Mechanisms that Impact Cancer Risk after Bariatric Surgery PAR

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

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- 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.
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)
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-KB, 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.