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Communication

# Advancing the Science of Weight Loss and Cancer Risk: A Framework for Future Investigation

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## Abstract

**Background:** Obesity is a leading modifiable risk factor for cancer, and metabolic and bariatric surgery consistently reduce cancer incidence among individuals with severe obesity. However, the mechanisms underlying this protection remain poorly characterized, limiting the development of targeted cancer prevention strategies. **Objectives:** To identify critical knowledge gaps in understanding how weight loss reduces cancer risk and to propose a framework for coordinated investigation across the research spectrum. **Methods:** We reviewed current evidence on metabolic surgery and cancer outcomes, evaluated existing data resources, and assessed methodological and infrastructure limitations constraining progress in this field. **Results:** Key gaps include an incomplete understanding of whether cancer protection derives from weight loss per se or surgery-specific metabolic changes; limited ability to compare surgical and pharmacologic weight loss approaches; absence of standardized outcome definitions across studies; and insufficient infrastructure for data sharing and integration. The emergence of highly effective GLP-1 receptor agonists creates unprecedented opportunities for mechanistic comparison but introduces new uncertainties regarding long-term cancer effects. **Conclusions:** Progress requires coordinated investment across basic science, clinical trials, electronic health record-based research, and epidemiologic studies. Priorities include developing interoperable data standards, supporting privacy-preserving data sharing methods, expanding access to multiomics tissue repositories, and building collaborative networks capable of adequately powdered cancer outcomes research.

**Keywords:** bariatric surgery; metabolic surgery; cancer prevention; obesity; GLP-1 receptor agonists; data interoperability

## Introduction

Obesity affects over 40% of American adults and has become the second leading modifiable risk factor for cancer after tobacco use [1–4]. The International Agency for Research on Cancer has identified at least 13 cancer types with established causal links to excess body weight [1]. These include cancers of the breast (postmenopausal), colon, rectum, endometrium, esophagus (adenocarcinoma), gallbladder, kidney, liver, ovary, pancreas, stomach (cardia), thyroid, and multiple myeloma [1,2]. Obesity-associated cancers account for approximately 8% of all cancers diagnosed in the United States annually, representing a substantial and potentially preventable burden of disease [4].

Metabolic and bariatric surgery represents the most effective intervention for sustained weight loss in people with severe obesity [5–8]. These procedures produce durable reductions of 25–35% of total body weight, substantially exceeding outcomes achieved through lifestyle intervention or pharmacotherapy alone [6,7]. Over 250,000 bariatric procedures are performed annually in the United States, with sleeve gastrectomy now accounting for approximately 60% of procedures and Roux-en-Y gastric bypass comprising most of the remainder [6]. Beyond weight reduction, these procedures induce profound metabolic changes through weight-independent mechanisms, including rapid

improvements in glucose homeostasis, alterations in bile acid metabolism, restructuring of the gut microbiome, and normalization of the chronic inflammatory state characteristic of obesity [7,8].

Large cohort studies have consistently demonstrated substantial reductions in cancer incidence following bariatric surgery [9–13]. The Swedish Obese Subjects study, with over 20 years of follow-up, reported a 33% reduction in overall cancer incidence among surgical patients compared to matched controls [9]. A 2022 JAMA study of over 30,000 patients with obesity found that bariatric surgery was associated with significantly lower cancer incidence and cancer-related mortality compared with matched non-surgical patients [10]. Meta-analyses suggest an overall risk reduction of approximately 40% for obesity-associated cancers [13]. However, the mechanisms underlying cancer protection remain incompletely understood, limiting our ability to identify which individuals benefit most, to optimize surgical approaches for cancer prevention, and to develop alternative strategies that might replicate these protective effects [14–16].

The emergence of highly effective glucagon-like peptide-1 (GLP-1) receptor agonists represents both an opportunity and an uncertainty for this field [17–22]. Agents such as semaglutide and tirzepatide produce weight loss of 15–22% of body weight, approaching surgical outcomes in some patients [17–19]. For the first time, pharmacologic therapy offers a comparator capable of achieving substantial weight loss without anatomic rearrangement of the gastrointestinal tract [17]. This creates unprecedented opportunities to distinguish weight loss effects from surgery-specific metabolic changes. However, the biological complexity of the mechanisms by which these agents produce their effects and whether they will confer similar cancer protection remains unknown [15,16].

This update examines current knowledge gaps and proposes a framework for advancing investigation into the relationship between weight loss and cancer risk. We argue that progress requires coordinated investment across the full research spectrum, from basic mechanistic studies through large-scale population investigations, supported by enhanced data infrastructure and collaborative networks.

## Current State of Evidence

The epidemiologic evidence linking bariatric surgery to reduced cancer incidence is substantial but generates more questions than it answers [9–13]. Cancer site-specific analyses reveal heterogeneous effects that hint at underlying mechanistic complexity [23–26]. Substantial risk reductions are consistently observed for postmenopausal breast cancer, endometrial cancer, and hepatocellular carcinoma, conditions strongly linked to estrogen exposure and metabolic dysfunction [24]. Breast cancer risk reductions of 40–50% have been reported across multiple cohorts, with the effect appearing strongest for estrogen receptor-positive tumors [23]. Endometrial cancer, the malignancy most strongly linked to obesity through estrogen-mediated pathways, shows among the largest reductions following surgery, with some studies reporting over 70% risk reduction [24].

In contrast, the effect on colorectal cancer remains controversial [25,26]. Some studies suggest increased risk following Roux-en-Y gastric bypass, potentially related to elevated bile acid exposure or microbiome alterations, while others demonstrate protective effects [25–28]. A systematic review found substantial heterogeneity by surgical procedure type, follow-up duration, and geographic region [25]. Clarifying the colorectal cancer question is particularly important given prevalence of colorectal cancer and the biological plausibility of increased risk through bile acid exposure [29–31].

Multiple plausible biological pathways have been proposed to explain the surgery-cancer relationship [14–16,27,28]. The adiposity-reduction hypothesis posits that decreased fat mass reduces circulating estrogens through diminished peripheral aromatization, normalizes adipokine profiles, and attenuates chronic inflammation, thereby reducing the tumor-promoting environment characteristic of obesity [15,16]. Adipose tissue produces inflammatory cytokines including interleukin-6 and tumor necrosis factor- $\alpha$  that promote tumorigenesis through NF- $\kappa$ B signaling and oxidative stress [14,15]. Weight loss reduces circulating levels of these factors [14].

The metabolic improvement hypothesis emphasizes weight-independent effects on glucose-insulin homeostasis [7,15]. Bariatric surgery produces rapid glycemic improvements often preceding

substantial weight loss, and hyperinsulinemia promotes cancer cell proliferation through insulin-like growth factor-1 signaling [15,16]. Type 2 diabetes remission rates of 60-80% at 2 years post-RYGB substantially exceed those achieved by equivalent weight loss through non-surgical means, suggesting mechanisms beyond adiposity reduction [7,8].

The gut-alteration hypothesis focuses on surgery-specific changes in bile acid metabolism, gut hormone secretion, and microbiome composition that occur with anatomic rearrangement but not with non-surgical weight loss [27,28]. RYGB dramatically increases circulating bile acid concentrations by 2-4 fold, primarily through altered enterohepatic circulation [32,33]. Post-RYGB patients demonstrate substantially restructured intestinal microbiomes with increased Proteobacteria and decreased Firmicutes [34,35].

These hypotheses are not mutually exclusive, and the relative contribution of each pathway likely varies by cancer site, surgical procedure, and patient characteristics [36]. A critical unanswered question is whether cancer protection is driven primarily by weight loss per se, or whether surgery-specific metabolic changes provide additional protection beyond what weight reduction alone would confer [7,9]. This question is particularly important for advancing precision care, as it could help guide patients in selecting the most effective weight loss method tailored to their individual needs and risk profiles.

## The GLP-1 Receptor Agonist Opportunity

The development of GLP-1 receptor agonists capable of producing substantial weight loss has transformed obesity treatment and created new possibilities for mechanistic insight into weight loss and cancer relationships [17–19,37,38]. Prior comparisons between surgical and non-surgical populations were confounded by the modest weight loss typically achieved through lifestyle intervention of 5-10% of body weight, making it impossible to determine whether observed differences reflected the magnitude of weight change or the method by which it was achieved [39]. GLP-1 agonists now enable comparisons of cancer outcomes between surgical patients and pharmacologically-treated individuals who achieve similar absolute weight loss [17,18].

The STEP trials demonstrated that semaglutide 2.4mg weekly produces mean weight loss of 15-17% of body weight, while tirzepatide achieves 20-22% in some populations [17–19]. These magnitudes approach the lower range of surgical weight loss outcomes and far exceed historical pharmacologic benchmarks [40]. Millions of patients are now initiating these medications, creating an invaluable natural experiment for comparative effectiveness research [41].

However, GLP-1 receptor agonists are not metabolically neutral comparison agents [20–22]. In addition to producing clinically meaningful weight loss, these drugs exert direct effects on glucagon secretion, gastric emptying, hepatic glucose production, and satiety signaling that may independently influence cancer biology [21,22,42,43]. GLP-1 receptors are expressed in multiple tissues, including the pancreas, thyroid, and gastrointestinal tract, raising questions about direct effects on neoplasia [44,45]. Concerns about thyroid C-cell tumors and pancreatitis led to black box warnings and have prompted ongoing surveillance [20,21]. They alter gut hormone profiles in ways that partially overlap with, but also differ from, the changes induced by bariatric surgery [46,47]. Despite these limitations, the scale and rapid uptake of GLP-1 agonists create a timely opportunity to study cancer outcomes in patients achieving substantial weight loss pharmacologically.

The research community thus faces a window of opportunity. Patients initiating GLP-1 therapy today represent a natural comparison cohort for studies examining cancer outcomes over the coming decade. Realizing this opportunity requires prospective planning: establishing standardized outcome definitions, implementing systematic data collection, and creating infrastructure for long-term follow-up.

## Critical Knowledge Gaps

Several fundamental questions remain unanswered despite decades of epidemiologic research [1,48]. First, what is the temporal relationship between weight change and cancer risk modification? Is cancer protection proportional to the magnitude of weight loss, or do specific trajectories such as rapid initial loss, sustained maintenance, or absence of regain confer differential benefit [9,49,50]? Weight loss patterns vary substantially: some patients lose weight rapidly and maintain it, others experience gradual loss followed by partial regain, while still others achieve modest initial loss that continues over time [51,52]. Addressing whether the pattern of weight loss matters requires longitudinal data with serial weight measurements linked to cancer outcomes, data that are rarely available in existing studies [50,53].

Second, do different surgical procedures confer differential cancer protection through distinct physiologic mechanisms [36,54]? Roux-en-Y gastric bypass and sleeve gastrectomy differ substantially in their effects on bile acid metabolism, gut hormone profiles, and microbiome composition [24,46,47]. If these differences translate into differential cancer outcomes, it would provide strong evidence for surgery-specific mechanisms beyond weight loss [36,55]. However, existing comparative data are limited by modest sample sizes, short follow-up, and inconsistent outcome definitions [54,56].

Third, how do patient characteristics modify surgical benefit [57]? Genetic susceptibility to obesity-associated cancers varies across individuals, captured by polygenic risk scores aggregating the effects of hundreds of common variants [58,59]. Women in the highest decile of breast cancer polygenic risk have approximately 3-fold higher baseline risk than those in the lowest decile [60]. Whether bariatric surgery provides greater, lesser, or equivalent relative risk reduction across the spectrum of genetic risk is unknown [57,61].

Fourth, what is the mechanistic significance of metabolic improvements that precede weight loss [62]? Bariatric surgery, particularly Roux-en-Y gastric bypass, produces rapid improvements in glycemic control within days of surgery, before substantial weight reduction occurs [7,8,63]. If these early metabolic changes contribute to cancer protection, it would suggest pathways distinct from adiposity reduction and potentially implicate insulin-IGF-1 signaling as a therapeutic target [64,65].

Fifth, can biomarkers predict or explain differential cancer outcomes [66]? Routine post-operative monitoring provides longitudinal data on hemoglobin A1c, lipid profiles, and nutritional parameters. Whether trajectories of these biomarkers mediate the surgery-cancer relationship has not been systematically examined using modern causal inference methods [66].

## Infrastructure and Methodological Challenges

Answering these questions confronts substantial infrastructure development and methodological challenges. Cancer is a relatively rare outcome, even among people with obesity, and detecting procedure-specific effects or subgroup interactions requires sample sizes far exceeding what single institutions can provide [67,68]. The Longitudinal Assessment of Bariatric Surgery (LABS) study and Teen-LABS cohort represent valuable resources with detailed phenotyping, but their sample sizes limit statistical power for cancer endpoints [67–78]. Conversely, larger cohorts typically lack the granular longitudinal data needed for mechanistic investigation [69].

Data interoperability presents a critical barrier. Electronic health record (EHR) systems vary in their data models, coding practices, and completeness. The Observational Medical Outcomes Partnership (OMOP) Common Data Model offers a path toward standardization but has not been widely adopted specifically for bariatric surgery research [69]. Developing and validating phenotype algorithms that reliably identify bariatric surgery patients, characterize surgical procedures, and ascertain cancer outcomes across heterogeneous data sources is essential for multi-site investigation. Initiatives such as the National Institutes of Health's All of Us Research Program, which combines genomic data with longitudinal health records from diverse populations, may enable studies not feasible within single health systems [70].

Privacy considerations further constrain data sharing, even when scientific and ethical justifications are strong [71]. Federal support for privacy-preserving analytic methods, including federated learning approaches that enable analysis across distributed datasets without centralizing sensitive information, would substantially advance the field. Such methods allow institutions to contribute to collective knowledge while maintaining control over individual-level data. Patient engagement in research design and governance can enhance both the ethical foundation and practical feasibility of data sharing initiatives [72].

Methodological limitations extend beyond data availability [73]. Confounding by indication remains the fundamental challenge in observational bariatric surgery research, as patients who choose and qualify for surgery differ systematically from those who do not in ways that may independently influence cancer risk.[74]. While propensity score methods address measured confounders, they cannot eliminate bias from unmeasured factors [75]. Triangulating evidence across multiple comparison strategies, including the emerging GLP-1-treated population, strengthens causal inference but cannot definitively establish causation [74–76].

The need for biological samples linked to clinical outcomes represents another infrastructure gap. Tissue repositories enabling multiomics analysis in relation to cancer outcomes are sparse [77]. Pre-operative and longitudinal post-operative sample collection is not standard practice outside research protocols. Expanding access to whole genome sequencing would enable comprehensive evaluation of genetic modifiers of surgical benefit [78].

## A Framework for Future Investigation

Progress requires coordinated effort across the research spectrum. We propose a framework organized around four complementary investigative approaches, each addressing distinct aspects of the weight loss-cancer relationship.

Basic science research must continue to elucidate the molecular mechanisms linking adiposity, metabolic dysfunction, and carcinogenesis [15]. Animal models enable experimental manipulation impossible in human studies, including controlled examination of weight loss methods, temporal dynamics, and tissue-specific effects [79]. Human tissue studies can validate findings from model systems [14]. Key priorities include understanding how adipose tissue inflammation promotes tumor initiation, how insulin and IGF-1 signaling affects cancer cell biology, how bile acids and the microbiome influence gastrointestinal carcinogenesis, and how sex hormones mediate the obesity-cancer relationship [14,15].

Clinical trials offer the most rigorous approach to causal inference but face practical constraints given the timeline required for cancer endpoints [80]. Trials with intermediate biomarker endpoints, examining effects of surgical procedures and weight-loss medications on circulating factors implicated in carcinogenesis, can provide relatively rapid mechanistic insights [81]. Longer-term trials with cancer incidence as the primary endpoint may ultimately be necessary to definitively establish whether different weight-loss approaches confer equivalent cancer protection [80].

EHR-based research enables large-scale observational studies at relatively low cost but requires careful attention to bias and confounding [73,74]. Priorities include developing and validating standardized phenotype definitions for surgical procedures, weight-loss trajectories, and cancer outcomes that can be applied across health systems. Implementing common data models such as OMOP would facilitate multi-site analyses. The growing population of patients treated with GLP-1 receptor agonists represents an invaluable natural comparison cohort that should be systematically studied [17].

Population-based epidemiologic studies complement clinical research by examining cancer outcomes in real-world populations with long follow-up [82]. Linkage of surgical registries to cancer registries and mortality databases enables examination of outcomes not captured within single health systems [68]. International collaborations extend the diversity of populations studied and increase statistical power [82].

## Enabling Collaborative Science

Realizing this framework requires infrastructure investments that transcend individual studies. Data sharing mechanisms that protect privacy while enabling collaborative analysis are essential. Federated approaches, where analyses conducted locally at each institution and only aggregate results are shared, offer one model. Trusted research environments with appropriate governance can enable more comprehensive data integration. Patients themselves have expressed willingness to contribute their data for research when the potential benefits are clear and privacy protections are robust [72].

Standardization efforts warrant sustained investment. Developing consensus definitions for key exposures such as surgical procedure type, weight loss magnitude and trajectory, and pharmacologic treatment exposure, and for outcomes including cancer diagnosis, histologic subtype, and stage, would enable meaningful comparison across studies and aggregation of evidence. The metabolic and bariatric surgery community's experience with quality registries provides a foundation for expanded outcome collection [68]. Integrating cancer endpoints into existing data collection frameworks would yield substantial returns.

Support for methodological innovation should accompany clinical research investment. Developing and validating statistical methods appropriate for the complex data structures in this field, including approaches for time-varying exposures, competing risks, mediation with survival outcomes, and causal inference from observational data, would strengthen the evidence base [83].

Finally, funding for long-term, collaborative investigation are essential. Cancer outcomes require extended follow-up that exceeds typical grant cycles [ref]. Multi-site studies require coordination infrastructure and standardization investments that precede data collection. Consortium grants, cooperative agreements, and other mechanisms designed for team science can better support the scope of investigation needed than individual investigator awards alone.

## Conclusions

The observation that bariatric surgery substantially reduces cancer incidence in people with severe obesity represents one of the most compelling findings in cancer prevention epidemiology [9–13]. Yet critical caps remain in our mechanistic understanding, limiting our ability to optimize this benefit, identify which individuals gain most, or determine whether non-surgical approaches might replicate these effects [14–16,27,28].

The emergence of highly effective GLP-1 receptor agonists creates both opportunity and urgency: opportunity to distinguish weight loss effects from surgery-specific mechanisms through comparative studies, and urgency to establish the infrastructure for systematic investigation before this natural experiment passes [17–19].

Answering the fundamental questions in this field requires coordinated investment across the research spectrum [85]. Basic science, clinical trials, EHR-based research, and population epidemiology each contribute unique and complementary evidence [66,86]. Supporting this effort demands enhanced data infrastructure, including interoperability standards, privacy-preserving sharing mechanisms, and comprehensive tissue repositories, alongside methodological innovation in causal inference and longitudinal modeling [66,86].

The potential public health impact justifies this investment. With over 40% of American adults affected by obesity and millions undergoing weight-loss interventions annually, understanding how to optimally reduce cancer risk in this population could prevent thousands of cancer cases each year [48,87,88]. Coordinated, sustained effort from the research community, supported by funding agencies and enabled by appropriate infrastructure, can transform current epidemiologic observations into actionable cancer prevention strategies.

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