus: A Systematic Review and Meta-Analysis," *Pharmacological Research* 177 (2022): 106094, <https://doi.org/10.1016/j.phrs.2022.106094>.
125. G. Bushi, S. Gaidhane, S. Ballal, et al., "Association Between GLP1 RAs Use and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis," *Health Science Reports* 2 (2025): e70490, <https://doi.org/10.1002/hsr.2.70490>.
126. Y. Sun, Y. Liu, Y. Dian, et al., "Association of Glucagon-Like Peptide-1 Receptor Agonists With Risk of Cancers—Evidence From a Drug Target Mendelian Randomization and Clinical Trials," *International Journal of Surgery* 8 (2024): 4688–4694, <https://doi.org/10.1097/js.0000000000001514>.
127. G. Figlioli, D. Piovani, S. Peppas, et al., "Glucagon-Like Peptide-1 Receptor Agonists and Risk of Gastrointestinal Cancers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *Pharmacological Research* 208 (2024): 107401, <https://doi.org/10.1016/j.phrs.2024.107401>.
128. Q. Wu, Y. Zeng, Y. Liu, et al., "A Meta-Analysis on the Risk of Esophageal Cancer in Type 2 Diabetes Patients Treated With GLP-1 Receptor Agonists," *Front Endocrinol (Lausanne)* 16 (2025): 1532587, <https://doi.org/10.3389/fendo.2025.1532587>.

129. K. Hidayat, Y. Y. Zhou, H. Z. Du, et al., "A Systematic Review and Meta-Analysis of Observational Studies of the Association Between the Use of Incretin-Based Therapies and the Risk of Pancreatic Cancer," *Pharmacoeconomics and Drug Safety* 2 (2023): 107–125, <https://doi.org/10.1002/pds.5550>.
130. A. Pasta, A. Facciorusso, M. C. Plaz Torres, E. G. Giannini, and R. Sacco, "Effects of Glucagon-Like PEPTIDE-1 Receptor Agonists on Incidence of Hepatocellular Carcinoma and Liver Decompensation in Patients With Diabetes: A Systematic Review and META-Analysis," *European Journal of Clinical Investigation* 6 (2025): e70000, <https://doi.org/10.1111/eci.70000>.
131. M. Shabil, M. N. Khatib, S. Ballal, et al., "Risk of Hepatocellular Carcinoma With Glucagon-Like Peptide-1 Receptor Agonist Treatment in Patients: A Systematic Review and Meta-Analysis," *BMC Endocrine Disorders* 1 (2024): 246, <https://doi.org/10.1186/s12902-024-01775-2>.
132. G. F. Piccoli, L. A. Mesquita, C. Stein, et al., "Do GLP-1 Receptor Agonists Increase the Risk of Breast Cancer? A Systematic Review and Meta-Analysis," *Journal of Clinical Endocrinology and Metabolism* 3 (2021): 912–921, <https://doi.org/10.1210/clinem/dgaa891>.
133. C. Lin, X. Cai, W. Yang, et al., "Glycemic Control and the Incidence of Neoplasm in Patients With Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials," *Endocrine* 2 (2020): 232–242, <https://doi.org/10.1007/s12020-020-02376-4>.
134. H. Dai, Y. Li, Y. A. Lee, et al., "GLP-1 Receptor Agonists and Cancer Risk in Adults With Obesity," *JAMA Oncology* 10 (2025): 1186–1193, <https://doi.org/10.1001/jamaoncol.2025.2681>.
135. C. M. Prado, S. M. Phillips, M. C. Gonzalez, and S. B. Heymsfield, "Muscle Matters: The Effects of Medically Induced Weight Loss on Skeletal Muscle," *Lancet Diabetes & Endocrinology* 11, no. 24 (2024): 785–787, [https://doi.org/10.1016/s2213-8587\(24\)00272-9](https://doi.org/10.1016/s2213-8587(24)00272-9).
136. J. P. H. Wilding, R. L. Batterham, S. Calanna, et al., "Impact of Semaglutide on Body Composition in Adults With Overweight or Obesity: Exploratory Analysis of the STEP 1 Study," *Journal of the Endocrine Society Supplement_1* (2021): A16–A17, <https://doi.org/10.1210/jendso/bvab048.030>.
137. I. J. Neeland, J. Linge, and A. L. Birkenfeld, "Changes in Lean Body Mass With Glucagon-Like Peptide-1-Based Therapies and Mitigation Strategies," *Diabetes, Obesity & Metabolism* 26 (2024): 16–27, <https://doi.org/10.1111/dom.15728>.
138. A. J. Sinclair and A. H. Abdelhafiz, "Metabolic Impact of Frailty Changes Diabetes Trajectory," *Metabolites* 2 (2023), <https://doi.org/10.3390/metabo13020295>.
139. M. J. Müller, M. Lagerpusch, J. Enderle, B. Schautz, M. Heller, and A. Bosy-Westphal, "Beyond the Body Mass Index: Tracking Body Composition in the Pathogenesis of Obesity and the Metabolic Syndrome," *Obesity Reviews* 13 (2012): 6–13, <https://doi.org/10.1111/j.1467-789X.2012.01033.x>.
140. Y. Liu, B. Ruan, H. Jiang, et al., "The Weight-Loss Effect of GLP-1RAs Glucagon-Like Peptide-1 Receptor Agonists in Non-Diabetic Individuals With Overweight or Obesity: A Systematic Review With Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials," *American Journal of Clinical Nutrition* 3 (2023): 614–626, <https://doi.org/10.1016/j.ajcnut.2023.04.017>.
141. J. P. H. Wilding, R. L. Batterham, M. Davies, et al., "Weight Regain and Cardiometabolic Effects After Withdrawal of Semaglutide: The STEP 1 Trial Extension," *Diabetes, Obesity & Metabolism* 8 (2022): 1553–1564, <https://doi.org/10.1111/dom.14725>.
142. L. J. Aronne, N. Sattar, D. B. Horn, et al., "Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial," *JAMA* 1 (2024): 38–48, <https://doi.org/10.1001/jama.2023.24945>.
143. S. B. K. Jensen, M. B. Blond, R. M. Sandsdal, et al., "Healthy Weight Loss Maintenance With Exercise, GLP-1 Receptor Agonist, or Both Combined Followed by One Year Without Treatment: A Post-Treatment Analysis of a Randomised Placebo-Controlled Trial," *EClinicalMedicine* 69 (2024): 102475, <https://doi.org/10.1016/j.eclim.2024.102475>.
144. P. J. Rodriguez, V. Zhang, S. Gratzl, et al., "Discontinuation and Reinitiation of Dual-Labeled GLP-1 Receptor Agonists Among US Adults With Overweight or Obesity," *JAMA Network Open* 1 (2025): e2457349, <https://doi.org/10.1001/jamanetworkopen.2024.57349>.
145. R. O'Connor, "Navigating the Benefits and Harms of GLP-1 and GLP-1/GIP Agonists in Obesity," *Drug and Therapeutics Bulletin* 2 (2026): 19–23, <https://doi.org/10.1136/dtb.2025.000039>.
146. P. A. Hubert, C. Coleman, G. J. Grosicki, et al., "Mind the Plateau: A Mathematical Modeling Analysis of Long-Term GLP-1 Receptor Agonist Treatment," *Journal of the Academy of Nutrition and Dietetics* 126 (2026): 156366, <https://doi.org/10.1016/j.jand.2026.156366>.
147. X. Zhang, J. Rhoades, B. J. Caan, et al., "Intentional Weight Loss, Weight Cycling, and Endometrial Cancer Risk: A Systematic Review and Meta-Analysis," *International Journal of Gynecological Cancer* 9 (2019): 1361–1371, <https://doi.org/10.1136/ijgc-2019-000728>.
148. V. L. Stevens, J. Priest, J. Wilkerson, A. A. D'Aloisio, and D. P. Sandler, "Weight Cycling and Cancer Risk in the Sister Study," *American Journal of Epidemiology* (2025), <https://doi.org/10.1093/aje/kwaf191>.
149. S. J. Marathe, E. W. Grey, M. S. Bohm, et al., "Incretin Triple Agonist Retatrutide (LY3437943) Alleviates Obesity-Associated Cancer Progression," *NPJ Metabolic Health and Disease* 1 (2025): 10, <https://doi.org/10.1038/s44324-025-00054-5>.
150. T. A. Wadden, A. M. Chao, M. Moore, et al., "The Role of Lifestyle Modification With Second-Generation Anti-Obesity Medications: Comparisons, Questions, and Clinical Opportunities," *Current Obesity Reports* 4 (2023): 453–473, <https://doi.org/10.1007/s13679-023-00534-z>.
151. T. P. Wycherley, L. J. Moran, P. M. Clifton, M. Noakes, and G. D. Brinkworth, "Effects of Energy-Restricted High-Protein, Low-Fat Compared With Standard-Protein, Low-Fat Diets: A Meta-Analysis of Randomized Controlled Trials," *American Journal of Clinical Nutrition* 6 (2012): 1281–1298, <https://doi.org/10.3945/ajcn.112.044321>.
152. A. M. Verreijen, M. F. Engberink, R. G. Memelink, S. E. van der Plas, M. Visser, and P. J. Weijs, "Effect of a High Protein Diet and/or Resistance Exercise on the Preservation of Fat Free Mass During Weight Loss in Overweight and Obese Older Adults: A Randomized Controlled Trial," *Nutrition Journal* 1 (2017): 10, <https://doi.org/10.1186/s12937-017-0229-6>.
153. G. M. Tinsley and S. Nadolsky, "Preservation of Lean Soft Tissue During Weight Loss Induced by GLP-1 and GLP-1/GIP Receptor Agonists: A Case Series," *SAGE Open Medical Case Reports* 13 (2025): 2050313x251388724, <https://doi.org/10.1177/2050313x251388724>.
154. D. Mozaffarian, M. Agarwal, M. Agarwal, et al., "Nutritional Priorities to Support GLP-1 Therapy for Obesity: A Joint Advisory From the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and the Obesity Society," *American Journal of Clinical Nutrition* 1 (2025): 344–367, <https://doi.org/10.1016/j.ajcnut.2025.04.023>.
155. N. Shivappa, S. E. Steck, T. G. Hurley, J. R. Hussey, and J. R. Hebert, "Designing and Developing a Literature-Derived, Population-Based Dietary Inflammatory Index," *Public Health Nutrition* 8 (2014): 1689–1696, <https://doi.org/10.1017/s1368980013002115>.
156. W. Marx, N. Veronese, J. T. Kelly, et al., "The Dietary Inflammatory Index and Human Health: An Umbrella Review of Meta-Analyses of Observational Studies," *Advances in Nutrition* 5 (2021): 1681–1690, <https://doi.org/10.1093/advances/nmab037>.
157. N. Shivappa, J. Godos, J. R. Hébert, et al., "Dietary Inflammatory Index and Colorectal Cancer Risk-A Meta-Analysis," *Nutrients* 9 (2017), <https://doi.org/10.3390/nu9091043>.

158. L. H. Willis, C. A. Slentz, L. A. Bateman, et al., “Effects of Aerobic and/or Resistance Training on Body Mass and Fat Mass in Overweight or Obese Adults,” *Journal of Applied Physiology* 12 (2012): 1831–1837, <https://doi.org/10.1152/jappphysiol.01370.2011>.
159. B. Strasser and W. Schobersberger, “Evidence for Resistance Training as a Treatment Therapy in Obesity,” *Journal of Obesity* 2011 (2011): 1–9, <https://doi.org/10.1155/2011/482564>.
160. K. L. Way, D. A. Hackett, M. K. Baker, and N. A. Johnson, “The Effect of Regular Exercise on Insulin Sensitivity in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis,” *Diabetes and Metabolism Journal* 4 (2016): 253–271, <https://doi.org/10.4093/dmj.2016.40.4.253>.
161. J. M. Jakicic, R. J. Rogers, K. K. Davis, and K. A. Collins, “Role of Physical Activity and Exercise in Treating Patients With Overweight and Obesity,” *Clinical Chemistry* 1 (2018): 99–107, <https://doi.org/10.1373/clinchem.2017.272443>.
162. D. Mozaffarian, M. Agarwal, M. Aggarwal, et al., “Nutritional Priorities to Support GLP-1 Therapy for Obesity: A Joint Advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and the Obesity Society,” *Obesity Pillars* (2025): 100181, <https://doi.org/10.1016/j.obpill.2025.100181>.
163. T. A. Wadden, V. L. Webb, C. H. Moran, and B. A. Bailer, “Lifestyle Modification for Obesity: New Developments in Diet, Physical Activity, and Behavior Therapy,” *Circulation* 9 (2012): 1157–1170, <https://doi.org/10.1161/circulationaha.111.039453>.
164. N. M. Lindberg, S. Vega-López, E. S. LeBlanc, et al., “Lessons Learned From a Program to Reduce Diabetes Risk Among Low-Income Hispanic Women in a Community Health Clinic,” *Front Endocrinol (Lausanne)* 11 (2020): 489882, <https://doi.org/10.3389/fendo.2020.489882>.
165. T. A. Wadden, T. S. Bailey, L. K. Billings, et al., “Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial,” *JAMA* 14 (2021): 1403–1413, <https://doi.org/10.1001/jama.2021.1831>.
166. T. A. Wadden, J. S. Tronieri, D. Sugimoto, et al., “Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT Randomized Controlled Trial,” *Obesity (Silver Spring, Md)* 3 (2020): 529–536, <https://doi.org/10.1002/oby.22726>.
167. E. Fallows, “Malnutrition With Use of GLP-1 Agonists Is an Underestimated Real World Harm,” *BMJ* 390 (2025): r1512, <https://doi.org/10.1136/bmj.r1512>.
168. A. M. Jastreboff, L. J. Aronne, and A. Stefanski, “Tirzepatide Once Weekly for the Treatment of Obesity. Reply,” *New England Journal of Medicine* 15 (2022): 1434–1435, <https://doi.org/10.1056/NEJMc2211120>.
169. S. J. Wherry, R. M. Miller, S. H. Jeong, and K. M. Beavers, “The Ability of Exercise to Mitigate Caloric Restriction-Induced Bone Loss in Older Adults: A Structured Review of RCTs and Narrative Review of Exercise-Induced Changes in Bone Biomarkers,” *Nutrients* 4 (2021), <https://doi.org/10.3390/nu13041250>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Recent human studies examining the impact of GLP-1 RAs on cancer risk.