Mechanisms that Impact Cancer Risk after Bariatric Surgery PAR

(R01-Clinical Trial Optional; R21-Clinical Trial not Allowed)

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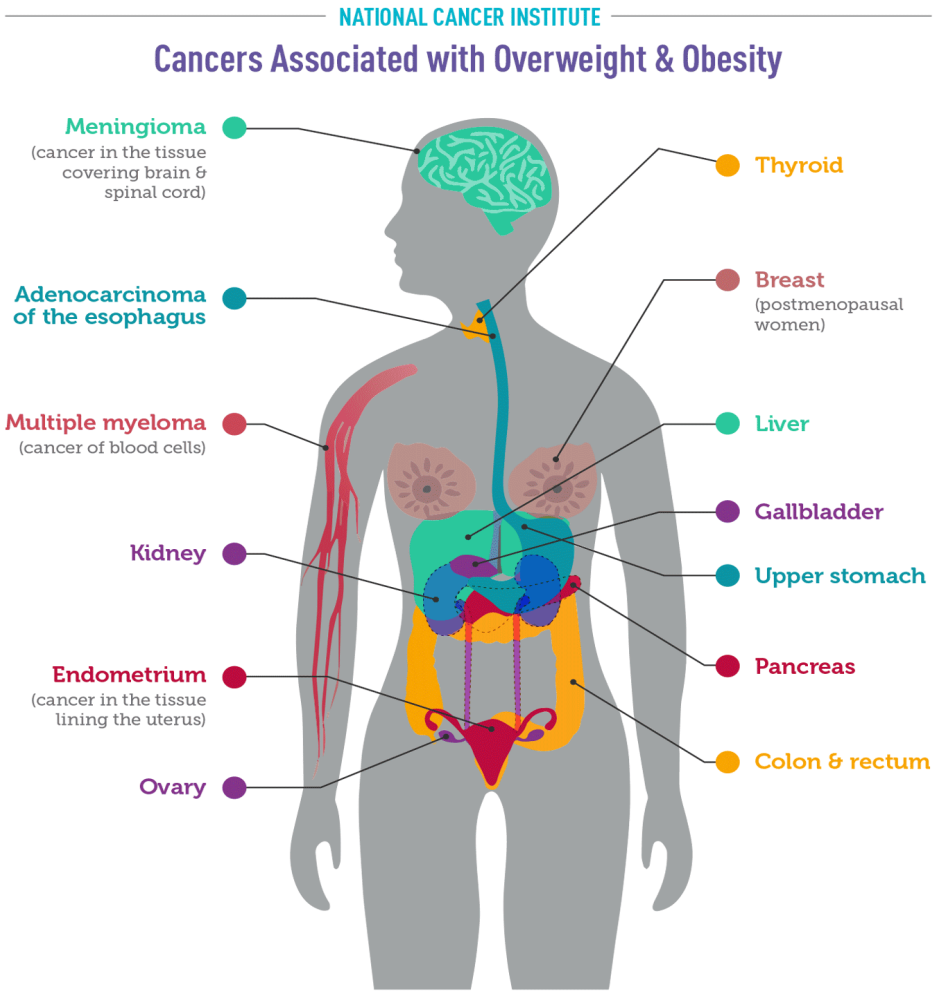
Division of Cancer Prevention

Trans-NCI Partnership

- Trans-NCI Obesity and Cancer Working Group
- Division of Cancer Prevention (DCP)
  - Breast and Gynecologic Cancer Research Group
  - Nutritional Science Research Group
  - Biometry Research Group
- Division of Cancer Biology (DCB)
  - Cancer Cell Biology Branch
  - Cancer Immunology, Hematology, and Etiology Branch

Obesity and Cancer

- Obesity increases the risk of multiple cancers.
- Obesity will soon surpass tobacco smoking as the leading preventable cause of cancer.
- Bariatric surgery demonstrates the most convincing evidence that weight loss leads to reductions in cancer risk and mortality.



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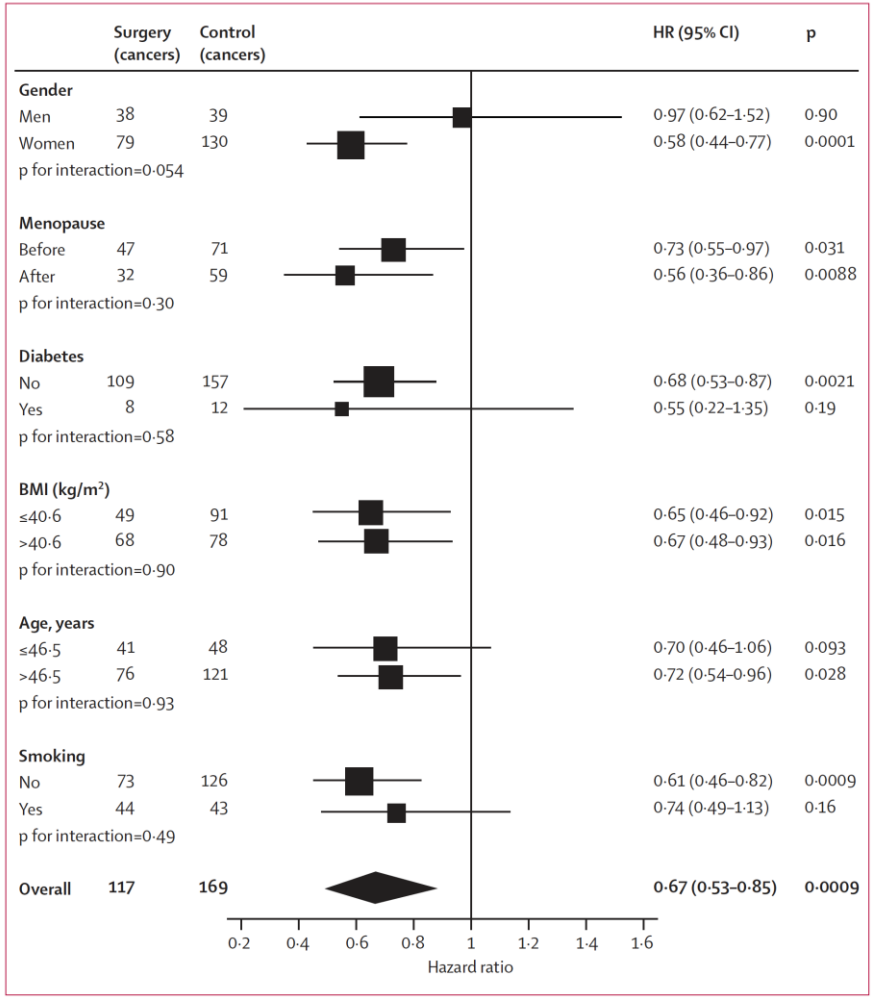
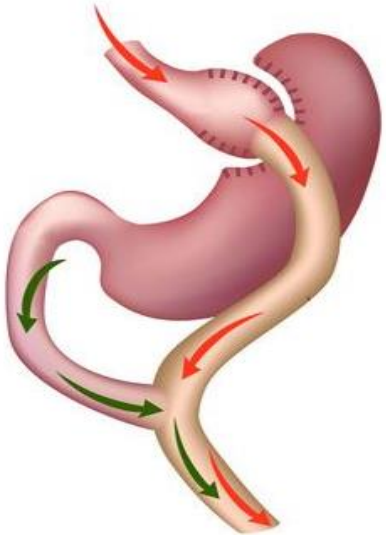
Bariatric Surgery and Cancer Risk

- Swedish Obese Subjects Study is the only prospective, controlled intervention trial to look at cancer incidence
- After a median of 10.9 years of follow-up, bariatric surgery resulted in
  - sustained mean weight reduction of 19.9 kg compared to gain of 1.3 kg in the control group
  - cancers incidence was lower in the surgery group (n=117) than in the control group (n=169; HR 0.67, 95% CI 0.53–0.85,p=0.0009)



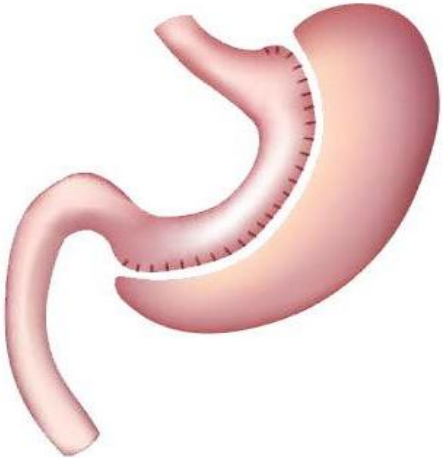
Are Bariatric Surgery Procedures Equal?

Gastric Bypass



Restrictive and Malabsorptive

Vertical Sleeve Gastrectomy



Restrictive

Gastric bypass has generally demonstrated greater benefit (more weight loss, more metabolic improvement) than the vertical sleeve gastrectomy.

Bariatric Surgery is Better than Lifestyle Interventions in Morbidly Obese Subjects

- Over 250,000 procedures performed in the U.S. in 2019, a 38% increase from 2011
- More initial and sustained weight loss
- Dramatic improvement or elimination of type 2 diabetes mellitus
  - The improvement precedes significant weight loss
- Reduction in cardiovascular risk
- Reduces the risk of certain obesity related cancers, although the mechanism(s) driving this risk reduction are mostly speculative.

NIH and Bariatric Surgery

- 1978-2008: NIDDK & NHLBI sponsored consensus conferences and expert panels
  - summarized the state of knowledge of bariatric surgery
  - experts make recommendations as to which patients most likely to benefit (BMI > 40 mg/kg^2, 35-40 mg/kg^2 if patient has an obesity related comorbidity)
- 2003: NIDDK established the Longitudinal Assessment of Bariatric Surgery (LABS)
  - LABS-1: short term safety study; LABS-2/-3: measured clinical/lab changes, focus on diabetes parameters
- NIH has funded research projects to address the safety/clinical impact/ mechanism(s) by which bariatric surgery impacts type II diabetes mellitus and cardiovascular risk
- FY 2022 NCI Annual Plan and Budget Proposal
  - The report points out the importance of “uncovering the biology at the intersection of obesity and cancer”
  - The report mentions bariatric surgery as an approach to control obesity leading to lower risk of multiple cancers

Possible Mechanisms Driving Obesity Related Cancer

- Chronic low-level inflammation
- Increased blood levels of insulin and insulin-like growth factor-1 (IGF-1)
- Fat cells produce adipokines (e.g. leptin, adiponectin), hormones that may stimulate or inhibit cell growth.
- Increased AMP-activated protein kinase (AMPK) signaling
- Changes in cancer cell scaffolding, altered immune responses, effects on the NF-Kß, and oxidative stress
- Alterations in the gut microbiome
- Decreased intestinal gluconeogenesis
- Epigenetic changes occur in adipocytes after weight loss
- Increased levels of aromatase

What is the Mechanistic Link between Bariatric Surgery and Cancer Risk Reduction?

Currently, **very little has been published** to answer this question, either in animal models or in humans.

The focus thus far has been on benefits seen more quickly after surgery

- Reduction in body weight
- Reduction in type II diabetes mellitus
- Reduction in metabolic syndrome
- Reduction in cardiovascular risk

Purpose of PAR

- Promote studies examining the mechanism(s) through which bariatric surgery impacts cancer risk
- Attract talented scientists who understand the dynamic changes caused by bariatric surgery
- R21 mechanism will allow for early stage or resource development projects (clinical trial not allowed)
- R01 mechanism will accommodate broader scoped or in-depth mechanistic studies (clinical trial optional)

Questions that need to be addressed include, but are not limited to:

- Do alterations in risk biomarkers occur before weight loss? If so, in what organ, tissue, or cell type do they originate?
- Is maximum weight loss or long term weight loss more important for cancer risk reduction? If so, how do the two differ at a cellular and/or biochemical level?
- What mechanism(s) explain the evidence that bariatric surgery is more beneficial in cancer risk reduction in women than men?
- Does bariatric surgery increase or decrease the risk of colorectal cancer, and if so, what are the mechanism(s)?
- Which cancers are favorably impacted by bariatric surgery, and what are the mechanism(s) that explain the effect?
- Does the specific bariatric surgery procedure influence cancer impact? If so, what are the mechanism(s) driving the difference in impact?

Portfolio Analysis

- 3/28 grants funded between 2009-2021, 2 R21s and one R01

- Current NCI obesity research funding opportunities:
  - PAR-18-893: Physical Activity and Weight Control Interventions Among Cancer Survivors: Effects on Biomarkers of Prognosis and Survival (R01 Clinical Trial Optional). Does not include surgical interventions.
  - Recently approved RFA: Metabolic Dysregulation and Cancer Risk Program: a Transdisciplinary Approach to Obesity-Associated Research (U01 Clinical Trial Optional). Human studies are required.

Justification for PAR

- Greater visibility with PAR than NOSI. Only 28 grants submitted on the topic over an 11 year period.
- Referral: clustered referral to a single CSR study section with additional expertise in bariatric surgery.
- Special review criteria: prior experience with bariatric surgery research by one or more of the investigators; for clinical trials, one or more of the collaborators should be a bariatric surgeon.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