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THE 2011-2016 TRANSDISCIPLINARY RESEARCH IN ENERGETICS AND CANCER (TREC) INITIATIVE: RATIONALE AND DESIGN

Ruth E. Patterson¹, Graham A. Colditz², Frank B. Hu³, Kathryn H. Schmitz⁴, Rexford S. Ahima⁴, Ross C. Brownson², Kenneth R. Carson², Jorge E. Chavarro³, Lewis A. Chodosh⁴, Sarah Gehlert², Jeff Gill², Karen Glanz⁴, Debra Haire-Joshu², Karen Louise Herbst¹, Christine M. Hoehner², Peter S. Hovmand², Melinda L. Irwin⁵, Linda A. Jacobs⁴, Aimee S. James², Lee W. Jones⁶, Jacqueline Kerr¹, Adam S. Kibel³, Irena B. King⁷, Jennifer A. Ligibel⁸, Jeffrey A. Meyerhardt⁸, Loki Natarajan¹, Marian L. Neuhauser⁹, Jerrold M. Olefsky¹, Enola K. Proctor², Susan Redline¹⁰, Cheryl L. Rock¹, Bernard Rosner¹¹, David B. Sarwer⁴, J. Sanford Schwartz⁴, Dorothy D. Sears¹, Howard D. Sesso¹⁰, Meir J. Stampfer³, S. V. Subramanian³, Elsie M. Taveras¹², Julia Tchou⁴, Beti Thompson⁹, Andrea B. Troxel⁴, Marianne Wessling-Resnick³, Kathleen Y. Wolin², and Mark D. Thornquist⁹

¹ University of California, San Diego, La Jolla, CA, USA

² Washington University in St. Louis, St. Louis, MO, USA

³ Harvard University, Boston, MA, USA

⁴ University of Pennsylvania, Philadelphia, PA, USA

⁵ Yale University, New Haven, CT, USA

⁶ Duke Cancer Institute, Durham NC, USA

⁷ University of New Mexico, Albuquerque, NM, USA

⁸ Dana-Farber Cancer Institute, Boston, MA USA

⁹ Fred Hutchinson Cancer Research Center, Seattle, WA, USA

¹⁰ Brigham and Women's Hospital, Boston, MA, USA

¹¹ Channing Laboratory, Boston, MA, USA

¹² Harvard Pilgrim Health Care Institute, Boston, MA, USA

Abstract

Purpose—Recognition of the complex, multidimensional relationship between excess adiposity and cancer control outcomes has motivated the scientific community to seek new research models and paradigms.

Corresponding author: Mark D. Thornquist, mthornqu@fhcrc.org, phone: 206-667-2931, fax: 206-667-5964.

Suggested Reviewers:

Elizabeth Eakin, University of Queensland

Robert Hiatt, UCSF Helen Diller Family Comprehensive Cancer Center

Neville Owen, Baker IDI Heart and Diabetes Institute

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Conflict of interest:

The authors declare that they have no conflict of interest.

Methods—The National Cancer Institute developed an innovative concept to establish a centers grant mechanism in nutrition, energetics, and physical activity; referred to as the Transdisciplinary Research on Energetics and Cancer (TREC) Initiative. This paper gives an overview of the 2011-2016 TREC Collaborative Network and the 15 research projects being conducted at the Centers.

Results—Four academic institutions were awarded TREC center grants in 2011: Harvard University, University of California San Diego, University of Pennsylvania, and Washington University in St. Louis. The Fred Hutchinson Cancer Research Center is the Coordination Center. The TREC research portfolio includes 3 animal studies, 3 cohort studies, 4 randomized clinical trials, 1 cross-sectional study, and 2 modeling studies. Disciplines represented by TREC investigators include basic science, endocrinology, epidemiology, biostatistics, behavior, medicine, nutrition, physical activity, genetics, engineering, health economics, and computer science. Approximately 41,000 participants will be involved in these studies, including children, healthy adults, and breast and prostate cancer survivors. Outcomes include biomarkers of cancer risk, changes in weight and physical activity, persistent adverse treatment effects (e.g., lymphedema, urinary and sexual function), and breast and prostate cancer mortality.

Conclusion—The NIH Science of Team Science group will evaluate the value-added by this collaborative science. However, the most important outcome will be whether this transdisciplinary initiative improves the health of Americans at risk for cancer as well as cancer survivors.

Keywords

energetics; obesity; diet; physical activity; cancer; transdisciplinary

INTRODUCTION

In 2010, approximately 70% of US adults were overweight or obese [1]. While weight gain, overweight and obesity rates appear to have stabilized for adults [1], trend analyses over a 12-year period indicate a significant increase in obesity in males aged 2-19 years but not in females [2]. Racial and ethnic differences remain, with the highest rates of overweight and obesity among Hispanics and non-Hispanic black adults (77% for both) [1]. The annual medical burden of obesity increased from 6.5 percent in 1998 to 9.1 percent in 2006 [3]. In 2008, the annual healthcare cost of obesity in the US was estimated to be \$147 billion a year [3].

Recent reviews and meta-analyses provide strong evidence from a number of research designs that overweight/obesity and adipose tissue distribution are associated with increased risk of many cancers [4-7]. Similar evidence exists that increased physical activity is associated with a reduced risk of certain cancers [6,8-11]. In addition, there is compelling evidence that obesity, physical activity, and diet influence the incidence and clinical course of multiple adverse effects of cancer treatment, quality of life, cancer recurrence, and mortality among those with a diagnosis of cancer [12-16].

Evaluation of biomarkers has enabled investigators to assess the biological factors thought to be involved in the causal pathway between carcinogenesis and lifestyle factors such as excess adiposity, physical activity, and dietary intake. Obesity may increase cancer risk by several mechanisms including increased estrogens and testosterone leading to increased risk of breast and endometrial cancers; hyperinsulinemia and insulin resistance leading to increased risks of colon, breast, prostate, and pancreatic cancers; and increased inflammation and depressed immune function [4,7,8,10,17-20]. Recent research also indicates that regular activity is associated with reduced risk of breast cancer via interrelated

biologic pathways that involve adiposity, sex hormones, insulin resistance, adipokines, chronic inflammation and immune function [8,21].

The increasing recognition of the complex, multidimensional relationship between excess adiposity and cancer risk, coupled with the high prevalence of obesity in the US, has motivated the scientific community to seek new research models and paradigms. Compared to traditional unidisciplinary research, transdisciplinary research is seen as having the potential to accelerate both discovery and its translation to practice [22,23]. Previous NIH transdisciplinary research initiatives include the National Institutes of Health Centers for Population Health and Health Disparities [24] and the Transdisciplinary Tobacco Research Use Centers (TTURCs) [25]. The TTURCs were the first transdisciplinary science initiatives and consequently have had more time to be evaluated. A recent bibliographic evaluation of TTURCs in comparison to R01s found that after an initial lag period, TTURCs had higher overall publication rates over a 10-year comparison period [26]. However, as noted by Rimer and Abrams in a companion commentary, the ultimate impact and value-added nature of transdisciplinary frameworks are likely decades away from being placed properly in the history of science [27]. In response, the National Cancer Institute (NCI) developed a concept to establish a centers grant mechanism in nutrition, energetics, and physical activity; referred to as the Transdisciplinary Research on Energetics and Cancer (TREC) Initiative (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-10-006.html>). The primary mission of the TREC Centers is to foster collaboration among transdisciplinary teams of scientists with the goal of accelerating progress towards reducing cancer incidence, morbidity and mortality associated with obesity, low levels of physical activity, and poor diet (see **Figure 1**. TREC Conceptual Model). The second mission of these centers is to provide training opportunities for new and established scientists who can carry out integrative research on energetics and cancer risk. The TREC Research Objectives are to:

Enhance knowledge of the mechanisms, from cellular, animal or human models to genetics and genomics, underlying the association between energy balance and carcinogenesis across a range of cancer-relevant areas from causation to prevention throughout the human life cycle.

Explore and integrate the etiology of obesity behavior and relevant health behavior theories, with broad population impact at the social-environmental and policy levels for prevention and control of obesity, focusing on children, groups at high risk for obesity, and cancer survivors.

The purpose of this article is to describe the 2011-2016 TREC Collaborative Network. Some detail is provided on the scientific rationale and underlying theoretical construct of this major undertaking. The scientific and logistic complexity of the TREC initiative has leadership and management challenges. Therefore a description is given of the organizational and management approach to this initiative, including mention of a committee structure designed to ensure adequate communications and decision-making procedures. The paper then turns to a summary of the 15 research projects that compose TREC. Finally, the evaluation components that will be applied to the TREC initiative are presented. This transdisciplinary approach to addressing the role of energetics in cancer risk provides a model for future initiatives addressing complex public health problems in the US.

METHODS

In 2004, the NCI issued the *original* TREC Request for Applications (RFA) using a U54 cooperative agreement grant mechanism. Applicants were required to demonstrate a transdisciplinary approach, propose 3-5 individual and connected research projects organized around a unifying research theme. Applications also included several cores (e.g.,

administration, bioinformatics, developmental pilot projects, education/training) as well as strategies to synthesize efforts across centers and plans to disseminate results to the medical, public health, policy, and cancer research community. The education/training component was included in recognition of the urgent need for new investigators in the area of energetics-cancer research. The provision of developmental/pilot funds supports exploration of novel directions, especially those that might arise with the progression of the major projects.

In 2005, four TREC Centers were selected by a national peer review process. The four Centers (principal investigators) originally funded under this mechanism were: Case Western Reserve University (Nathan A. Berger, MD), Fred Hutchinson Cancer Research Center (Anne McTiernan, MD, PhD), University of Minnesota (Robert W. Jeffery, PhD), and University of Southern California (Michael I. Goran, PhD). The Fred Hutchinson Cancer Research Center was funded to be the Coordination Center. These TREC Centers were highly productive, transdisciplinary in focus and contributed greatly to the understanding of transdisciplinary team science [28-30]. TREC research finds have been reported elsewhere and cover a wide scope of results. Select highlights include: findings on the effects of diet quality on inflammatory and adipokine profiles of overweight and obese individuals [31], to the impact of adipocytes on leukemia treatment [32], to the effects of exercise on oxidative stress in overweight or obese women [33], as well as the relationship of sleep duration to increased cancer risk [34]. TREC research highlights are available at <http://treescience.org/trec/bin/scientist/pubs.aspx?j=21>. A comprehensive publication list and further details describing the initial TREC Centers are publicly available on the TREC project website (<http://treescience.org/trec/bin/about/archive05.aspx?j=21>).

In 2009, the NCI issued a revised TREC Request for Applications (RFA). The focus of the 2009 RFA was expanded to reflect the current state of the evidence, which had grown dramatically since 2004. The TREC RFA 2009 was released for open competition, and included modifications to strengthen the RFA's transdisciplinary focus between the relationships of obesity, cancer etiology and mechanisms and the cancer survivorship population. This second phase of TREC continued using a U54 cooperative agreement grant mechanism, including a limited competition U01 RFA for the Coordination Center. This manuscript is focused on the results of the 2009 TREC RFA. Below we provide an overview of the 2011-2016 TREC Collaborative Network as well as the 4 Centers and the 15 research projects being conducted at the Centers.

RESULTS

Overview

After a competitive review of proposals, 4 academic institutions were awarded center grants by NIH in 2011: Harvard University, University of California San Diego, University of Pennsylvania, and Washington University in St. Louis. The Fred Hutchinson Cancer Research Center is the TREC Coordination Center. As shown in **Figure 2**, TREC is a collaborative network composed of the research centers, the Coordination Center, and program staff from NCI and other NIH institutes. The Network is governed by the TREC Steering Committee, which is composed of the NCI program director, the principal investigator (PI) of the Coordination Center, and the PI of each TREC Center. As shown, there are currently 13 TREC Working Groups, made up of scientists from all the TREC sites. These Working Groups are a key part of the dynamic approach to TREC collaborations and are a source of expertise to all TREC partners and advise the TREC Steering Committee on protocol, policy and scientific issues. These groups are also encouraged to develop training opportunities and scientific workshops. Finally, to encourage the use of common

measures, the Coordination Center is collecting and sharing information on measures being used in the TREC research studies, such as diet and physical activity assessment and assays.

Underlying the TREC Initiative is the premise that communication, exchange of ideas and resources, and collaborations among scientists and across disciplines increase the potential for transdisciplinary scientific breakthroughs. In particular, cross-center collaborations are seen as critical to enhancing the capacity of the TREC Initiative, to catalyze problem solving, and to lead to more rapid advances in knowledge. Therefore, one of the primary goals of the Fred Hutchinson Cancer Research Center Coordination Center (Mark D. Thornquist, PI) is to support the TREC Initiative by facilitating regular cross-TREC conference calls, semi-annual in-person meetings of the TREC scientists, and monthly conference calls for TREC Working Groups. The 13 TREC Working Groups allow scientists interested in similar topic areas (e.g., physical activity measurement, cost-effectiveness, survivorship) to meet regularly to discuss scientific challenges in study implementation, more consistent use of measures, potential collaborative papers, and other cross-center collaborations. The Coordination Center also plays a key role in helping to manage the cross-TREC pilot project program. Annually, an RFA is issued across the TREC Centers asking for proposal involving 2 or more Centers working together on a single project. These projects are funded in Years 2-5 of the initiative and provide an avenue for introducing and integrating new investigators and innovative technologies, methodologies, and/or research in the TREC infrastructure. Finally, the Coordination Center plays an important role in developing training modules, and evaluating progress.

For the 2011-2016 TREC Collaborative Network, 15 independent, but interrelated, research projects are being conducted. As shown in **Table 1**, this research portfolio includes 3 animal studies, 3 cohort studies, 4 randomized clinical trials in humans, 1 cross-sectional study, and 2 modeling studies (see below for additional details). A wide variety of disciplines are included among the TREC investigators, including basic science, endocrinology, epidemiology, biostatistics, behavior, medicine, nutrition, physical activity, genetics, engineering, health economics, and computer science.

Cancers targeted by the TREC Centers include prostate, breast, and colorectal cancer. Overall, approximately 41,000 participants will be involved in these studies, including children, healthy adults of all ages, breast cancer and prostate cancer survivors. Outcomes are diverse and include biomarkers of cancer risk, weight loss, changes in physical activity, persistent adverse treatment effects (e.g., lymphedema and post-prostatectomy urinary and sexual function), and breast and prostate cancer mortality.

Harvard University (PI: Frank B. Hu, MD, PhD)

The Harvard TREC Center will address how genetic, behavioral, and structural factors influence obesity and the biologic mediators between obesity and cancer at multiple stages of life (infants, adolescents, healthy adults and cancer survivors). Toward this end, four complementary and interrelated research projects have been developed to form a cohesive, transdisciplinary center focused on training, the generation of knowledge, and its translation and dissemination. **Table 2** provides a summary of the four research projects contained within this Center.

University of California, San Diego (PI: Ruth E. Patterson, PhD)

The overall objective of the UCSD TREC Center is to enhance knowledge regarding insulin resistance and inflammation underlying the association of energetics with breast cancer carcinogenesis, from the cell to the community. The results of these studies are anticipated to contribute to understanding the link between obesity and breast cancer as well as provide

insight about interventions with broad population impact for prevention and control of disease. **Table 3** provides a summary of the Center's four research projects.

University of Pennsylvania (PI: Kathryn H. Schmitz, PhD, MPH)

The central mission of the Penn TREC Survivor Center is to advance science on energetics and cancer survivorship, toward the goal of improving both the length and quality of cancer survivorship. The three major projects address both categories of major challenges faced by survivors (risk of recurrence and persistent adverse treatment effects) and link research questions from bench to policy work. The three projects described below are viewed as a platform of methodologies that can be used to develop a sustainable research program on obesity and cancer survivorship and train new scientists to answer the multitude of questions remaining regarding energetics and cancer survivorship. **Table 4** provides a summary of the Center's three research projects.

Washington University in St. Louis (PI: Graham A. Colditz, MD, DrPH; Co-PI: Sarah Gehlert, PhD)

This TREC Center aims to answer the question: What are the factors in the molecular and social environments that influence energetics to produce cancer throughout the lifespan from predisposition to survival? In answering this question, the Center will extend findings to state-level modeling of cancer risk using biological, social, environmental and other inputs to determine areas with the maximum pay off for cancer prevention and control. Further, dissemination and implementation of research findings is key to this Center, incorporated as a core to enable faster adoption of research findings by multiple stakeholders from researchers, to worksites and policy makers, to geographic regional planners, to individuals and more. **Table 5** provides a summary of the Center's four research projects.

There are numerous opportunities for collaborations within and across TREC Centers. The TREC Initiative includes developmental research funds to expand the scope of research as new opportunities and directions arise; to bring in new investigators and new fields of research to the TREC team; and to integrate new and innovative technologies and/or methodologies into the TREC infrastructure. Developmental projects may be collaborative among scientists of one or more TREC Centers, or with scientists outside the TREC Initiative. In addition, based on alignment of research interests, the TREC Steering Committee has identified institutions that will function as Affiliate TREC Centers: Case Western Reserve University, Nathan Berger, MD; Johns Hopkins Global Center for Childhood Obesity, Youfa Wang, MD, PhD; and National Centre for Tumour Diseases and the German Cancer Research Centre, Neli Ulrich, PhD (www.trecscience.org).

DISCUSSION

The TREC initiative was designed to accelerate science by integration of social, behavioral and biological sciences to address obesity, physical inactivity and poor diet within a cancer prevention context. The transdisciplinary research model is incorporated at multiple levels, including within each of the TREC Centers where applicants were required to demonstrate a transdisciplinary approach; across the Centers via cross-TREC investigator and working group conference calls and in-person meetings; and via structural TREC activities such as cross-Center pilot studies and an Investigator Exchange Program. It is notable that the first such transdisciplinary initiative (Transdisciplinary Tobacco Research Use Centers or TTURCs) did not include a Coordinating Center. Learnings from the TTURCs indicated that a Coordinating Center could be an important enhancement of the collaborative process by facilitating and driving collaborations among the Centers and supporting evaluation processes.

Evaluation is a key component of the TREC Initiative. Outcomes to be assessed will include peer-reviewed publications, educational and outreach programs, and effectiveness of a collaborative research development model. This evaluation will be conducted by the Coordination Center in collaboration with the TREC Collaborations and Outcomes Working Group and the NCI Science of Team Science (SciTS) team. The SciTS team was formed in 1999 with a primary charge to better understand the processes, outcomes and impacts of large transdisciplinary center grant initiatives supported by the NCI [30]. As part of evaluating the effectiveness of the collaborative research model in TREC, the SciTS team will participate in Collaboration and Outcomes Working Group calls and provide expert consultation in order to (1) support the group in achieving self-identified goals related to capturing the collaborative processes involved in TREC and the broad impacts of transdisciplinary team science in TREC, (2) collect examples of collaborative processes: cross-disciplinary collaborations, expansion of collaboration networks, cross-center collaborations, and (3) document examples of these impacts in scientific advancements, career trajectory for trainees and investigators, and emerging areas of transdisciplinary science. SciTS program staff will also conduct an external evaluation based on information available through the TREC self-evaluation process, but with the emphasis on assessing the overall progress in achieving the scientific goals of the entire TREC Initiative. Finally, an important aspect of evaluation is to assess whether the transdisciplinary nature of the TREC Initiative results in increased scientific productivity (e.g., publication rates, impact factors). To this end, the SciTS team will be using surveys, bibliometric analyses, networking analyses, and other tools to evaluate the value-add of collaborative science in comparison to the traditional R01 model of research starting in 2013.

In conclusion, there is increasing evidence to support a substantive role of obesity and energetics in cancer control outcomes. Significant progress regarding obesity and disease risk will require continued commitment to both unidisciplinary and multidisciplinary research. The overall impact of this transdisciplinary initiative will not be known for years. For now, success will be defined by the degree to which these Centers produce novel and innovative research approaches and discoveries. However, the most important outcome will be whether the TREC Initiative improves the health of Americans at risk for cancer as well as cancer survivors.

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*Physiological and Behavioral Factors contribute to the additional factors of Personality (e.g., extraversion), Psychological Factors (e.g., stress), and Cognitive Factors (e.g., beliefs)

Figure 1.
National Cancer Institute Conceptual Model for the Transdisciplinary Research in
Energetics and Cancer Initiative

Abbreviations: PI = Principal Investigator; CC = Coordination Center, NCI = National Cancer Institute, PO = Project Officer

Figure 2.

The 2011-2016 Transdisciplinary Research in Energetics and Cancer (TREC) Initiative

Table 1
Overview of Research Projects Being Conducted by the Transdisciplinary Research in Energetics and Cancer (TREC) Centers, 2011-2016.

TREC Center	Project Title (Leader)	Age	Sex	N	Study Design	Anthropometrics	Physical Activity	GIS	Diet	Blood Biomarkers	Genetics
Harvard	Sleep Duration, Energy Balance, and Insulin Resistance in Children (Taveras)	0-12	M/F	~1300	Cohort	x	x	x	x	x	x
	Environmental and Lifestyle Factors, Obesity and Cancer-related Biomarkers (Hu)	45-80	M/F	8750	Cohort	x	x	x	x	x	x
	Energetics, Fatal Prostate Cancer, and Overall Survivorship (Ma)	40-84	M	22,071	Cohort	x	x	x	x	x	x
	Impact of Exercise and Metformin on Hyperinsulinemia in Colorectal Cancer Survivors (Meyerhardt)	21	M/F	200	RCT	x	x	x	x	x	
UCSD	Role of Inflammation and Insulin Resistance in Mouse Models of Breast Cancer (Olefsky)	NA	F	NA	Animal				x	x	
	Diet Composition and Genetics: Effects on Weight, Inflammation, and Biomarkers (Rock)	21	F	234	RCT	x	x	GPS	x	x	x
	Weight Loss, Mechanisms, and Mortality among Breast Cancer Survivors (Patterson)	>50	F	340	RCT	x	x	GPS		x	
	Advancing Assessment of Energy Expenditure in Women with Increased Cancer Risk (Kerr)	21	F	NA ^a	NA ^a	x	x	GPS		x	
UPenn	Impact of Exercise and Caloric Restriction on Cancer Recurrence in Mice (Chodosh)	NA	F	NA	Animal				x	x	
	Women in Steady Exercise Research (WISER) Survivor Trial (Schmitz)	>50	F	555	RCT	x	x		x	x	
WUSTL	Breast Cancer-related Lymphedema: Cost of Illness and Cost Effectiveness of Alternative Management Strategies (Schwartz)	30-70	F	NA ^b	Model	x	x		x		
	Transgenerational Animal Models of Nutritional Impact on Cancer Predisposition (Moley)	NA	M/F	NA	Animal				x	x	
	Energy Balance and Post-Radical Prostatectomy Urinary and Sexual Function: PIE (Prostatectomy, Incontinence, Erectile function (Volin))	All	M	500	Cohort	x	x				

TREC Center	Project Title (Leader)	Age	Sex	N	Study Design	Anthropometrics	Physical Activity	GIS	Diet	Blood Biomarkers	Genetics
	SHOW-ME Study (Supports at Home and Work for Maintaining Energy Balance) (Hoehner)	21-65	M/F	~2000	Cross-sectional	x	x	x	x		
	Social Determinants in the Link Between Obesity and Cancer (Hovmand)	All	M/F	5000	Model	TBD	TBD	TBD	TBD	TBD	TBD

Abbreviations: Harvard = Harvard University; UCSD = University of California, San Diego; UPenn = University of Pennsylvania; WUSTL = University of Washington in St. Louis; NA = Not Applicable; RCT = Randomized Clinical Trial; GIS = Geographic Information Systems; GPS = Global Positioning System; TBD = To Be Determined.

^aThis study provides objective energy expenditure measurements to the 2 RCTs being conducted at UCSD.

^bThis study will conduct cost-effectiveness of the RCT being conducted at Penn.

Table 2

Projects in the Harvard University TREC Center (Principal Investigator: Frank B. Hu, MD, PhD)

<p><i>Project 1: Sleep duration, energy balance, and insulin resistance in children</i> <i>Project Leader: Elsie M. Taveras, MD, MPH</i> This project will investigate the role of sleep duration and sleep patterns in early childhood as novel risk factors for obesity and markers of adipose tissue and metabolic dysfunction in adolescence, using data from Project Viva, a prospective pre-birth cohort study (birth to age 12 years). The specific aims are: 1) to examine the extent to which short sleep duration in infancy, chronic insufficient sleep from infancy to mid-childhood, and sleep duration and efficiency at age 12 years are associated with adiposity and cancer-related biomarkers; 2) to examine the extent to which these associations are mediated by dietary behaviors, the composition of diet, and physical activity/inactivity behaviors (e.g., television viewing); and 3) to examine the extent to which these associations are modified by genetic factors.</p>
<p><i>Project 2: Environmental and lifestyle factors, obesity and cancer-related biomarkers</i> <i>Project Leader: Frank Hu, MD, PhD</i> This project will examine the association of behavioral and environmental factors with circulating levels of cancer-related biomarkers among 750 middle aged women in the <i>Nurses' Health Study</i>, and will evaluate whether selected genetic characteristics modify the associations between behavioral and environmental factors and risk of obesity. The aims that will be specifically addressed in this project are: 1) to examine associations between energetic factors and cancer-related biomarkers (insulin/IGF pathway, adipokines, and sex hormones); 2) to examine the relationships of neighborhood social economical status (SES) and built environment (assessed by the county sprawl index) with cancer-related biomarkers; and 3) to examine whether genetic factors modify the associations between behavioral and structural factors and risk of obesity and long-term weight gain.</p>
<p><i>Project 3: Energetics, fatal prostate cancer, and overall survival. Project Leaders: Jing Ma, MD, PhD and Howard Sesso, ScD</i> The overall goal of this project is to gain a better understanding of the biological mechanisms linking obesity with prostate cancer survival, with a focus on biomarkers of the insulin/IGF pathway and adipocyte function. This project will investigate how geospatial and genetic variables are related to biomarker levels and prostate cancer survival in the Physicians' Health Study, allowing for thematic continuity across projects. The findings of these studies will provide new insights into the role of energy metabolism in prostate cancer progression, will guide the identification of novel cancer therapeutic targets, and will help the development of cancer prevention strategies spanning urban planning, diet, and lifestyle modification.</p>
<p><i>Project 4: The impact of exercise and metformin on hyperinsulinemia in colorectal cancer survivors.</i> <i>Project Leaders: Jeffrey Meyerhardt, MD, MPH, Jennifer Ligibel, MD and Lee W. Jones, PhD</i> The primary goal of this project is to determine changes in fasting insulin levels after 6 months of either supervised exercise training alone, metformin alone, or a combination of the two interventions in stage I-III colorectal cancer survivors. The study design is a 2 × 2 randomized trial of supervised aerobic exercise guided by validated behavioral support techniques versus attention control and metformin versus placebo. This trial will provide data that will be very useful in designing large-scale trials to explore the impact of these interventions upon colorectal cancer recurrence and survival.</p>

Table 3

Projects in the UCSD TREC Center titled Energetics & Breast Cancer: Obesity, Inflammation, Insulin Resistance & Risk (Principal Investigator: Ruth E. Patterson PhD)

<p><i>Project 1: Role of Inflammation and Insulin Resistance in Mouse Models of Breast Cancer. Project Leader: Jerrold Olefsky, MD</i> Diets rich in saturated and omega-6 ($\omega 6$) fatty acids (FAs) are pro-inflammatory and increase breast cancer risk, but diets rich in omega-3 ($\omega 3$) fatty acids are anti-inflammatory and decrease cancer risk. We hypothesize that the receptor, GPR120, is the critical mediator of the protective effects of $\omega 3$ FAs in breast cancer. This will be tested in 4 specific aims that combine (1) studies using orthotopic tumor cell transplants, (2) spontaneous tumors in obese wild type (WT) and GPR120 knockout (KO) mice, with and without $\omega 3$ FA supplementation; (3) studies using orthotopic mouse and human tumor cell transplants into RAG2 knockout mice, and (4) studies of metastasis using genetically marked tumor cells in obese WT and GPR120 KO mice.</p>
<p><i>Project 2: Diet Composition and Genetics: Effects on Weight, Inflammation and Biomarkers. Project Leader: Cheryl L Rock, PhD, RD</i> This project will examine whether there is a differential response to dietary macronutrient composition in a weight loss intervention in healthy obese women, depending on insulin resistance status. Outcomes include weight loss; hormonal factors and markers of inflammation that may link obesity to breast cancer mortality; and nutrient-gene interactions that contribute to differential response of cytokines to weight loss and diet composition associated with polymorphisms in IL-6 and TNF-α genes. The study will address these aims in a randomized controlled trial involving 234 obese women randomly assigned to a high-carbohydrate (65% energy) low-fat (20% energy); a low-carbohydrate (45% energy) high-monounsaturated fat (35% energy) diet; or a walnut-rich, lower carbohydrate (45%), higher fat (35% of energy) diet in a 12-month behavioral weight loss program.</p>
<p><i>Project 3: Weight Loss, Mechanisms, and Mortality Among Breast Cancer Survivors. Project leader: Ruth E. Patterson, PhD</i> Biomarkers will be assayed in archived blood samples from a cohort of overweight/obese, postmenopausal cancer survivors with long-term follow-up for mortality. Biomarkers will represent the major proposed mechanisms by which obesity is associated with postmenopausal breast cancer: (1) insulin-IGF axis, (2) endogenous sex hormones, and (3) inflammation. The joint role of these biomarkers will be examined to develop a Biomarker Risk Score that predicts breast cancer mortality. These Risk Score biomarkers will then be assayed in blood samples collected in a randomized controlled trial of metformin and/or weight loss. This 6-month weight loss and exercise intervention trial will randomize 340 overweight/obese postmenopausal breast cancer survivors into four groups: weight loss and metformin, weight loss and placebo, metformin, or placebo. Change in the Biomarker Risk Score from baseline will be used to predict change in the risk of breast cancer mortality in response to the interventions.</p>
<p><i>Project 4: Advancing Assessment of Energy Expenditure in Women with Increased Cancer Risk. Project Leader: Jacqueline Kerr, PhD</i> Participants in the UCSD randomized trials described above will participate in Project 4, by wearing an accelerometer, GPS device, and heart rate monitor for 7 days at study entry and follow-up. Machine Learning algorithms will be applied to the data collected by these devices. Machine Learning is a process whereby computer algorithms are developed and validated in comparison to a training data set (i.e., a gold standard). The training data set will be developed in a separate but parallel study where obese women will wear the physical activity assessment devices and a SenseCam: a small device worn like a necklace that passively collects ~3000 images per day. These images will be manually coded to create the annotated truth file (gold standard) for comparison to the data collected via accelerometers, GPS, and heart rate monitors. The algorithms will be used to assess behavior types as well as activity intensity and their relation to insulin resistance.</p>

Table 4

Projects in the University of Pennsylvania TREC Survivor Center (Principal Investigator: Kathryn Schmitz, PhD, MPH)

Project 1: Impact of Exercise and Caloric Restriction on Cancer Recurrence in Mice.

Project leader: Lewis Chodosh, MD, PhD

Project 1 will use an innovative genetically engineered mouse model for breast cancer recurrence to determine the direct effects of exercise, caloric restriction, or their combination on breast cancer recurrence and surrogate biomarkers of recurrence risk. Mammary tumors will be induced in overweight mice by the doxycycline-dependent activation of an oncogene relevant to human breast cancer in the mammary glands of mice fed a high fat diet. Regression of the resulting tumors will be induced by oncogene down-regulation to generate cohorts of mice bearing dormant residual tumor cells. Overweight mice bearing residual disease will be randomly assigned to exercise, caloric restriction, both of these interventions, or neither and followed for cancer recurrence. Biomarkers will be evaluated to explore the hypothesized relationship between energy balance and recurrence and will include markers reflecting the PI3K-Akt-mTOR pathway, insulin resistance, IGF-1, HGF, adipokines, inflammation, tumor angiogenesis and oxidative stress.

Project 2: Women In Steady Exercise Research (WISER) Survivor Trial.

Project Leader: Kathryn Schmitz, PhD, MPH

The WISER Survivor Trial is a follow-on to the WISER Trial from TREC1 [35-38], the ongoing WISER Sister Trial (R01-CA131333 to Schmitz), and the PAL trial [39,40]. The goals of the WISER Survivor trial are to assess the effects of exercise and/or weight loss through caloric restriction on a common long term adverse effect of treatment (lymphedema), biomarkers for recurrence, and quality of life. Blood samples will be stored until results from project 1 are available. Surrogate biomarkers for the molecular pathways that mediate observed effects in project 1 will be analyzed. This one year controlled weight loss and exercise intervention trial will randomize a multi-ethnic cohort of overweight and obese breast cancer survivors with clinically confirmed lymphedema into four groups: exercise, caloric restriction, both of these interventions, or neither (control group), with a sample size of 125 per group (N=500).

Project 3: Breast Cancer-Related Lymphedema: Cost of Illness and Cost Effectiveness of Alternative Management Strategies. Project leader: J. Sanford Schwartz, MD

Breast cancer related lymphedema (BCRL), characterized by arm swelling, impaired function and bothersome symptoms, is a common, persistent adverse event of breast cancer therapy. BCRL incurs substantial health care costs (significant portions of which are borne by patients), reduces productivity and reduces quality of life. Effective behavioral interventions such as exercise training and weight loss may mitigate its impact and prevent progression, but often are not reimbursed. There is a compelling need to better characterize the medical economic impact of BCRL, as well as its short- and long-term health consequences. Project 3 will: (1) assess BCRL direct medical care costs; (2) assess the incremental cost-effectiveness of the Project 2 interventions; and (3) model the impact of the Project 2 interventions over an extended time frame.

Table 5

Projects in the Washington University in St Louis Transdisciplinary Research on Energetics and Cancer Center (Principal Investigator: Graham Colditz, MD; Co-Principal Investigator: Sarah Gehlert, PhD)

<p><i>Project 1: Transgenerational animal models of nutritional impact on cancer predisposition. Project Leader: Kelle H. Moley, MD</i> This project will examine the effect of maternal high-fat diet and changes in metabolic bioenergetics on prostate gland development and susceptibility to prostate cancer in male offspring. This team will address exposures across epigenetic changes that arise among offspring of obese females, leading to abnormal expression of key genes involved in the development of the prostate gland, which predispose the offspring to develop cancer. Findings from this project will be positioned to inform molding of cancer in populations as implemented in Project Four.</p>
<p><i>Project 2: Energy balance and post-radical prostatectomy urinary and sexual function: PIE (Prostatectomy, Incontinence and Erectile function). Project Leaders: Kathleen Wolin, ScD and Adam S. Kibel, MD</i> Concerns regarding the loss of urinary and sexual function are major drivers of treatment decisions in men with prostate cancer. This prospective observational cohort study will recruit n=500 men prior to radical prostatectomy and follow them for 12 months post-operatively to evaluate the role of physical activity and obesity in trajectories of urinary and sexual function following surgical treatment for prostate cancer, thus addressing an important patient-reported outcome. Furthermore, this team addresses the TREC goal of expanding translational research to cancer survivors.</p>
<p><i>Project 3: SHOW-ME Study (Supports at Home and Work for Maintaining Energy Balance). Project Leaders: Christine Hoehner, PhD, MSPH and Ross Brownson, PhD</i> This project addresses worksite environments and policies relevant for physical activity and diet behaviors and evaluates whether worksite supports for physical activity and healthy eating are predictive of obesity. Assessing worksite in the context of built environment will provide actionable knowledge about what policy changes in communities and worksites would have the greatest impact on healthy lifestyles to prevent obesity and related cancers. This team will begin designing for dissemination early in the study period to bring their findings to local worksites, governments and practitioners.</p>
<p><i>Project 4: Social determinants in the link between obesity and cancer. Project Leaders: Peter Hovmand, PhD and Graham A. Colditz, MD, DrPH</i> This project focuses on understanding the role that social determinants play in the link between obesity and cancer at the population level across the lifespan. This team will develop a multi-cohort computer simulation model of obesity and non-Hodgkin's lymphoma (NHL). The influence of social determinants on the link between obesity and NHL will then be studied through a series of factual/counter-factual comparison. Once the simulation approach is established, additional cancers can be added to the model using data from this or other TREC Centers.</p>