Exercise and nutrition interventions to improve treatment-related outcomes in cancer survivors (Clinical Trial Required)

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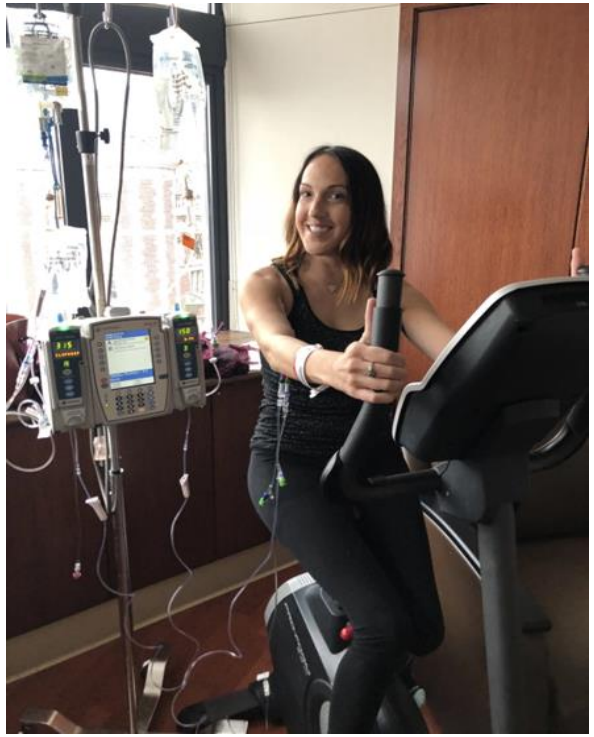
Background

- Adverse physical consequences among survivors can increase risk for treatment interruptions
  - Adiposity/low muscle mass, poor fitness, and diet can lead to worse outcomes in survivors, including dose interruptions and toxicities
  - 35% of US cancer survivors are obese and
    <17% meet general physical activity guidelines

- Exercise and nutrition interventions:
  - Improve fitness, body composition, and nutritional status
  - Are generally well-tolerated and can be tailored
  - Can be delivered in conjunction with cancer therapies

- Few studies have focused on:
  - The time period shortly before or during cancer treatment
  - Treatment-related outcomes



Purpose of this RFA

- To understand how exercise and nutrition interventions (alone or combined) affect treatment-related outcomes for curative/life-extending therapies
  - Treatment-related outcomes include:
    - Dose interruption, reduction, or delays
    - Related healthcare utilizations (e.g., hospital admissions, length of stay, ED visits)
    - Severe adverse events (e.g., CTCAE ≥ 3, dose-limiting and organ-specific toxicities)

- To address research gaps concerning:
  - Specific exercise and nutrition interventions across cancer sites and treatment protocols

- Goal: to help patients successfully complete planned treatment with good overall outcomes

Exercise Intervention

- ACSM Exercise Guidelines for Cancer Survivors:
  - Reviewed existing literature
  - Exercise deemed safe and provided considerations
- Strength of evidence
  - **Strong:** improved fitness, lean mass, fatigue, QOL, and functioning
  - **Safe/moderate benefit:** lymphedema and bone health
  - **Requiring further study:** cardiotoxicity, peripheral neuropathy, treatment tolerance
- Limitations: studies of treatment-related outcomes
  - Secondary data analyses of a parent trial
  - Lacked specificity regarding exercise guidance ("dose") by **F**requency, **I**ntensity, **T**ime, and **T**ype (FITT) and determination of optimally-effective exercise level

Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable

Download Clinical Guidelines

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Nutrition Interventions Before and During Treatment

Before Treatment "Prehab"	Results
Nutritional interventions (some with exercise) prior to colorectal surgery (Gillis et al. 2018)	↑- presurgical functional capacity and lean body mass ↓- length of hospital stay
During Treatment	**Results**
Protein Supplementation (colorectal cancer patients during 5-fluorouracil-based chemotherapy) (Mazzuca et al. 2019)	↓ - hematological and gastrointestinal toxicities ↑ - nutritional status
Fasting-mimicking diets in combination with therapies were associated with: (Bauersfeld et al. 2018, Nencioni et al. 2018)	↑- treatment efficacy and tolerability ↓- toxicities
High-fiber diet (compared with habitual-fiber intake) during pelvic radiotherapy (Wedlake et al. 2017)	↓- gastrointestinal toxicity

Required Elements of RFA

- Identify the gaps in knowledge to be addressed
- RCT, initiated before or during cancer treatment, with power to test intervention effects on a treatment-related outcome as the primary endpoint and secondary endpoints i.e., patient reported outcomes
- Justify the biological plausibility of the intervention on the treatment-related outcomes
- Specify population of cancer survivors treated for curative or life-extending intent
- Include robust treatment data - planned and delivered dose and type for all treatment modalities, and where appropriate, supportive care measures (e.g., anti-emetics)
- Include validated measures of body composition, diet, general physical activity, and where appropriate, metabolic biomarkers
- Cooperate with Coordinating Center in identification of common data elements and standardization procedures

Additional Requirements: Studies with Exercise Component

- Specify details of exercise prescriptions (e.g., FITT criteria)
- Include validated measure of exercise adherence and exercise-related biomarkers relevant to treatment outcomes (e.g., CRF, functional status)

Possible Research Questions

- What is the minimally and optimally effective “dose” of exercise to mitigate organ-specific toxicity in cancer survivors receiving a specific therapy?
- Does exercise and/or access to medical nutritional therapy improve immediate post-surgical outcomes, including length of hospital stay and readmissions?
- Does a tailored weight loss intervention for overweight/obese cancer survivors that is designed to preserve muscle improve completion of the planned course of treatment in cancer survivors?
- Does intermittent fasting around the time of chemotherapy improve ability to deliver the planned course of treatment?

RFA Justification

U Mechanism
• Focuses work to address the research gap identified in the portfolio and ensure studies are aligned with NCI priorities • Promotes trans-disciplinary exchange and collaboration among awardees • Facilitates NCI expertise and involvement • Requires collection and harmonization of common measures and standardized procedures across projects to maximize opportunities for data pooling and pilot projects
Research Coordinating Center
• Supports collection of common data, standardization of platform and procedures for the collection, pooling, and analysis of common data across projects for current and future use • Provides expertise to support collection of novel data (e.g., cost or implementation feasibility) • Facilitates communication within the cooperative group and serves as a resource for extramural community

Budget: $1.275M total cost per grant per year. 5 research sites and 1 coordinating center.

Reviewer Comments and Clarifications (Drs. Robison, Seewaldt, & Colditz)

- Remove age ≥ 18-years as requirement
- Include patient report outcomes as a secondary outcome
- Collect, where appropriate, supportive care measures (e.g., anti-emetics, pain medication)
- Clarification of responsive study design features
  - Study population
    - Overweight/obesity status is a consideration but not a required sample selection criterion
    - Inclusion of minority and socioeconomically underserved populations strongly encouraged
  - Study design
    - Study enrollment initiated shortly before or during treatment, but intervention may extend beyond treatment
    - Collect common data elements facilitated by Coordinating Center:
      - metabolic biomarkers/profile of participants and set of patient reported outcomes
      - Collection of intervention implementation and feasibility data
- Coordinating Center
  - Establish common data terms, definitions, platforms and standardized procedures for common data collection and harmonization across all projects to facilitate future data pooling and analysis
  - Support collection of novel data (e.g., implementation feasibility, cost) and data analyses