National Cancer Institute

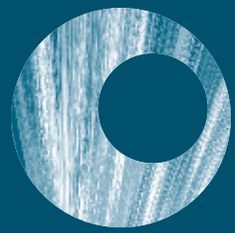
MARCH 2009

Transdisciplinary Research on Energetics and Cancer

39TH REGULAR MEETING OF THE BOARD OF SCIENTIFIC ADVISORS

Division of Cancer Control and Population Sciences

TREC



U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

Transdisciplinary Research on Energetics and Cancer (TREC)

MIDCOURSE UPDATE

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MARCH 2009

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NATIONAL CANCER INSTITUTE

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Foreword

The rising incidence of obesity worldwide and the suspected role that obesity plays in the development of many types of cancer have created a new challenge for the cancer research community in the 21st century. The National Cancer Institute (NCI) has responded to this challenge by expanding support for collaborative science concerning diet and physical activity, energy balance, and cancer prevention.

In its 2007 report, *Promoting Healthy Lifestyles: Policy, Program, and Personal Recommendations for Reducing Cancer Risk,* the President's Cancer Panel recognized that the prevention of obesity, overweight, and sedentary behavior are major challenges for cancer control and that proven methods to address these issues have not yet been established. Almost two-thirds of the US population is overweight, and approximately half of those individuals are obese. If current trends continue, an estimated 74% of the adult population will be overweight or obese by 2010.

The data linking overweight and obesity to physical inactivity, poor dietary choices, and adverse health outcomes are significant. Obesity rates vary, with higher rates observed among groups of lower socioeconomic status and in some racial/ethnic groups. The escalating rates of overweight and obesity among children and adolescents are especially concerning. Significant advances are required to optimize treatment and prevention strategies for these populations.

In 2005, NCI launched the Transdisciplinary Research on Energetics and Cancer (TREC) initiative to foster the integration of social, behavioral, and biological sciences to address obesity, physical inactivity, and poor diet within a cancer prevention context. Working under a cooperative agreement, the four TREC Research Centers and the Coordination Center have developed a comprehensive network of talented investigators and made outstanding scientific progress. The Research Centers are Case Western Reserve University, Fred Hutchinson Cancer Research Center, the University of Minnesota, and the University of Southern California. The Fred Hutchinson Cancer Research Center serves as the Coordination Center as well.

The work of TREC investigators complements NCI's other energy balance research endeavors, as well as the many programs supported across the National Institutes of Health (NIH) and stimulated by the NIH Obesity Research Strategic Plan of 2004. The TREC initiative was developed to help us understand and reduce the increasing prevalence of overweight and obesity in the United States by enhancing our understanding of the mechanisms underlying the association between energy balance and carcinogenesis. TREC researchers are answering critical questions that will help guide our nation's public health efforts.

I am pleased to issue this Midcourse Update for TREC, which provides highlights of the evidence being generated by the TREC transdisciplinary researchers and partnership. The science that has evolved promises breakthrough discoveries in mechanisms of metabolism and in the behavioral, social, and environmental models. This Midcourse Update illustrates how the transdisciplinary science supported by TREC can accelerate progress and contribute toward NCI's goal of reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet.

Sincerely,

Robert T Croyle, PhD
Director

DIVISION OF CANCER CONTROL AND POPULATION SCIENCES
NATIONAL CANCER INSTITUTE

1

Overview

The National Cancer Institute (NCI), in response to the growing public health concern with overweight and obesity in the United States, established the Transdisciplinary Research on Energetics and Cancer (TREC) Centers in nutrition, energy balance, and physical activity. The Centers include scientists from multiple disciplines and encompass projects spanning the biology and genetics of behavioral, socio-cultural, and environmental influences on nutrition, physical activity, weight, energy balance, and energetics.

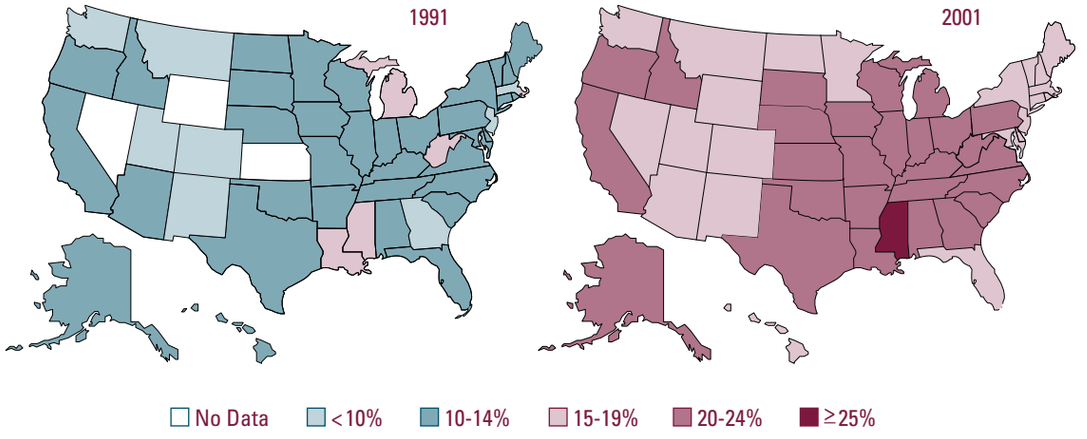
Introduction

Overweight and Obesity in the United States

The prevalence of overweight and obesity continues to rise to epidemic rates for both adults and children in the United States. Data for adults ages 20 to 74 from two National Health and Nutrition Examination Surveys (NHANES) have shown that the prevalence of obesity increased from 15% (in 1976-1980) to 32.9% (in the 2003-2004 survey) (see Figures 1 and 2). Data from the 2003-2004 NHANES indicate that 26.2% of youth ages 2 to 5 years, 37.2% of youth ages 6 to 11 years, and 34.3% of youth ages 12 to 19 years are overweight, are obese, or have a body mass index (BMI) equal to or greater than their age- and gender-adjusted 85th percentile (Koplan et al., 2005). As an overall health problem, obesity due to unhealthy lifestyle has an adverse public health impact, is associated with shortened life expectancy similar in scope to tobacco use, and is perhaps the most important risk factor among non-smokers.

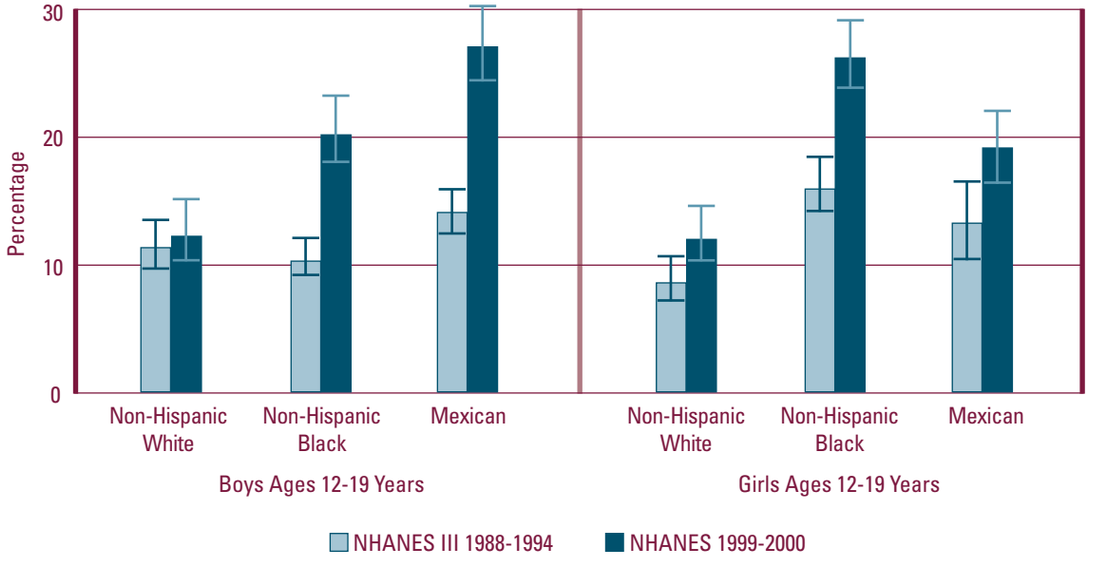
In 2002, the International Agency for Research on Cancer (IARC) report *Weight Control and Physical Activity* indicated that the avoidance of adult weight gain, in combination with efforts to improve diet, may have protective effects against selected cancers such as cancers of the colon, uterus, and kidney; postmenopausal breast cancer;

FIGURE 1: The Epidemic of Obesity in the United States



Source: Ogden et al., 2006

FIGURE 2: Overweight Prevalence by Race/Ethnicity for Adolescent Boys and Girls



Source: Ogden et al., 2006

and adenocarcinoma of the esophagus (see sidebar below). The report estimated that between 25% and 34% of these cancers may be attributable to the combined effects of increased body weight and inadequate physical activity (IARC, 2002). Yet, in 2004, research was limited largely to the discovery of single-cancer prevention-related factors, such as diet, nutrient intake, body mass, or physical activity. Few studies embraced a multidisciplinary approach to examine these factors simultaneously and address their health impact. Another limitation was the lack of evidence on which social-environmental, policy, or structural-level changes would be the most cost-effective approaches for prevention and weight control.

From the 1990s onward, levels of childhood overweight and obesity have continued to rise dramatically (National Task Force, 2000; IOM, 2005). This increase has ominous implications for the development of serious diseases such as type 2 diabetes, heart disease, certain cancers, and depression during youth and into adulthood (Mokdad et al., 2003; Kumanyika et al., 2008). Overweight and obesity disproportionately affect racial and ethnic minority populations and people of lower socioeconomic status (Flegal et al., 2002; Sedjo et al., 2007). Further studies were recommended to explore how behaviors involving body weight, physical activity, and diet may affect the development of cancer as well as prognosis for cancer survivors (Calle and Kaaks, 2004; Calle and Thun, 2004; McTiernan, 2008). This was particularly relevant for populations and communities with the highest rates of childhood obesity, which continues today to be a high-priority research area.

Cancers Associated with Obesity

Established or suspected obesity-related cancers include:

- Breast (postmenopausal)
- Prostate (advanced)
- Pancreas
- Esophagus (adenocarcinoma)
- Gastric cardia (adenocarcinoma)
- Endometrium
- Colon and rectum
- Liver
- Gallbladder
- Kidney (renal cell)
- Non-Hodgkin's lymphoma
- Multiple myeloma
- Leukemia
- Stomach (males)
- Ovary
- Uterus
- Cervix

Source: President's Cancer Panel, 2007

The term *energy balance* refers to the integrated effects of diet, physical activity, and genetics on growth and body weight over an individual's lifetime. Evidence continues to demonstrate the importance of understanding the effects of energy balance on the development and progression of cancer and on cancer patients' quality of life (WCRF/AICR, 2007). As NCI expands its leadership to advance population-based energy balance research, this approach has been broadened to include more complex models of discovery in behavior, environment, mechanisms, and genetics, with special emphasis on pediatric obesity and prevention. This approach is the foundation for discovery behind the TREC initiative.

Strategic Planning

Given the complexity and multiplicity of the forces driving the obesity epidemic, the National Institutes of Health (NIH) established a Strategic Plan for Obesity Research in 2004. Developed by the NIH Obesity Research Task Force, of which NCI is a partner, the Strategic Plan was framed to thoughtfully engage an obesity research agenda. Key priorities include preventing and treating

obesity through lifestyle modification; preventing and treating obesity through pharmacological, surgical, and other medical approaches; breaking the link between obesity and its associated health conditions; and conducting research on cross-cutting topics, including health disparities, technology, fostering of interdisciplinary research teams, investigator training, translational research, and education/outreach (HHS/NIH, 2004).

"TREC has helped me build new bridges with colleagues from other disciplines as well as strengthen my existing collaborative network."

— JAYNE A FULKERSON, PHD
UNIVERSITY OF MINNESOTA SCHOOL OF NURSING

In response to the growing obesity epidemic and public health concern, NCI developed the TREC initiative. This 5-year, $54 million effort is designed to integrate the study of diet, weight, and physical activity; energy balance; and their effects on cancer. It draws from basic to clinical sciences, to influence population-focused research. TREC has a central role in NCI's obesity-focused research portfolio. Four Research Centers and one Coordination Center were funded in September 2005. The award recipients include Case Western Reserve University, the Fred Hutchinson Cancer Research Center, the University of Minnesota, and the University of Southern California. The Fred Hutchinson Cancer Research Center is also the site for the Coordination Center. Collaboration across these transdisciplinary teams of scientists fosters an accelerated rate of progress toward reducing cancer incidence, morbidity, and mortality. As noted in NCI's FY2009 report, *The Nation's Investment in Cancer Research: Connecting the Cancer Community,* significant advances are required to better understand and integrate the complex pathways and systems into a population perspective that will allow use of such knowledge for cancer prevention and control (HHS/NIH, 2008, p. 27).

The TREC initiative has benefited from prior NCI multidisciplinary and transdisciplinary initiatives, such as the Transdisciplinary Tobacco Use Research Centers (TTURC), the Centers of Excellence in Cancer Communication Research (CECCR), and the Breast Cancer Surveillance Consortium (web links to these projects are provided in the References section at the end of this chapter).

Continuum of Disciplinarity

Unidisciplinary – Researchers from a single discipline work together to address a common problem.

Multidisciplinary – Researchers from different disciplines *work independently* or sequentially, each from his or her own discipline-specific perspective, to address a common problem.

Interdisciplinary – Researchers from different disciplines *work jointly* to address a common problem, and, although some integration of their diverse perspectives occurs, participants remain anchored in their own fields.

Transdisciplinary – Researchers from different disciplines *work jointly to create a shared conceptual framework* that integrates and moves beyond discipline-specific theories, concepts, and approaches, to address a common problem.

Source: Rosenfield, 1992.

Based on the lessons learned from these earlier initiatives, NCI developed the TREC concept to enhance the options for rapid collaboration and productivity (Morgan et al., 2003; Stokols et al., 2003) (see sidebar on previous page). Progress has been exceptional to date and is described in detail within this report. The TREC initiative draws from the collective expertise of NCI scientists across the Division of Cancer Control and Population Sciences (DCCPS), the Division of Cancer Prevention, and the Division of Cancer Biology, as well as members of the NCI Energy Balance Task Force. TREC is led by Linda Nebeling, PhD, MPH, RD, FADA, Chief of the Health Promotion Research Branch in the Behavioral Research Program, DCCPS, NCI. Ms Yvonne Grant, Program Analyst, is the Administrative Program Director.

"The openness of TREC investigators to consider the importance of sleep disturbances as an obesity risk factor has generated many new ideas and approaches. My own work has been enriched."

— SUSAN REDLINE, MD, MPH
CASE WESTERN RESERVE UNIVERSITY

This urgency surrounding the childhood obesity epidemic continues today and requires further consideration. To this end, NCI and NIH will partner with the nation's leading research funders – the Centers for Disease Control and Prevention and the Robert Wood Johnson Foundation – in an effort to improve the efficiency and effectiveness of childhood obesity research through increased coordination and collaboration. Recently launched, the National Collaborative on Childhood Obesity Research is working together to build capacity for multilevel, integrated research; increase the effectiveness of research, translation, and evaluation initiatives; and enhance capacity for translation and dissemination of effective interventions. The TREC initiative is a valuable component of this emerging effort.

Organization of This Report

This report begins with a description of the TREC initiative and features the accomplishments and activities of the five TREC Centers during the first 3 years of funding. Chapters 2 to 6 provide individual synopses of the research projects and midpoint outcomes within, and across, each of the four TREC Research Centers and the Coordination Center. Chapter 7 summarizes the overall evaluation of the TREC initiative that has been set into place. Chapter 8 provides summaries of the activities and accomplishments of the TREC Working Groups and Task Forces. Chapter 9 includes highlights of the cross-Center research collaborations that have evolved since the initiative was funded. They are examples of the expanding transdisciplinary approach to key research opportunities that have developed during the past 3 years. The report concludes with a compilation of all TREC relevant presentations and publications to date.

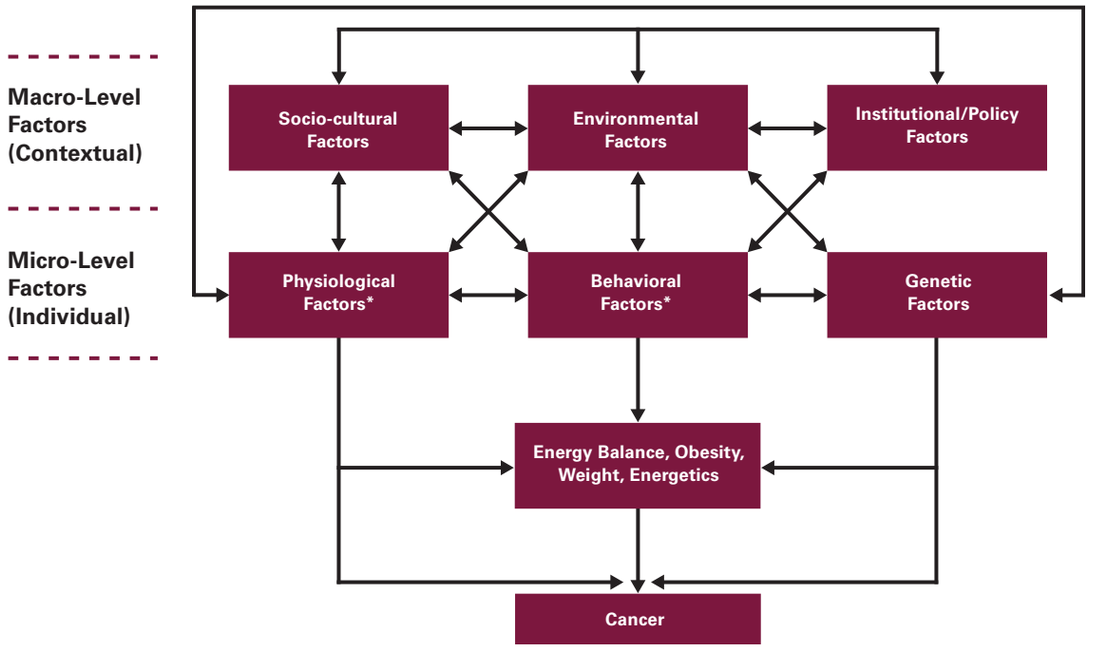
This synopsis frames the unique and distinctive nature of the TREC Research Centers and Coordination Center and identifies the research questions and challenges addressed by the initiative, the various research methodologies used, and the breadth of disciplinary research fields needed to solve the complex problem of obesity and its relationship to cancer.

Section 1
Purpose and Goals of the TREC Initiative
Purpose of the TREC Initiative

Prior to the development of the TREC initiative, an overarching framework that highlighted the interactive nature of the various factors that contribute to obesity and overweight, and how they may influence obesity-related carcinogenesis, was lacking. Figure 3, the TREC conceptual model, displays the classifications of factors that potentially contribute to energy balance, obesity, weight status, and energetics within the context of cancer prevention. These classifications are arranged into micro-level (or individual) factors and macro-level (or contextual) factors. This conceptual model highlights the complex and interactive factors that may contribute to obesity (i.e., energy imbalance) and influence the relationship between obesity and carcinogenesis. While macro-level factors are noted to be more distal from obesity-related carcinogenesis, it is important to note that macro-level factors are viewed as critical factors that likely shape individual-level factors and the relationship between obesity and carcinogenesis.

The NCI funding concept established a U54/U01 cooperative agreement in nutrition, energetics, and physical activity, referred to as the TREC initiative. It was designed to foster transdisciplinary studies that will enable the integration

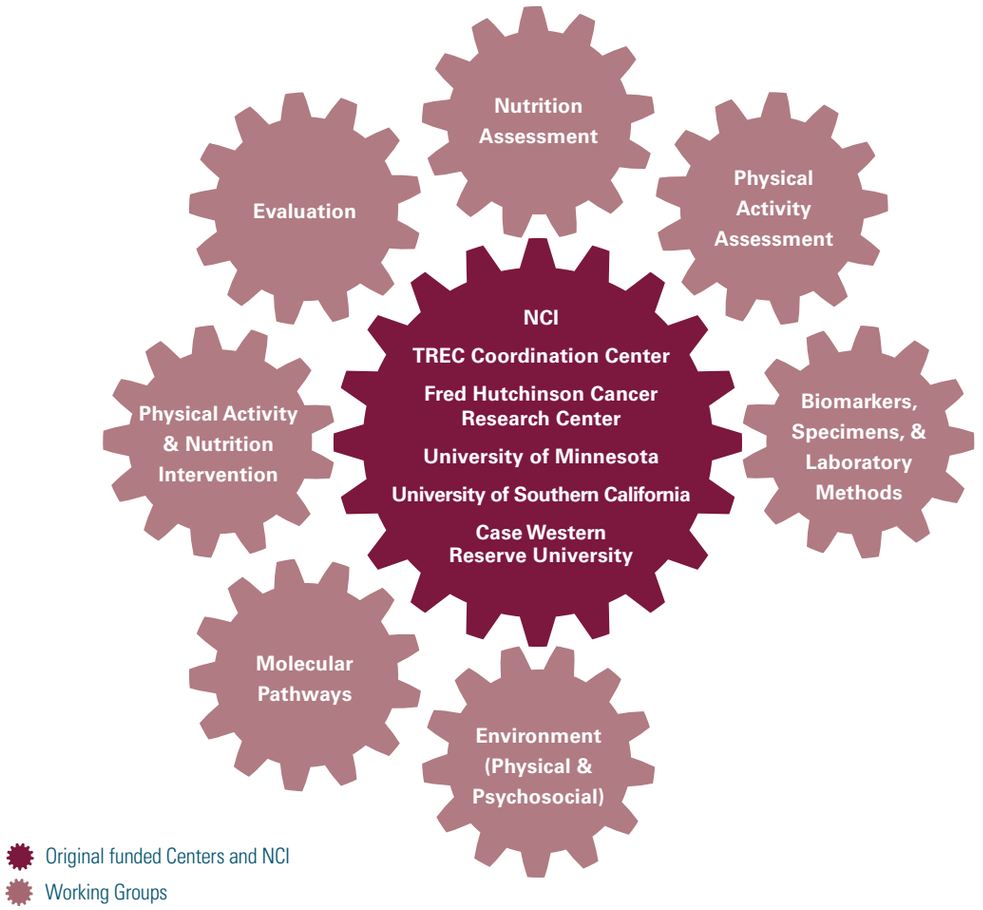
FIGURE 3: TREC Conceptual Model



* 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).

Macro-level factors represent variables outside the individual that serve as the contexts in which obesity and energy imbalance develop. Micro-level factors represent variables within the individual that contribute to obesity, energy imbalance, and the links between energy balance and carcinogenesis. These macro- and micro-level factors are complex and interactive. Physiological and behavioral factors also form psychological (e.g., stress), personality, and cognitive factors (e.g., efficacy) that contribute to energy balance (not displayed).

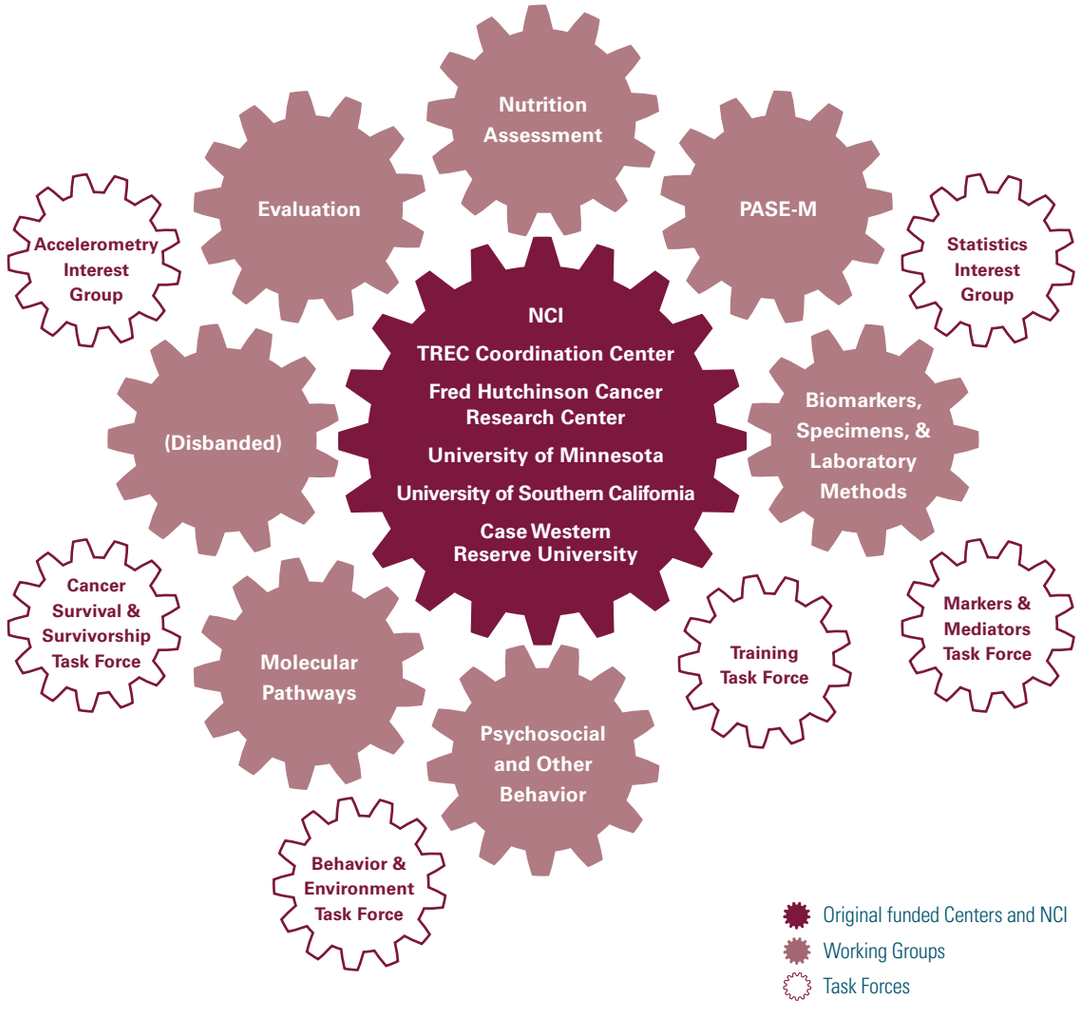
FIGURE 4: TREC Network Original Funded Structure in 2005



The center wheel depicts the core of the TREC network. It is comprised of the five funded sites and NCI. The seven smaller wheels depict the seven Working Groups formed in year 1 to address common research interests and promote cross-collaboration.

of social, behavioral, and biological science into more comprehensive study designs. Research Centers were selected through a national peer review process. The selected Research Centers include a large number of scientists from multiple disciplines and encompass projects ranging from the biology and genetics of energy balance to behavioral, sociocultural, and environmental influences on nutrition, physical activity, weight, energy balance, energetics, and cancer (see Figure 4). A Steering Committee was formed to lead and govern the scientific collaborations and projects. Seven Working Groups were established by the TREC Steering Committee during the first year to focus on specific research questions that would arise as the initiative moved forward. The Working Groups advise the TREC Steering Committee on protocol, policy, and procedural issues pertaining to their respective areas of expertise. They have been a major factor in the identification and framing of cross-Center collaborations that have evolved since the TREC initiative started. Over

FIGURE 5: Growth of TREC Network, 2008



As the TREC network continued to evolve, the Working Groups were modified to meet the scientific challenges. Two Working Groups modified their research focus (Physical Activity, Sleep, and Environmental Measurement, or PASE-M, and Psychosocial and Other Behavior), and one was disbanded. Six new groups were established as special Task Forces or Special Interest Groups. These newer additions (see the outlying wheels) were formed to address specific cross-collaborative research priorities.

time, the number of Working Groups has evolved to reflect the scientific priorities that have developed across the initiative. Special Task Forces were established to address key research questions and needs identified by the TREC Steering Committee and the TREC investigators (see Figure 5).

These measures were taken to improve TREC's collaboration and impact.

TREC's Mission

Significant advances are required to integrate our current and future understanding of these pathways

into a population perspective that will allow use of such knowledge for cancer prevention and control. Such advances depend critically on programs that bring together researchers with diverse perspectives and give them the support needed to facilitate collaboration. TREC Centers are expected to elucidate how these factors interrelate in transdisciplinary, integrative approaches that span the cancer continuum and that range from basic and clinical metabolic studies to behavioral and population-based studies. A unique aspect is that TREC Centers must establish a developmental research program with processes for conceiving and evaluating studies that allow exploration of novel directions, especially those that might arise with the progression of major projects.

Goals and Objectives

Each TREC Center was required to address at least three of the four goals below and to effectively integrate basic and population sciences within its research initiatives. These four goals build on the lessons learned from the Transdisciplinary Tobacco Use Research Centers, an example of a successful transdisciplinary program (Morgan et al., 2003).

1. To enhance the understanding of the mechanisms underlying the association between energy balance and carcinogenesis across the cancer continuum, from causation and prevention through survival.
2. To develop effective, innovative approaches for the prevention of obesity with broad population impact at the social-environmental and policy levels, focusing on children and critical periods during adulthood where weight gain is likely to occur. High-risk periods include times of smoking cessation, cancer treatment, and major life transitions involving work or family.
3. To bring together diverse disciplines in creative new ways by facilitating collaborative endeavors between researchers from cancer centers, schools of public health, and academic departments from diverse disciplines such as molecular biology, genetics, psychology, anthropology, urban planning, informatics, social sciences, and communications.
4. To create significant new opportunities for interdisciplinary training in energy balance and cancer for scientists at every stage in their careers.

TREC Sites and Coordination Center

In addition to state-of-the-art research, a TREC Center must provide career development opportunities for new and established investigators who wish to pursue active research careers in transdisciplinary nutrition, physical activity, weight, and energy balance and must provide developmental funds for innovative developmental projects. Essential parts of this initiative are the interactions among the TREC Centers on research collaborations, the exchange of scientists on a visiting basis, the establishment of special Working Groups, resource sharing, and other innovative mechanisms.

All TREC Centers participate in two semi-annual meetings. The purpose of these meetings is to share scientific information, assess scientific progress in the field, identify new research opportunities, and facilitate cross-collaborations to promote discovery and resolve areas of controversy. Where pertinent,

TREC Priority Research Topic Areas

Examples illustrative of research priorities featured in TREC:

- Energy balance & carcinogenesis throughout the life cycle
- Ecological models of health behaviors
- Racial/ethnic health disparities
- Methodologies, biomarkers, & mechanisms
- Population-level effects
- Transdisciplinary partnerships

the five TREC Centers are encouraged to use common measures that allow pooling of data. Since evaluation of the progress of large initiatives is an increasing priority for NCI, all TREC Centers are required to participate in a variety of evaluation activities that have been developed jointly by the TREC Evaluation Working Group and the NCI Evaluation of Large Initiatives (ELI) team (Hall et al., 2008; Stokols et al., 2008). Further details on the evaluation design are provided in Chapter 7. As part of the TREC research goal to address cross-cutting health disparity concerns, the TREC Centers are encouraged to form partnerships with public health agencies and other health organizations that have strong ties to minority communities with high rates of obesity and cancer.

Section 2
Description of the TREC Centers: What We Do

TREC scientists are studying how the combined effects of obesity, poor diet, and lack of physical activity increase cancer risk. They are also searching for effective ways to prevent obesity. The TREC Research Centers conduct diverse projects that involve scientists from disciplines such as molecular biology, genetics, proteomics, nutrition, physical activity, psychology, sociology, environment, public policy, and statistics. Along with primary research projects, each Center contains a number of cores that support administrative, statistical, and training activities. The TREC Coordination Center facilitates interactions across and between the Research Centers and NCI. It also provides common services and can support a central data repository tracking system for all TREC partners. Further details on each TREC Center and the Coordination Center can be found in Chapters 2 to 6.

Case Western Reserve University
Lead PI: Nathan A Berger, MD

The Case Western Reserve University (CASE) TREC Center concentrates on cellular mechanisms, using laboratory models and clinical research that focus on obesity, metabolic dysfunction, and colorectal cancer risk.

- Obesity and Molecular Pathways Leading to Colon Cancer (Co-PIs: Sanford Markowitz, MD, PhD, and Joseph Nadeau, PhD) seeks to determine the intestinal tumor-inducing effect and molecular signaling pathways associated with a high-fat diet versus obesity in unique strains of mice with chromosomal substitutions rendering them susceptible or resistant to the obesigenic effects of high-fat diets.
- Insulin Resistance Syndrome Pathway Factors and Colon Polyps (PI: Li Li, PhD) examines candidate gene variance and haplotype, associated biomarkers, and insulin resistance syndrome-related serum markers to understand how insulin resistance syndrome, related genes, and dietary factors work in concert in the etiology of human colon neoplasia.
- Determination of Obesity and Metabolic Dysfunction in Adolescents (PI: Susan Redline, MD) explores the determinants of obesity and metabolic dysfunction during the critical life-transition period of adolescence. This study will capitalize on a unique population cohort followed as part of the Cleveland Children's Sleep and Health Study and will investigate sleep phenotype and sleep disturbances as novel and important determinants of obesity and its relation to metabolic dysfunction.

Fred Hutchinson Cancer Research Center
Lead PI: Anne McTiernan, MD, PhD

The TREC Research Center at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle is focused on the prevention of breast and colorectal cancers, with particular emphasis on diet and physical activity. The Seattle TREC Center includes an integrated research program examining energy balance and its consequences in cells, animal models,

and human subjects. Novel laboratory work in proteomics and metabolomics includes testing the effects of dietary and exercise intervention in order to identify biological signals of adiposity.

- Mechanisms Linking Nutrient Supply and Cell Cycle/Survival (PI: David Hockenbery, MD) will bring together basic research efforts under way in FHCRC laboratories in an innovative approach to analyzing the cellular effects of hyperglycemia, hyperinsulinemia, and inflammation on growth, proliferation, and survival pathways relevant to oncogenesis.
- Energy Balance and Cancer: Markers and Mechanisms in Rats (PI: Henry Thompson, PhD) will determine, in an animal model, the effects of caloric restriction and exercise, alone and in combination, on the carcinogenic response in the mammary gland and on the mechanisms by which changes in energy balance modulate the development of cancer.
- Glycemic Load and Obesity Effects on Cancer Biomarkers (Co-PIs: Johanna Lampe, PhD, and Marian Neuhouser, PhD) will investigate the metabolic and cancer biomarker response to experimental high- and low-glycemic load diets in lean and obese adults in a controlled feeding study using a randomized crossover design.
- Exercise and Diet: Biomarkers and Mechanisms in Humans (Co-PIs: Cornelia Ulrich, PhD, and Anne McTiernan, MD, PhD) will investigate the effects of dietary weight loss and exercise, alone and together, on biomarkers of inflammation and DNA damage and repair, as well as the influences of genetic polymorphisms on these associations.
- Preventing Obesity in Low-Income Working Adults (PI: Shirley Beresford, PhD) will test a worksite obesity prevention intervention in a geographic area with a large representation of low-income and minority individuals, to determine whether the intervention has any impact on BMI and markers of insulin resistance and inflammation.

University of Minnesota

Lead PI: Robert W Jeffery, PhD

The University of Minnesota TREC Research Center is focused on population studies that examine the causes of, and effective prevention strategies for, obesity in youth and families.

- Etiology of Adolescent Obesity (IDEA) (PI: Leslie Lytle, PhD, RD) is a multifactorial, cross-sectional, prospective observational study examining predictors of obesity development in adolescents, including sociocultural factors, family factors, environmental factors, and individual factors.
- Take Action: Household Environmental Weight Gain Prevention (PI: Simone French, PhD) is evaluating a family-based weight gain prevention intervention that emphasizes intervention on environmental contributors to weight gain.
- Women In Steady Exercise Research (WISER) (PI: Mindy Kurzer, PhD) is studying the effects of physical activity on estrogen metabolism, oxidative stress, and DNA repair mechanisms in young women.

University of Southern California

Lead PI: Michael I Goran, PhD

The University of Southern California (USC) TREC Research Center explores physiologic, metabolic, genetic, behavioral, and environmental influences on obesity and cancer risk in minority children.

- Obesity-Related Metabolic Risk for Cancer: Ethnicity and Response to Exercise in Minority Youth (PI: Michael Goran, PhD) examines the ethnic differences in obesity-related metabolic

risk factors for cancer in Hispanic and African American youth and the potential role of strength training as an innovative intervention for improving these risk factors.

- Insulin Resistance and Declining Physical Activity Levels in African American and Latina Girls (PI: Donna Spruijt-Metz, PhD) studies the biological and behavioral bases for the decline in physical activity during puberty in minority girls.
- Influence of Built Environments on Obesity During Childhood (Co-PIs: Michael Jerrett, PhD, and Kiros Berhane, PhD) will examine the built environment and urban sprawl as risk factors for the development of obesity in children.

TREC Coordination Center

Lead PI: Mark Thornquist, PhD

FHCRC also serves as the Coordination Center for the TREC initiative. The Coordination Center supports communication, dissemination, data sharing, and collaboration among the TREC Research Centers and NCI.

The TREC Coordination Center:

- Collaborates with the TREC Research Centers to lead the scientific development of data methods and systems to promote collaborative research on energetics and cancer.
- Provides centralized operational support for the TREC initiative by organizing regular TREC meetings and establishing a communication infrastructure for information exchange.
- Facilitates the training of new investigators through the identification and coordination of training workshops.
- Disseminates TREC research knowledge through the creation of a public website and the organization of sessions at scientific meetings.
- Collaborates with NCI to develop evaluation metrics for the TREC initiative and performs evaluation on a regular basis.

Section 3
Overview of TREC Accomplishments to Date

The progress of the five TREC Centers has been exceptional during the first 3 years, while avoiding many of the hurdles seen previously. Gleaning the benefits of the lessons learned from prior transdisciplinary initiatives within DCCPS, TREC investigators have taken maximum advantage. The result is the exceptional pace and progress this group has achieved in 3 short years, both in building expanding partnerships and in conducting developmental and cross-collaboration research. *The TREC initiative has been able to accomplish more at this stage of its funding cycle than prior initiatives of its kind in DCCPS.*

Cross-Center Research Opportunities

Cross-Center collaboration has been a vital part of the TREC initiative. A major force has been the developmental projects that started in the first funding year. The developmental projects have enabled TREC scientists to explore new research opportunities and directions as they arise. A total of 96 developmental projects have been awarded since TREC started (see Table 1). The developmental project funds support new investigators and encourage new fields of research. This resource allows TREC to integrate new and innovative technologies and/or methodologies into existing research infrastructure. Developmental projects are collaborative among scientists within one or more TREC sites or with scientists outside the TREC initiative (see Figure 6). Developmental projects have developed as a result of preliminary results from a Center's primary project and from emerging discoveries.

TABLE 1: Developmental Projects Awarded 2006-2008

YEAR 1

Case Western Reserve University

134 Metabolomic Studies of Mice Susceptible to Obesity and/or Colon Cancer (PI: Henri Brunengraber)

135 Regulation of Obesity and Endoplasmic Reticulum Stress by Salicylates (PI: Bryan Williams)

Seattle

136 Fitness, Fatness, and Cancer Biomarkers in Youth (closed) (PI: Glen Duncan)

137 Development of a Serum-Based Marker of Apoptosis and Assessment of Responses to Dietary and Exercise Interventions (PI: David Hockenbery)

138 The Gut Microbiota as a Cancer Biomarker Influenced by Glycemic Load and Obesity (PI: Meredith Hullar)

139 Characterization of Diet- and Exercise-Dependent Metabolic Phenotypes: Evaluating Responses to Interventions (PI: Terry Kavanagh)

140 Ancillary Data and Sample Collection in Seattle TREC Project 3, the CARB Study (PI: Johanna Lampe)

141 Effect of a 12-Month Exercise Intervention on Inflammatory Markers in Men and Women (PI: Anne McTiernan)

142 Effect of Exercise and Caloric Restriction on Adipose Tissue Biomarker Specimen Collection Pilot (PI: Cornelia Ulrich)

143 Obesity, Menopausal Status, and Mammary Carcinogenesis: Model and Mechanisms (PI: Zongjian Zhu)

University of Minnesota

144 Biological Determinants of Obesity in Teens (PI: Donald Dengel)

145 Social, Cultural, and Contextual Dimensions of Young Women's Physical Activity (PI: Maureen O'Dougherty)

146 Validation of Internet-Based Dietary Assessment (PI: Mark Pereira)

147 Effects of Exercise on Breast Cancer Biomarkers in Nipple Aspirate Fluid (closed) (PI: Andrea Plate)

148 Physical Activity and Media in the Home Environment (PI: John Sirard)

University of Southern California

149 Combining Strength and Cardiovascular Exercise (Circuit Training) to Reduce Obesity and Associated Diseases in Overweight Latina Youth (PI: Jaimie Davis)

150 Hip Hop 2 Health (HH2H) (PI: Lester Jones)

151 Colon Cancer-Related Epigenetic Changes in Obesity (PI: Howard Kaufman)

152 SportBrain™ Pedometer and GPS Logging Technology: Better Tools for Evaluating Physical Activity in Children and an Application to the Impact of Neighborhood Land Use and Children's Commuting Time (PI: Rob McConnell)

The unique three-digit reference number is part of a code assigned to each project when it is awarded. This reference number will enable the reader to link the specific projects listed in Table 1 to Figure 6.

All developmental projects are listed by the year of initial funding. In some cases, developmental projects, such as the TREC Coordination Center projects, are ongoing from the year of initial funding through year 4.

TABLE 1: Developmental Projects Awarded 2006-2008 – Continued

153 Exploring the Link Between Obesity and Poor Prognosis of Childhood Acute Lymphoblastic Leukemia Using a Murine Model (PI: Steve Mittleman)

154 Ola No Ke Kino (The Body Enjoys Health!) (PI: Victor Pang)

155 Food for Thought: A Community-wide Strategic Summit for Reducing Overweight/ Obesity Among Latino and African American Families (PI: Michael Ruble)

156 Functional Brain Responses After Satiety in Normal Weight and Overweight Adolescent Girls (PI: Dawna Salter-Venzon)

157 "Kid Healthy" Steps to Healthy Living (PI: Jackie Teichmann)

158 Social Network Influences on Diet and Physical Activity (PI: Thomas Valente)

Coordination Center
(Fred Hutchinson Cancer Research Center)

159 Specimen Tracking System for the Seattle TREC Center (PI: Mark Thornquist)

YEAR 2

Cross-Center

160 Autonomic and Metabolic Dysfunction in Obese Children with Sleep-Disordered Breathing (Co-PIs: Michael CK Khoo, University of Southern California; Susan Redline, Case Western Reserve University)

161 Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-ethnic Sample of Children: A Transdisciplinary Cross-Site Developmental Project (Co-PIs: Mark Pereira, University of Minnesota; Donna Spruijt-Metz, University of Southern California)

162 Pediatric Primary Care Obesity Prevention (Co-PIs: Rona Levy, Fred Hutchinson Cancer Research Center; Nancy Sherwood, University of Minnesota)

164 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (Co-PIs: Sanford Markowitz and Li Li, Case Western Reserve University; Cornelia Ulrich, Fred Hutchinson Cancer Research Center)

165 Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations (Co-PIs: Melissa Nelson, University of Minnesota; Jaimie Davis, University of Southern California)

220 Scientific Support: Conference Calls (PI: Mark Thornquist, Coordination Center)

Case Western Reserve University

166 Genetic Dissection of Insulin Resistance in Insulin-like Growth Factor-1 in Cancer and Metabolic Function (PI: Courtney Gray-McGuire)

167 Efficacy of Sleep Extension in Conjunction with Pediatric Obesity Intervention (PI: Carolyn Ievers-Landis)

168 Voltage-Dependent Anion Channel Control of Cancer Cell Energetics (PI: Anna-Liisa Nieminen)

169 Improving Energy Balance Assessment Using Biomarkers and Genetic Determinants of Resting Metabolic Rate (PI: Nora Nock)

170 The Role of the *Ski* Proto-oncogene in the Control of Energy Metabolism (PI: Ed Stavnezer)

Seattle

171 Energy Balance, Polychlorinated Biphenyl (PCB) Exposure, and Possible Toxicologic Effects (PI: Anneclaire DeRoos)

TABLE 1: Developmental Projects Awarded 2006-2008 – Continued

172 Family-Based Physical Activity Intervention for Preschool-Age Cancer Survivors (PI: Debra Friedman)

173 A Twin Study of the Role of Gut Bacteria in Obesity and Inflammation (PI: Johanna Lampe)

174 Effect of Yoga on Weight, Fatigue, and Quality of Life in Breast Cancer Patients (PI: Anne McTiernan)

University of Minnesota

175 Identifying Novel Roles of Lipocalin 2 in Insulin Action and Glucose Metabolism (PI: Xiaoli Chen)

176 Hypothalamic Acyl-CoA Metabolism and Food Intake Regulation (PI: Douglas Mashek)

177 Obesity, Elevated Blood Pressure, and Insulin Resistance Among American Indian School-children: Identifying Family- and Environment-Level Determinants (PI: Melissa Nelson)

178 ZEB1 and the Development of Obesity (PI: Michel Sanders)

180 Comparing Childhood Weight-for-Age to Body Mass Index in the Prediction of Adolescent Obesity and Chronic Disease Risk Factors (PI: Steven Stovitz)

181 GIRK4: A New Obesity Gene? (PI: Kevin Wickman)

University of Southern California

182 Translation of a Novel Resistance Training Intervention to a Home Environment for Overweight Hispanic Youth (PI: Louise Kelly)

183 Global Gene Expression in White Blood Cells from Hispanic and African American Adolescents (PI: Christian Roberts)

YEAR 3

Cross-Center

184 Obesity-Associated Molecular Changes in Barrett's Esophagus (Co-PIs: Amitabh Chak, Case Western Reserve University; William Grady, Fred Hutchinson Cancer Research Center) [Chak funded in Year 2]

207 The Effect of Sleep Apnea on Adipose Gene Expression (Co-PI: Sanjay Patel, Case Western Reserve University)

Effects of a 6-Month Diet and Exercise Randomized Intervention Trial Among Overweight and Obese Postmenopausal Women on Adipose Gene Expression (Co-PI: Karen Foster-Schubert, Fred Hutchinson Cancer Research Center)

Effects of Ethnicity on Lipomic Profile and Adipokines: Relation to Adipose Tissue Morphology and mRNA Expression (Co-PI: Christian Roberts, University of Southern California)

208 Insulin Resistance and Breast Cancer Prognosis (Co-PIs: Anne McTiernan, Fred Hutchinson Cancer Research Center; Leslie Bernstein, University of Southern California)

215 The Interaction of Childhood Height and BMI on the Prediction of Adiposity and Insulin Resistance (Co-PIs: Steven Stovitz, University of Minnesota; Louise Kelly, University of Southern California)

216 Scientific Support: Schmitz Collaboration (PI: Mark Thornquist, Coordination Center)

219 Scientific Support: TREC Knowledge & Education Expansion Project (KEEP) (PI: Mark Thornquist, Coordination Center)

TABLE 1: Developmental Projects Awarded 2006-2008 – Continued

226 The Effects of Information in the Media on Antecedents of Weight Control (Co-PIs: Marco Yzer, University of Minnesota; Carolyn Ievers-Landis, Case Western Reserve University)

Case Western Reserve University

201 The Role of Genetic Backgrounds in Varying Susceptibility to Obesity and Tumorigenesis in Intestine Using a Proteomics Approach (PI: Jinsook Chang)

203 Role of a Novel Muscle Phosphatase (mtmr14) in Muscle Function, Obesity, and Cancer (PI: Thomas Nosek)

210 Investigating the Relationship Between Exercise, Physical Activity, and Cancer with PEPCK-C^{mus} Mouse Models (PI: Marco Cabrera)

211 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (PI: Sanford Markowitz)

212 Gut Microbes, Host Genetics and Diet, Metabolic Disease, and Cancer Susceptibility (PI: Joseph Nadeau)

213 Retinol Binding Protein-4 (RBP4): A Novel Biomarker for Colon Neoplasia (PI: Cheryl Thompson)

214 Functionally Define the Role of P85α Met326Il3 Single Nucleotide Polymorphism in Colon Cancer (PI: Zhenghe John Wang)

234 PEPCK-C^{mus} Mice to Study the Relationship Between Exercise, Aging, and Cancer (PI: Richard Hanson)

Seattle

217 The Impact of Diet and Physical Activity on the Number and Type of Macrophages in Subcutaneous Abdominal Adipose Tissue (PI: Mario Kratz)

218 The Meals and Grazing Study (MAG) (PI: Marian Neuhouser)

227 Successful Weight Loss Maintenance Following a Year-Long, Randomized Diet and Exercise Intervention (PI: Karen Foster-Schubert)

228 Eating and Weight-Related Behaviors Associated with Weight Loss Success Among Postmenopausal Sedentary Overweight Women (PI: Anne McTiernan)

University of Minnesota

199 Changes in Inflammatory Markers of Young Women Following Exercise (PI: Andrea Arikawa)

200 The Neighborhood and Home Food Environment Study (PI: Scott Shimotsu)

University of Southern California

221 Impact of Gestational Diabetes Mellitus on Fetal and Postnatal Hypothalamic Development (PI: Sebastien Bouret)

222 Fine-Mapping of *FTO* and *TCF2* in African Americans (PI: Christopher Haiman)

223 Investigating the Relationships Between Obesity and Leukemia Relapse (PI: Steven Mittelman)

224 Rapid and Non-invasive Quantitation of Abdominal Fat Distribution Using Magnetic Resonance Imaging (PI: Krishna Nayak)

Coordination Center

225 Balance of Energy in Chemotherapy (BALANCE) (PI: Kathryn Schmitz)

TABLE 1: Developmental Projects Awarded 2006-2008 – Continued

YEAR 4

Cross-Center

233 Effect of Physical Activity on Melatonin Levels in Previously Sedentary Men and Women (Co-PIs: Catherine Duggan, Fred Hutchinson Cancer Research Center; Sanjay Patel, Case Western Reserve University)

Case Western Reserve University

235 Mitochondrial Function in Obesity and Hepatocellular Carcinoma (PI: Charles Hoppel)

236 Maternal Obesity and Fetal Patterning of Breast Cancer Risk (PI: Ruth Keri)

237 Effect of Weight Loss on Oxidative Stress and Inflammation Markers and Gut Microbial Ecology (PI: Li Li)

238 Role of Leptin and High-Fat Diet in Development of Breast Cancer in Mice (PI: Ofer Reizes)

239 FOXP1, Obesity, and Gastrointestinal Cancer (PI: Can Shi)

240 Physical Activity and Tumor Incidence in Azoxymethane-Treated PEPCK-C^{mus} Mice (PI: James Swain)

241 Effect of Obesity and Insulin Resistance on the Activation of ^{IR}S1, AKT, and mTOR and the Development of Colon Adenomas (PI: Cheryl Thompson)

242 A Prospective Pilot Study of Endometrial Neoplasia Screening in Morbidly Obese Women (PI: Vivian Von Grueningen)

Seattle

229 Quantitation of the Metabolically Active Gut Microbial Community in a Twin Study of Inflammation and Obesity (PI: Meredith Hullar)

230 The Fat and Inflammation Study (PI: Mario Kratz)

231 Effects of Yoga on Insulin, Glucose, and Other Metabolic Hormones in Breast Cancer Survivors (PI: Alyson Littman)

232 Modulation of Mammary Carcinogenesis by Glycemic Index: A Mechanism-Based Metabolomics Approach (PI: Elizabeth Ryan)

University of Minnesota

243 Perinatal Influences on Infant Adiposity: The Minnesota Infant Nutrition, Neurodevelopment, and Obesity (MINNOwS) Study (PI: Ellen Demerath)

244 Obesity Prevention for Overweight Children by Targeting Parent Behaviors, the Home Environment, and Family Functioning (PI: Simone French)

245 Weight Loss and Biological Parameters in Obese Breast Cancer Survivors (PI: Mindy Kurzer)

246 Informing Measurement Strategies to Assess Relevant Food Environments Among Young Adults (PI: Melissa Nelson)

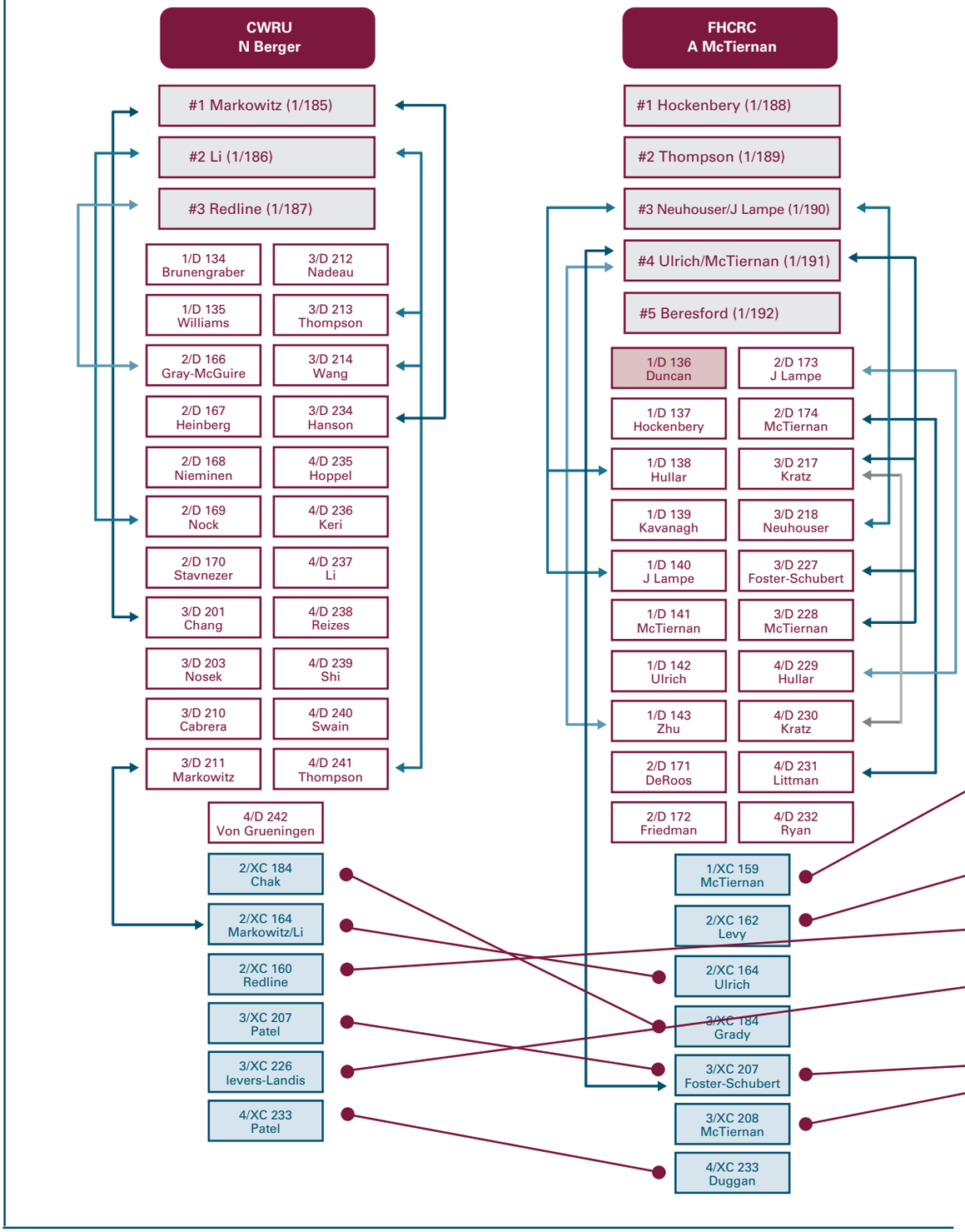
University of Southern California

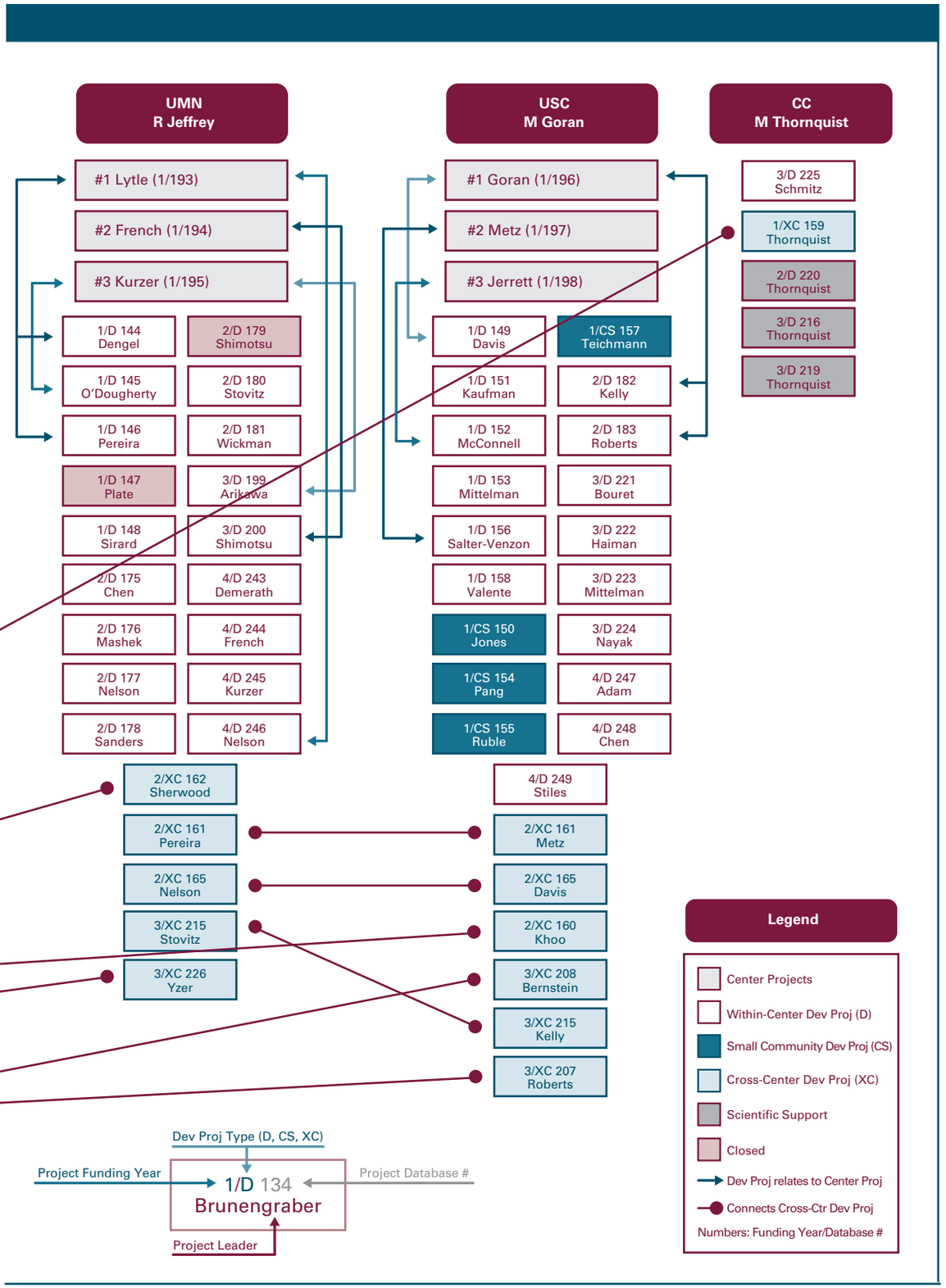
247 Effect of Insulin Resistance on the Brain and the Implications for Weight Regulation (PI: Tanja Adam)

248 Roles of Sex Hormones in Obesity and Breast Cancer (PI: Shiuan Chen)

249 The Role of Energy Sensor AMPK in Liver Cancer Development (PI: Bangyan Stiles)

FIGURE 6: Developmental Projects Diagram




UMN
R Jeffrey
USC
M Goran
CC
M Thornquist
#1 Lytle (1/193)
#2 French (1/194)
#3 Kurzer (1/195)
1/D 144 Dengel
2/D 179 Shimotsu
1/D 145 O'Dougherty
2/D 180 Stovitz
1/D 146 Pereira
2/D 181 Wickman
1/D 147 Plate
3/D 199 Arikawa
1/D 148 Sirard
3/D 200 Shimotsu
2/D 175 Chen
4/D 243 Demerath
2/D 176 Mashek
4/D 244 French
2/D 177 Nelson
4/D 245 Kurzer
2/D 178 Sanders
4/D 246 Nelson
#1 Goran (1/196)
#2 Metz (1/197)
#3 Jerrett (1/198)
1/D 149 Davis
1/CS 157 Teichmann
1/D 151 Kaufman
2/D 182 Kelly
1/D 152 McConnell
2/D 183 Roberts
1/D 153 Mittelman
3/D 221 Bouret
1/D 156 Salter-Venzon
3/D 222 Haiman
1/D 158 Valente
3/D 223 Mittelman
1/CS 150 Jones
3/D 224 Nayak
1/CS 154 Pang
4/D 247 Adam
1/CS 155 Ruble
4/D 248 Chen
3/D 225 Schmitz
1/XC 159 Thornquist
2/D 220 Thornquist
3/D 216 Thornquist
3/D 219 Thornquist
2/XC 162 Sherwood
2/XC 161 Pereira
2/XC 165 Nelson
3/XC 215 Stovitz
3/XC 226 Yzer
4/D 249 Stiles
2/XC 161 Metz
2/XC 165 Davis
2/XC 160 Khoo
3/XC 208 Bernstein
3/XC 215 Kelly
3/XC 207 Roberts
Legend
Center Projects
Within-Center Dev Proj (D)
Small Community Dev Proj (CS)
Cross-Center Dev Proj (XC)
Scientific Support
Closed
Dev Proj relates to Center Proj
Connects Cross-Ctr Dev Proj
Numbers: Funding Year/Database #
Dev Proj Type (D, CS, XC)
Project Funding Year
1/D 134
Brunengraber
Project Database #
Project Leader

Expanding Scientific Outreach in Energetics and Cancer

The TREC Centers have become a visible presence. They are expanding transdisciplinary perspectives and interest in research on energetics and cancer at both local and national meetings and conferences (see sidebar). The TREC Markers and Mediators Task Force organized an international think tank conference, AACR-NCI-TREC Mediators and Mechanisms of Energy Balance and Cancer, held in February 2008 and sponsored by the American Association for Cancer Research (AACR) and NCI (see Chapter 8). A second international conference, Energy Balance and Cancer Prognosis and Survivorship, is planned for October 2009 in Seattle, WA. Other meetings with prominent TREC representation were the 2008 AACR-NCI Prevention Meeting and the Prevention Think Tank. The TREC Centers have successfully developed and presented symposia sessions on a variety of topics at numerous national and international professional meetings during the past 3 years. TREC Centers have sponsored local conferences to convened researchers, policymakers, community organizations, and health systems interested in obesity prevention and cancer as well. Examples include a childhood obesity symposium hosted by the USC TREC and an annual scientific meeting hosted by the FHCRC TREC.

Affiliations of TREC Scientists

- North American Association for the Study of Obesity
- Experimental Biology
- International Society for Behavioral Nutrition & Physical Activity
- American Public Health Association
- Society of Behavioral Medicine
- American Association for Cancer Research
- American College of Sports Medicine
- American Federation for Aging Research
- HHS Physical Activity Guidelines Advisory Committee
- 2007 President's Cancer Panel
- International Conference on Physical Activity & Public Health
- Breast Global Health Initiative
- Childhood Obesity Think Tank
- NIH Transdisciplinary Research Working Group
- State/Local Community Partnerships
- AACR-NCI Prevention Meeting & Prevention Think Tank
- NCI Mouse Models Conference
- NCI Translational Science Conference
- Other NIH Institutes

TREC scientific leaders have been involved in a wide number of committees and professional associations (see sidebar). These organizations include the US Department of Health and Human Services Physical Activity Guidelines Advisory Committee, the 2006-2007 President's Cancer Panel, the International Conference on Physical Activity and Public Health, the International Society for Behavioral Nutrition and Public Health, the Federation of American Societies for Experimental Biology (FASEB), AACR, and the Breast Global Health Initiative, to name a few.

Career Development

Across sites, TREC supports the transdisciplinary training of a total of 73 scholars at various levels, including master's of public health students, doctoral students, postdoctoral scholars, and junior faculty. Trainees come from various disciplines, including nutrition, epidemiology, food science and nutrition, kinesiology, exercise physiology, neuroscience, biostatistics, medical oncology, molecular biology, health behavior research, psychology, and geography.

Developing the infrastructure for an environment that promotes transdisciplinary science has produced an array of Center-specific and cross-Center products promoting continuing education, state-of-the-art training, and knowledge exchange. Highlights of such activities include new websites at FHCRC and USC that allow investigators to easily share and access information on upcoming meetings and events, funding opportunities, statistical programming languages, and other research tools.

"Through the TREC conferences and meetings, I have been introduced and exposed to different investigators with very different backgrounds and expertise. This exposure has resulted in several new publications and grant submissions over the past 3 years."

— JAIMIE DAVIS, PHD, RD
KECK SCHOOL OF MEDICINE
UNIVERSITY OF SOUTHERN CALIFORNIA

Each TREC Research Center has established a journal club to discuss current research as well as explore new disciplines. Regularly scheduled face-to-face meetings promote transdisciplinary collaboration. Examples include the Training, Education, and Mentoring (TEAM) meetings at USC, a distinguished speaker seminar series at CASE, Energy Balance Working Group trainee seminars at the University of Minnesota, and a monthly scientific seminar series at FHCRC. At a local level, the University of Minnesota hosted a manuscript writing retreat in 2008 and developed a system for tracking manuscripts and proposals to facilitate collaborative publications and the integration of ideas.

In addition to seminars, research support, and mentoring, TREC Centers have developed other TREC-specific training opportunities. Responding to a need for transdisciplinary training in energetics and cancer, CASE has developed a semester-long graduate course, Energetics, Obesity, and Cancer: Transdisciplinary Views from Molecules to Health Policy. CASE also developed a structural equation modeling summer seminar for TREC researchers and graduate students. This training provides a powerful tool for transdisciplinary researchers in estimating and testing complex association/causal models. USC offers continuing medical education courses, including Pediatric Obesity Updated from Clinic to Community and a Food 4 Thought Summit (see sidebar on next page). Innovative training activities that link trainees across sites and geography include webinars, monthly conference calls, and workshops held in conjunction with the biannual TREC Scientific Meetings. Centers work together to share training opportunities. Finally, the TREC Coordination Center provides training and travel resources to new investigators by way of the TREC Knowledge & Education Expansion Project (KEEP) (see Aim 3 in Chapter 6). These modest resources, coordinated through the TREC Coordination Center, enable trainees to access support for educational activities and travel. A more detailed and comprehensive list is provided in the Training Task Force section in Chapter 8.

Products from TREC Collaborations

TREC investigators have produced several innovative products. These include methods for statistical modeling of nonlinear growth trajectories, a system for coding health messages in the media, new measurement tools (e.g., the Meanings of Eating Index and the Dietary Contextual Self-Regulation Scales), databases for physical activity and sleep measures, and biological resource

developments such as the next-generation (Cre-loxP) GIRK4 knockout line and generation of a mouse with floxed SLC5A8 alleles. Such products are shared across the TREC Centers and are examples of how the Centers work together to expand transdisciplinary approaches (see sidebar on next page). For example, the database established to identify and track sleep behavior measures led to the integration of these behavior measures across multiple population-focused projects across TREC. This development will support wider data collection and strengthen the ability of TREC investigators to evaluate the relationship between sleep patterns and behavior, hormonal and metabolic effects, and obesity in adolescents.

TREC Relevant Training Activities

Special TREC Seminar Series (National/International)

Journal Clubs/Webinars/Tutorials

CASE TREC
- Energetics, Obesity, & Cancer: Transdisciplinary Views from Molecules to Health Policy (graduate course)
- Structural Equation Modeling (summer seminar)
- Strategic Retreats (Advanced Statistics & Techniques)

Expanded Partnerships
- USC Child Obesity Symposium: Genes, Brains, & Behavior
- USC Community Medical Health Series (continuing medical education)
- USC Community Policy Leaders/ Organizations

University of Minnesota
- Manuscript Writing Retreat

TREC Training Workshops

Funding Opportunities

Across all TREC Centers, investigators have applied for a variety of additional funding opportunities. To date, TREC investigators have received four K-Awards (three from NCI and one from the National Institute of Diabetes and Digestive and Kidney Diseases), an R03 grant from NCI, an R21 grant from NCI, two R01 grants from NCI (plus one application pending in FY09), an R13 award from NCI, and two grants from not-for-profit organizations (the American Heart Association and the California Breast Cancer Research Program) (see Table 2).

Although investigator-initiated research projects represent a significant portion of the NIH funding portfolio, efforts are underway, as part of the NIH Strategic Plan for Obesity Research, to coordinate research efforts initiated across NIH. NCI has been actively engaged in this process, and the TREC initiative has been an exemplary model. The TREC Scientific Meetings have included many NIH scientists both as participants and as speakers. Their presence enhances networking and scientific discussion and helps broaden how investigators think about the science. At the most recent TREC Scientific Meeting (October 14-15, 2008), NIH scientists, including the speakers listed below, were invited to provide thoughtful discussion on NIH obesity research directions and challenges:

- Transforming the Research Paradigm for Understanding and Preventing Childhood Obesity, by Dr Terry Huang, Director of the Obesity Research Strategic Core, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

- Neurobiology of Obesity and Its Links to Addictive Behavior and Therapeutic Implications, by Dr Nora Volkow, Director of the National Institute on Drug Abuse.

TREC Database Resources

Resource databases developed within and across TREC Centers:

- TREC Coordination Center Data Tracking System and Calendar
- Physical Activity and Sleep Measures
- Comprehensive Specimen Tracking System: Laboratory Information Management Systems
- TREC Secure SQL
- USC-CTREC Web Tool
- USC-Green Visions Interactive Web Mapping Facility

- Endocannabinoids as Regulators of Energy Homeostasis, by Dr George Kunos, Scientific Director of the National Institute on Alcohol Abuse and Alcoholism.

The TREC initiative has become a model that other Institutes want to learn from and build on. Since the TREC initiative started, three new funding opportunities have been released that complement the TREC research agenda. In 2006 and 2007, NCI released two program announcements titled Studies of Energy Balance and Cancer in Humans (PA-06-405 and PA-07-176). This concept was designed to enable analyses of new and existing data sets, along with the collection of data and biological specimens to define factors and mechanisms influencing energy balance and cancer risk. The five investigators who have received grants are now linked to TREC and participate at TREC biannual meetings. In 2008, the National Heart, Lung, and Blood Institute (NHLBI) announced a new funding opportunity (RFA-HL-08-013) titled Translating Basic and Behavioral and Social Science Discoveries into Interventions to Reduce Obesity: Centers for Behavioral Intervention Development (U01). This NHLBI-led initiative, in partnership with NCI, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Office of Behavioral and Social Sciences Research, is designed to translate findings from basic research on human behavior into more effective clinical, community, and population interventions to reduce obesity and obesity-related behaviors. Yet to be awarded, this funding opportunity has been designed to bridge areas of research not tapped by the existing TREC. Once established, it will support possible future research collaborations between TREC investigators and NHLBI initiative awardees. These funding examples highlight how the TREC initiative has made a pivotal impact on the NIH obesity community and on its development and promotion of a transdisciplinary approach to science.

Presentations and Publications

The TREC initiative has produced numerous scientific products within its first 3 years. TREC investigators have delivered more than 90 presentations at various local, national, and international conferences between 2005 and 2008. More than 180 manuscripts have been published in scientific journals, with 63 additional manuscripts in press. These publications reflect TREC's progress in scientific collaboration across multiple disciplines,

TABLE 2: Types of New Grants Awarded to TREC Investigators Since 2005

Funding Mechanism	Number
K Awards	4
R03	1
R21	1
R01	2 (1 pending)
R13	1
Others	2
Total Awarded	11

including public health, medicine, social sciences, dietetics, geography, health promotion, exercise science, environmental health, biology, chemistry, and genetics. The number of publications will rise as more projects and manuscripts are completed.

"The TREC has facilitated a new interaction between researchers interested in adipose biology and cancer risk. Within this group we have made major headway to investigating several aspects of adipokines and inflammation in the context of energy balance and cancer."

— CORNELIA ULRICH, PHD
FRED HUTCHINSON CANCER RESEARCH CENTER

In an exciting development, Springer Science and Humana Press have invited CASE TREC investigator Dr Nathan Berger to lead a book series on cancer and energy balance. Six volumes are in progress, with planned contributions from many TREC investigators and from experts around the globe. Likewise, the USC investigators have developed a special issue of *Urban Geography* that is focused on "Geobesity." This supplement will include many invited papers from TREC investigators. Finally, the USC TREC Center has published three special reports on issues of park access, park equity, and park resources.

Evaluation

Given the complexities of large, multicenter, transdisciplinary initiatives, NCI has initiated a broad evaluation plan to assess whether initiatives like TREC are effective in promoting scientific collaboration that ultimately results in public health benefit. The TREC initiative is unique in the breadth of evaluation activities planned to assess scientific productivity across all levels of the TREC organization. Of greatest importance, the evaluation plan for TREC has included the measurement of key assessment parameters at baseline and throughout the entire project timeline (Hall et al., 2008). The TREC Evaluation Working Group, along with NCI's ELI team, has established a research metric, research goals, and models that will be used for the duration. The model and evaluation goals are described in detail in Chapter 7.

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2

Case Western Reserve University Transdisciplinary Research on Energetics and Cancer (TREC) Center

Principal Investigator: Nathan A Berger, MD

Obesity has reached global pandemic proportions, is increasing across all age groups, and is now considered a major public health crisis. Cancer is among the many comorbid conditions associated with and possibly etiologically related to obesity, with strong epidemiologic associations identified between obesity and several malignancies, including esophageal adenocarcinoma, colon cancer, postmenopausal breast cancer, renal cell carcinoma, and uterine cancer. These and other cancers are likewise affected by other aspects of energy balance, including exercise and caloric restriction.

The TREC program at Case Western Reserve University (CASE), led by Nathan A Berger, MD, draws on the expertise and resources of the Case Comprehensive Cancer Center and the molecular biologic, genetic, metabolic, and patient and population health expertise at the Case Western Reserve University School of Medicine to conduct a spectrum of hypothesis-driven, mechanism-based laboratory, clinical, and population-based studies to identify genetic, molecular, and behavioral processes and mechanisms contributing to the development of obesity, as well as mediators of its relation to cancer, and to identify targets for prevention and control of these processes.

The scientific aims of the CASE TREC are defined by three full research projects and a spectrum of highly interactive and multidisciplinary developmental projects, which are supported by 3 core facilities – Administration and Biostatistics, led by Ralph O'Brien, PhD, and Bioassays, led by Russell P Tracy, PhD – as well as 17 core facilities of the Case Comprehensive Cancer Center. Developmental projects conducted both within

and across TREC Centers provide opportunities for participation by and training of new investigators, development of new insights from investigators representing diverse disciplines, and development of innovative, transdisciplinary, scholarly approaches to address these complex and refractory problems. To more effectively investigate the association between energy balance and cancer, the CASE TREC program has developed a comprehensive and intense series of educational programs and training exercises to stimulate transdisciplinary research approaches among faculty and trainees at all levels, including undergraduates, pre- and postdoctoral students, and junior faculty members.

CASE Scientific Meeting

TREC Grantees met at CASE in October 2006 to review the progress and revise the Working Group and Task Force activities across TREC.

Primary Research Projects

Primary research is conducted in three interrelated projects focused on the determination of antecedents of obesity and their relation to cancer, employing (1) molecular and animal models of gastrointestinal malignancies, (2) genetic epidemiology studies of the relation between insulin resistance syndromes and colon polyps, and (3) population cohort studies to determine risk factors for obesity in adolescents and the association of obesity with biomarkers that may affect the neoplastic process.

Project 1

Obesity and Molecular Pathways Leading to Colon Cancer

Led by Sanford Markowitz, MD, PhD, and Joseph Nadeau, PhD

Project 1 employs genetically engineered mice to assay the risk of gastrointestinal tumors contributed by increased dietary fat versus obesity. Investigations of the relation between long-chain fatty acid metabolism and colon carcinogenesis have identified an enzyme in the arachidonic acid pathway, 15-prostaglandin dehydrogenase (15-PGDH), as a suppressor of colon cancer. Ongoing studies are investigating the mechanisms by which this pathway contributes to carcinogenesis and how it may be most effectively interrupted. In another part of Project 1, C57 black 6 mice, which serve as a model of high-fat diet-induced obesity and related syndromes, and AJ mice, which are resistant to diet-induced obesity, have been used to engineer a unique series of consomic mice with single-chromosome substitutions conferring sensitivity or resistance to diet-induced obesity. These mice provide a powerful tool to investigate signaling pathways and processes involved in diet-induced obesity and the diet versus obesity impact on colon cancer and hepatocellular cancer. More importantly, they provide an excellent tool to investigate the impact of genetic, environmental, and behavioral interactions on energy balance and cancer.

Project 2

Insulin Resistance Syndrome Pathway Factors and Colon Polyps

Led by Li Li, MD, PhD

This project is a genetic epidemiology study of the relation between colon adenomatous polyps (precursors of colon neoplasia) and candidate gene variants and haplotypes, associated biomarkers, and the insulin resistance syndrome, including related serum biomarkers, in order to understand how these components work in concert in the etiology of human colon neoplasia.

Project 3

Determination of Obesity and Metabolic Dysfunction in Adolescents

Led by Susan Redline, MD, MPH

This project capitalizes on a unique population cohort of adolescents, followed since birth as part of the Cleveland Children's Sleep and Health Study, to investigate both sleep physiology and sleep disturbances, as well as factors associated with low birth weight, as determinants of obesity and metabolic dysfunction, especially some of the mediators that influence neoplastic growth processes. The overall cohort contains over 600 children, of whom more than 250 adolescents and 420 of their parents have been extensively evaluated as part of this study.

Developmental Research Projects

In addition to the primary studies described earlier, the CASE TREC, with supplemental resources provided by the Case Western Reserve University School of Medicine and the Case Comprehensive Cancer Center, has carefully identified 29 developmental projects to encourage participation by faculty from different disciplines to focus on problems of energy balance and cancer. Six of these represent collaborations with investigators at other TREC Centers. Many other informal cross-Center collaborations and interactions have developed as a result of TREC activities, especially those that occur during the semi-annual TREC meetings. Among the TREC-funded development projects are the projects shown in Table 1.

TABLE 1: Developmental Projects Funded Through TREC

YEAR 1

Case Western Reserve University

134 Metabolomic Studies of Mice Susceptible to Obesity and/or Colon Cancer (PI: Henri Brunengraber)

135 Regulation of Obesity and Endoplasmic Reticulum Stress by Salicylates (PI: Bryan Williams)

YEAR 2

Cross-Center

160 Autonomic and Metabolic Dysfunction in Obese Children with Sleep-Disordered Breathing (Co-PIs: Michael CK Khoo, University of Southern California; Susan Redline, Case Western Reserve University)

The unique three-digit reference number is part of a code assigned to each project when it is awarded. This reference number will enable the reader to link the specific projects listed here to Figure 6 in Chapter 1.

All developmental projects are listed by the year of initial funding. In some cases, developmental projects, such as the TREC Coordination Center projects, are ongoing from the year of initial funding through year 4.

TABLE 1: Developmental Projects Funded Through TREC – Continued

164 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (Co-PIs: Sanford Markowitz and Li Li, Case Western Reserve University; Cornelia Ulrich, Fred Hutchinson Cancer Research Center)

Case Western Reserve University

166 Genetic Dissection of Insulin Resistance in Insulin-like Growth Factor-1 in Cancer and Metabolic Function (PI: Courtney Gray-McGuire)

167 Efficacy of Sleep Extension in Conjunction with Pediatric Obesity Intervention (PI: Leslie Heinberg)

168 Voltage-Dependent Anion Channel Control of Cancer Cell Energetics (PI: Anna-Liisa Nieminen)

169 Improving Energy Balance Assessment Using Biomarkers and Genetic Determinants of Resting Metabolic Rate (PI: Nora Nock)

170 The Role of the *Ski* Proto-oncogene in the Control of Energy Metabolism (PI: Ed Stavnezer)

YEAR 3

Cross-Center

184 Obesity-Associated Molecular Changes in Barrett's Esophagus (Co-PIs: Amitabh Chak, Case Western Reserve University; William Grady, Fred Hutchinson Cancer Research Center) [Chak funded in Year 2]

207 The Effect of Sleep Apnea on Adipose Gene Expression (Co-PIs: Sanjay Patel, Case Western Reserve University; Karen Foster-Schubert, Fred Hutchinson Cancer Research Center; Christian Roberts, University of Southern California)

226 The Effects of Information in the Media on Antecedents of Weight Control (Co-PIs: Marco Yzer, University of Minnesota; Carolyn Ievers-Landis, Case Western Reserve University)

Case Western Reserve University

201 The Role of Genetic Backgrounds in Varying Susceptibility to Obesity and Tumorigenesis in Intestine Using a Proteomics Approach (PI: Jinsook Chang)

203 Role of a Novel Muscle Phosphatase (mtmr14) in Muscle Function, Obesity, and Cancer (PI: Thomas Nosek)

210 Investigating the Relationship Between Exercise, Physical Activity, and Cancer with PEPCK-C^{mus} Mouse Models (PI: Marco Cabrera)

211 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (PI: Sanford Markowitz)

212 Gut Microbes, Host Genetics and Diet, Metabolic Disease, and Cancer Susceptibility (PI: Joseph Nadeau)

213 Retinol Binding Protein-4 (RBP4): A Novel Biomarker for Colon Neoplasia (PI: Cheryl Thompson)

214 Functionally Define the Role of P85α Met326Il3 Single Nucleotide Polymorphism in Colon Cancer (PI: Zhenghe John Wang)

234 PEPCK-C^{mus} Mice to Study the Relationship Between Exercise, Aging, and Cancer (PI: Richard Hanson)

TABLE 1: Developmental Projects Funded Through TREC – Conitnued

YEAR 4

Cross-Center

233 Effect of Physical Activity on Melatonin Levels in Previously Sedentary Men and Women (Co-PIs: Catherine Duggan, Fred Hutchinson Cancer Research Center; Sanjay Patel, Case Western Reserve University)

Case Western Reserve University

235 Mitochondrial Function in Obesity and Hepatocellular Carcinoma (PI: Charles Hoppel)

236 Maternal Obesity and Fetal Patterning of Breast Cancer Risk (PI: Ruth Keri)

237 Effect of Weight Loss on Oxidative Stress and Inflammation Markers and Gut Microbial Ecology (PI: Li Li)

238 Role of Leptin and High-Fat Diet in Development of Breast Cancer in Mice (PI: Ofer Reizes)

239 FOXP1, Obesity, and Gastrointestinal Cancer (PI: Can Shi)

240 Physical Activity and Tumor Incidence in Azoxymethane-Treated PEPCK-C^{mus} Mice (PI: James Swain)

241 Effect of Obesity and Insulin Resistance on the Activation of ^{IR}S1, AKT, and mTOR and the Development of Colon Adenomas (PI: Cheryl Thompson)

242 A Prospective Pilot Study of Endometrial Neoplasia Screening in Morbidly Obese Women (PI: Vivian Von Grueningen)

Career Development for Young Investigators

An important goal of the CASE TREC is to engage, enhance, and expand the number of investigators conducting transdisciplinary research on energy balance and cancer. This systematic approach to training and research development includes a regular series of weekly seminars, annual symposia, monthly retreats, didactic courses, visiting consultant lectureships, semi-annual national TREC meetings, focused mentoring programs, research fellowships, faculty training and travel stipends, and developmental project awards. These trainees come from a broad range of disciplines, including internal medicine, family medicine, pediatrics, reproductive biology, biochemistry, genetics, genomics, proteomics, psychology, epidemiology and biostatistics, and bioengineering, with representation from the Schools of Medicine, Arts and Sciences, and Engineering. In addition to 7 senior faculty investigators, the CASE TREC has contributed developmental research funding for an additional 7 senior investigators and to the career development and academic enhancement of 9 junior faculty, 5 residents and clinical fellows, 18 postdoctoral fellows, 15 graduate students, and 1 undergraduate student.

Key Partnerships and Collaborations

The CASE TREC is an integral component of the NCI-designated Case Comprehensive Cancer Center, which provides important research resources that include support services from 17 shared facilities. The TREC program is interactive with institutional T32, K12, and R25 training awards and collaborates with the National Institutes of Health-funded institutional Clinical-Translational Science Award. During 2008, members of the CASE TREC have been organizers and/or invited participants in the American Association for Cancer Research (AACR)-TREC-NCI Think Tank Conference: Energy Balance and Cancer Mechanisms and Mediators; the American Federation

for Aging Research's Aging and Cancer: Two Sides of the Same Coin? Conference; the NCI Translational Science Meeting; and the AACR-NCI Think Tank: Charting the Future of Cancer Prevention. In 2009, CASE TREC members are invited participants and/or organizers of the NCI Mouse Models of Human Cancers Consortium Steering Committee Meeting and the TREC-NCI Think Tank Conference: Energy Balance, Cancer Prognosis, and Survivorship. The CASE TREC is providing leadership for a book series on energy balance and cancer to be published by Springer Science and Humana Press.

Organized by Dr Li Li, a collaboration with China has been established between the CASE TREC and the Shanghai-Zhabei District Department of Health, China's Center for Disease Control, and Fudan University School of Public Health. In October 2007, four members of the CASE TREC, working with Shanghai colleagues, coordinated and participated in the Shanghai Symposium on Community-Based Disease Prevention Research, which included a series of presentations on energy balance and cancer. Five members of the Shanghai-Zhabei District Department of Health came to Case Western Reserve University for a 3-month training period in the conduct and analysis of large epidemiologic cohort studies. A collaborative community-based study of chronic disease, diet, physical activity, and disease end points, including obesity, metabolic syndrome, diabetes, cardiovascular disease, cancer, and aging, has been initiated in Shanghai.

PRIMARY RESEARCH PROJECT 1A

Obesity and Molecular Pathways Leading to Colon Cancer

Problem

Intake of dietary fat has been implicated as an important determinant of both obesity and colon cancer risk. But there has been little molecular understanding of how fatty acid metabolism can affect colon cancer risk. We have focused on determining if one significant pathway of fatty acid metabolism, the pathway by which the 20-carbon arachidonic acid fatty acid is metabolized to bioactive prostaglandins, is a target for deregulation in colon cancer.

Disciplines Involved

Molecular biology, molecular genetics, mouse models of cancers, pathology, gastroenterology, population genetics, cancer prevention

What We Know

15-Prostaglandin dehydrogenase (15-PGDH) is a novel colon cancer tumor suppressor gene that, by degrading prostaglandins, acts to negatively regulate the levels of colonic prostaglandins that build up downstream of the arachidonic acid pathway. In effect, 15-PGDH is the body's natural genetic celecoxib for prevention of colon cancer.

Research Questions

1. Is 15-PGDH lost in colon cancer?
2. Does loss of 15-PGDH increase colonic prostaglandin levels?
3. Does loss of 15-PGDH cause colon cancer susceptibility?
4. Does increasing 15-PGDH protect against colon cancer?
5. Does genetic variation in 15-PGDH levels among different individuals confer increased colon cancer risk?

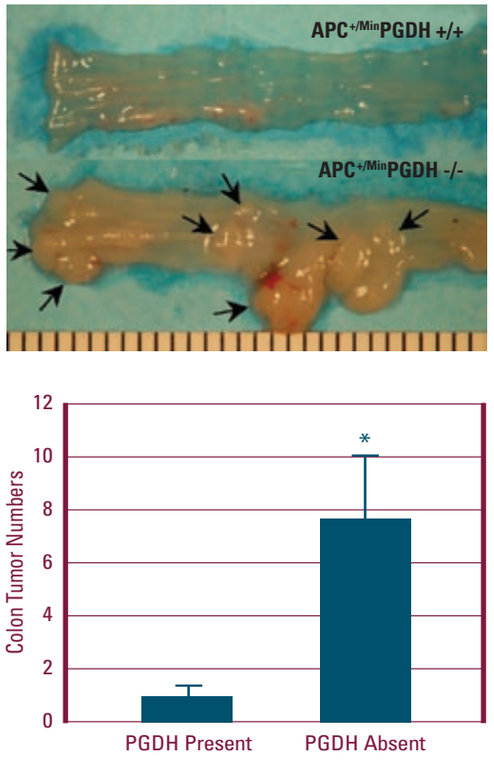
Methods

1. 15-PGDH levels were determined in normal colon and in colon cancers.
2. Colonic prostaglandin levels were determined in 15-PGDH knockout mice.
3. The colon tumor susceptibility of the 15-PGDH knockout mouse was determined.
4. The 15-PGDH transgenic mouse was constructed, and colonic prostaglandin levels and tumor susceptibility were determined.
5. Genetic variants across the 15-PGDH locus were determined in independent large cohorts of individuals with colon cancer versus control individuals who were cancer free.

Results

15-PGDH proves to be highly expressed in the normal human colon and is essentially undetectable in nearly all human colon cancers. Genetic knockout of 15-PGDH in the mouse rendered mice markedly colon tumor susceptible, converting mice strains that were completely resistant to colon carcinogens into mice that were markedly susceptible to tumor induction (Figure 1). Moreover, increasing levels of colonic 15-PGDH, via construction of a 15-PGDH transgenic mouse, resulted in conferring resistance to colon tumor development in a sensitive mouse strain.

FIGURE 1: Colon Tumors in 15-PGDH Null Mice



The pictogram (top) shows the absence of colon tumors in the colon of the 15-PGDH wild-type but tumor-predisposed Min mouse. In marked contrast, the bottom half of the pictogram shows the marked number of colon tumors arising in the 15-PGDH null littermates (which also bear the Min allele). Quantitation of the sevenfold increase in colon tumor development across the cohort of mice is shown in graphical summary (bottom).

Next Steps

Having gone from human into mouse models, the key next steps are to now translate these findings back to humans. Key questions to now sort out are whether some human beings mimic mice in having low 15-PGDH levels and in being colon cancer susceptible. We must further determine whether low levels of 15-PGDH in some humans are directly encoded by 15-PGDH genetic variants within the 15-PGDH gene itself. And we must model in mice, and determine in humans, whether the risk imparted by low 15-PGDH levels is modifiable by reducing dietary intake of arachidonic acid and of fatty acid precursors in the arachidonic acid pathway, or by intervention with drugs that antagonize prostaglandin generation by the COX enzymes. Last, as discussed below, the development of drugs that can increase the normal 15-PGDH levels in the colon would potentially offer a major new strategy for prevention of colon cancer development in humans.

Implications for Cancer Prevention and Control

These findings rewrite the diagram of the role of the prostaglandin pathway in human colon cancer. While it was previously known that colon cancers increase prostaglandin generation by upregulation of COX-2, we now find that colon cancers, equally importantly, also need to shut off the natural prostaglandin degradation pathway mediated by 15-PGDH. 15-PGDH thus becomes a major new target for development of drugs that may prevent colon cancer. The use for colon cancer prevention of drugs that inhibit COX-2 (such as celecoxib) has in large clinical trials proved problematic, due to the finding that chronic use of COX-2 inhibitors increases risks of heart attacks. This is thought to be due to these drugs lowering levels of the "good prostaglandin" prostacyclin in the blood vessels. In contrast, drugs that could increase 15-PGDH would be predicted to decrease risk of colon cancer development (through suppressing prostaglandin levels in the colon), while having no effect on the heart and blood vessels (as 15-PGDH does not regulate prostacyclin levels).

Selected Publications

1. Myung SJ, Rerko RM, Yan M, Platzer P, Guda K, Dotson A, Lawrence E, Dannenberg AJ, Lovgren AK, Luo G, Pretlow TP, Newman RA, Willis J, Dawson D, Markowitz SD. 15-Hydroxyprostaglandin dehydrogenase is an in vivo suppressor of colon tumorigenesis. *Proc Natl Acad Sci USA.* 2006;103(32):12098-102.

2. Guo C, Sah JF, Beard L, Willson JK, Markowitz SD, Guda K. The noncoding RNA, miR-126, suppresses the growth of neoplastic cells by targeting phosphatidylinositol 3-kinase signaling and is frequently lost in colon cancers. *Genes Chromosomes Cancer.* 2008;47(11):939-46.

PRIMARY RESEARCH PROJECT 1B

Obesity and Molecular Pathways Leading to Colon Cancer

Problem

The incidence and severity of colon cancer are associated with high-fat diets and obesity in humans. However, the strong correlation between diet and obesity makes it difficult to distinguish direct effects of diet on tumorigenesis versus secondary effects resulting from obesity and related metabolic diseases. Chromosome substitution strains (CSSs) of mice that are heterozygous for the Apc*min mutation provide a model for testing the relative contributions of diet versus obesity and metabolic effects on colon cancer risk. On an ad libitum high-fat diet, some CSSs show marked obesity whereas others remain lean. By using a combination of lean and obese Apc*min/+ CSSs, the effects of diet and obesity can be tested.

Disciplines Involved

Oncology, genetics, molecular biology, genomics, nutrition

What We Know

High-fat diets, obesity, and metabolic diseases are strongly associated with the incidence and severity of colon polyps, which represent a transitional step from normal gastrointestinal biology to colon cancer.

Research Questions

1. Is a high-fat diet, regardless of obesity, sufficient to increase polyp number in genetically disposed mice?

2. Is cancer risk a secondary consequence of diet-induced obesity and metabolic disease?

Methods

1. We selected two CSSs (CSS-1 and -2) that are obese when maintained on a high-fat diet and two CSSs (CSS-7 and -17) that are resistant to diet-induced obesity.
2. The Apc*min mutation was transferred to each of these CSSs to make congenic CSSs that are homosomic for the substituted chromosome and that segregate for the predisposing mutation that increases polyp numbers in heterozygous mice.
3. These Apc*min/+ congenic CSS and C57BL/6J test males, as well as their wild-type controls, were then maintained on a high-fat or a low-fat diet until they were ~60 days of age.
4. At autopsy, the number of polyps was counted, and samples of polyps from mice in each group were verified histologically.

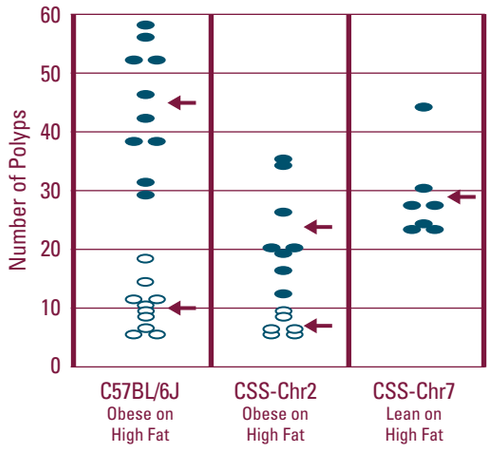
Results

A strong diet effect was found in C57BL/6J and the two congenic CSSs whose testing is complete; significantly more polyps were found in mice that were maintained on the high-fat versus the low-fat diet (Figure 2). Obese and lean congenic CSSs had comparable numbers of polyps, suggesting that diet rather than obesity and related metabolic conditions was the primary determinant of polyp number.

Next Steps

We will test whether the Apc*min/+ congenic CSS males consume similar amounts of high-fat chow. We will test the effects of alternative kinds of fat on cancer risk. We will test whether the high-fat diet leads to changes in the kinds, numbers, and functions of gut microbes and whether these might contribute to polyp risk.

FIGURE 2: Effects of Diet and Obesity on Intestinal Polyp Numbers



This figure shows the number of polyps in C57BL/6 and CSS Apc*min heterozygous males that were raised on a high-fat diet (filled symbols) or low-fat diet (open symbols).

Implications for Cancer Prevention and Control

These preliminary results suggest that individuals who are genetically at risk for colon cancer should avoid high-fat diets.

PRIMARY RESEARCH PROJECT 1C

Obesity and Molecular Pathways Leading to Colon Cancer

Problem

Hepatocellular carcinoma (HCC) occurs frequently in humans and is a leading cause of cancer death. An increasing number of cases are associated with fatty liver disease. Although many animal models of diet-induced obesity and metabolic disease have been described, the hypothesis that obesity and fatty liver disease, which result from a long-term high-fat diet, are sufficient for hepatocellular carcinogenesis has not been tested.

Disciplines Involved

Oncology, genetics, molecular biology, genomics, nutrition

What We Know

Short-term exposure to high-fat diet leads to obesity and liver damage.

Research Questions

1. Does long-term use of a high-fat diet lead to fatty liver disease and HCCs?

Methods

C57BL/6J and A/J males were raised on a high-fat or low-fat diet (ad libitum), with groups of C57BL/6J males undergoing a diet switch after 100 days on the initial diet. Mice were followed until ~450 days of age, when they were autopsied and examined for pathology and for biochemical and molecular features.

Results

1. C57BL/6J but not A/J males showed a dramatic increase in obesity, fatty liver disease, and the incidence of HCCs (Figure 3).
2. By contrast, HCCs were not found in genetically susceptible C57BL/6J males that were switched from a high-fat to a low-fat diet during the course of the study.
3. Histological analysis confirmed the presence of steatosis, hepatitis, fibrosis, occasional cirrhosis, dysplasias, and HCCs, all features of non-alcoholic steatohepatitis, which is a fatty liver disease associated with obesity.
4. Biochemical analysis showed evidence for liver damage and inflammation.
5. Molecular profiling showed two classes of mouse HCCs that correspond to the two major HCC classes in humans.
6. In summary, diet-induced HCC in C57BL/6J males is an important model for a rapidly growing class of HCCs in humans.

Next Steps

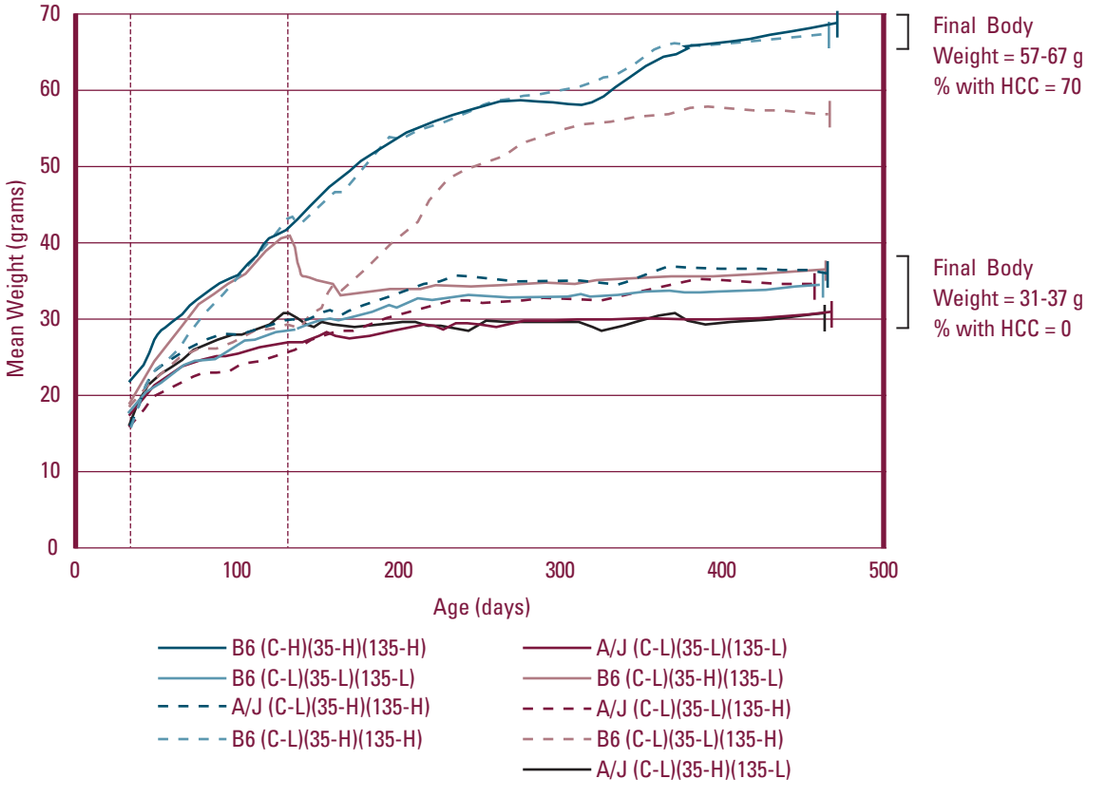
Genetic and other biomarkers of cancer onset can be identified and mechanisms of pathogenesis can be characterized. The mechanisms by which diet switch prevents development of HCCs can be studied. The effects of other kinds of fatty diets can be tested.

Implications for Cancer Prevention and Control

We found a classic example of gene-environment interactions where a high-fat diet was sufficient to induce HCC in the genetically susceptible C57BL/6J strain, but not the resistant A/J strain, without carcinogens or genetic engineering and with only long-term exposure to a high-fat diet.

A diet switch from high fat to low fat during the course of the study reversed outcome with respect to development of both fatty liver disease and HCC.

FIGURE 3: Effects of Diet on Body Weight and Hepatocellular Carcinoma



This figure shows that only B6 male mice that had been raised on a high-fat diet since conception or since 35 days of age had HCCs at the end of the study. High-fat (H) and low-fat (L) diets were introduced at one of three time points: prior to conception (C), at 35 days of age (35), and at 135 days of age (135). At the end of the study, mean body weights in the three groups of obese B6 mice ranged from 57 g to 67 g, with 70% of mice in the two most obese groups having an HCC. In the five groups of lean mice, mean body weights ranged from 31 g to 37 g, with none having an HCC. (The third group of obese B6 mice died suddenly before an autopsy could be performed, so their disease status is unknown.)

PRIMARY RESEARCH PROJECT 2

Insulin Resistance Syndrome Pathway Factors and Colon Polyps

Problem

Hyperinsulinemia, a compensatory response to insulin resistance, is believed to drive the development of the insulin resistance syndrome and has been associated with colon carcinogenesis. How the risk of colon neoplasia may be affected by genetic and lifestyle factors and biomarkers involved in the pathogenesis of the insulin resistance syndrome has not been well elucidated.

Disciplines Involved

Cancer epidemiology, gastroenterology, molecular genetics, nutrition, biochemistry and metabolism

What We Know

Insulin resistance is hypothesized to be the underlying mechanistic link between colon neoplasia and a Western lifestyle characterized by excess energy intake, physical inactivity, and obesity. The complex interplay between genetic predisposition and lifestyle factors drives the development of colon neoplasia.

Research Questions

1. How does the insulin resistance syndrome as an integral entity affect risk of colon adenomatous polyps?
2. How do genetic variants of candidate genes, biomarkers, and dietary factors in the insulin resistance syndrome pathways affect risk of colon adenomatous polyps?
3. What are the joint and interactive effects of these factors on the development of colon adenomatous polyps?

Methods

These questions are addressed in a colonoscopy-based incident case-control study of colon polyps, where 1,500 patients without known personal history of colorectal cancer or polyps are being recruited at the time of their screening colonoscopy from the University Hospitals Health System. Lifestyle risk factors and blood samples are collected prior to colonoscopic examinations. Cases and controls are then identified and confirmed by histopathology. Latent structure equation models will be used to synthesize information on candidate gene polymorphisms, biomarkers, and diet by jointly looking at their direct and indirect (mediated by the insulin resistance syndrome) effects on colon polyps.

Results

Data collection has been completed for 1,107 patients. Preliminary results for the first 627 participants (195 cases and 432 controls) have generated some novel and intriguing data.

FIGURE 4: Distribution of RBP4 Levels in Cases and Controls

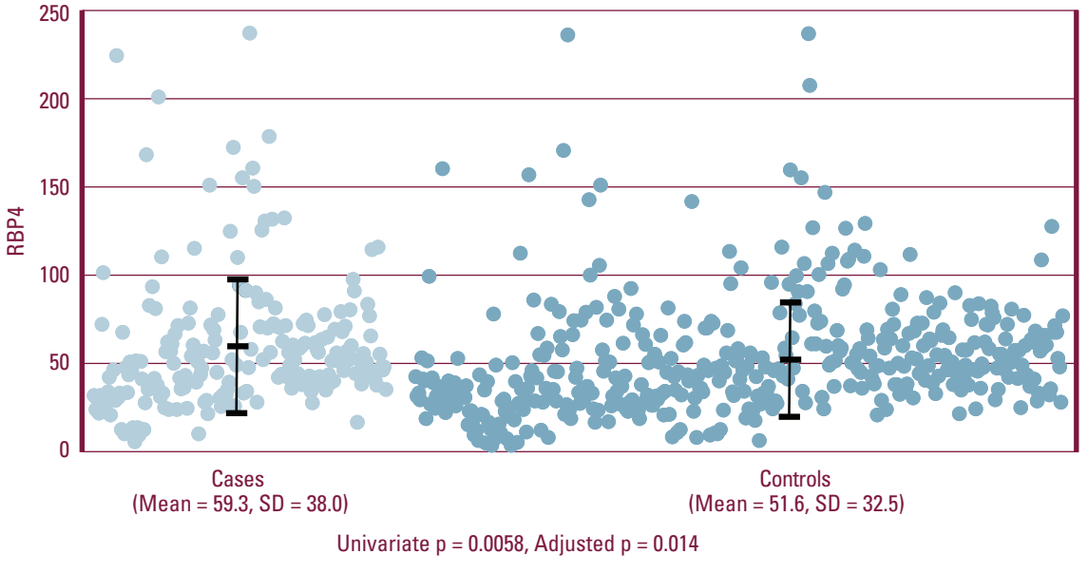


Figure shows association of RBP4 with waist-to-hip ratio in cases with colon polyps and in controls.

FIGURE 5: Odds Ratios for Association of RBP4 with Colon Polyps

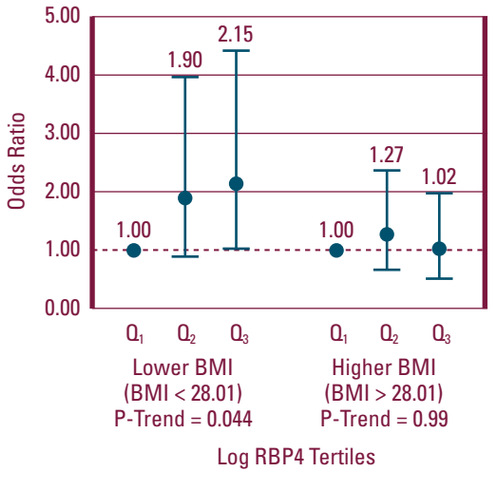


Figure shows association of RBP4 tertiles with colon polyps in subjects with BMI < 28.01 (left) or BMI > 28.01 (right).

Serum retinol binding protein-4 (RBP4) and colon polyps

Patients with adenomatous polyps have significantly higher levels of RBP4 than the controls (Figure 4). Stratified analyses by body mass index (BMI) showed a linear dose-response relationship between RBP4 and colon polyps among subjects with BMI lower than the median (28.01), but not among those with BMI higher than 28.01 (Figure 5). Analyses stratified by waist-to-hip ratio showed similar results. These data are the first to suggest that RBP4, a novel biomarker (and potentially a cause) for insulin resistance, is associated with risk of colon polyps, in particular among non-obese persons.

Waist-to-hip ratio (WHR) and colon polyps

WHR is positively associated with risk of colon polyps [odds ratios for the 1st, 2nd, and 3rd tertiles of WHR are 1.0 (referent), 1.47 (0.89-2.41), and 1.97 (1.19-3.27), respectively; P-trend = 0.0005]; in contrast, there is no association for BMI for either men or women. These data support that WHR is a better marker for central obesity and visceral adiposity than BMI in the investigation of the obesity–colon neoplasia link.

Lysophosatidylcholines (LPCs) and colon neoplasia

In a substudy of 165 patients with colon polyps, 191 controls, and 139 patients with colon cancers, we found significantly lower plasma levels of LPCs in colon cancer cases than in controls or patients with polyps. These data are consistent with our previous report of plasma LPCs as potential markers for colorectal cancer (Zhao et al., 2007).

Next Steps

We will continue recruitment and data collection to reach our accrual goal of 1,500 participants. Genotyping and other biomarker assays will begin in the summer of 2009. Analysis will address all aims to test our central hypothesis that variants in candidate genes, biomarkers, and diet may directly or indirectly (mediated by the insulin resistance syndrome) affect the development of colon polyps.

Implications for Cancer Prevention and Control

Elucidation of the mechanistic link between the insulin resistance syndrome and colon adenomatous polyps will advance our understanding of the etiologic role of obesity and insulin resistance in the development of colon neoplasia.

Evidence of the insulin resistance syndrome–colon polyp mechanistic link will support interventions to reduce obesity and insulin resistance as new avenues for early prevention of colon neoplasia.

Selected Publications

1. Zhao Z, Xiao Y, Elson P, Tan H, Plummer SJ, Berk M, Aung PP, Lavery IC, Achkar JP, Li L, Casey G, Xu Y. Plasma lysophosphatidylcholine levels: Potential biomarkers for colorectal cancer. *J Clin Oncol.* 2007;25:2696-701.

PRIMARY RESEARCH PROJECT 3

Determination of Obesity and Metabolic Dysfunction in Adolescents

Problem

The developed world has witnessed a progressive rise in the prevalence of obesity and obesity-related complications in children and adults despite community efforts at improving diet and activity. Concurrently, there has been a progressive decline in average sleep time. Adolescents in particular are progressively sleep deprived, with 45% of teens reporting less than 8 hours of average nightly sleep. Experimental and observational data indicate that sleep deprivation alters appetite-regulating hormones and glucose metabolism, potentially contributing to risk of overweight.

Disciplines Involved

Sleep medicine, pediatrics, pulmonary medicine, psychology, epidemiology, endocrinology, biostatistics

What We Know

Insufficient sleep is a strong risk factor for obesity in both prepubertal and postpubertal children. Insufficient sleep also is relatively more common in children with other health risk factors, such as neighborhood disadvantage and minority race. Health interventions aimed at improving health behaviors should address healthy sleep in addition to interventions aimed at improving diet and exercise.

Research Questions

1. What is the prevalence of obesity and rate of change in obesity prevalence across childhood in an urban sample? Which subgroups of children (defined by sex, birth weight, ethnicity) are at highest risk for obesity?
2. Do variations in sleep behaviors and sleep disorders influence weight, weight gain during childhood, and biomarkers associated with cancer?
3. Which children are most likely to be sleep deprived?
4. Are certain subgroups of children more vulnerable to both weight gain and sleep disorders?
5. Through what mechanisms does sleep deprivation influence weight: through alterations in energy expenditure or energy consumption?

Methods

We examined a birth cohort (1988-1993), 50% of whom were preterm and 32% of whom were African Americans. Cohort members were examined on three to four occasions, from ages 3 to 19 years.

Measurements of body size, sleep, and psychological variables were collected when the children (n = 907) were ages 8 to 11 years (middle school examination). A sample of 300 children was restudied at ages 16 to 19 years (late adolescent examination).

Measurements at the late adolescent examination included anthropometry, physical activity, and sleep-wake patterns measured by 5- to 7-day actigraphy, overnight polysomnography, fasting venipuncture and 2-hour oral glucose tolerance testing, and dietary assessment using two 24-hour food recalls, coded using the Minnesota Nutrition Data System for Research.

The relationships of BMI with measures of sleep at both the middle school and late adolescent examinations were examined. The influence of other factors, including socioeconomic status, birth weight, ethnicity, sex, and psychological functioning, also were examined as potential effect modifiers.

Results

The prevalence of obesity (BMI > 95 percentile) increased from 14.4% to 18.6% over the 8-year period between the middle childhood and late adolescent examinations (when mean age changed from 9.8 years to 17.7 years). BMI early in childhood predicted obesity in later childhood ($r = 0.74$; $p < 0.001$).

Overweight was most common in children who were from poor neighborhoods, were African American, and had sleep apnea.

Gain in weight over the 8-year period was highest in low birth weight children (median BMI percentile increasing from 60.8 to 71.2 vs. 66.7 to 69.0, $p < 0.01$, for the low birth weight vs. normal birth weight children, respectively).

Mean weekday sleep duration decreased from 9.3 hours to 7.5 hours between the ages of 9.8 and 17.7 years. Short or poor quality sleep was most common among minorities and those from poor neighborhoods.

FIGURE 6: BMI Percentile by Sleep Duration

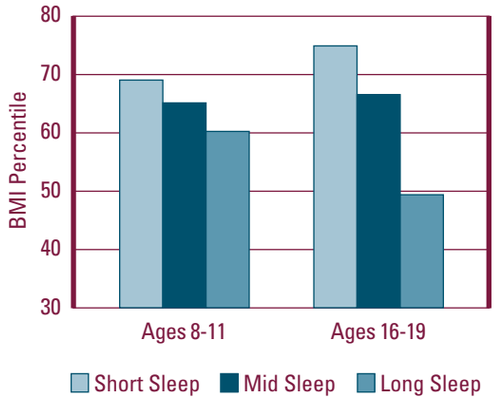


Figure shows association of BMI percentile with sleep duration in children at ages 8 to 11 and ages 16 to 19. From the Cleveland Children's Sleep and Health Study.

Short sleep duration was a risk factor for obesity at both the middle childhood and late adolescent examinations. At ages 8 to 11 years, BMI percentile varied from a median of 69.7 to 60.5 for children in the lowest tertile of sleep duration (< 8.7 hours) to the highest tertile (> 10 hours) (Figure 6). Adjusted analyses showed that each hour of decreased sleep predicted a 41% increased odds of obesity. In late adolescence, decreased sleep duration also was associated with a higher BMI (BMI percentile varying from 75 to 49.6 in children with sleep durations of < 7 hours to > 9 hours, respectively).

As Figure 7 shows, shorter sleep duration was associated with an increased consumption of fat relative to total calories ($r = 0.14$; $p < 0.05$) but was not associated with differences in physical activity levels or with indices of behavioral problems.

Next Steps

1. To fully model the associations between sleep and other behavioral risk factors and, in the larger targeted sample, to test for subgroup (low birth weight, minority status) susceptibility (interactions).
2. To test the effectiveness of a sleep extension intervention on appetite, food choices, and weight management.
3. To examine the associations between biomarkers, including those implicated in cancer, that may mediate the associations between sleep-related stressors and energetics.
4. To examine differences in circadian timing and obesity.

Implications for Cancer Prevention and Control

These data underscore the importance of sleep as a mediator of weight control. Increased attention to improving sleep early in life may be as important in preventing obesity-related cancers as are more traditional approaches aimed at diet and exercise.

FIGURE 7: Mean Percentage of Calories from Fat as a Function of Average Sleep Duration

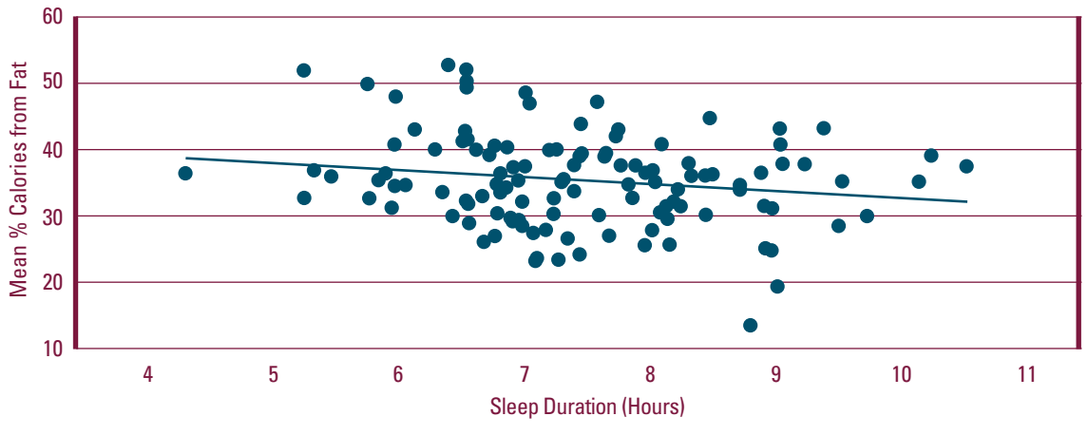


Figure shows association of fat caloric consumption with sleep duration. From the Cleveland Children's Sleep and Health Study.

Selected Publications

1. Javaheri S, Storfer-Isser A, Rosen CL, Redline S. Sleep quality and elevated blood pressure in adolescents. *Circulation.* 2008;118(10):1034-40.

2. Ievers-Landis CE, Storfer-Isser A, Rosen C, Johnson NL, Redline S. Relationship of sleep parameters, child psychological functioning and parenting stress to overweight status among preadolescent children. *J Dev Behav Pediatr.* 2008;29(4):243-52.

3. Ievers-Landis C, Redline S. Pediatric sleep apnea: Implication of the epidemic of overweight. *Am J Respir Crit Care Med.* 2007;175:436-41.

3

Seattle Transdisciplinary Research on Energetics and Cancer (TREC) Center

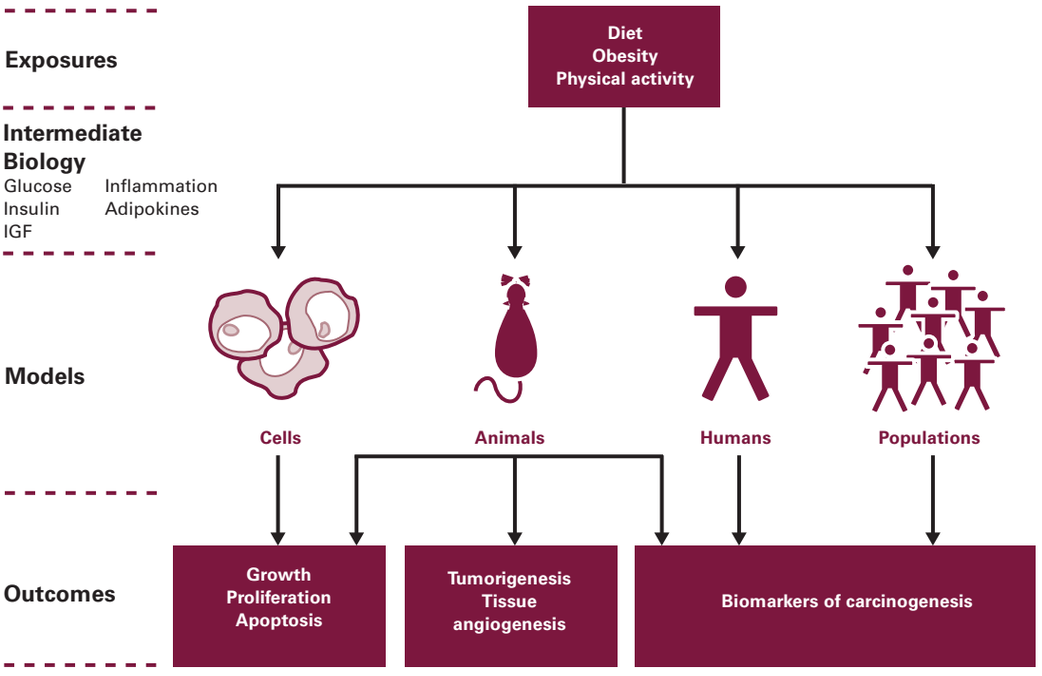
Principal Investigator: Anne McTiernan, MD, PhD

The primary goal of the Seattle TREC Center is to elucidate the pathways linking components of energy balance to the cancer process, using several different study designs, and with the involvement of scientists from such diverse fields as medicine, cell biology, animal models, epidemiology, nutrition, gastroenterology, molecular biology, obesity, cardiology, immunology, statistics, exercise physiology, and behavioral science.

The Seattle TREC Center fosters the cross-fertilization of ideas involving scientists from disciplines that do not often collaborate. This multidisciplinary collaboration has led to a fruitful exchange of ideas over the first 3 years of TREC funding. Thus, we have achieved the main goals of the TREC Centers as stated in the original NCI Request for Applications: "to foster collaboration among transdisciplinary teams of scientists with the goal of accelerating progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet." The Seattle TREC builds on our already strong history of interdisciplinary work at the Fred Hutchinson Cancer Research Center, the University of Washington, and Colorado State University.

Our central theme is to explore, using a variety of methodologies in integrated projects, the roles that several consequences of overweight, obesity, and a sedentary lifestyle play in the carcinogenic process. In particular, we are studying the interplay among energy balance, change in components of energy balance, hyperglycemia, hyperinsulinemia, inflammation, and cancer biomarkers and models, as depicted in Figure 1. The cancer biomarkers and models range from apoptosis and proliferation in cell cultures, to preclinical models with tumor incidence and timing, to markers of cellular damage and repair in humans, and, finally, to human proteomics and genomics. Although our focus is primarily on biomarkers and models that are relevant to breast and colon cancer incidence, our research results are pertinent to the risk of

FIGURE 1: Schematic of Seattle TREC Research Themes



other types of cancer. The Seattle TREC projects pertain to cancer risk across the lifespan. The basic science projects (Projects 1 and 2) are relevant to carcinogenesis at any age. A human feeding study (Project 3) focuses on adults ages 18 to 45 years, a time when lifetime eating patterns are formed and weight gain is common (e.g., the college years). A biomarker study (Project 4) is testing the effects of weight loss and exercise on cancer risk factors in postmenopausal women, a group at high risk for overweight and obesity. A public health project (Project 5) is testing an obesity prevention intervention at small worksites that are populated with young and middle-aged adults from minority racial/ethnic groups at risk for weight gain.

Thus, the Seattle TREC Center is garnering information on the effects of treating overweight and obesity through dietary pattern, calorie restriction, and exercise, as well as the effects of obesity prevention in at-risk persons. By conducting related (in both design and focus) studies using different models (cell/animal/human), we are able to explore a breadth of the carcinogenesis process that is not possible in human intervention studies alone.

The Seattle TREC includes three central and closely linked activities: five primary major research projects; a comprehensive program of developmental projects; and our structured program for training and mentoring new researchers in energy balance and cancer, including predoctoral, postdoctoral, and junior investigators.

The specific aims of the Seattle TREC Center as a whole are to:

- Build a multidisciplinary group of investigators into a transdisciplinary team exploring the mechanisms linking energy balance and carcinogenesis using basic cellular, animal, and human model systems.
- Develop and test interventions that can be translated into the public health setting, with the goal of reducing the cancer burden by reducing overweight and obesity and increasing physical activity.
- Train new scientists to focus on these interdisciplinary areas of research.
- Establish collaborations with scientists across the TREC community to develop and implement new research ideas.
- Build resources for future studies in energy balance and cancer, within the Seattle TREC Center, across the TREC community, and beyond.

Primary Research Projects

The primary research at the Seattle TREC Center is conducted in five main projects. While each project has one to two project leaders, the Seattle TREC investigators are involved across projects and review progress regularly at Executive Committee meetings.

Project 1

Mechanisms Linking Nutrient Supply and Cell Cycle/Survival

Led by David Hockenbery, MD

This project brings together basic research efforts in an innovative approach to analyzing the cellular effects of hyperglycemia on growth, proliferation, and survival pathways relevant to oncogenesis. It investigates the mechanisms of glucose activation of proliferative (c-myc) and survival/pro-inflammatory (NF-κB) pathways in endothelial cells and extends these studies to cancer-susceptible epithelial cells and to immortalized and cancer cell lines. Finally, it examines whether glucose-regulated pathways have tumor-promoting effects on initiated human mammary epithelial cells. This project includes basic science researchers from the cancer, obesity/endocrinology, and cardiology fields and will speed development in basic cancer research while increasing knowledge of the effects of obesity on different cell lineages.

Project 2

Energy Balance and Cancer: Markers and Mechanisms in Rats

Led by Henry Thompson, PhD

Project 2 is determining, in a chemically induced (1-methyl-1-nitrosourea) rat model of breast cancer, the effects of caloric restriction alone and exercise alone and in combination on the carcinogenic response in the mammary gland. This project will also elucidate the mechanisms by which changes in energy balance modulate the development of cancer. This project parallels the designs of Projects 3 and 4, which are testing, in human participants, the effects of interventions on cancer biomarkers. The investigators are extending the methods of those studies to the spectrum of carcinogenesis in an animal model, including caloric restriction and exercise effects on cancer biomarkers (serum hormones, peptides, cytokines, plasma proteomics), cancer intermediates (tissue proliferation and apoptosis), and mammary tumorigenesis (number and latency of tumors). This cross-talk between animal and human researchers is helping us understand the value of these types of model systems in predicting responses to similar interventions in humans. It also allows us to investigate both biomarkers and cancer endpoints in a well-characterized model system.

Project 3

Glycemic Load and Obesity Effects on Cancer Biomarkers

Led by Marian Neuhouser, PhD, and Johanna Lampe, PhD

This project investigates the metabolic response to experimental diets that have a low- or high-glycemic load in normal weight and overweight/obese young adults (ages 18-45) in a crossover clinical trial design. It builds on observational studies that indicate a role of high-glycemic index diets in the etiology of several cancers, by employing an experiment where individual food intake is controlled for a defined period of time. The investigators are testing the effect of these diets in lean and overweight/obese persons on various biomarkers in the glucose and insulin pathways, adipokines, and proteomics. This human nutrition experiment closely parallels the work conducted in Project 2 (including a shared specific aim) and provides nutritional expertise and resources to Projects 2, 4, and 5.

Project 4

Exercise and Diet: Biomarkers and Mechanisms in Humans

Led by Cornelia Ulrich, PhD, and Anne McTiernan, MD, PhD

Project 4 investigates which intermediate biomarkers in key pathways are affected by exercise and by weight loss achieved through a reduced-calorie diet. It focuses on biomarkers of inflammation, DNA damage and repair, and insulin pathways and is examining the effect modification of several common gene polymorphisms related to these biomarkers. This cost-efficient study is an ancillary study to an NCI-funded randomized, controlled clinical trial testing the effects of 1-year moderate-intensity exercise and reduced-calorie diet, individually and combined, on several hormonal biomarkers of breast cancer in postmenopausal women (NCI R01 CA105204, PI: A McTiernan). The results from this study, in which the effects on biomarkers of more intensively monitored weight loss and exercise interventions are being tested, will ultimately identify biomarkers useful to test in stored specimens in Project 5, a public health-oriented intervention trial.

Project 5

Preventing Obesity in Low-Income Working Adults

Led by Shirley Beresford, PhD

This project tests a worksite obesity prevention intervention in a geographic area with a large representation of low-income and minority individuals. It builds on the resources of an ongoing worksite obesity prevention trial being conducted in large worksites in Western Washington State (NIH R01 HL79491, PI: S Beresford). The diet part of the intervention employs a simple method for teaching employees about the caloric content of foods, using a system of identifying foods in 100-calorie portions. The exercise program consists of encouragement and incentives to increase daily physical activity to 30 or more minutes per day, 5 days per week, of moderate activity. We will also test the effects of this intervention on weight, body mass index (BMI), and fasting insulin, glucose, leptin, adiponectin, C-reactive protein (CRP), serum amyloid A (SAA), and fatty acids. This project benefits from other TREC scientists by incorporating their experience with exercise and diet interventions in controlled experiments into a public health setting. Project 5 represents our “mechanistic validation,” that is, whether we find evidence that what is observed in Projects 1 to 4 in terms of mechanisms and markers actually has relevance in the “real world environment” of Project 5.

Developmental Research Projects

In addition to the primary studies described earlier, the Seattle TREC Center has carefully selected and funded 26 developmental research projects in energy balance and cancer (Table 1) and has successfully competed for external funding to support several new projects within the Seattle TREC. More detailed descriptions of many of these developmental research projects are provided in Chapter 9.

TABLE 1: Developmental Projects Funded Through TREC

YEAR 1

Seattle

136 Fitness, Fatness, and Cancer Biomarkers in Youth (closed) (PI: Glen Duncan)

137 Development of a Serum-Based Marker of Apoptosis and Assessment of Responses to Dietary and Exercise Interventions (PI: David Hockenbery)

138 The Gut Microbiota as a Cancer Biomarker Influenced by Glycemic Load and Obesity (PI: Meredith Hullar)

139 Characterization of Diet- and Exercise-Dependent Metabolic Phenotypes: Evaluating Responses to Interventions (PI: Terry Kavanagh)

140 Ancillary Data and Sample Collection in Seattle TREC Project 3, the CARB Study (PI: Johanna Lampe)

141 Effect of a 12-Month Exercise Intervention on Inflammatory Markers in Men and Women (PI: Anne McTiernan)

142 Effect of Exercise and Caloric Restriction on Adipose Tissue Biomarker Specimen Collection Pilot (PI: Cornelia Ulrich)

143 Obesity, Menopausal Status, and Mammary Carcinogenesis: Model and Mechanisms (PI: Zongjian Zhu)

YEAR 2

Cross-Center

162 Pediatric Primary Care Obesity Prevention (Co-PIs: Rona Levy, Fred Hutchinson Cancer Research Center; Nancy Sherwood, University of Minnesota)

164 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (Co-PIs: Sanford Markowitz and Li Li, Case Western Reserve University; Cornelia Ulrich, Fred Hutchinson Cancer Research Center)

Seattle

171 Energy Balance, Polychlorinated Biphenyl (PCB) Exposure, and Possible Toxicologic Effects (PI: Anneclaire DeRoos)

172 Family-Based Physical Activity Intervention for Preschool-Age Cancer Survivors (PI: Debra Friedman)

173 A Twin Study of the Role of Gut Bacteria in Obesity and Inflammation (PI: Johanna Lampe)

174 Effect of Yoga on Weight, Fatigue, and Quality of Life in Breast Cancer Patients (PI: Anne McTiernan)

The unique three-digit reference number is part of a code assigned to each project when it is awarded. This reference number will enable the reader to link the specific projects listed here to Figure 6 in Chapter 1.

All developmental projects are listed by the year of initial funding. In some cases, developmental projects, such as the TREC Coordination Center projects, are ongoing from the year of initial funding through year 4.

TABLE 1: Developmental Projects Funded Through TREC – Continued

YEAR 3

Cross-Center

184 Obesity-Associated Molecular Changes in Barrett's Esophagus (Co-PIs: Amitabh Chak, Case Western Reserve University; William Grady, Fred Hutchinson Cancer Research Center) [Chak funded in Year 2]

207 Effects of a 6-Month Diet and Exercise Randomized Intervention Trial Among Overweight and Obese Postmenopausal Women on Adipose Gene Expression (Co-PIs: Karen Foster-Schubert, Fred Hutchinson Cancer Research Center; Sanjay Patel, Case Western Reserve University; Christian Roberts, University of Southern California)

208 Insulin Resistance and Breast Cancer Prognosis (Co-PIs: Anne McTiernan, Fred Hutchinson Cancer Research Center; Leslie Bernstein, University of Southern California)

Seattle

217 The Impact of Diet and Physical Activity on the Number and Type of Macrophages in Subcutaneous Abdominal Adipose Tissue (PI: Mario Kratz)

218 The Meals and Grazing Study (MAG) (PI: Marian Neuhouser)

227 Successful Weight Loss Maintenance Following a Year-Long, Randomized Diet and Exercise Intervention (PI: Karen Foster-Schubert)

228 Eating and Weight-Related Behaviors Associated with Weight Loss Success Among Postmenopausal Sedentary Overweight Women (PI: Anne McTiernan)

YEAR 4

Cross-Center

233 Effect of Physical Activity on Melatonin Levels in Previously Sedentary Men and Women (Co-PIs: Catherine Duggan, Fred Hutchinson Cancer Research Center; Sanjay Patel, Case Western Reserve University)

Seattle

229 Quantitation of the Metabolically Active Gut Microbial Community in a Twin Study of Inflammation and Obesity (PI: Meredith Hullar)

230 The Fat and Inflammation Study (PI: Mario Kratz)

231 Effects of Yoga on Insulin, Glucose, and Other Metabolic Hormones in Breast Cancer Survivors (PI: Alyson Littman)

232 Modulation of Mammary Carcinogenesis by Glycemic Index: A Mechanism-Based Metabolomics Approach (PI: Elizabeth Ryan)

Externally Funded Projects

Effect of Exercise and Weight Loss on Adipose Tissue Biology, R21 CA131676 (PI: Cornelia Ulrich)

In April 2008, we received R21 funding (PI: Cornelia Ulrich) for an ancillary study of adipose tissue biology in relation to TREC Project 4. The R21 enabled us to collect adipose tissue biopsies from women who remained to be recruited for a randomized, controlled trial (parent study of Project 4). The goals of the R21 are to investigate, in overweight/obese sedentary postmenopausal women, the effects of a 6-month exercise intervention, reduced-calorie diet, and combined exercise-diet intervention vs. control on (1) mRNA and protein expression of specific pro-inflammatory cytokines and adipokines, (2) mRNA expression

related to sex steroid hormone production, and (3) overall gene expression patterns (using the Affymetrix U133 plus 2.0 Gene Chip microarray) in subcutaneous adipose tissue. Further, we plan to explore the impact of changes in body weight on these outcomes. Forty-nine women were recruited, and the first 6-month follow-up visits began in October 2008. This combination of biomarkers funded as part of TREC Project 4, in conjunction with this novel examination of effects on adipose biology, provides novel insights into multiple pathways linking energy balance to cancer risk. The R21 also builds on several Seattle-funded developmental projects designed to develop the biopsy methodology used here (PI: Cornelia Ulrich) and other aspects of adipose tissue biology (PI: Karen Foster-Schubert; PI: Mario Kratz).

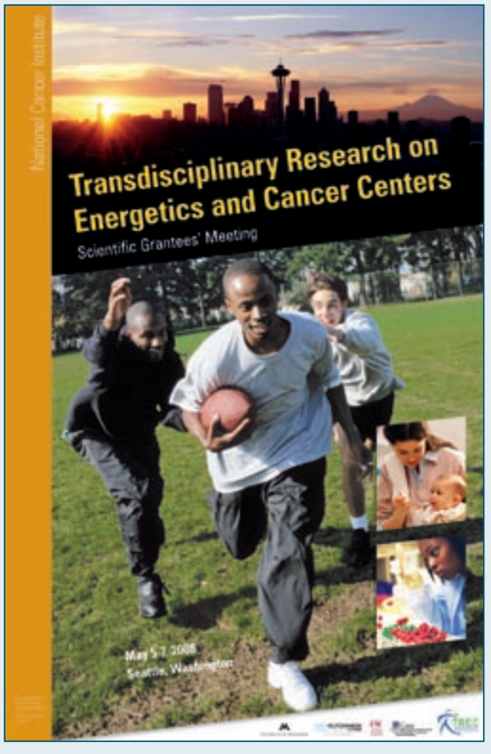
Exercise Effects on Oxidative Damage Among Women, R03 CA130043 (PI: Cornelia Ulrich)

We also received ancillary R03 funding to investigate the effects of exercise on oxidative damage in a completed randomized, controlled trial of 173 postmenopausal women. This grant application was developed jointly between TREC trainee Dr Peter Campbell and Dr Cornelia Ulrich. Findings suggest that exercise training can reduce the levels of F2-isoprostane in urine. We are following up with a more comprehensive dose-response analysis by different parameters of adherence, as well as cross-sectional analyses predicting levels of this biomarker of oxidative stress.

Postprandial Glycemic Response to 4-Week Low- and High-Glycemic Load Diets, R03 CA132158 (PI: Marian L Neuhouser; Co-Investigator: Johanna Lampe)

This study builds on Project 3 from the Seattle TREC Center. The overall goal of this project is to understand the postprandial metabolic response to meals that are low or high in glycemic load and how the nature of the response may be related to understanding mechanisms related to carcinogenesis. While meal effects on glucose and insulin have been well characterized, less is understood about the postprandial effect of habitual meal patterns on other molecules that may be more directly related to carcinogenesis, such as the insulin-like growth factors and their binding proteins. A subset of Project 3 study participants (n = 20) will be asked to consume two additional low- or high-glycemic load meals at the end of each feeding period and remain in the clinic for 8 hours for serial blood draws to assess the postprandial metabolic response. As of December 16, 2008, 18 participants had enrolled in the postprandial study and 14 had completed both study periods. The four who were enrolled but had not completed the protocol will complete study activities in February-March

Seattle Scientific Meeting



TREC Grantees met at the Fred Hutchinson Cancer Research Center to review progress and status of the overall evaluation to date.

2009. All intervention activities should be completed by June 2009.

Exercise, Mammary Cancer, and Mechanisms, R01 CA 100693 (PI: Henry Thompson)

The goal of this project is to determine the direct effects of exercise on the process of mammary carcinogenesis in a rodent model of breast cancer.

Diet, Weight Control, and Breast Carcinogenesis, R01 CA 126704 (PI: Henry Thompson)

This study is designed to answer questions about how dietary glycemic load and fat loss influence metabolic and hormonal processes that may affect breast cancer recurrence. We hypothesize that, in addition to the anticipated effects of fat loss on circulating levels of bioavailable sex steroids, the effects of excess fat on breast cancer prognosis can be attributed to three interrelated metabolic processes: altered glucose metabolism (IGF-1, IGFBP-3, glycated proteins), chronic inflammation (C-reactive protein, IL-6, TNF-alpha), and excessive cellular oxidation (8-hydroxy-2-deoxyguanosine and 8-isoprostane F-2 alpha). A 6-month intervention study involving 370 postmenopausal women who have been treated for breast cancer is proposed. Randomized women, stratified by resected stage, systemic adjuvant therapy, and BMI (> 25 and < 35), will either serve as a non-intervention control group or follow a tailored diet-physical activity program designed to create a weekly negative energy balance equivalent to 3,500 kcal. The intervention groups will receive the same physical activity protocol but one of two diets that differ in glycemic load. The specific aims are shown below:

Aim 1
Does dietary glycemic load alter the pattern of change observed in circulating factors involved in glucose homeostasis, chronic inflammation, cellular oxidation, and steroid hormone metabolism during progressive loss of body fat? We will also examine how observed changes in these circulating factors relate to changes in indicators of breast cancer recurrence.

Aim 2
Do circulating factors associated with glucose homeostasis, chronic inflammation, and cellular oxidation display the same pattern of change in response to progressive fat loss as circulating analytes associated with sex steroid metabolism? Analytes of interest will be measured monthly throughout the study.

Aim 3
Does dietary glycemic load affect the magnitude or rate of fat loss? Plasma adipokines such as leptin and adiponectin and plasma ghrelin will be measured to provide biological determinants that may help explain differences in response. The work proposed in this application should provide quantitative data about the importance of the magnitude of fat loss on metabolic and hormonal processes involved in cancer recurrence and provide guidance about effective dietary approaches that maximize weight loss benefits on breast cancer prognosis.

PRIMARY RESEARCH PROJECT 1

Mechanisms Linking Nutrient Supply and Cell Cycle/Survival

Problem

Hyperglycemia is related to risk of several cancers, but the exact mechanisms related to carcinogenesis are unknown. Project 1 analyzes the cellular effects of hyperglycemia on growth, proliferation, and survival pathways relevant to oncogenesis. It investigates the mechanisms of glucose activation of proliferative (c-myc) and survival/pro-inflammatory (NF-κB) pathways in endothelial, epithelial, and immortalized and cancer cell lines.

Disciplines Involved

Molecular biology, gastroenterology, obesity, endocrinology, cardiology

What We Know

Energy surplus, defined as (caloric intake – caloric expenditure), is associated with increased cancer risk in humans, and both dietary caloric restriction and exercise are protective in several animal models of cancer. Systemic factors such as IGF-1 and adrenal corticosteroids were proposed to mediate the effects of energy restriction on carcinogenesis; however, experimental manipulations of circulating IGF-1 and corticosterone levels have not reproduced the dietary effects. Increased glucose availability due to energy surplus is not expected to have direct effects on cancer-prone tissues, since the glucose transporter and hexokinase family members expressed in most tissues have Km values in the range of physiologic blood glucose concentrations. However, the dynamic range of metabolizable glucose concentrations has not been reported for most cell types.

Research Questions

1. How do myc and NF-κB, both involved in positive feedback regulation of glycolytic metabolism in cancer cells, affect glucose metabolism in non-transformed cells?

2. What is the role of glucose metabolism in signaling/transcriptional responses to elevated glucose concentrations in non-transformed cells?

3. Are there differences in cell responses to high glucose between normal cell types and normal vs. transformed cells?

Methods

Aim 1

We have investigated the role of c-myc expression in substrate utilization using U13C-labeled glucose and analysis of 13C-enriched metabolites by nuclear magnetic resonance spectroscopy.

Aim 2

In the past year, we have completed our studies on responses to high glucose in human microvascular endothelial cells (HMECs), a representative proliferating normal cell type. Lactate production and cell respiration were measured in real time using a perifusion system.

Aim 3

Responses of cellular metabolism and NF-κB activation to different glucose concentrations were determined for several primary cell types, immortalized and malignant breast epithelial cell lines (MCF-10A, MCF-7, MDA-MB-231).

Implications for Cancer Prevention and Control

If a mechanism for hyperglycemia inducing carcinogenesis can be determined, it will provide supporting evidence that excessive glucose concentrations are implicated in the etiology of cancer and may provide important information for developing therapies for cancer prevention or treatment. Thus, this project has high translational potential.

Selected Publications

1. Schwartz PS, Manion MK, Emerson CB, Fry JS, Schulz CM, Sweet IR, Hockenbery DM. 2-Methoxy antimycin reveals a unique mechanism for Bcl-xL inhibition. *Mol Cancer Ther.* 2007;6:2073-80.
2. Sweet IR, Gilbert M, Maloney E, Hockenbery D, Schwartz M, Kim F. Endothelial inflammation induced by excess glucose is linked to intracellular accumulation of glucose-6-phosphate. *Diabetologia.* Under review.
3. Maloney E, Sweet IR, Hockenbery DM, Pham M, Rizzo NO, Tateya S, Schwartz MW, Kim F. NADPH oxidase and toll-like receptor-4 are necessary for palmitate-induced inflammatory responses in human endothelial cells. *Arterioscler Thromb Vasc Biol.* Submitted.

PRIMARY RESEARCH PROJECT 2

Energy Balance and Cancer: Markers and Mechanisms in Rats

Problem

Epidemiological studies indicate that obesity and a sedentary lifestyle increase risk for several cancers, including postmenopausal breast and breast cancer-associated mortality irrespective of menopausal status. Because of the limitations inherent in the measurement of both energy intake and physical activity behaviors over the time course required for cancer to develop, the investigation of these questions in epidemiological studies is difficult. Moreover, the effect of the glucose availability from dietary carbohydrate on weight control-mediated protection against cancer has not been studied.

Disciplines Involved

Nutrition, exercise science, cell and molecular biology, computational biology, carcinogenesis, pathology

What We Know

In a mammary carcinogenesis model, caloric restriction and exercise have been shown to reduce number of tumors and increase the time to development. In the evaluation of published preclinical data, how the effects on carcinogenesis compare when energy balance is altered to the same extent by energy restriction or physical activity has never been addressed.

Research Questions

1. What are the effects of energy restriction or physical activity alone or in combination on the carcinogenic response in the mammary gland?
2. What is the effect of carbohydrate availability on the carcinogenic response and systemic biomarkers when weight control is mediated by energy restriction?

3. What are the effects of energy restriction and physical activity dose on candidate mechanisms and markers using genomic and proteomic technologies?

Methods

Aim 1

The objective of this experiment was to compare the effects on mammary carcinogenesis of similar limitations in energy availability either by energy expenditure due to increased physical activity or by restricting dietary energy intake. A total of 90 female Sprague Dawley rats were injected with 1-methyl-1-nitrosourea (50 mg/kg) and 7 days thereafter were randomized to either a sedentary control group, a physical activity group given free access to a running wheel, or a group whose food intake was restricted by an amount that would limit growth to the rate observed in the physical activity group. Individually housed rats were given free access to a motorized activity wheel, and running behavior was reinforced by food reward. The amount of food given to each animal was precisely regulated by a computer-controlled microcontroller linked to a food dispenser, and food intake was recorded.

Aim 2

Work conducted during this reporting period was done in collaboration with the laboratory of Marian Neuhouser and Johanna Lampe (Project 3). Two composite human diets, one with a low glycemic load and the other with a high glycemic load, were prepared in bulk (50 kg of each) and were fed to rats in a carcinogenesis experiment (n = 30/group). The human diets are the same as those being fed to human participants in Project 3.

Next Steps

We will investigate the cellular processes, molecular mechanisms, and biochemical mediators that account for the observed effects.

Implications for Cancer Prevention and Control

Determining the independent and combined effects on cancer incidence of calorie restriction and physical activity can provide important data for developing and testing weight loss/maintenance and physical activity interventions for cancer prevention in humans.

Selected Publications

1. Thompson HJ, Neuhouser M, Lampe J, Zhu Z, Jiang W. Glycemic load: Its impact on carcinogenesis and candidate mechanisms. *J Natl Cancer Inst.* In preparation.

PRIMARY RESEARCH PROJECT 3

Glycemic Load and Obesity Effects on Cancer Biomarkers

Problem

Obese individuals have increased risk for several types of cancer, yet the components of energy balance that are carcinogenic have not been clearly defined.

Disciplines Involved

Nutrition, epidemiology, molecular biology

What We Know

Many obese individuals eat foods that are low in fiber and high in refined carbohydrates, which are characteristics of high-glycemic index foods. Yet the effects of a high-glycemic load diet on biomarkers of cancer risk are unknown.

Research Questions

We hypothesize that the associations of obesity with cancer risk are mediated by a specific dietary pattern (i.e., high glycemic load) that causes an unfavorable metabolic profile. The consequences of this obesity-related metabolic dysregulation are changes in the production of peptide growth factors, cytokines, and cell-signaling molecules, which influence a cascade of events related to carcinogenesis. Thus, examination of a set of diet-related biomarkers of obesity that are in the pathway to cancer will provide important information about mechanisms of obesity-associated cancers. Specifically, we hypothesize that high-glycemic load diets are associated with greater synthesis of a panel of biomarkers related to carcinogenesis and that low-glycemic load diets are associated with lower synthesis of these biomarkers in a manner that is independent of weight loss.

Methods

Using a 4-week crossover design, this project is investigating the effect of low- and high-glycemic load experimental diets on cancer-related biomarkers. The biomarkers to be examined include insulin, glucose, IGF-1, IGFBP-3, leptin, adiponectin, interleukin-6, CRP, and SAA. This project also examines the extent to which overweight/obesity modifies the association of the experimental diet interventions with the cancer-related biomarkers insulin, glucose, IGF-1, IGFBP-3, leptin, adiponectin, interleukin-6, CRP, and SAA. Finally, it investigates dietary intervention-induced changes in plasma proteomic patterns and tests whether these patterns differ for overweight/obese individuals compared to lean individuals.

Results

As of December 31, 2008, 99 of 114 people screened were eligible to enroll in the study, with 91 consenting to participate. Five people are currently being screened or scheduled for information sessions. Seventy-six people completed all study baseline activities. Four people dropped out between completing baseline activities and starting the feeding study.

Seventy-two people started the feeding study. Compliance has been excellent, and only four participants have dropped out after beginning the feeding study. To date, 62 people have completed both study arms and 6 are currently on protocol. One of our recruitment goals is to enroll both normal weight and overweight/obese participants. To date, 38 (86% of goal) of those who are currently enrolled or have completed the study are normal weight and 30 (70% of goal) are overweight. Another goal was to enroll Hispanic and African American participants. To date, the study has enrolled 16 (73% of goal) Hispanic and 16 (73% of goal) African American participants.

Next Steps

All intervention activities should be completed by June 2009.

Implications for Cancer Prevention and Control

If a high-glycemic load diet adversely affects cancer biomarkers in the setting of weight maintenance, this may help with developing cancer prevention or treatment interventions to be tested.

Selected Publications

1. Noar K, Schwarz Y, Breymeyer K, Lampe JW, Neuhouser ML. Design of low- and high-glycemic load diets for a randomized cross-over feeding study. *J Am Diet Assoc*. Under review.

PRIMARY RESEARCH PROJECT 4

Exercise and Diet: Biomarkers and Mechanisms in Humans

Problem

The mechanisms explaining the associations of overweight/obesity and a sedentary lifestyle with cancer risk are unknown. This project aims to explore these mechanisms by testing effects of weight loss and increased physical activity on several novel biomarkers of cancer risk in postmenopausal overweight/obese sedentary women.

Disciplines Involved

Molecular epidemiology, internal medicine, nutrition, obesity, immunology, molecular biology

What We Know

Exercise and caloric restriction are related to a reduced risk of multiple cancer types, yet the underlying mechanisms are poorly defined. It is also not clear whether there are joint positive effects of both exercise and caloric restriction on biomarkers of cancer risk and whether weight loss is necessary for exercise to have beneficial effects. Exercise causes bouts of oxidative stress, and initial studies suggest that training may positively affect a person's DNA repair capacity.

Research Questions

As part of an ongoing randomized, controlled trial, this TREC project investigates the effects of an exercise program, a reduced-calorie diet, and a combined exercise and reduced-calorie diet program on cancer-related biomarkers, specifically biomarkers of inflammation (CRP, SAA, and IL-6), DNA damage sensitivity, and DNA repair capacity in response to gamma irradiation. We also investigate intervention-induced changes in plasma proteomic patterns to characterize the proteins that change with the interventions in order to identify new biomarkers. Finally, this research will enable us to examine modification of the effects by body composition changes during the course of the interventions, BMI and body fat mass at baseline, and genetic characteristics relevant to inflammation.

Methods

Project 4 is ancillary to a funded clinical trial, R01 CA105204, Exercise, Diet, and Sex Hormones in Postmenopausal Women [Nutrition and Exercise for Women (NEW)], PI: Anne McTiernan. Participant recruitment for this parent trial (NEW study) was accomplished via mass mailing and the media. A total of 439 women have been randomized to the NEW study and serve as the population for the Project 4 studies.

Biomarkers
A total of 439 women have had lymphocytes collected in preparation for DNA damage and repair assays. Biospecimens for gene expression (with "RNA later" added) have been collected from 281 participants.

DNA Repair Assays (Comet Assay)
The Comet assay will be performed in the Public Health Sciences Molecular Epidemiology laboratory to measure DNA repair function. Because of the extremely high volume of slides to be read (n = 439 x 3 time points x 7 slides = 9,219 slides), we decided to acquire a Metafer Slide Scanning Station (Metasystems, Belmont, MA) to complete this work ($105,283). We have optimized the assay according to the new specifications for reading on the instrument and have also arranged for data transfer and read-in to the TREC databases. In 2007 we commenced assays of study participants.

Results

As of December 15, 2008, we had completed 414 assays (207 participant sets at 2 timepoints each). We continue assays at a rate of six assays per week. Some repeats will be necessary due to lymphocyte viability issues, but, in general, we are well on track to complete assays as the NEW participants complete their intervention.

Next Steps

We plan to perform our other study assays in year 4 and continue into year 5. We plan these assays to be completed within a 6-month time period to reduce potential error from laboratory drift. Future research directions will depend on results from our primary aims. However, of particular note, Dr Cornelia Ulrich has secured additional NIH funding based on her early work in TREC, including an R21 grant focused on adipose tissue gene expression changes with energy balance and an R03 grant testing the effects of exercise change on urinary isoprostanes.

Implications for Cancer Prevention and Control

This study will provide important information about the combined and independent effects of exercise and caloric restriction on cancer biomarkers in humans. If we can identify mechanisms relating energy balance and cancer, it will provide important information for supporting the observational data linking energy balance to cancer. If we can show that changes in energy balance variables change cancer biomarkers in a protective manner, it will provide important evidence of a true biological effect of energy balance change on cancer risk.

The optimal dose of energy balance change can be estimated from this study's results. If we determine that the weight loss intervention results in measurable effects on cancer biomarkers, this will tell us that a weight loss intervention with goal weight loss of 10% body weight has measurable cancer risk-reduction effects. Furthermore, if we see effects on cancer biomarkers in the exercise-alone arm, this tells us that a moderate-intensity aerobic exercise program of 225 minutes per week results in measurable effects on cancer biomarkers. Furthermore, for both the dietary weight loss and exercise interventions, we will determine dose-response effects because there will be a gradient of adherence among study participants.

Selected Publications

1. Meyers JA, McTiernan A, Ulrich CM. Leptin and immune function – integrating the evidence. *Nutr Res.* 2005;9:791-803.

2. Mohanka M, Irwin M, Heckbert SR, Yasui Y, Sorensen B, Chubak J, Tworoger SS, Ulrich CM, McTiernan A. Serum lipoproteins in overweight/obese postmenopausal women: A one year exercise trial. *Med Sci Sports Exerc.* 2006;38:231-9.

PRIMARY RESEARCH PROJECT 5

Preventing Obesity in Low-Income Working Adults

Problem

More than two-thirds of American adults are overweight or obese, yet methods for preventing weight gain and effecting long-term weight loss in adults are not widely available.

Disciplines Involved

Epidemiology, nutritional science, social and behavioral science, nutritional biochemistry, exercise physiology, internal medicine

What We Know

In light of the obesity epidemic in the United States and elsewhere, a focus on treatment and weight loss for the overweight and obese at the individual level is too limited to have a population-wide impact on the epidemic. The traditional approaches to weight loss have included dietary and exercise interventions, often with short-term success, but reductions in weight often do not last more than a year or so after the intervention has stopped. Health professionals have used various techniques to recommend restrictive dieting and exhortations to increase regular physical activity, again with only limited success. Calorie restriction has been achieved through reducing fat intake or reducing carbohydrate intake (both macronutrients directly contribute calories). Behavioral change at the population level often begins with a small change that increases over time. Worksites offer accessibility to large numbers of people, so interventions at the worksite level have a wide reach into the adult population. Intervention approaches can use the worksite social environment and structural changes to complement individual-level strategies. Nonetheless, proven methods to achieve the goal of preventing obesity are lacking, and few studies have included small worksites that have high proportions of lower income, minority workers.

Research Questions

1. Will an obesity prevention program that includes simple messages of reduced-calorie intake and increased physical activity result in reduced BMI compared to control participants (no program) in a randomized trial of small worksites?

Methods

This project is developing and evaluating a 2-year intervention that will maintain or decrease BMI in a randomized trial of 30 worksites. Intervention goals are (1) to influence the worksite environment, including policies and procedures, by increasing worksite access to healthy foods and physical activity opportunities; (2) to promote individual behavior change by increasing awareness of energy balance; and (3) to build a dietary intervention that will promote decreased calorie intake. BMI will increase less in intervention worksites than in control worksites between baseline and the 2-year follow-up.

Results

Thirty-one worksites have been randomized. From the first three waves of recruitment, 24 worksites have 571 employee surveys available for analysis. Baseline data were examined for individual-level associations, between daily servings of fruits and vegetables, physical activity, and BMI (predictors) and obesity and weight loss quality of life scores and productivity loss scores calculated from the Work Limitations Questionnaire (outcomes).

Our results suggest that obese men, and particularly obese women, experience a significantly impaired obesity-related quality of life. If the intervention supports these findings, there may be additional work-related and general health benefits from reducing weight and increasing physical activity.

Next Steps

The trial activities are continuing, and assays will be performed to determine intervention effects on cancer biomarkers.

Implications for Cancer Prevention and Control

If this intervention is shown to have beneficial effects on BMI, interventions could be designed and tested for implementation in additional settings, including public health settings.

Selected Publications

1. Whisnant SA, Beresford SAA, Henderson JA, Patrick D, Xiao L, McTiernan A. Obesity risk shown to be related to quality of life: baseline results from a worksite trial. Submitted.

4

University of Minnesota Transdisciplinary Research on Energetics and Cancer (TREC) Center

Principal Investigator: Robert W Jeffery, PhD

The Minnesota TREC Center focuses on the prevention end of the continuum connecting obesity and cancer. Current studies within the Center involve only cancer-free human populations. We are primarily focusing on family and youth transitioning into young adulthood as our populations of interest, and we include research aims that span biological through environmental questions.

We choose this emphasis because it reflects the unique strengths of the University of Minnesota, including population-based interventions in diet, obesity, and other behavioral conditions; disease prevention through behavior change; and a strong team of researchers interested in youth, family, and population-based health.

The specific aims of the Minnesota TREC Center are:

- To bring together scientists of diverse disciplines to increase our understanding of obesity and cancer risk factors related to diet and activity during the life transition from childhood to young adulthood. Specifically, we are interested in understanding the etiologic factors that contribute to the development of obesity in youth, in developing and evaluating innovative primary prevention interventions for families and youth, and in examining potential relationships between exercise and cancer-related hormones in young women.
- To provide mechanisms and opportunities for transdisciplinary research and to foster career development in the field of obesity and cancer risk.
- To strengthen existing links and create new links between investigators from public health, medicine, nursing, the basic sciences, food science and nutrition, liberal arts, the behavioral sciences, and public policy and urban design in order to enhance the study of obesity.

Center activities include three scientific projects; a developmental research program targeted at funding small projects to train developing scientists and to provide experience that leads to future career development and independent R01 funding; training programs to develop young investigators in the field, including participation in formal and informal instruction and mentoring; and a program of outreach and dissemination through public forums and participation in local, regional, and national policy discussions about the problem of obesity. Overall, the Center aims to create an active, transdisciplinary, participatory environment for research, training, and translation to promote the understanding and prevention of obesity in youth and families.

Two cores were established as part of the Minnesota TREC Center:

Administrative Core
Responsible for the overall coordination of the activities of the TREC Center and administration of the training and research development components.

Data and Statistical Services Core
Responsible for helping investigators and trainees with the development of assessment tools, data entry, and statistical support.

Primary Research Projects

The commitment of our group to transdisciplinary collaboration and training can be expressed on two levels, a conceptual level and an operational level. On a conceptual level, we use the TREC conceptual model developed by NCI to guide our research (http://cancercontrol.cancer.gov/TREC). This multilevel model describes variables ranging from broad environmental and cultural factors, to intermediate variables describing specific aspects of the environment (such as family, school, and neighborhood), to individual factors of behaviors, psychological conditions, beliefs, and attitudes; biological characteristics such as genetics and biochemical status; and energy balance/obesity. At different levels, these variables are conceptualized as interacting in multiple ways with each other over time, both individually and synergistically, to influence obesity-related behaviors and the risk of developing obesity and cancer. The individual projects range in scope and are briefly described below.

Overall, these studies employ multiple disciplines: sociology, communications, geography, psychology, kinesiology, nutrition, biostatistics, and biochemistry. They also bridge a substantial range of domains that are related to energy balance and carcinogenesis. We believe that these studies present a rich opportunity for interdisciplinary collaboration among investigators with diverse backgrounds and that each project has demonstrated the potential to make unique scientific contributions.

Project 1

Etiology of Adolescent Obesity (IDEA)

Led by Leslie Lytle, PhD, RD

This observational cohort study is examining etiologic factors in the development of obesity in youth. It assesses both macro-level and micro-level factors as they relate to energy balance in adolescents. The research examines the potential influence of sociocultural, environmental, and institutional policy factors in the family, home, school, and neighborhood, as well as individual psychosocial factors and eating and activity behaviors of youth related to risk for becoming overweight or obese. This project engages an existing cohort of youth being followed for tobacco-related behaviors through another NCI-funded research project. This study includes investigators from four different units at the University of Minnesota (i.e., the School of Public Health, the School of Nursing, the School of Kinesiology, and the College of Architecture and Landscape Architecture) and from the following disciplines: nutrition, health behavior,

exercise physiology, epidemiology, psychology, education, policy, urban planning, and statistics.

Project 2

Take Action: Household Environmental Weight Gain Prevention

Led by Simone French, PhD

This project examines a specific environment, namely the home, and attempts to systematically examine the effects of changing food exposures and exposure to activity opportunities on individual eating and exercise habits and body weight. It focuses on both macro-level and micro-level factors but limits those to the home and family environment. It uses an innovative primary prevention approach using both household- and individual-level change strategies to positively influence the energy balance of households, including the adult and youth members, ages 12 and older. This study includes investigators trained in social psychology, clinical psychology, nutrition, and child development.

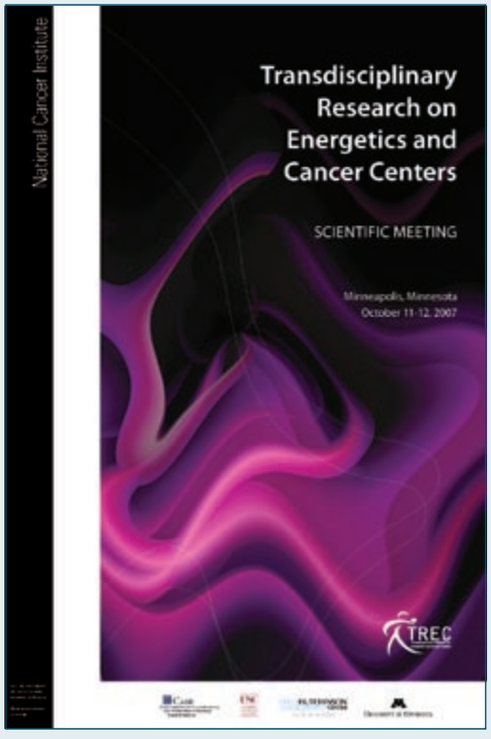
Project 3

Women In Steady Exercise Research (WISER)

Led by Mindy Kurzer, PhD

This project is toward the more biological end of the model continuum. It focuses on micro-level factors by examining the relationship between physiological hormonal factors and aerobic exercise training in young women ages 18 to 30, and also assesses changes in other metabolic factors that may explain the association between physical activity and breast cancer. This study includes investigators from across the Minnesota Cancer Center, including investigators from public health, food science and nutrition, and the Medical School. This project is the only one of our three projects with a laboratory component.

Minnesota Scientific Meeting



TREC Grantees met at the University of Minnesota to review the progress and engage other scientists in TREC-related research collaborations.

Developmental Research Projects

The purpose of the Minnesota TREC developmental projects program is to attract new investigators to the field of obesity research, with a focus on youth and cancer. An emphasis has been placed on supporting young developing investigators first. Secondarily, the Center has funded established investigators who wish to initiate work in a new field. All resources of the Minnesota TREC Center are available to individuals who have been awarded developmental research projects to further develop their subject matter and research methods skills.

TABLE 1: Developmental Projects Awarded 2006-2008

YEAR 1

University of Minnesota

144 Biological Determinants of Obesity in Teens (PI: Donald Dengel)

145 Social, Cultural and Contextual Dimensions of Young Women's Physical Activity (PI: Maureen O'Dougherty)

146 Validation of Internet-Based Dietary Assessment (PI: Mark Pereira)

147 Effects of Exercise on Breast Cancer Biomarkers in Nipple Aspirate Fluid (closed) (PI: Andrea Plate)

148 Physical Activity and Media in the Home Environment (PI: John Sirard)

YEAR 2

Cross-Center

161 Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-ethnic Sample of Children: A Transdisciplinary Cross-Site Developmental Project (Co-PIs: Mark Pereira, University of Minnesota; Donna Spruijt-Metz, University of Southern California)

162 Pediatric Primary Care Obesity Prevention (Co-PIs: Rona Levy, Fred Hutchinson Cancer Research Center; Nancy Sherwood, University of Minnesota)

165 Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations (Co-PIs: Melissa Nelson, University of Minnesota; Jaimie Davis, University of Southern California)

University of Minnesota

175 Identifying Novel Roles of Lipocalin 2 in Insulin Action and Glucose Metabolism (PI: Xiaoli Chen)

176 Hypothalamic Acyl-CoA Metabolism and Food Intake Regulation (PI: Douglas Mashek)

177 Obesity, Elevated Blood Pressure, and Insulin Resistance Among American Indian School-children: Identifying Family- and Environment-Level Determinants (PI: Melissa Nelson)

178 ZEB1 and the Development of Obesity (PI: Michel Sanders)

180 Comparing Childhood Weight-for-Age to Body Mass Index in the Prediction of Adolescent Obesity and Chronic Disease Risk Factors (PI: Steven Stovitz)

181 GIRK4: A New Obesity Gene? (PI: Kevin Wickman)

YEAR 3

Cross-Center

215 The Interaction of Childhood Height and BMI on the Prediction of Adiposity and Insulin Resistance (Co-PIs: Steven Stovitz, University of Minnesota; Louise Kelly, University of Southern California)

226 The Effects of Information in the Media on Antecedents of Weight Control (Co-PIs: Marco Yzer, University of Minnesota; Carolyn levers-Landis, Case Western Reserve University)

The unique three-digit reference number is part of a code assigned to each project when it is awarded. This reference number will enable the reader to link the specific projects listed here to Figure 6 in Chapter 1.

All developmental projects are listed by the year of initial funding. In some cases, developmental projects, such as the TREC Coordination Center projects, are ongoing from the year of initial funding through year 4.

TABLE 1: Developmental Projects Awarded 2006-2008 – Continued

University of Minnesota

199 Changes in Inflammatory Markers of Young Women Following Exercise (PI: Andrea Arikawa)

200 The Neighborhood and Home Food Environment Study (PI: Scott Shimotsu)

YEAR 4

University of Minnesota

243 Perinatal Influences on Infant Adiposity: The Minnesota Infant Nutrition, Neurodevelopment, and Obesity (MINNOwS) Study (PI: Ellen Demerath)

244 Obesity Prevention for Overweight Children by Targeting Parent Behaviors, the Home Environment and Family Functioning (PI: Simone French)

245 Weight Loss and Biological Parameters in Obese Breast Cancer Survivors (PI: Mindy Kurzer)

246 Informing Measurement Strategies to Assess Relevant Food Environments Among Young Adults (PI: Melissa Nelson)

To further facilitate transdisciplinary collaboration and foster cooperative research, the three obesity centers at the University of Minnesota [Minnesota Obesity Center (supported by the National Institute of Diabetes and Digestive and Kidney Diseases), Obesity Prevention Center (University of Minnesota supported), and TREC (NCI supported)] have combined resources over the past 3 years to initiate a single annual request for developmental research proposals. The overall goal is to provide seed money with the intent that investigators will successfully pursue extramural funding. Through a competitive review process, five developmental research grants were awarded in year 1, nine grants in year 2, four grants in year 3, and four to date in year 4 (Table 1). All funded projects are transdisciplinary in approach and involve cross-unit participation. Five projects involve cross-Center collaborations that include investigators from at least two TREC Centers. Progress reports for selected developmental projects are provided in Chapter 9.

Overall, the developmental projects program has proven to be a successful vehicle for promoting and developing translational research on obesity, youth, and cancer. It is based on procedures demonstrated to be effective in developing obesity research programs for the last 10 years, and it is rigorous in its attention to scientific rigor, objectivity, and honesty. The likelihood of continuing stimulating transdisciplinary collaborative interaction and synergy with existing programs and centers at the University of Minnesota is extremely high.

Career Development for Young Investigators

Another aim of the Minnesota TREC Center is to contribute to the training and professional development of the next generation of obesity prevention researchers and practitioners. Through enhanced coursework, combined with seminars and research emphasizing a transdisciplinary perspective, our Center strives for students and new investigators to gain the skills and knowledge necessary to successfully address the obesity epidemic. The career development program for junior faculty, postdoctoral fellows, and current doctoral students has proven to be an extremely

successful component of the grant. The program provides trainees with exposure to advanced methods and experimental approaches in transdisciplinary obesity research and with the skills needed to pursue independent research careers in this area. Fourteen trainees from five departments are currently participating in the program. Two trainees have received National Institutes of Health K12 grants due in large part to TREC support.

In addition, the Energy Balance Research Group was formed and meets regularly under the direction of senior TREC investigators. The meeting format was adapted to specifically assist junior investigators with new grant submissions and data analysis for publications. Attendees and presenters have included faculty and students from several academic units, including the Medical School, Pediatrics, Nursing, Psychiatry, Psychology, Epidemiology and Community Health, and Kinesiology.

Key Partnerships and Collaborations

The Minnesota TREC Center brings together the resources of the Minnesota Cancer Center, the Minnesota Obesity Center, and the University of Minnesota Obesity Prevention Center to share support services to increase our understanding of obesity and cancer risk related to obesity. The Center also provides an opportunity to expand on our existing community partnerships with schools, worksites, and the health care delivery system. We have continued to foster research collaborations with several key partners through grant submissions, development research, and provision of expert technical assistance. These efforts are intended to stimulate research on obesity-related issues in a real world setting.

PRIMARY RESEARCH PROJECT 1

Etiology of Adolescent Obesity (IDEA)

Problem

The purpose of the TREC IDEA study is to examine the etiology of adolescent obesity as a risk of future cancer using a socio-ecological approach and considering possible risk and protective factors at the individual, family, school, and neighborhood levels. TREC IDEA uses a transdisciplinary approach to study this complex issue, engaging researchers who span areas of expertise from physiologists to urban planners. This study is helping to lay groundwork for ecological research through the development and testing of valid environmental measures to assess the obesogeneity of homes, schools, and neighborhoods and through the testing of analytic approaches applied to new fields.

Disciplines Involved

Social science (health behavior, psychology), nutrition, exercise physiology, epidemiology, biology, biostatistics

What We Know

We know that obesity is an epidemic in both adults and children and that obesity incurs significant health risk in the population, both directly and through co-morbidities. We know much less about the etiology of obesity. We believe that obesity is “caused” by a variety of complex factors that occur at multiple levels, including the individual, family, home, school, and neighborhood. However, without a better sense of the most potent and mutable factors, our ability to intervene and reverse the trend of obesity is stymied.

Research Questions

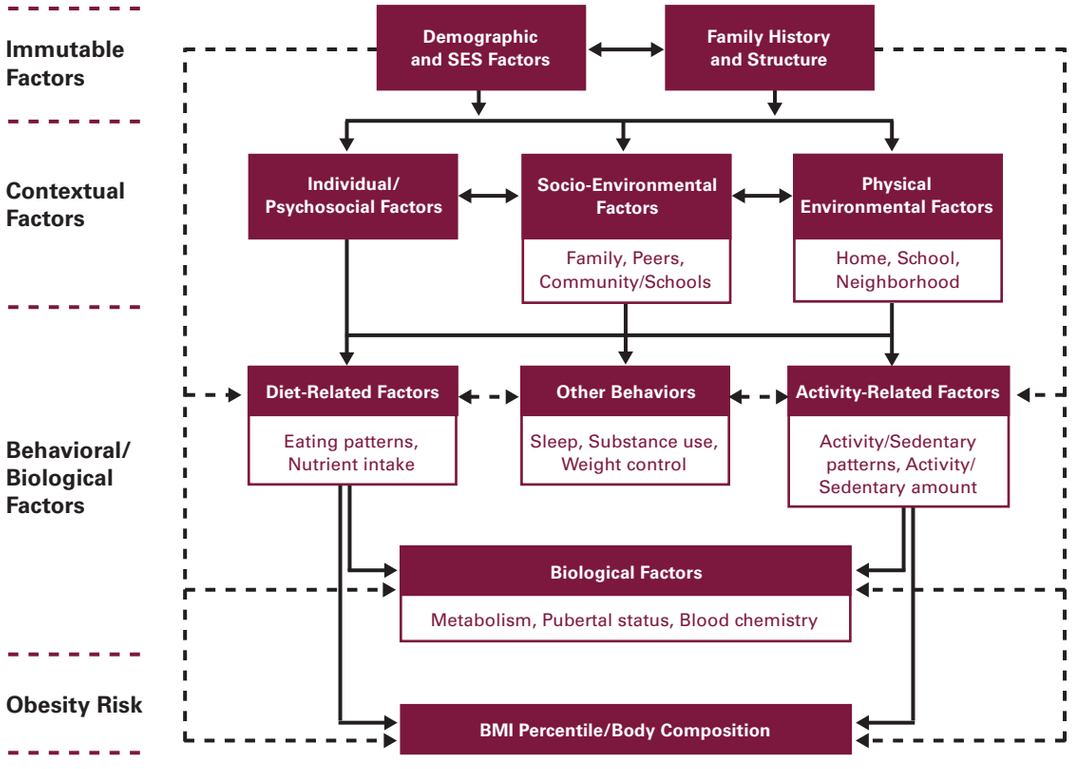
Using a longitudinal cohort design with a sample of youth and parent dyads, we are examining factors at multiple levels that may contribute to the increase in the prevalence of obesity in youth.

Methods

The TREC IDEA study is a longitudinal cohort study of youth ages 10 to 16 (n = 349) and one parent or other primary caregiver. It has three measurement periods, including a baseline assessment and two assessment periods 12 and 24 months after baseline. The primary endpoint is change in BMI z-scores and movement between weight categories over time, but the ecological design permits many outcomes to be examined in both the youth and adult cohort, including dietary intake, levels of physical activity, and other weight-related health behaviors. Figure 1 shows the conceptual model guiding this research.

At baseline, our youth sample had a mean age of 15.4 years, was 51% female, and was 93% non-Hispanic White; 80% lived with both their mother and father. Twenty percent of the youth sample was at or above the 85th percentile for BMI. The average age of the adult sample was 46.7; this sample was 76% female and 98% non-Hispanic White. Thirty percent of the sample was overweight (25 > BMI < 30) and 24% was obese (BMI > 30). The majority of adults had at least a college education (63%). We successfully measured 95% of the cohort of youth and adults at time 2 and are currently collecting data for the third time period.

FIGURE 1: TREC IDEA Study Conceptual Model



Results

School Environment

Our data collection includes assessment of the school environment, and at baseline our cohort attended 127 schools. Of the 116 schools that allowed us entry for data collection, 79% were public schools and 61% were high schools. School data collection included observation and documentation of competitive foods in the schools, including foods and beverages available through vending, a la carte, and school stores. In addition, a principal interview was conducted in each school to collect data on policies and practices related to foods used in fundraising and as incentives, opportunities to be active in school, levels of physical activity and physical education in schools, and whether the school had a wellness council. The following are some highlights of the findings:

- Ninety-one percent of schools have vending machines, with an average of 128.7 food/beverage items per school. On average, 57.6% of the foods and beverages offered meet the Institute of Medicine (IOM) calorie criteria, 79.3% meet the IOM percentage of calories from fat criteria, and 49.9% meet both the IOM calorie and fat criteria.
- Eighty-nine percent of schools have an a la carte food program. In the TREC IDEA middle schools, 83.7% of the foods and beverages offered meet the IOM calorie criteria, 80.4% meet the IOM percentage of calories from fat criteria, and 73.6% meet both the IOM calorie and fat criteria.
- Twenty-two percent of schools have school stores that sell food or beverages.
- Fifty percent of schools reported policies to regulate food used for fundraising. Most policies supported healthy practice, particularly in middle schools. However, the use of foods high in fat and added sugars remains a prevalent fundraising practice, especially for student clubs and sports teams.
- The average requirement of physical education was 202 minutes per week (range = 45-450 minutes).
- Sixty-five percent of schools have policies regarding the provision of individualized physical activity/fitness plans.
- Forty-eight percent of schools have policies regarding the provision of opportunities to participate in community physical activities.
- Public schools (vs. private schools) and high schools (vs. middle schools) were significantly more likely to have physical activity-promoting policies and practices. Additionally, students in public schools and high schools were more likely to receive an average of 150 minutes of physical education per week.

Neighborhood Environment

Geographic information systems (GIS) are being used to assess the neighborhood environments surrounding each youth's home and school (http://www.designforhealth.net/techassistance/trec.html). While a great deal of research has been published on how the built environment is measured and may be associated with levels of physical activity, the use of GIS data to describe the neighborhood food environment is earlier in its development. We are studying the unique challenges that are faced when trying to make sense out of the neighborhood food environment data, including (1) identification of the appropriate geographies that define a neighborhood; (2) the level of reliability, completeness, and detail that is available in food-related GIS data; (3) important issues around data reduction; and (4) consideration of the level of associations that we may expect from assessment of the physical environment.

Next Steps

This rich data set provides the opportunity for examining a wide range of questions related to the etiology of childhood obesity. In addition to

examining associations with myriad relationships portrayed in our conceptual model, we will be examining longitudinal relationships between early exposures via the home, school, and neighborhood environments and weight change in both youth and adults, as well as how social influences from family and peers influence change in dietary and eating behaviors, biological outcome, and change in weight status. We will be examining the mediating influences of individual behavioral choices on weight change and will also be examining latent class analysis techniques as a way to understand typologies of risk factors that may affect unhealthy weight gain.

Implications for Cancer Prevention and Control

The TREC IDEA study has implications for cancer control and prevention through its emphasis on the environmental and behavioral factors that influence individuals', families', and communities' eating and activity choices. The TREC IDEA study focuses on primary prevention of cancers by building the evidence for what factors are most significant in influencing behavioral and biological factors related to cancer prevention.

Selected Publications

1. Sirard J, Nelson M, Pereira M, Lytle L. Validity and reliability of a home environment inventory for physical activity and media equipment. *Int J Behav Nutr Phys Act.* 2008;5:24.
2. Nelson M, Lytle L, Pasch K. Nutrition literacy: The need for a better understanding of energy balance and related concepts among adolescents and their parents. *J Am Diet Assoc.* In press.
3. Fulkerson JA, Nelson MC, Lytle LA, Moe SG, Heitzler C, Pasch KE. The validation of a home food inventory. *Int J Behav Nutr Phys Act.* 2008;5(1):55.

PRIMARY RESEARCH PROJECT 2

Take Action: Household Environmental Weight Gain Prevention

Problem

Overweight and obesity are a serious, modern epidemic that affects the majority of US adults and a growing proportion of youth. Effective primary prevention programs are urgently needed to address this public health issue. The literature shows that television viewing, energy-dense restaurant and prepackaged foods, sugar-sweetened beverages, and the family unit are important environmental influences on weight-related behaviors and the development of obesity. However, few studies have been conducted to intervene on these environmental influences.

The present study is a novel and innovative obesity prevention intervention. The study is innovative in its intervention on all individual household members, and it focuses on the known influences of television viewing and energy-dense foods in the home and eating out.

The results of the study will provide important information on the effectiveness of a broad-reaching weight gain prevention program that is appropriate for use with families in community settings. The study will also provide unique data about whether changing these environmental influences will have an impact on preventing weight gain. Currently, few data are available to evaluate this important question.

Disciplines Involved

Nutrition, psychology, epidemiology

What We Know

The home environment is an important influence on food choices, television viewing, and physical activity. These behaviors are known to contribute to energy balance and weight gain. It is important to intervene in the entire household environment and with all family members to promote healthy food choices, reduce sedentary behavior such as television viewing, and promote more physical activity.

Research Questions

1. Does an intervention that includes the entire family and targets the household food environment, television viewing, and physical activity behaviors promote healthier food choices, less television viewing and greater physical activity, and less excess weight gain among all household members?

Methods

The primary aim of this study is to evaluate a household-level weight gain prevention intervention that includes both environmental change and individual-level behavior change components. Ninety households were recruited and randomized to one of two groups for a 1-year period: (1) a face-to-face group program that focuses on household environmental changes plus individual-level behavior changes targeting specific foods and physical activity behaviors or (2) a no-contact control group. The primary outcome is percentage change in household-level BMI over the 1-year intervention period.

The household environmental weight gain prevention program includes components to reduce access to television viewing via a television time-limiting device; reduce household availability of energy-dense prepackaged foods and sugar-sweetened beverages; increase household availability of fruits and vegetables; reduce frequency of fast food restaurant use; and increase frequency of self-weighing (adults only). In addition, the individual-level behavioral change component targets specific eating and exercise behaviors that dovetail with the household environmental changes to promote weight control.

The intervention program format consists of 6 monthly face-to-face group meetings, 12 monthly newsletters, 12 home-based activities, and 6 encouragement telephone calls. The control group receives no contact until the 12-month follow-up measurement session.

The primary outcome is household-level percentage weight change measured 1 year following the initiation of treatment. Secondary outcomes are changes in food choices, physical activity, television-viewing time, and frequency of self-weighing. It is hypothesized that intervention households will gain significantly less weight over the 1-year intervention period than households randomized to the control group.

Results

Ninety households were recruited from the community. Fifty-one percent included two adults and two or more children. Household annual income was distributed as follows: 35% reported ≤ $45,000; 30% reported $50,000 to ≤ $95,000; and 35% reported ≥ $100,000. Sixty-one percent of household heads reported a college degree or greater education. Household heads were on average aged 41 years, with a BMI equal to 29.7 kg/m^2; 25% were overweight, 35% percent were obese, and 30% were normal weight. Seventy-two percent of household heads reported television viewing 2 or more hours per day, and households reported eating out 3.4 times per week.

Households randomized to the intervention group (n = 45) participated at high levels in the intervention sessions and in the home activities. Eighty-six

percent of the households attended three or more of the six face-to-face sessions; 75% attended five or more sessions. Eighty-three percent of the households completed 10 or more of the 12 home activities. Ninety-one percent of the households had television-monitoring devices placed on all of the televisions in their homes. Households kept the television-monitoring devices on their home televisions an average of 10 months of the possible 12 months of the intervention.

Follow-up measures are currently being collected and are estimated to be completed by January 2009. Clinic completion rates are approximately 90%.

Next Steps

The primary outcome analysis is currently underway. Change in BMI, food choices, television-viewing time, and physical activity will be examined. Household food purchase changes during the intervention will be analyzed using the food purchase receipt data collected from households at baseline and follow-up.

Implications for Cancer Prevention and Control

The household is an ideal setting for obesity prevention efforts aimed at the entire family unit. All household members are targeted, the home environment is intervened upon, and household members act as an interconnected social team to change behaviors related to energy balance.

PRIMARY RESEARCH PROJECT 3

Women In Steady Exercise Research (WISER)

Problem

With over 200,000 diagnoses of breast cancer each year in the United States, there is tremendous interest in discovery of a modifiable risk factor for breast cancer. Many, but not all, of the observational studies show exercise to be associated with a reduced risk for breast cancer, but how this occurs is little understood. There is a long latent period between cancer initiation and diagnosis. Even if a cancer is diagnosed after menopause, it may be premenopausal exposures that affect breast cancer. It is thus important to examine biological processes by which exercise may lower breast cancer risk in a population of young healthy women.

This study is an exercise intervention designed to examine the efficacy of aerobic exercise training for changing oxidative stress, estrogen levels, estrogen metabolism, and metabolic factors in the direction of reduced cancer risk. The study also investigates interactions among these hypothesized mechanisms and how exercise effects may be moderated by some social and individual characteristics (such as socio-demographics, social support for exercise, or time constraints). This study is the first adequately powered randomized controlled trial to assess whether aerobic exercise training among premenopausal women can alter leading hypothesized mechanisms through which exercise is thought to reduce cancer risk.

Disciplines Involved

Nutrition, exercise science, analytical chemistry, behavioral science, biochemistry

What We Know

Population studies have shown that exercise is associated with a reduction in breast cancer risk.

Research Questions

1. What are the mechanisms by which aerobic exercise reduces breast cancer risk in premenopausal women?
2. Will premenopausal women following the current recommendations for aerobic exercise show alterations in breast cancer biomarkers?
3. What are the usual patterns of physical activity and motivations for physical activity in premenopausal women?

Methods

Women In Steady Exercise Research (WISER) is a randomized, parallel-arm, controlled trial recruiting 320 women ages 18 to 30. Participants need to have regular menstrual cycles, be sedentary, not be taking any hormonal contraceptives, and be generally healthy. The primary aim of the WISER study is to assess the effects of exercise on changes in oxidative stress measured via plasma F2-isoprostanes. Secondary aims include assessing the effects of exercise on other metabolic factors that may explain the purported inverse association between exercise and breast cancer risk, as well as on menstrual cycle characteristics. In addition to plasma F2-isoprostanes, measurements include reproductive hormones, urinary estrogen metabolites, insulin, glucose, insulin-like growth factor (IGF)-1 and IGF binding proteins (IGFBPs), body composition, dietary intake, and fitness level. Women are randomized into a control group or an exercise intervention (n = 160) consisting of aerobic exercise sessions of 30 minutes five times a week over four menstrual cycles. The intervention begins with 4 weeks of five-times-weekly weight-bearing aerobic exercise training at 65-70% of age-predicted maximum heart rate. With each successive 4 weeks, exercise intensity is increased by 5% of age-predicted maximum heart rate, so that, from the 13th week onward, the participants exercise at 80-85% of age-predicted maximum heart rate. Participants are supervised weekly by certified fitness professionals and record their average heart rate (via heart rate monitors) at each session. This exercise prescription is consistent both with current public health recommendations on the amount of exercise required to promote and maintain health and to prevent chronic disease and with International Agency for Research on Cancer recommendations for the amount of exercise that may prevent breast cancer.

Results

The WISER trial began recruitment in May 2006. As of October 13, 2008, 206 participants had completed all measurements and 62 were in the process of completing measurements. The overall adherence to the exercise protocol is 89%; rates have shown a gradual decline from the first 4 weeks (94%) to the last 4 weeks (81%). The overall drop-out rate is 17.5%. In summer 2008, we analyzed biological samples from 160 participants who completed the study. Blood hormones such as estrone, estradiol, progesterone, testosterone, and sex-hormone binding globulin (SHBG), as well as IGF-1, IGFBP-1, IGFBP-2, and IGFBP-3, were assayed. Plasma F2-isoprostane analyses were also conducted. The mean age of participants who finished the WISER study (n = 206) is 25 years, and mean BMI is 24.8 kg/m^2. Sixty-six percent of the finished participants had either a college degree or a professional or graduate degree, 81% had never been married, and 6% had children. The majority of the participants who finished were White (63.5%), 15.4% were Asian, 7.4% were Black, and 13 % were of other race or ethnicity. Baseline data for a few selected endpoints are shown in Table 2.

TABLE 2: Baseline Values of Major Biochemical Endpoints from the WISER Study[1]

Endpoint	Mean ± SD	
	Control Subjects (n = 80)	Exercise Subjects (n = 80)
F2-isoprostanes (pg/mL)	50.5 ± 16.9	57.9 ± 23.9
IGF-1 (ng/mL)	387.5 ± 106.7	372.7 ± 98.2
IGFBP-3 (ng/mL)	4,708.7 ± 793.9	4,702.5 ± 872.8
Estradiol (ng/mL)	66.8 ± 27.8	63.4 ± 21.7
SHBG (ng/mL)	25.2 ± 13.4	23.5 ± 9.5
Progesterone (ng/mL)	19.4 ± 10.5	18.1 ± 11.5

[1] Values are means ± standard deviations. The data are preliminary, in that they are from half the subjects who will eventually complete the study. Thus, no statistical tests were performed.

Next Steps

Samples from 160 subjects have been analyzed up to this point, and we plan to have the other 160 samples analyzed for all endpoints by December 2009. Statistical analyses of the data will occur in spring 2010, following the laboratory analyses. We would also like to expand our understanding of the effects of physical activity on breast cancer risk by examining sleep and melatonin, because lower levels of melatonin have been shown to be associated with an increased risk for breast cancer. (An R21 grant application has been submitted to NCI.)

Implications for Cancer Prevention and Control

The WISER study is an ongoing trial aimed at finishing recruitment by December 2008. We will recruit approximately 75 more participants to ensure having 320 participants who complete all measurements by December 2009. Laboratory analyses are being conducted as planned, and we expect to have all samples analyzed by December 2009, followed by data analysis and manuscript preparation. This large, randomized, controlled study, which is testing the hypothesis that regular aerobic exercise can result in positive physiological changes associated with reduced risk for hormonally related cancers, is of potentially great significance for cancer prevention. It can add force to the recommendations on the health benefits of lifestyle changes through physical activity.

Selected Publications

1. Arikawa A, O'Dougherty M, Kaufman B, Kurzer M, Schmitz K. Exploring behavioral and body composition changes in young women after a 16-week exercise intervention. In *Sixth Annual Conference of the International Society of Behavioral Nutrition and Physical Activity*, Oslo, 2007, p. 211.

5

University of Southern California Transdisciplinary Research on Energetics and Cancer (TREC) Center

Principal Investigator: Michael I Goran, PhD

The University of Southern California Center for Transdisciplinary Research on Energetics and Cancer (USC C-TREC) is built on the concept that long-term cancer control can be addressed through the prevention and control of obesity during childhood. Our approach is based on the premise that obesity is a modifiable risk factor for some forms of cancer and that reduction of obesity in childhood has the potential for making an impression on lifelong cancer risk reduction.

Therefore, it is important to understand the early life factors that contribute to the causes and consequences of obesity. Bringing together a team of transdisciplinary scientists, the USC C-TREC is examining the causes and consequences of childhood obesity during the pubertal transition, especially in high-risk minority groups. The USC C-TREC consists of three interactive and interdisciplinary research projects that are supported by core facilities in administration, data management and analysis, human measurement, and training and career development. These cores also support a variety of developmental studies.

Primary Research Projects

Project 1

Obesity-Related Metabolic Risk for Cancer: Ethnicity and Response to Exercise in Minority Youth

Led by Michael I Goran, PhD

Project 1 is examining the ethnic differences in body fat distribution, insulin resistance, insulin-like growth factors and binding proteins, inflammatory markers, and oxidative stress in overweight African American and Hispanic children during the critical period of adolescent growth. In addition, Project

1 is examining the efficacy of nutrition education and a strength training intervention in improving these risk factors. The significance of Project 1 is to shed new light on differences in metabolic risk factors for cancer between African Americans and Hispanics and to examine their response to nutrition education and strength training. The contrast between African Americans and Hispanics is of particular interest because these groups have a similar predisposition to obesity and insulin resistance and a similar risk for type 2 diabetes; however, for the major types of cancer, African Americans have substantially greater risk than Hispanics.

To date, we have completed studies with 54 overweight Latino adolescents (15.5 ± 1.0 years), who were randomly assigned to (1) a control condition (n = 16), (2) nutrition education (n = 21), or (3) nutrition education plus strength training (n = 17). The nutrition education group received weekly modified carbohydrate nutrition classes, with a focus on decreasing sugar intake and increasing fiber intake, while the nutrition plus strength training group received the same nutrition classes plus twice-weekly strength training. We found a significant overall intervention effect for improvement in bench press ($p < 0.001$), as well as reductions in energy, carbohydrate intake, and fat intake ($p \leq 0.05$). However, there were no significant intervention effects on insulin sensitivity, body composition, or most glucose/insulin indices, except that glucose incremental area under the curve ($p = 0.05$) decreased in both the nutrition education and nutrition education plus strength training groups (by 18% and 6.3%, respectively) compared to the control group (32% increase). We also examined whether the individual degree of improvement in dietary sugar or fiber after the 16 weeks was related to improvements in metabolic outcomes related to type 2 diabetes risk. This analysis showed that 55% of all participants reduced their intake of added sugar (mean decrease = 47 g/day) and that 59% improved their fiber intake (mean increase = 5 g/day). There was no difference across intervention groups in the percentage of participants who made these improvements, including the control group. Those who reduced their sugar intake had significant improvements in glucose and insulin response to an oral glucose challenge. Those who improved their fiber intake had significant improvements in body mass index (BMI) and visceral adipose tissue. Collectively, these results show that, despite the absence of overall intervention effects, youth who decreased their sugar intake by the equivalent of one can of soda per day or increased their fiber intake by the equivalent of one-half cup of beans showed improvements in key risk factors for type 2 diabetes that have also been implicated as risks for cancer, specifically improvements in insulin secretion and visceral fat. Improvements occurred independent of group assignment and were equally likely to occur in control group participants.

Project 2

Insulin Resistance and Declining Physical Activity Levels in African American and Latina Girls

Led by Donna Spruijt-Metz, PhD

This project aims to identify the physiological and psychological determinants of the decline in physical activity in Latina (n = 50) and African American (n = 50) girls during puberty. Annual metabolic evaluations and quarterly accelerometry and psychosocial evaluations are completed for 3 years. The main objective is to assess whether the decline in physical activity in girls emanates from the "trigger" of insulin resistance, which is linked to affective determinants of physical activity such as mood and energy levels, and whether these metabolic and psychological changes contribute to the marked decline in physical activity that occurs during puberty. This study is the first to examine the temporal relationship between pubertal insulin resistance and the sharp decline in physical activity experienced by Latina and African American girls.

Results from this study will redefine our understanding of the physiological and behavioral basis of the decline in physical activity in girls during puberty and will be useful in shaping future interventions for promoting increased physical activity in pubertal girls.

More than 60 girls (77% Latina) have now completed the initial overnight stay, and approximately 15 have completed year 2 overnight stays. We have analyzed baseline data in more detail for 38 of these girls (28 Latina and 10 African American; mean age = 9.3 years, 47% Tanner stage 1 and 53% Tanner stage 2). Girls at Tanner stage 2 reported more school-related negative life events ($p = 0.04$) and more light and sedentary activity ($p = 0.008$) compared to girls at Tanner stage 1. Insulin sensitivity was not significantly different by Tanner stage after controlling for ethnicity and adiposity. Girls at Tanner stage 2 had a 30% higher acute insulin response to glucose, and this remained significant ($p = 0.04$) after controlling for ethnicity and adiposity. In a regression model, variation in sedentary behavior was explained by body fat and negative life events at school ($R2 = 0.70$). In this cross-sectional analysis, adiposity and negative life events at school seem to be driving the increase in sedentary behavior in girls during early pubertal transition.

Project 3

Influence of Built Environments on the Development of Obesity During Childhood

Led by Kiros Berhane, PhD, and Michael Jerrett, PhD

This project has two specific aims: (1) To assess the effects of the neighborhood built environment on the development of childhood obesity over time and (2) to explore whether individual (i.e., gender, race, socioeconomic status) and contextual (i.e., air pollution) variables modify the association between the built environment and the development of childhood obesity over time. Project 3 is in the unique position of capitalizing on the rich data resources from the Southern California Children's Health Study (CHS), funded by the National Institute of Environmental Health Sciences (NIEHS). CHS is a longitudinal cohort study involving several multi-ethnic cohorts of more than 11,000 children from 16 Southern California communities with diverse socioeconomic, built environment, and demographic profiles. CHS provides extensive information on objective yearly measurements of weight and height for these cohorts, as well as a wealth of information at the community, school, individual, and temporal levels. Specific strengths of the data include the examination of the effects of the built environment on children's prospective change in weight status, direct assessment of children's weight status annually, efficient use of existing environmental and individual data, and the ability to evaluate potential differential effects across race/ethnicity on the relationship between built environment and obesity.

As a result of Project 3, the CHS data have been greatly enriched by an extensive compilation of built environment factors, using geographic information systems (GIS) and land-use regression techniques. We developed a novel and flexible multilevel modeling paradigm and applied it to assess the effect of built environment, social, environmental, demographic, and health variables, at various levels of aggregation, on various aspects of BMI trajectories in children. Based on an extensive analysis of data from the two fourth-grade cohorts, we have made several important findings:

- Roadway network connectivity is associated with BMI levels, but these associations were modified by gender and indicators of safety, such as population density and neighborhood-level crime indices.
- Chronic disease status and respiratory disease are large contributors to the longitudinal increases of BMI in children ages 10 to 18.

- Access to recreational programming, green spaces, parks, and canopy tree cover is associated with decreased BMI levels at age 18.
- There are significant associations between measures of traffic intensity around the child's home and BMI growth. These associations are consistent across different buffer sizes and different types of roads.
- Surprisingly, any access to food, either through over-the-counter takeout or grocery stores, is associated with increased BMI growth in both boys and girls ages 10 to 18. The only protective variable is lack of food in the local neighborhood environment.

Developmental Research Projects

The USC C-TREC has structured the Developmental Research program to grow into an exciting and competitive mechanism that provides opportunities, resources, and support to junior researchers, as well as established scientists new to the field of obesity, who want to explore novel areas relating to obesity and cancer. In addition, the Developmental Research program has been a springboard for several R01 applications, numerous collaborations (including cross-Center collaborations with other TREC sites; see Table 1), and growth in terms of investigators directly and indirectly involved with the TREC program's overall aim of addressing the physiological, metabolic, behavioral, genetic, and environmental influences of obesity, metabolic health, and cancer risk, with a focus on minority children. The Developmental Research program has proved a success on many fronts and continues to inspire and energize the leaders and collaborators of the USC C-TREC.

Career Development for Young Investigators

The USC C-TREC has a major focus in training, mentoring, and career development. Our training core directly supports five PhD students from various academic programs, but numerous trainees from all levels and multiple disciplines (e.g., biostatistics, biomedical engineering, epidemiology, and behavior) have benefited greatly from the TREC Center, including 12 PhD students, 9 postdoctoral fellows, and 6 junior faculty affiliated with the various USC C-TREC projects and developmental studies, as well as other related projects.

As part of the training, mentoring, and career development core, the USC C-TREC hosts biweekly seminars, providing opportunities for trainees to hear from, and meet with, scientists from around the country who are involved in obesity- and cancer-related research. The seminars include networking, roundtable discussions, and one-on-one meetings. In addition, each PhD student is assigned a speaker to host, which includes conducting a tour of the laboratory, introducing the seminar, and facilitating the question-and-answer session. Trainees are also eligible to apply for funds from the Knowledge & Education Expansion Project (KEEP) to attend or receive training that goes beyond coursework and standard conference attendance. USC C-TREC KEEP funding has been provided for training opportunities such as a workshop to train new trainers on motivational interviewing; a workshop on neuroimaging in obesity research, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases; training on GIS analytical techniques; and a course on the theory and application of generalized linear mixed models across disciplines from a non-Bayesian perspective. USC C-TREC trainees are encouraged to attend and participate in TREC Scientific Meetings and are involved in several of the TREC Working Groups. Recently, trainees were given a unique training opportunity at the USC C-TREC retreat, which featured top scientists from USC and surrounding universities. PhD students were invited and assigned to breakout tables, where they had the opportunity to hear and be involved in discussions of current work and future directions. USC C-TREC trainees have been successful in obtaining extramural research support, including

TABLE 1: Developmental Projects Funded Through TREC

YEAR 1

University of Southern California

149 Combining Strength and Cardiovascular Exercise (Circuit Training) to Reduce Obesity and Associated Diseases in Overweight Latina Youth (PI: Jaimie Davis)

150 Hip Hop 2 Health (HH2H) (PI: Lester Jones)

151 Colon Cancer-Related Epigenetic Changes in Obesity (PI: Howard Kaufman)

152 SportBrain™ Pedometer and GPS Logging Technology: Better Tools for Evaluating Physical Activity in Children and an Application to the Impact of Neighborhood Land Use and Children's Commuting Time (PI: Rob McConnell)

153 Exploring the Link Between Obesity and Poor Prognosis of Childhood Acute Lymphoblastic Leukemia Using a Murine Model (PI: Steve Mittleman)

154 Ola No Ke Kino (The Body Enjoys Health!) (PI: Victor Pang)

155 Food for Thought: A Community-wide Strategic Summit for Reducing Overweight/Obesity Among Latino and African American Families (PI: Michael Ruble)

156 Functional Brain Responses After Satiety in Normal Weight and Overweight Adolescent Girls (PI: Dawna Salter-Venzon)

157 "Kid Healthy" Steps to Healthy Living (PI: Jackie Teichmann)

158 Social Network Influences on Diet and Physical Activity (PI: Thomas Valente)

YEAR 2

Cross-Center

160 Autonomic and Metabolic Dysfunction in Obese Children with Sleep-Disordered Breathing (Co-PIs: Michael CK Khoo, University of Southern California; Susan Redline, Case Western Reserve University)

161 Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-ethnic Sample of Children: A Transdisciplinary Cross-Site Developmental Project (Co-PIs: Mark Pereira, University of Minnesota; Donna Spruijt-Metz, University of Southern California)

165 Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations (Co-PIs: Melissa Nelson, University of Minnesota; Jaimie Davis, University of Southern California)

University of Southern California

182 Translation of a Novel Resistance Training Intervention to a Home Environment for Overweight Hispanic Youth (PI: Louise Kelly)

183 Global Gene Expression in White Blood Cells from Hispanic and African American Adolescents (PI: Christian Roberts)

YEAR 3

Cross-Center

207 The Effect of Ethnicity on Lipomic Profile and Adipokines: Relation to Adipose Tissue Morphology and mRNA Expression (Co-PIs: Christian Roberts, University of Southern

The unique three-digit reference number is part of a code assigned to each project when it is awarded. This reference number will enable the reader to link the specific projects listed here to Figure 6 in Chapter 1.

All developmental projects are listed by the year of initial funding. In some cases, developmental projects, such as the TREC Coordination Center projects, are ongoing from the year of initial funding through year 4.

TABLE 1: Developmental Projects Funded Through TREC – Continued

California; Sanjay Patel, Case Western Reserve University; Karen Foster-Schubert, Fred Hutchinson Cancer Research Center)

208 Insulin Resistance and Breast Cancer Prognosis (Co-PIs: Anne McTiernan, Fred Hutchinson Cancer Research Center; Leslie Bernstein, University of Southern California)

215 The Interaction of Childhood Height and BMI on the Prediction of Adiposity and Insulin Resistance (Co-PIs: Steven Stovitz, University of Minnesota; Louise Kelly, University of Southern California)

University of Southern California

221 Impact of Gestational Diabetes Mellitus on Fetal and Postnatal Hypothalamic Development (PI: Sebastien Bouret)

222 Fine-Mapping of *FTO* and *TCF2* in African Americans (PI: Christopher Haiman)

223 Investigating the Relationships Between Obesity and Leukemia Relapse (PI: Steven Mittelman)

224 Rapid and Non-invasive Quantitation of Abdominal Fat Distribution Using Magnetic Resonance Imaging (PI: Krishna Nayak)

YEAR 4

Cross-Center

None funded

University of Southern California

247 Effect of Insulin Resistance on the Brain and the Implications for Weight Regulation (PI: Tanja Adam)

248 Roles of Sex Hormones in Obesity and Breast Cancer (PI: Shiuan Chen)

249 The Role of Energy Sensor AMPK in Liver Cancer Development (PI: Bangyan Stiles)

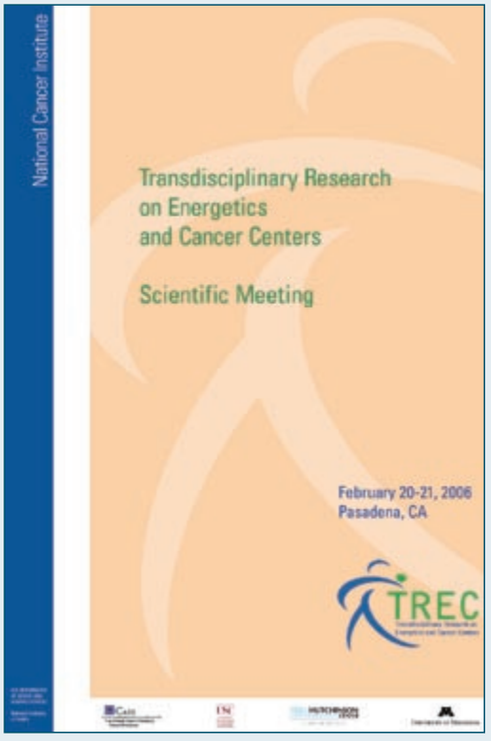
a K01 grant, an Innovative Developmental and Exploratory Award (IDEA) grant from the California Breast Cancer Research Program, a supplement from the National Center on Minority Health and Health Disparities, and R21 grants.

Key Partnerships and Collaborations

The USC C-TREC is centered in the Department of Preventive Medicine at the Keck School of Medicine, but it also incorporates expertise and critical collaborations from numerous faculties and schools at USC, including the Norris Comprehensive Cancer Center; the Viterbi School of Engineering; the College of Arts, Letters, and Sciences; and the School of Pharmacy. In addition, our partner institutions include the USC-affiliated Children's Hospital of Los Angeles; the University of California, Berkeley, School of Public Health; and the City of Hope Medical Center, an NCI-designated Comprehensive Cancer Center and independent biomedical research, treatment, and education center dedicated to preventing and treating cancer. USC C-TREC investigators, junior faculty, and trainees continue to be actively involved in the TREC Working Groups, including helping in the development of new Working Groups and acting as Working Group chairs and co-chairs. New collaborations have emerged, and existing partnerships have been strengthened, as a result of the Working Groups. Attendance at each TREC Scientific Meeting has also proven instrumental in forging and furthering cross-collaborations with other TREC Center investigators, allowing for

face-to-face discussions and more meaningful updates on each Center's progress. A particularly effective mechanism for involving internal and external scientists and students in the USC C-TREC has been the biweekly seminar series, where invited speakers present work that is relevant to the goals of the Center. The seminar series includes networking and one-on-one and group meetings, where senior scientists and trainees can talk with a variety of researchers from around the world. The USC C-TREC also hosted a 1-day transdisciplinary symposium, Childhood Obesity Symposium: Genes, Brains, and Behavior, which featured prominent speakers from across the country and the spectrum of childhood obesity research. At the community level, the USC C-TREC has been able to raise awareness and receive valuable input from community partners such as the Los Angeles Unified School District, local Boys and Girls Clubs, medical clinics, and participants and their families. The partnerships and collaborations that have been built through the USC C-TREC are truly transdisciplinary and continue to grow in strength and substance as the aims and goals of the Center are realized.

USC Scientific Meeting



TREC Grantees met for the first time at USC for an orientation of the individual TREC Centers and to begin framing cross-collaboration opportunities.

PRIMARY RESEARCH PROJECT 1

Obesity-Related Metabolic Risk for Cancer: Ethnicity and Response to Exercise in Minority Youth

Problem

African Americans and Hispanics share a similar predisposition to obesity and insulin resistance, as well as risk for type 2 diabetes. However, for the major types of cancer, African Americans have substantially greater risk than Hispanics. Project 1 aims to shed new light on obesity-related biological and metabolic differences between these two ethnic groups as they relate to potential increased lifelong risk of cancer.

Disciplines Involved

Clinical research, human metabolism, exercise physiology, behavioral intervention

What We Know

We have previously shown that both African American and Latino children are more insulin resistant than Caucasian children, and this difference is not explained by differences in total body fat or visceral fat. Moreover, the metabolic compensation

for a similar degree of insulin resistance markedly differs between African American and Latino children. African Americans display profound hyperinsulinemia in response to a glucose challenge, which is partly explained by a lower insulin clearance in the liver, whereas Latinos have a more subdued increase in insulin levels, due to an increase in second-phase insulin secretion. We build upon these observations to hypothesize that the hyperinsulinemia in response to glucose in African American youth is associated with important metabolic differences that could increase long-term cancer risk.

Research Questions

1. How do the different body fat compartments contribute to insulin resistance in African American and Hispanic youth?
2. How does the metabolic compensation for insulin resistance differ between African American and Hispanic youth?
3. Are there differences in cancer biomarkers (body fat, insulin resistance, lipid peroxidation, and oxidative stress) that are already evident at a young age in obese Hispanics and African Americans?
4. Does nutrition education and/or strength training improve these cancer biomarkers, and do these intervention effects differ by ethnicity?

Methods

This project involves a cross-sectional comparison of obese adolescents (60 African Americans vs. 60 Hispanics) and a 16-week randomized, controlled trial of nutrition education with and without twice-weekly strength training. Major outcome variables include insulin sensitivity and insulin response to glucose by intravenous glucose tolerance test; whole-body composition by dual energy X-ray absorptiometry (DEXA); visceral fat and liver fat by magnetic resonance spectroscopy; blood collection for measures of oxidative stress, lipid peroxidation, plasma lipids, and genetic admixture; and physical activity by accelerometry.

Results

To date, we have completed studies in 54 overweight Latino adolescents (15.5 ± 1.0 years) who were randomly assigned to a control group (n = 16), nutrition education (n = 21), or nutrition education plus strength training (n = 17). The nutrition education group received modified weekly carbohydrate nutrition classes, with the focus on decreasing sugar and increasing fiber intake, while the nutrition education plus strength training group received the same nutrition classes plus strength training (twice weekly). A significant overall intervention effect was found for improvement in bench press ($p < 0.001$) and reductions in energy, carbohydrate, and fat intake ($p \leq 0.05$). However, there were no significant intervention effects on insulin sensitivity, body composition, or most glucose/insulin indices, except that glucose incremental area under the curve ($p = 0.05$) decreased in the nutrition education and nutrition education plus strength training groups by 18% and 6.3%, respectively, compared to a 32% increase in the control group. We also examined whether the individual degree of improvement in dietary sugar or fiber intake after 16 weeks was related to improvements in metabolic outcomes related to type 2 diabetes risk. This analysis showed that 55% of all participants reduced their added sugar intake (mean decrease = 47 g/d) and that 59% increased their fiber intake (mean increase = 5 g/d). There was no difference across intervention groups for the percentage of participants who made these improvements, including controls. Those who reduced their sugar intake had significant improvements in the glucose and insulin response to an oral glucose challenge. Those who increased their fiber intake had significant improvements in BMI and visceral adipose tissue. Collectively, these results show that, despite the absence of overall intervention effects, individuals who decreased their sugar intake by the equivalent of one can of soda per day or increased their fiber intake by the equivalent of one-half cup of beans showed

improvements in key risk factors for type 2 diabetes that have also been implicated as risks for cancer, specifically insulin secretion and visceral fat. Improvements occurred independent of group assignment and were equally likely to occur in control group participants.

Next Steps

We have also just completed studies in a similar group of obese African American youth, and our next steps involve analyzing this data to examine cross-sectional ethnic differences as well as ethnic differences in response to the same interventions.

Implications for Cancer Prevention and Control

Project 1 will shed new light on differences in metabolic risk factors for cancer between African Americans and Hispanics, as well as their response to nutrition education and strength training.

PRIMARY RESEARCH PROJECT 2

Insulin Resistance and Declining Physical Activity Levels in African American and Latina Girls

Problem

There is a profound decline in physical activity during puberty, especially among minority females. Project 2 asks whether the decline in physical activity in minority girls emanates from the "trigger" of pubertal insulin resistance, which is linked to affective determinants of physical activity, including mood and energy levels. This study is the first to examine the temporal relationship between pubertal insulin resistance and the sharp decline in physical activity experienced by Latina and African American girls during puberty.

Disciplines Involved

Clinical research, human metabolism, exercise physiology, behavioral psychology

What We Know

Physical activity can prevent or treat obesity, and physically active girls have substantially lower risk of developing breast and other cancers such as colon and endometrial cancer as adults. However, in US populations there is a profound pubertal decline in physical activity that is most pronounced in African American and Hispanic girls, two populations that are already at high risk for overweight and related diseases. We and others have shown that insulin resistance increases during puberty, peaking at Tanner stage 3, and returns to near-normal levels at Tanner stage 5. Several studies have identified sharp physical activity declines from age 12, the average age at which girls reach Tanner stage 3 and demonstrate peak pubertal insulin resistance, which suggests that pubertal insulin resistance may trigger a decline in physical activity. Some of the same biological factors that influence physical activity, such as insulin resistance and biological progression into puberty, appear to influence affective correlates of physical activity such as mood. We pull together these strands of research from different disciplines to hypothesize that the pubertal decline in physical activity in girls is partially biologically programmed, emanating from the "trigger" of insulin resistance—which is linked to affective determinants of physical activity, including mood and energy levels—and that these metabolic and psychological changes contribute to the marked decline in physical activity that occurs during puberty.

Research Questions

1. What is the direct impact of pubertal insulin resistance in Latina and African American adolescent girls on physical activity, mood, and other psychosocial correlates of physical activity across the pubertal transition from Tanner stage 1 to 3?
2. Is the impact of puberty-induced insulin resistance on physical activity mediated by changes in mood or other psychosocial correlates?
3. Are there ethnic differences in the impact of insulin resistance on mood or physical activity?

Methods

We will recruit 50 Latina girls and 50 African American girls, ages 9 to 11, at Tanner stage 1. Yearly metabolic evaluations and quarterly accelerometry and psychosocial evaluations will be completed for 3 years. A combination of path models and growth curve models will be used to understand the longitudinal impact of pubertal insulin resistance on mood, motivation, and physical activity levels in Latina and African American girls as they mature. Major outcome variables include insulin sensitivity and insulin response to glucose by intravenous glucose tolerance test; physical activity by accelerometry and recall; whole-body composition by air plethysmography (BodPod™); visceral fat and liver fat by magnetic resonance spectroscopy; blood collection for measures of leptin and inflammatory markers; and questionnaires for psychosocial measures.

Results

To date, more than 60 girls (77% Latina) have completed the initial overnight stay, and approximately 15 have completed year 2 overnight stays. We have analyzed baseline data in more detail for 38 of these girls (28 Latina and 10 African American; mean age = 9.3 years; 47% Tanner stage 1 and 53% Tanner stage 2). Girls at Tanner stage 2 reported more school-related negative life events ($p = 0.04$) and more light and sedentary activity ($p = 0.008$) compared to girls at Tanner stage 1. Insulin sensitivity was not significantly different by Tanner stage after controlling for ethnicity and adiposity. Girls at Tanner stage 2 had a 30% higher acute insulin response to glucose, and this remained significant ($p = 0.04$) after controlling for ethnicity and adiposity. In a regression model, variation in sedentary behavior was explained by body fat and negative life events at school ($R2 = 0.70$). In this cross-sectional analysis, adiposity and negative life events at school seem to be driving the increase in sedentary behavior in girls during early pubertal transition. We also recently completed a cross-sectional analysis in 51 girls to examine the relationship between C-reactive protein, leptin, BMI Z-score, percentage body fat assessed by air plethysmography (BodPod™), and insulin sensitivity and acute insulin response in 51 Latina and African American girls, mean age 9.2 (± 0.94) years, at either Tanner stage 1 ($n = 25$) or 2 ($n = 26$). Girls at Tanner stage 2 had higher BMI z-scores, percentage body fat, and fasting insulin and leptin levels than those at stage 1. There were no ethnic differences in any of the measured variables. A linear regression model showed that C-reactive protein independently explained 10% ($p = 0.00$) of the variance in leptin after adjusting for percentage body fat, Tanner pubertal stage, ethnicity, and insulin sensitivity. Hence, low-grade inflammation may contribute to prolonged leptin exposure and leptin resistance, even in healthy children.

Next Steps

We are completing recruitment and have just developed a database with data from more than 50 girls from Project 2 and more than 50 Hispanic girls from Project 1 to examine the cross-sectional relationships between physical activity, insulin resistance, and psychosocial correlates of physical activity across Tanner stages. We will also combine our data with data from Leslie Lytle's IDEA study and Susan Redline's sleep cohort to examine the

different correlates of objectively measured versus subjectively measured physical activity in youth across TREC Centers. The Coordination Center will assist with data analyses. This has been submitted as part of a symposium for the 2009 Obesity Society meeting, together with other members of the Physical Activity, Sleep, and Environmental Measurement Working Group.

Implications for Cancer Prevention and Control

Project 2 is the first study to examine the temporal relationship between pubertal insulin resistance and the sharp decline in physical activity experienced by Latina and African American girls during puberty. Results from this study will redefine our understanding of the physiological and behavioral basis of the decline in physical activity in girls during puberty and will be useful in shaping future interventions for promoting increased physical activity in pubertal girls.

PRIMARY RESEARCH PROJECT 3

Influence of Built Environments on the Development of Obesity During Childhood

Problem

Rates of overweight and obesity have nearly doubled in children over the past two decades, leading to increased risks of obesity as adults and short- and long-term risk of cancer as well as type 2 diabetes and cardiovascular disease. Recent metabolic and genetic research has deepened our understanding of the physiological aspects of body weight regulation. Very little evidence, however, supports the notion that the current epidemic of obesity and related diseases is explained directly by acute metabolic and/or genetic defects. The more likely explanation relates to societal and environmental changes that promote the expression of an obese phenotype (i.e., fewer requirements for physical activity and greater abundance and availability of calorie-rich food). Growing evidence now links the built environment to physical activity, dietary intake, and obesity. Most previous studies have been cross-sectional, and longitudinal studies tracking large populations of children over critical development periods are now needed to assess the influence of the built environment on the development of obesity in children.

Disciplines Involved

Epidemiologic research, medical geography, biostatistics, growth curve modeling

What We Know

There is growing evidence that now links the built environment to physical activity, dietary quality, and obesity. Most of this information is based on cross-sectional studies that may not have the richness of prospective and objective assessment of physiologic indices such as BMI. It is also well-recognized that preventing obesity during childhood could result in decreasing the rising tide of childhood-onset diabetes and may also lower the risk of cancer later in life.

Research Questions

1. How does the neighborhood built environment affect the development of childhood obesity over time?
2. How is the potential effect of the built environment on the development of childhood obesity over time modified by individual variables (e.g., gender, race, socioeconomic status) and contextual variables (e.g., air pollution)?

Methods

Based on objective assessment of BMI levels at several yearly measurements for each child, Project 3 assesses the impact of the built environment on childhood obesity (and how this impact might be modified by contextual factors) using a novel multi-level modeling paradigm that accounts for nonlinear trajectories in childhood BMI trajectories. Project 3 has the unique position of capitalizing on the rich data resources from the Southern California Children's Health Study (CHS) funded by the National Institute of Environmental Health Sciences. CHS is a longitudinal, multi-ethnic cohort study involving several multi-ethnic cohorts of more than 11,000 children from 16 Southern California communities with diverse socioeconomic, built-environment, and demographic profiles. These cohorts have extensive information on objective yearly measurements of weight and height, as well as a wealth of information at the community, school, individual, and temporal levels. Specific strengths of the data include examination of the effects of the built environment on children's prospective change in weight status, direct assessment of children's weight status annually, efficient use of existing environmental and individual data, and the ability to evaluate potential differential effects across race/ethnicity on the relation between built environment and obesity.

Results

As a result of Project 3, the CHS data have been greatly enriched by an extensive compilation of built-environment factors using geographic information systems. A novel and flexible multi-level modeling paradigm was developed and applied to assess the effect of built-environment, social, environmental, demographic, and health variables, at various levels of aggregation, on various aspects of BMI trajectories in children. Based on an extensive analysis of data from the two fourth grade cohorts, several important findings have been observed:

- Roadway network connectivity is associated with BMI levels, but these associations were modified by gender and indicators of safety such as population density and neighborhood-level crime indices.
- Chronic disease status and respiratory disease are large contributors to the longitudinal increase in BMI in children ages 10 to 18.
- Access to recreational programming, green spaces, parks, and canopy tree cover is associated with decreased BMI levels at age 18.
- There are significant associations between measures of traffic intensity around the child's home and BMI increase.

These associations are consistent across different buffer sizes and different types of roads. Surprisingly, any access to food, either through over-the-counter takeout or grocery stores, is associated with increased BMI growth in both boys and girls ages 10 to 18. The only protective variable is lack of food in the local neighborhood environment.

Next Steps

Additional analyses are underway to assess the effects of additional socioeconomic, demographic, and built-environment factors at various levels of aggregation (e.g., temporal, individual, school, community). Parallel analyses are being conducted for more than 5,000 members of another, younger cohort (recruited from kindergarten and first grade classrooms in 13 Southern California communities). This new cohort will allow us to examine the effects of the built environment at an even younger age and will also provide an opportunity to replicate key study findings as this currently active cohort starts to overlap in age with the other cohorts. Current results from the younger cohort generally replicate our findings from the older cohort.

Implications for Cancer Prevention and Control

Project 3 has the potential for informing policy on effective measures for preventing childhood obesity, and hence related cancers later in life. Given the strong evidence that childhood obesity likely persists into adulthood, it is important to understand how the built environment influences progression toward obesity in children before they become obese. The objective and prospective nature of the BMI assessment, the large sample size, and the richness of information on demographic, socioeconomic, dietary, activity, and built-environment factors at several levels of aggregation provides a unique opportunity to obtain crucial answers to important public health questions.

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TREC Coordination Center

Principal Investigator: Mark Thornquist, PhD

The TREC Coordination Center provides organizational and scientific leadership to facilitate interactions among the TREC Research Centers and NCI.

Our role as the Coordination Center in a collaborative consortium such as TREC is different from the more familiar role of coordination centers in multicenter trials, because there is no common standardized protocol to implement across sites. Compared to coordination centers of multicenter trials, our role is to be suggestive rather than prescriptive, supportive rather than directing, behind the scenes rather than in the forefront. Our success is demonstrated by the organizational support that happens seamlessly and allows the TREC Research Centers to focus on their research.

We foster communication and collaboration among teams of scientists; develop unified data management tools, including TREC common data elements (CDEs); and ensure that knowledge is disseminated both within and outside TREC. We perform all of the centralized work to make TREC more than just the sum of its parts.

In addition to our coordination role, we participate in the scientific research of TREC. The TREC Coordination Center includes investigators in biostatistics, nutrition science, kinesiology, epidemiology, and laboratory methods who are active in the TREC Working Groups and Task Forces and advancing their own scientific research through their collaborations with TREC investigators around the country. The science is an important element of the TREC Coordination Center's contribution to TREC. In addition to experienced investigators, the TREC Coordination Center has highly trained and experienced staff in the areas of project management, data management systems development, and CDE development. This mix of investigators and staff makes a team well-suited for the promotion and integration of transdisciplinary research.

Accordingly, the TREC Coordination Center has the following specific aims:

Aim 1
In collaboration with the TREC Centers, to lead the scientific development of data methods and systems to promote transdisciplinary collaborative research on energetics and cancer.

Aim 2
To provide centralized operational support for the TREC program by organizing regular TREC meetings and establishing a communication infrastructure for information exchange.

Aim 3
To facilitate the training of new investigators through the identification and coordination of training workshops.

Aim 4
To disseminate TREC research knowledge through creation of a public website and organization of TREC symposia at national and international scientific meetings.

Aim 5
In collaboration with NCI, to develop evaluation metrics for the TREC program and perform the evaluation on a regular basis.

Looking to the future, we envision several areas where the Coordination Center can continue to help bring transdisciplinary research together by:

- Further coordinating the development of CDEs to support data sharing (see sidebar).
- Providing centralized data management for cross-Center projects.
- Developing a web-based system to capture TREC project results and specimen information so that investigators can efficiently identify potential collaborators (for example, by helping investigators find other investigators who have specimens and data relevant to a proposed research question).
- Creating a data transfer and archiving tool to support the capture and distribution of TREC data.

Highlights

Aim 1
Data Methods and Systems
Web-Based Systems for Data Management and Specimen Tracking

The TREC Coordination Center has designed and built customized web-based applications for use in TREC studies where clinical data are captured, collected specimens are tracked, and laboratory assay results are annotated and uploaded into secure data repositories. These systems, combined with a centralized server for data

Common Data Elements (CDEs)

CDEs are data elements (e.g., answers to questions on a form or results of a laboratory assay) to which are attached extensive information (metadata) about the meaning of the data element and the form of the data that it holds. Examples of metadata include the specific wording of a question on a clinical form, a list of permissible values the data element may take on, and the format that the data element uses in storage. Metadata describe the collected data in such a way that their semantic meanings can be determined, allowing them to be compared to similar data collected at a different institution or from a different study. Well-annotated CDEs enable the possibility of merging and analyzing data from multiple studies as a single uniform data set.

storage, allow all study-related electronic data, captured from all facets of a study, to be centralized and available to everyone who requires access.

To date, two of our customized systems are used in TREC studies: the Participant Data Management (PDM) system and the Laboratory Information Management System (LIMS).

- The PDM system manages participant contacts and collects pertinent study-related data on web-based forms. The system uses CDEs to provide consistency in the way data are collected, formatted, and described. The PDM uses CDEs not only to assist with a single study and its associated data capture, analysis, and presentation but also to enhance and assure potential for future data sharing, a current focus of many funding sources. The PDM (see Figure 1) is currently used by the Balance of Energy in Chemotherapy (BALANCE) Study, a TREC Coordination Center developmental project.
- LIMS is specimen focused and assists research laboratories in managing project-related information, such as specimen location, specimen shipments, and laboratory methods. It includes laboratory results and a search feature to quickly identify specimens based upon customized participant and specimen search parameters. LIMS (see Figure 2) is currently used by the Seattle TREC Center for nine projects (three main projects and six developmental projects). The TREC Coordination Center's BALANCE Study also uses LIMS.

FIGURE 1: Participant Data Management (PDM) System

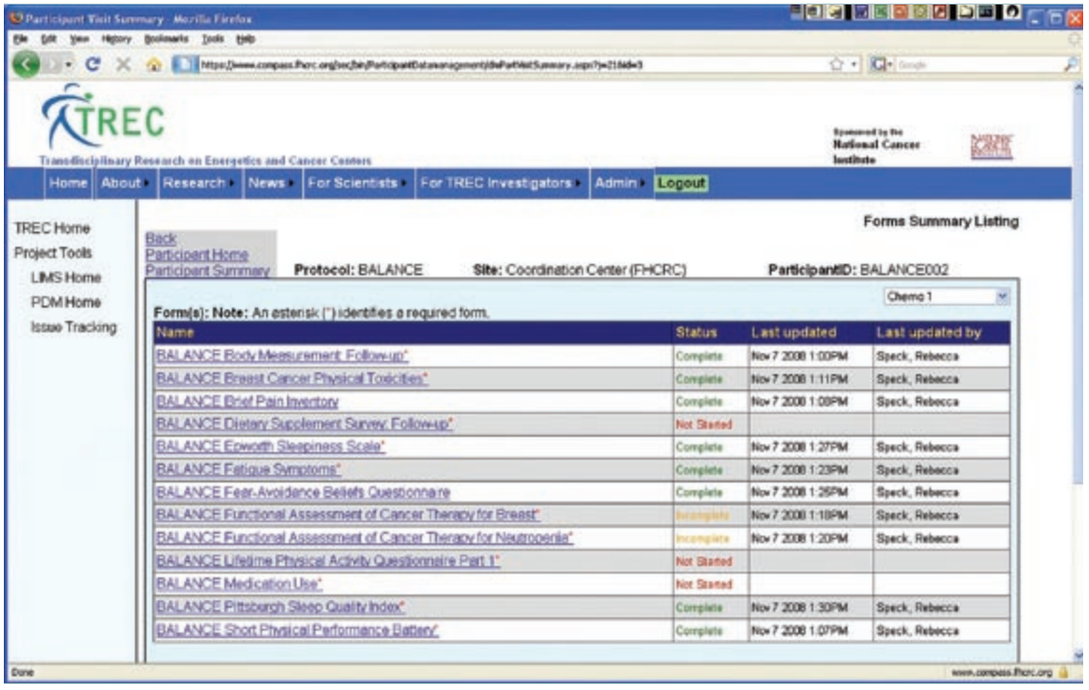
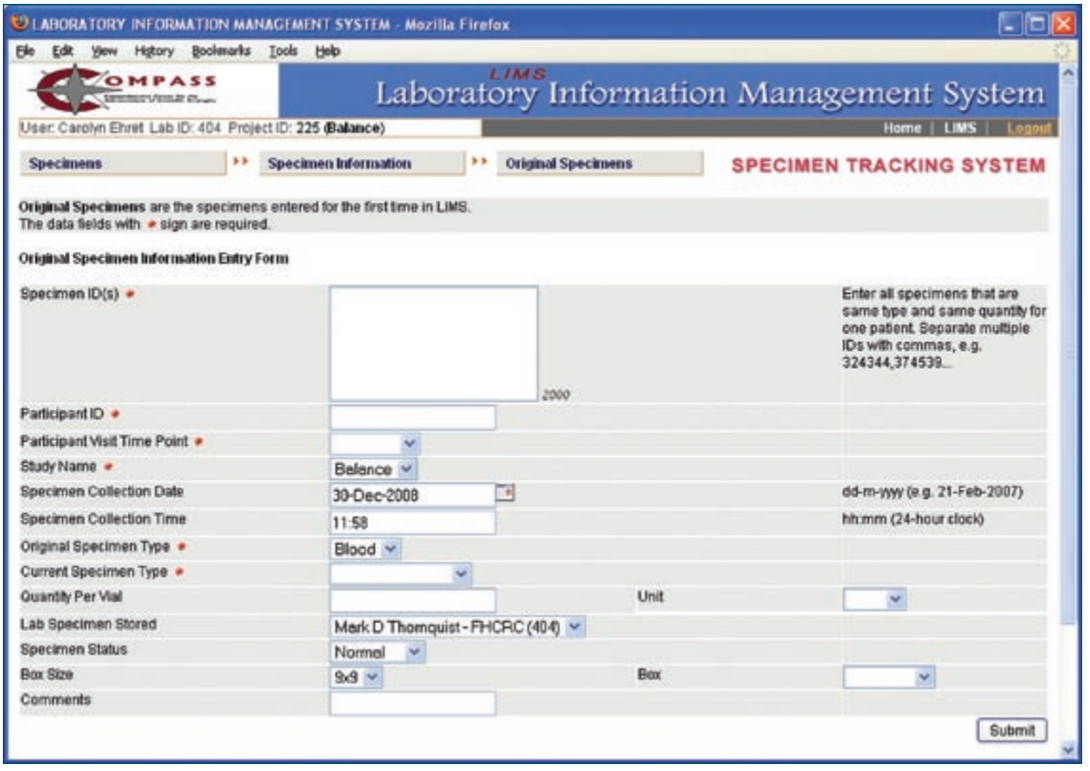


FIGURE 2: Laboratory Information Management System (LIMS)



Combined, these systems provide exceptional technological mechanisms for managing study-related data. Figure 3 depicts how the PDM, used to collect participant information during a scheduled visit, and the LIMS, used to track specimens and laboratory work performed on the collected specimens, interact to provide a shared platform to support data analysis. Participant and specimen data can be easily combined in preparation for statistical analysis.

Our systems are accessed through specifically designed secure web portals. Data are stored on secure servers at the TREC Coordination Center and are managed by network and database administrators. Thus, large quantities of data are available for secure sharing or data recovery if needed.

Investigation Into Benefits of Implementing Quality Assurance/Quality Control Program for Laboratory Assays

In March 2007, the TREC Steering Committee approved a proposal from the TREC Biomarkers Working Group to gather information about biospecimens to be collected in each of the TREC main and developmental projects. Goals for gathering this information were to:

- Enable investigators interested in ancillary studies to determine who might have appropriate samples available.
- Identify potential cross-Center collaborations regarding effects of various exposures on outcomes in common across studies.

FIGURE 3: TREC Coordination Center Web-Based Systems for Data Management and Specimen Tracking

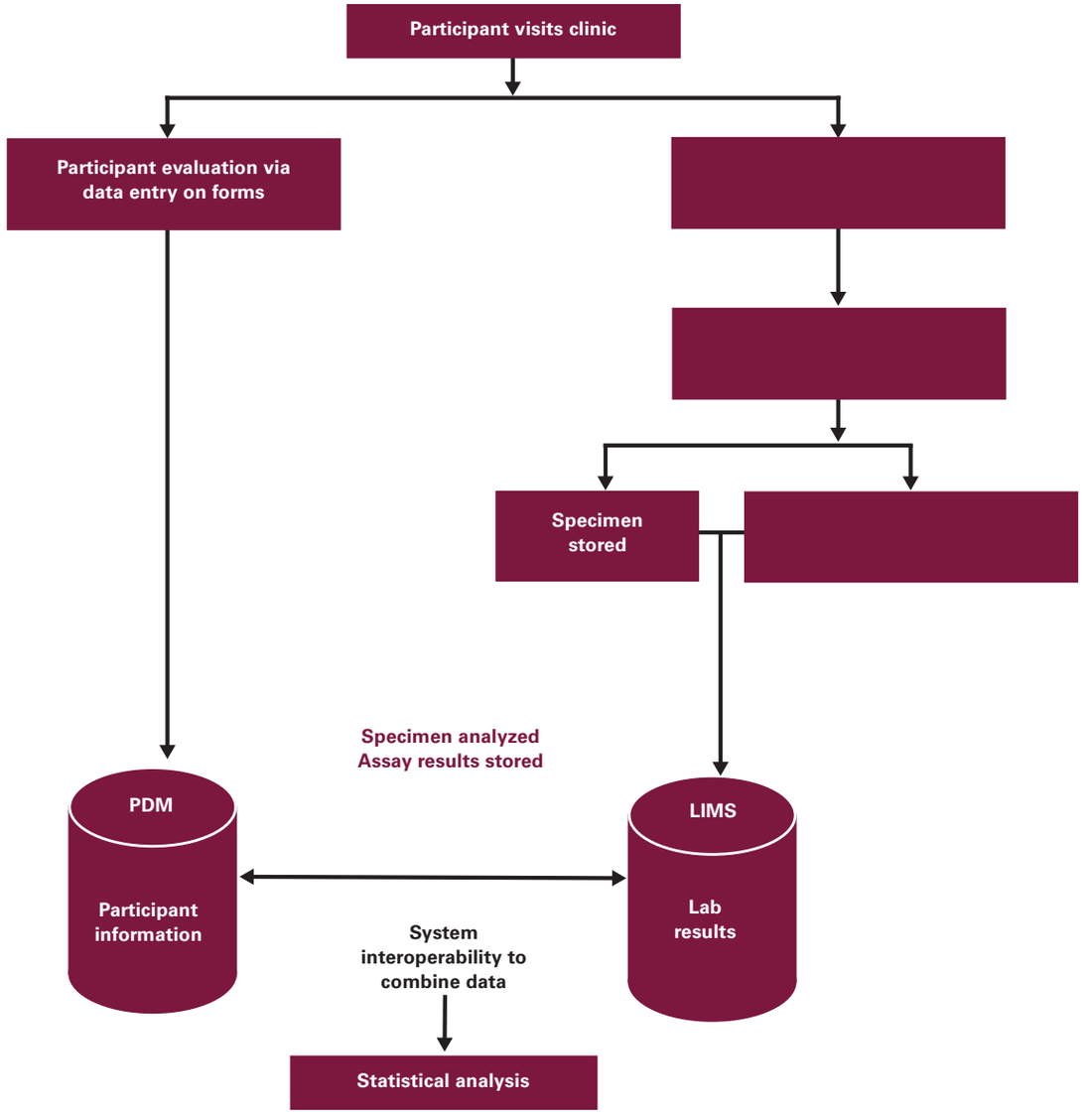


Figure depicts Participant Data Management (PDM) system, used to collect participant information during a scheduled visit, and Laboratory Information Management System (LIMS), used to track specimens and laboratory work performed on the collected specimens. Participant and specimen data can be easily combined in preparation for statistical analysis.

- Determine when an analyte was being measured by different assays at different laboratories, so that investigators could choose to converge on a single assay if feasible.
- Identify assays in common across different studies/Centers for which it might be useful to have a quality assurance/quality control (QA/QC) program to enable comparisons across laboratories.

To support this effort, the TREC Coordination Center designed and implemented a Biospecimen Survey and prepared comprehensive summary documents for the TREC membership. For example, Table 1 shows the blood assays most commonly performed in TREC projects involving human biospecimens. Based on the information obtained in this survey, TREC Coordination Center investigators have explored the potential for a "laboratory round-robin" developmental project to assess the extent to which results from multiple laboratories doing common assays for TREC projects are comparable. We focused on biomarkers that are primary or secondary outcomes in their studies and on assays for these markers being run contemporaneously at multiple laboratories to avoid issues of sample stability and laboratory drift. In 2008, the only biomarkers meeting our criteria that were being assayed in three or more laboratories with sufficient sample sizes (> 100 per laboratory) were insulin-like growth factor (IGF)-1 and IGF binding protein (IGFBP)-3. Implementing this QA/QC project for the IGF pathway alone was not cost-efficient so no round robin was performed in 2008. Feedback from TREC investigators indicates that there is ongoing enthusiasm for pursuing this activity as a real investment in validating cross-Center and cross-project comparisons, so the round-robin project will be considered again in 2009, when the larger number of laboratory assays being performed makes such a project more cost-efficient.

TABLE 1: Common Blood Assays Across TREC[1]

Blood Assay	TREC Centers (no.)	TREC Projects (no.)	Labs (no.)	Participants (no.)
Adiponectin	4	9	4	3,284
Cortisol	2	5	2	258
C-Reactive Protein	4	6	5	1,748
Estrogens	3	6	4	1,268
Glucose	4	13	4[2]	3,707
IGF Pathway Hormones	4	11	5	3,489
Interleukin-6	4	7	5	1,280
Insulin	4	12	3[2]	1,637
Leptin	4	11	4[2]	1,816
Oxidative Stress	2	6	3[2]	992

Source: TREC Biospecimen Survey, May 2007.

[1] Projects funded as of May 2007.

[2] "To be named" laboratories not included.

Group Activity to Promote Common Methods Across TREC

Several TREC Working Groups, Task Forces, and staff or interest groups have formed to facilitate the flow of research ideas and collaborations across TREC. The TREC Coordination Center has at least one participating member in each group and has provided leadership in several to promote common methods across TREC. The following are two examples:

- **Nutrition Assessment Working Group.** Dr Marian Neuhouser chaired the Nutrition Assessment Working Group from its inception in autumn 2005 to February 2007. Because several TREC Centers were conducting studies with dietary assessment, the group began meeting regularly by telephone shortly after TREC was funded, with the intent of utilizing common methods across sites prior to the beginning of data collection or interventions. An early product of this Working Group, under Dr Neuhouser's leadership, was the *Catalogue of Nutrition Assessment*, a document summarizing diet assessment methods in the eight TREC main projects that use dietary assessment.
- **Statistics Interest Group.** In 2008, as some of the main TREC projects approached the analysis phase, Dr Mark Thornquist led the formation of the Statistics Interest Group, with representatives from all TREC Centers. The focus of this group is to discuss statistical methodology appropriate for and necessitated by the multidimensional analytic viewpoints inherent in transdisciplinary research and to examine and critique statistical analyses of evolving project data. In harmony with the principles of transdisciplinarity, participants in the monthly conference calls of this interest group have included a cross-section of TREC disciplines, leading to a sharing of scientific viewpoints and more complex, multilayered analyses of data being proposed for TREC projects.

Conference Call Support

The TREC Coordination Center arranges and financially supports all of the bimonthly TREC Steering Committee conference calls. We also support one conference call per month for each of the TREC Working Groups and Task Forces. As of August 2008, we had supported more than 125 conference calls, including 13 teleconference training seminars organized by TREC Working Groups.

Aim 2
Operational Support

The TREC Coordination Center provides centralized operational support for the TREC initiative. Examples include establishing and maintaining a communication infrastructure, providing administrative and logistical support for Scientific Meetings, preparing and maintaining the TREC Manual of Operations, and coordinating communication for TREC Steering Committee review, approval, and monitoring of developmental projects.

Communication Infrastructure

We established and maintain the communication infrastructure for information exchange across the TREC network. Key components include the TREC website (see details under Aim 4); establishment of more than 20 electronic mailing lists for TREC Working Groups, Task Forces, the Steering Committee, and other investigator groups; and conference call support (see sidebar).

Meeting Support

The TREC Coordination Center provides logistical and administrative support to organize and conduct the biannual TREC Center Scientific Meetings. Some of our meeting support activities include facilitating the TREC Steering Committee's

preparation of the meeting agenda; arranging for hotel and meeting space; managing online meeting registration; preparing the meeting packet; managing all on-site logistics, including audiovisual support; and posting all available presentations to the TREC secure website as a permanent resource for TREC investigators.

Manual of Operations
We oversee the development, production, and ongoing maintenance of the TREC Manual of Operations. This 53-page document, which is posted to the TREC secure website, describes the policies and common procedures for implementing the TREC initiative.

Developmental Project Support
The TREC Coordination Center coordinates communication for TREC Steering Committee review, approval, and monitoring of developmental projects. The following are examples of the support we provide:

- Maintenance of the procedures, systems, and forms for standardized implementation of the cross-Center proposal application process (e.g., schedule for announcing availability of funds, template for requesting applications, format for proposals, evaluation scoring sheet).
- Coordination of Steering Committee review and approval of locally approved proposals.
- Coordination of Steering Committee review of progress for all approved cross-Center projects every 6 months.
- Maintenance of the following materials on the TREC secure website:
  - The proposal for every approved developmental project, and additional materials if available.
  - The TREC Projects List, which shows projects by Center with project title and investigator name.
  - The TREC Projects Diagram, which shows all projects by Center and indicates cross-Center collaborations.

Aim 3
Training

TREC Knowledge & Education Expansion Project (KEEP)
In August 2007, the TREC Coordination Center, together with the TREC Training Task Force, obtained TREC Steering Committee approval to allocate some of the TREC Coordination Center developmental funds to establish a $20,000 per annum TREC Knowledge & Education Expansion Project (KEEP), to be shared evenly among the four TREC sites. The KEEP funds give TREC trainees educational opportunities such as, but not limited to:

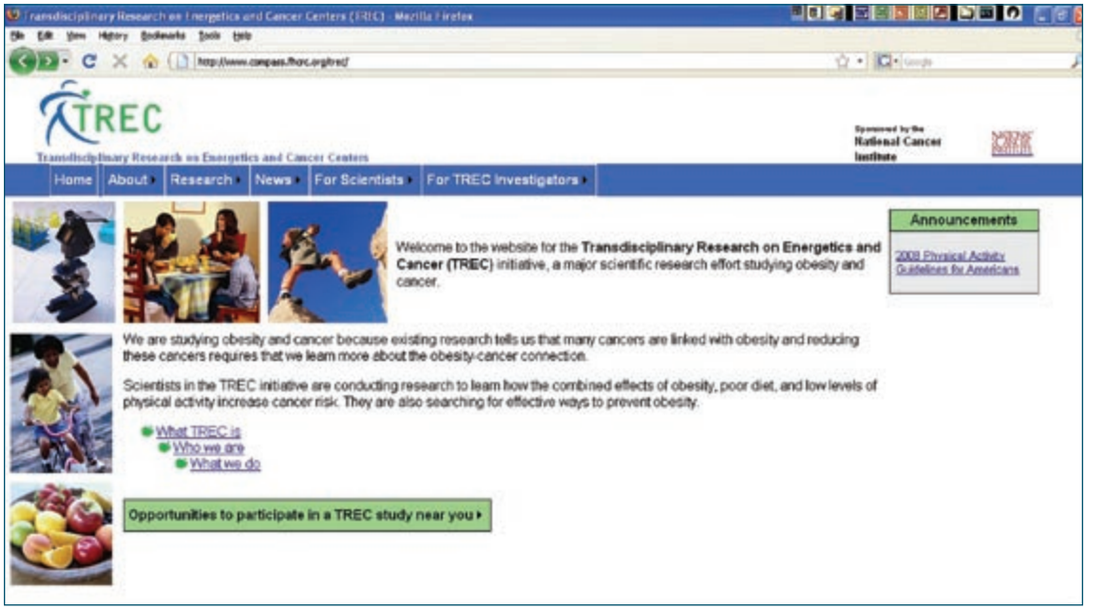
- Visiting other TREC Research Centers to expand their knowledge base in transdisciplinary research.
- Attending scientific conferences, such as the American Association for Cancer Research, as a means of continuing education.
- Receiving instruction on the use of one of the TREC datasets for purposes of expanding the knowledge base and possible collaborative research opportunities.
- Visiting non-TREC institutions to gain knowledge and skill in a specific technique or procedure.

We developed all policies, procedures, materials, and systems for implementing the TREC KEEP. As of August 31, 2008, 18 investigators from the four TREC Research Centers had received training support through this project (Table 2).

TABLE 2: TREC Knowledge & Education Expansion Project (KEEP) Recipients (Year 3, September 1, 2007–August 31, 2008)

Recipient	Educational Opportunity
Case Western Reserve University	
Jinsook Chang	American Society of Mass Spectrometry conference in Denver, CO, on June 1-6, 2008 (to attend and present data proposed and generated to date in TREC developmental grant)
Katarina Greer	6th TREC Centers Scientific Meeting in Seattle, WA, May 6-7, 2008
Sanjay Patel	6th TREC Centers Scientific Meeting in Seattle, WA, May 5-7, 2008
	Dr. Richard Pratley's laboratory at the University of Vermont, July 21-22, 2008 (to gain skills to develop a biorepository of adipose tissue samples at Case Western Reserve University)
Cheryl Thompson	6th TREC Centers Scientific Meeting in Seattle, WA, May 5-7, 2008
Fred Hutchinson Cancer Research Center	
Kristin Campbell	American College of Sports Medicine Annual Meeting in Indianapolis, IN, May 28-31, 2008
Meredith Hullar	Experimental Biology meeting in San Diego, CA, April 5-9, 2008
Alyson Littman	International Society for Behavioral Nutrition and Physical Activity Annual Meeting in Banff, AB, Canada, May 21-24, 2008
Elizabeth Poole	American Association for Cancer Research special conference, Candidate Pathways, Whole Genome Scans: Reconciling Results, Looking Into the Future, in Carefree, AZ, May 20-23, 2008
University of Minnesota	
Andrea Arikawa	6th TREC Centers Scientific Meeting in Seattle, WA, May 5-7, 2008
Melissa Nelson	International Society for Behavioral Nutrition and Physical Activity Annual Meeting in Banff, AB, Canada, May 21-24, 2008
Maureen O'Dougherty	Annual Meeting of Active Living Research in Washington, DC, April 10-12, 2008
Steven Stovitz	American College of Sports Medicine Annual Meeting in Indianapolis, IN, May 27-31, 2008
University of Southern California	
Courtney Byrd-Williams/ Britni Belcher	Online training provided by the SAS Institute, in Pasadena, CA, April 22-25, 2008 (to improve the techniques for manipulating SAS code used to reduce accelerometry data)
Chih-Chieh (Roger) Chang	Generalized Linear Mixed Models: Theory and Applications – Continuing Education at the Joint Statistical Meetings in Denver, CO, August 3-7, 2008
Rebecca Cherry	Digestive Disease Week in San Diego, CA, May 18-21, 2008 (to attend and present poster)
Jaimie Davis	6th TREC Centers Scientific Meeting in Seattle, WA, May 5-7, 2008
Claudia Toledo	3rd International Symposium: Integrated Biomarkers in Cardiovascular Diseases in Seattle, WA, July 9-11, 2008
Emily Ventura	2-Day visit at Fred Hutchinson Cancer Research Center, in Seattle, WA, May 8-9, 2008 (to meet with Marian Neuhouser and FHCRC staff regarding the TREC feeding study on glycemic load and obesity effects on cancer biomarkers)

FIGURE 4: TREC Public Portal Home Page

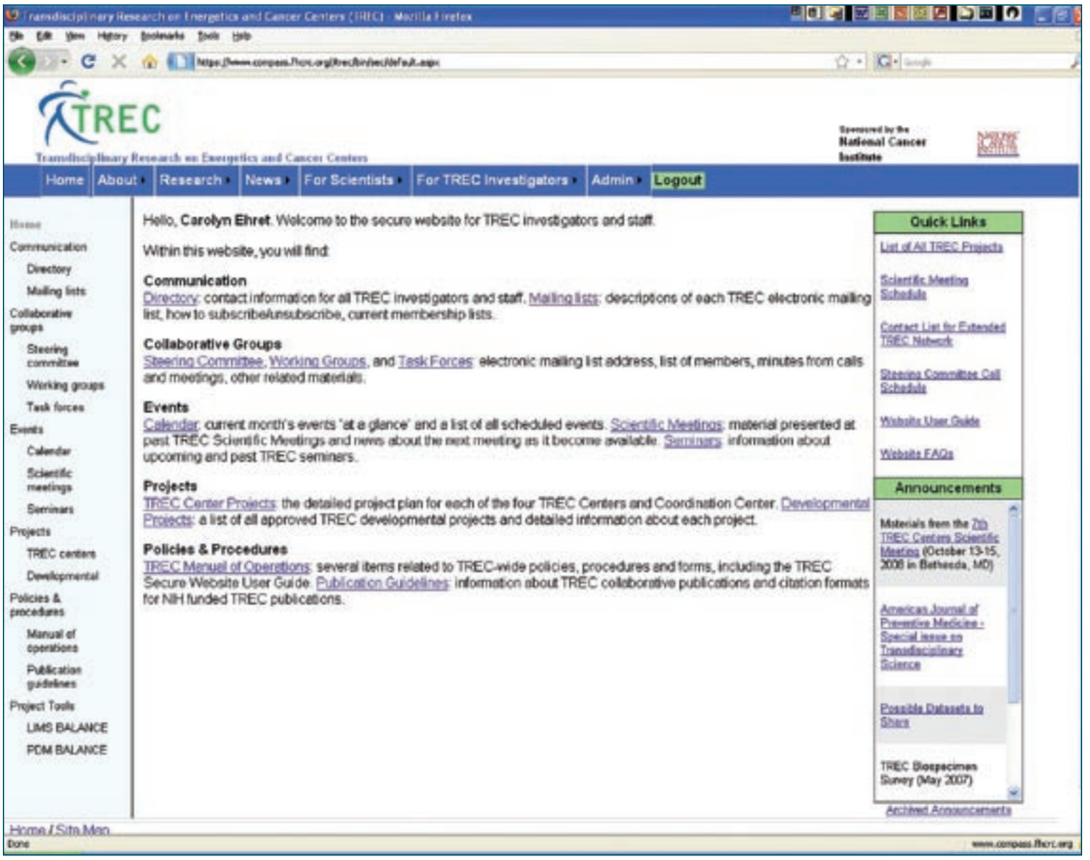


Center to update information in the directory. The result is a website that is easily kept up to date and that is a useful source of information for TREC investigators.

Together, these sites have links to over 2 gigabytes of information covering all aspects of TREC and acting as the repository of all information about TREC. The following types of information are available through the secure portal:

- **Communication.** Directory of TREC individuals, sortable by Center or study role, with complete contact information; lists of TREC mailing lists, with descriptions of their purpose, as well as lists of subscribed members and procedures for subscribing and unsubscribing.
- **Collaborative Groups.** For the TREC Steering Committee, Working Groups, and Task Forces, lists of members, agendas and materials for meetings/calls, and archives of all meeting minutes.
- **Events.** Calendar of events such as Scientific Meetings and Working Group webinars, archives of the presentations at these events, and agendas and meeting summaries for the biannual Scientific Meetings.
- **Projects.** The title, principal investigator, and detailed project plans for all TREC primary and approved developmental projects.
- **Policies and Procedures.** The TREC Manual of Operations and publication guidelines.
- **Project Tools.** Access to the specimen annotation, inventory, and tracking systems developed by the TREC Coordination Center to facilitate the specimen handling process at TREC Centers, currently being used by the Seattle TREC Center for all of its specimen activities (project-specific user rights are required for access).

FIGURE 5: TREC Secure Website Home Page



Sections that will be added to the secure TREC website include publications, with links to the PubMed Central versions of papers as they become available, and evaluation, detailing the activities and findings from the ongoing evaluation of the TREC Consortium.

Symposia and Workshops

TREC Coordination Center investigators actively participate in the preparation and delivery of symposia, workshops, and conferences to disseminate TREC knowledge. For example, the American College of Sports Medicine program committee invited Dr Kathryn Schmitz to submit a proposal for a featured session at the May 2009 meeting in Seattle, WA. The session accepted for presentation is titled Raging Hormones: Effects of Exercise on Hormones Across the Lifecycle in Girls and Women.

Dr Melinda Irwin was instrumental in organizing and planning the upcoming TREC conference, Energy Balance to Improve Cancer Prognosis and Survivorship. The primary goal of this transdisciplinary conference is to examine, at the molecular, animal, clinical, and epidemiological levels, the relationship between energy balance and cancer prognosis and survivorship. This conference will stimulate focused, but wide-ranging, discussion among experts in these fields, resulting in an agenda to guide future research in energy balance and cancer survival/survivorship.

Other Knowledge Dissemination Activities
The TREC Coordination Center has taken other steps to enhance communication and facilitate knowledge dissemination. We provide access to GoToMeeting™, an online meeting program that allows individuals attending a conference call to view the meeting convener's computer desktop on their own computer. The Statistics Interest Group has plans to use this system, as it will allow them to demonstrate live data analyses with the opportunity to explore immediately alternative models that may be suggested in the conference call and have all participants see the result. The TREC Coordination Center also took the lead in developing the initial form of the TREC publication guidelines, to ensure consistency in the dissemination and interpretation of TREC data as it appears in publications.

Aim 5
Evaluation

Large-scale initiatives such as TREC require regular evaluation to assess the extent to which the research being conducted is achieving the goals of the initiative and is doing so in a cost-effective manner. A major and ongoing focus of the TREC Coordination Center is to work collaboratively with the TREC Center Directors and NCI's Evaluation of Large Initiatives (ELI) team to perform rigorous assessment of the progress of TREC, as well as to work with the ELI team in researching the science of team science. The goals, strategic plan, and completed and future activities related to evaluation of TREC are discussed in Chapter 7. Here we highlight the TREC Coordination Center's role and activity in evaluating the TREC initiative and enhancing research into the science of team science.

The Coordination Center's activity in evaluation is led by the Center Director, Dr Mark Thornquist, who was the chair of the TREC Evaluation Working Group from 2005 to 2008; this group has representatives from all of the TREC Centers, including Center Directors from four of the five TREC Centers, plus representatives from NCI and the ELI team. The Working Group meets monthly, and from 2005 to 2008 the Coordination Center set the agenda and provided minutes. This Working Group has been productive, as evidenced in the report of the Evaluation Working Group (see Chapter 8).

In 2006, during year 1 of TREC, the ELI team and TREC Coordination Center investigators and staff implemented an online survey of TREC investigators to evaluate, among other factors, the readiness of the TREC Centers to initiate transdisciplinary research, the institutional support provided to the Centers that could enhance the prospect for successful execution of transdisciplinary science, and the experience and attitudes of the TREC investigators. The Coordination Center helped develop and test the survey and piloted the online implementation, which was created by Westat under a subcontract with NCI. Coordination Center staff developed the sampling frame and provided data for the creation of permissible values lists for several key variables. The Coordination Center also developed the protocol for the activity and oversaw its review by institutional review boards at both the Fred Hutchinson Cancer Research Center and Westat. The Coordination Center's Center Director collaborated with the ELI team in the analysis of the data from the baseline survey, leading to a presentation in 2006 at a conference on the science of team science and a recent publication (Hall et al., 2008). In 2008, a follow-up survey of TREC investigators was implemented with a similar Coordination Center role in development and planned analysis. Data from this survey provide the first measures of change from baseline of the TREC Centers and are thus invaluable to the TREC Center Directors in providing intermediate measures of success for many projects that have not yet reached the analysis stage.

The TREC Coordination Center has also conducted evaluations of each of the biannual TREC Scientific Meetings and has provided feedback from these evaluations to the TREC Steering Committee to help improve the value of these meetings to the TREC investigators. This feedback has led to a greater emphasis on time for small-group discussions, poster sessions, and breakout activities that have led to many of the collaborative cross-Center projects funded through the TREC Centers' developmental project funds.

Selected Publications

1. Hall KL, Stokols D, Moser RP, Taylor BK, Thornquist MD, Nebeling LC, Ehret CC, Barnett MJ, McTiernan A, Berger NA, Goran MI, Jeffery RW. The collaboration readiness of transdisciplinary research teams and centers: Findings from the National Cancer Institute's TREC year-one evaluation study. *Am J Prev Med.* 2008;35(2S):S161-72.

7

Evaluation of TREC

As with all large-scale initiatives, TREC includes evaluation taken from multiple directions and perspectives. Evaluation of the scientific productivity in TREC occurs in all aspects of TREC research and at all levels of the TREC organization. A unique aspect of the evaluation of TREC is the formal evaluation of the science of transdisciplinary research in TREC.

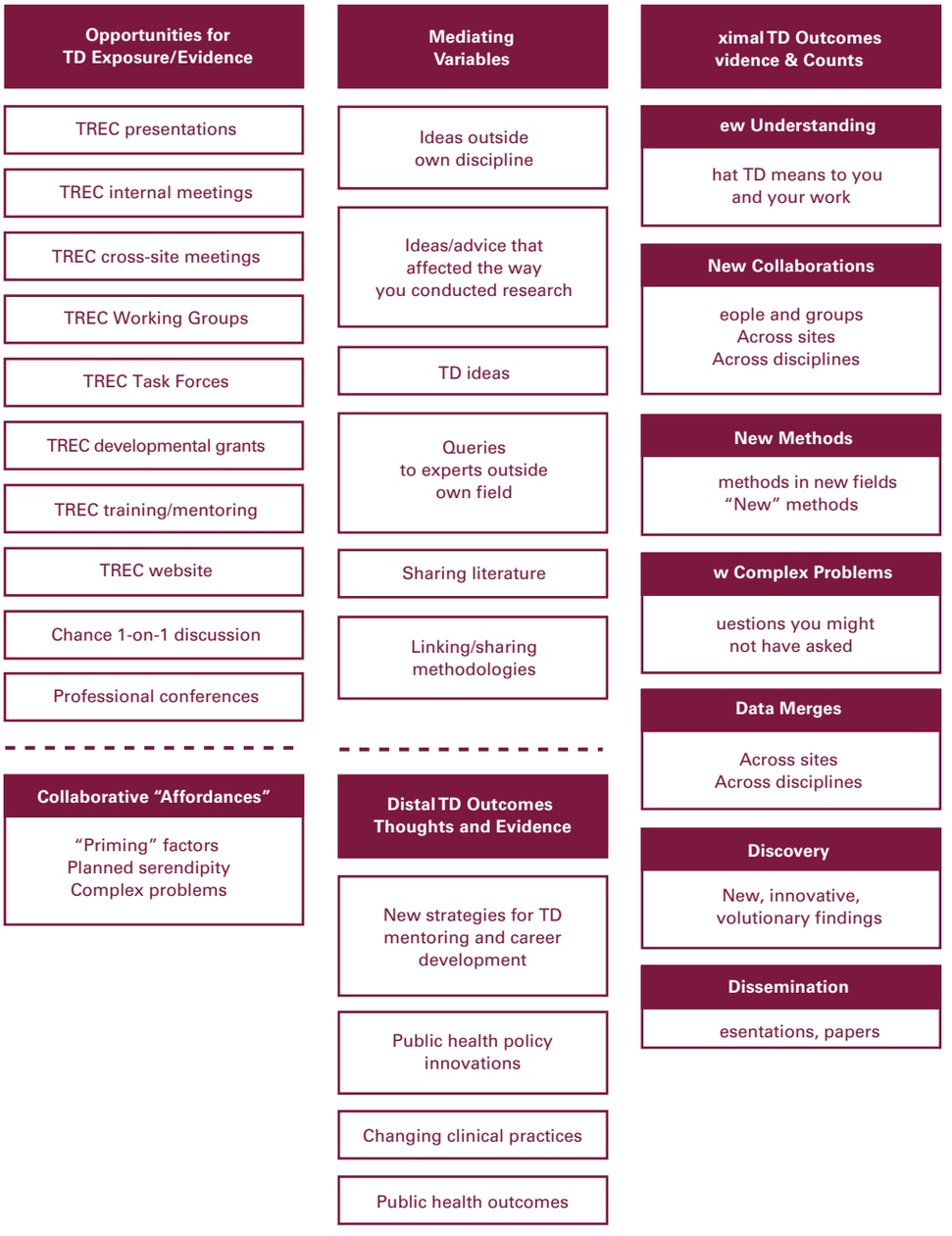
This evaluation is overseen by the TREC Evaluation Working Group; a collaboration between key NCI staff, referred to as NCI's Evaluation of Large Initiatives (ELI) team; and members of the TREC Coordination Center and the TREC Research Centers. Through this evaluative work, TREC is advancing the science of transdisciplinary science as well as the fields of energetics and cancer.

Goals of Evaluation

The original Request for Applications for TREC specified goals for evaluation of the initiative, focusing on the development of capacity for research and the cultivation of a transdisciplinary research culture among the initiative's participants. In the first years of the initiative, the TREC Evaluation Working Group refined these goals based on a conceptual framework of TREC's opportunities, mediating variables, and outcomes (Figure 1). The refined goals aim to provide objective evidence that TREC has been an effective means of advancing research by examining the relationships between energetics and cancer. Evaluation has provided TREC Centers with the information they need to improve their research excellence by identifying scientific gaps and collaborative opportunities. Evaluation goals in the first years of TREC include the following:

- Collecting data on the existing infrastructure and organization of the Centers to establish the baseline capacity and readiness of the Centers to engage in transdisciplinary research.
- Assessing the numbers and types of collaborative relationships and products developed within and among TREC Centers.

FIGURE 1: TREC Evaluation – Processes of Achieving Transdisciplinary (TD) Outcomes



- Measuring the success of the Centers in establishing a collaborative research environment (through, for example, facilitating communication among investigators and promoting trust among collaborators).
- Measuring the success of the Centers in establishing transdisciplinary training programs for new and established investigators.

Evaluation goals in the remaining years of this 5-year grant period include continued evaluation of the goals above, together with the following:

- Determining the level of utilization of shared resources across the TREC initiative (as a measure of the synergy achieved by funding TREC as a collaborative initiative instead of as a set of independent R01 awards).
- Assessing the quantity and quality of TREC publications and their influence in the fields of energetics and cancer.
- Measuring the success of TREC investigators in obtaining future National Institutes of Health (NIH) grants or funding from other sources.
- Assessing the numbers of disciplines and levels of analyses in TREC publications as measures of the degree of incorporation of transdisciplinarity.

The TREC Evaluation Working Group has also identified a longer term goal that cannot be addressed in this 5-year grant period but that directly reflects the effect of transdisciplinarity on the quality of research produced:

- Documenting the development of new, synergized fields of research that merge disciplines related to energetics and cancer.

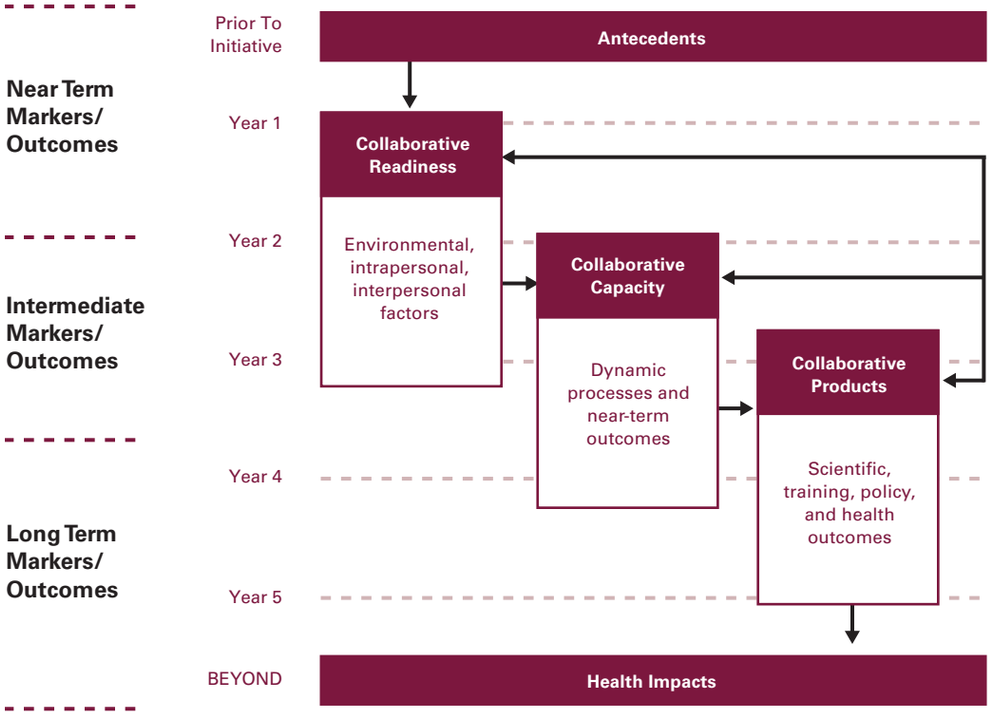
Strategic Plan for Evaluation

The TREC evaluation plan spans 5 years and accounts for the evolution of TREC as the initiative matures (Figure 2). When TREC was launched in September 2005 as a newly organized initiative, it involved sites with few previous collaborations between them, little existing infrastructure designed specifically to promote transdisciplinary research, and many investigators who were new to transdisciplinary science. Early evaluation of TREC focused on antecedents and near-term outcomes to determine how prepared the TREC Centers were to launch their transdisciplinary research agenda and how quickly they implemented their programs, such as through the establishment of scientific cores and training programs. The middle years of TREC have seen a tremendous increase in the number of developmental projects, an expansion of the number of investigators and trainees involved, and a marked increase in the number of cross-Center studies and collaborations, as described in other chapters of this document.

This dynamic increase is thought to be facilitated by collaboration and orientation toward transdisciplinarity has been strongly facilitated by three factors:

1. Deep involvement of TREC investigators with a history of prior involvement in interdisciplinary research.
2. Commitment of developmental funds to support faculty development, developmental projects, and cross-Center research.
3. Frequent cross-Center scientific exposure to, interaction with, and developing awareness of multidisciplinary strengths of TREC members through semi-annual TREC Scientific Meetings and regular telephone conferences of multiple TREC Working Groups and Task Forces.

FIGURE 2: Logic Model for Evaluating TREC Initiative



It is still early to assess primary health outcomes in many of the core TREC projects – particularly the epidemiological and intervention trials in humans, which need the full 5 years of data and follow-up to achieve their planned goals. Evaluation during this period has evolved to examine how the collaborative dynamic has changed and how that, in turn, has led to objective, documentable changes in the quality of research conducted at the TREC Centers. By year 5 of the initiative, the dominant evaluation metrics will be the traditional measures of scientific achievement, such as research publications and new research funding received. Evaluation of the process will continue, and there are plans to compare the types of research products produced by a transdisciplinary initiative such as TREC with other, non-transdisciplinary initiatives or more traditional R01-type grants. Future relevant research will clearly be required to evaluate the extent to which TREC research is affecting health outcomes related to obesity and physical activity and the potential effects on cancer at the individual, community, and policy levels.

TREC is the first of NCI's transdisciplinary initiatives in which the ELI team has been involved from the onset of the initiative's funding, and it is thus the first initiative in which it has been possible to plan systematized collection of baseline information and predictors that will be used in longitudinal analyses to examine their influence on more distal outcomes. The evaluation activity in TREC will prove invaluable to the advancement of the science of transdisciplinary science by enabling prospective analyses of the

effects of collaboration readiness factors measured during the first months of the initiative, rather than retrospective assessment of these effects as in the other NCI transdisciplinary initiative evaluations.

Evaluation Activities Completed and Ongoing

Formal evaluation activities conducted in the first 3 years by the TREC Evaluation Working Group include a baseline survey of TREC investigators conducted in spring 2006, a follow-up survey in spring-summer 2008, and analyses of the approved proposals for TREC developmental projects. In addition, TREC investigators conducted a strategic planning activity in summer and fall 2006, at the start of year 2 of the TREC initiative. Internal evaluation performed by the TREC Research Centers is described in their chapters of this document.

Baseline Survey

The web-based baseline survey of investigators at all four TREC Centers was conducted in spring 2006, with a 74% response rate (56/76). Respondents provided informed consent so that the data from this and future evaluation surveys could be published. The data collected can be grouped into two major categories. The first included current and antecedent collaborative readiness measures, such as research orientation, institutional resources, and research history (including prior collaborations and history of interdisciplinary or transdisciplinary research). The second category included near-term outcome measures, such as impressions of their Center's readiness, interpersonal collaborations and productivity, and likelihood of success in achieving early deliverables. The measures used can be found online at www.cancercontrol.cancer.gov/trec/TREC-Survey-2006-01-31.pdf.

The outcomes of the baseline evaluation have been published. As an example, one set of analyses examined associations between investigators' research orientation (on the continuum of disciplinarity) and measures of collaborative history and readiness (Hall et al., 2008). Figure 3 shows that the instruments had good success in distinguishing unidisciplinary, multidisciplinary, and interdisciplinary/transdisciplinary research (also see sidebar). Investigators who scored higher on the interdisciplinary/transdisciplinary factor had engaged in more cross-disciplinary and TREC-related research activities, reported better collaborative activity at their Center, and had better awareness of institutional resources. The data collected in this survey provide a baseline description of the TREC Centers against which follow-up analyses can be compared to document the progress in transdisciplinary research in TREC.

Continuum of Disciplinarity

Unidisciplinary – Researchers from a single discipline work together to address a common problem.

Multidisciplinary – Researchers from different disciplines *work independently* or sequentially, each from his or her own discipline-specific perspective, to address a common problem.

Interdisciplinary – Researchers from different disciplines *work jointly* to address a common problem, and, although some integration of their diverse perspectives occurs, participants remain anchored in their own fields.

Transdisciplinary – Researchers from different disciplines *work jointly to create a shared conceptual framework* that integrates and moves beyond discipline-specific theories, concepts, and approaches, to address a common problem.

Source: Rosenfield, 1992.

FIGURE 3: Path Diagram for the Research Orientation Scale, Including Factor Loadings and Factor Correlations

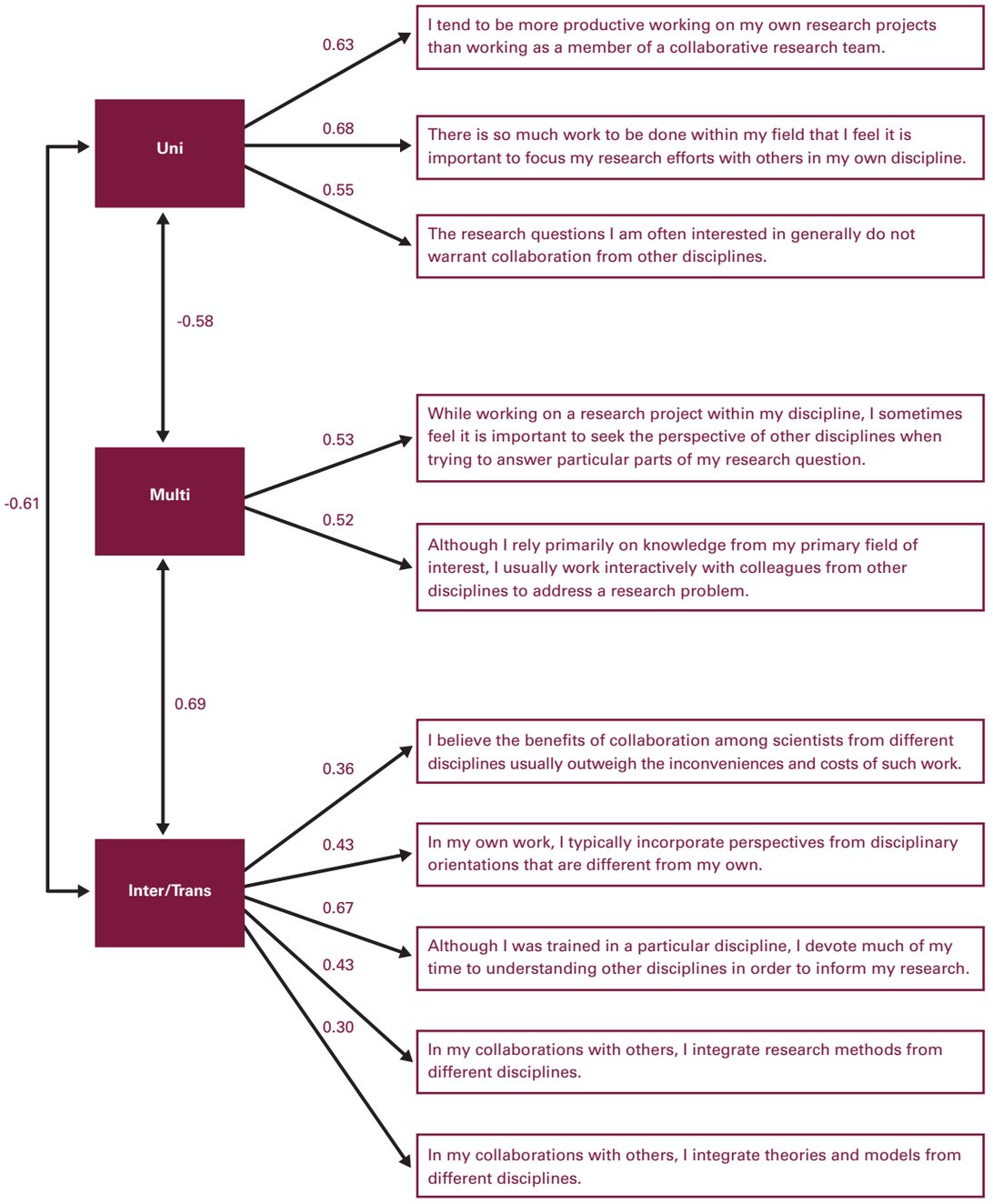


Figure shows results of a factor analysis of the research orientation scale, resulting in factors identified as unidisciplinary, multidisciplinary, and inter/transdisciplinary. Arrows between factors are labeled with the correlations between those factors. Arrows from factors to individual scale questions are labeled with the factor loading of that question on the factor.

Source: Hall et al., 2008.

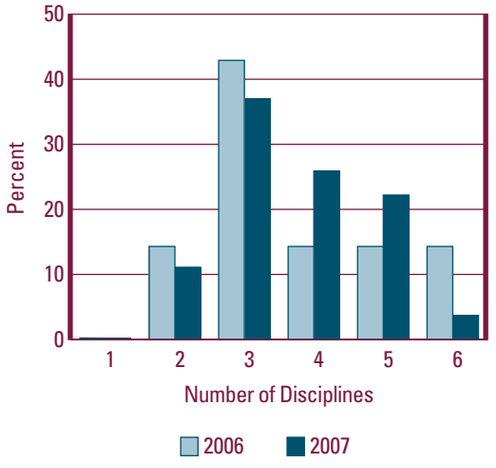
Follow-up Survey

The first follow-up survey in TREC was conducted in spring-summer 2008 using a protocol similar to the baseline survey. It evaluated some of the baseline measures to assess longitudinal change, along with new measures to assess more intermediate outcomes. The measures used can be found online at http://dccps.nci.nih.gov/brp/sci-res/eval_inst.html. Analyses are expected to be completed and reviewed by the Evaluation Working Group in early 2009.

Analysis of Written Products

As described in the strategic plan for evaluation, the timing of the research project in TREC meant that its first years would not be able to provide outcome measures of research findings. However, examination of the funded proposals for TREC developmental projects provided an early window into the progress of TREC, since changes in the types of research proposals being incorporated into TREC would show how the transdisciplinary science at the Centers was evolving. Two independent trained staff members read each approved TREC developmental project proposal from 2006 (the first year of new developmental project proposals) and 2007. The ELI team developed evaluation criteria based on an existing protocol for the analysis of written products. The protocol for the evaluation of TREC written products has been published (Hall et al., 2008).

FIGURE 4: Change in Number of Disciplines Represented in Proposals, 2006-07



Between 2006 and 2007, there was an increase in the number of disciplines represented in project proposals.

The interrater reliabilities of the measurements ranged from 0.24 to 0.69 and were generally above 0.50. The lowest reliability was for the type of cross-disciplinary integration, and this result is attributable to the difficulty in distinguishing interdisciplinary from transdisciplinary research (see sidebar on page 109). Comparison of the 2007 developmental project proposals to the 2006 proposals showed increases in number of disciplines represented in the proposals (Figure 4), increasing use of group/interpersonal analyses, and an increasing integration of disciplines, with a lower percentage of unidisciplinary analyses and higher percentages of multidisciplinary and interdisciplinary/transdisciplinary analyses. These analyses provide initial evidence for the evolution of TREC's science into a more highly transdisciplinary endeavor.

Strategic Planning

In 2006, the TREC Steering Committee embarked on a process of strategic planning, culminating in an investigator meeting in October 2006. NCI hired an organizational consultant, and the TREC Centers and NCI collaborated with the consultant to identify potential areas for growth and development of the TREC program. The consultant designed an interview protocol that was reviewed and approved by the TREC Steering Committee, conducted individual interviews with 38 TREC investigators and staff, held group interviews with 48 investigators and staff, and then facilitated the joint investigator meeting. The process, which used the Appreciative Inquiry method, helped create new collaborations among TREC investigators,

such as by the incorporation of measures of sleep into several main TREC projects. It also led to new directions of emphasis for TREC research, including markers/mediators and survival/survivorship. The subsequently created TREC Markers and Mediators Task Force took the lead in organizing an expert think tank symposium on markers and mediators connecting energy balance and cancer, convened February 24-26, 2008, and sponsored by TREC, NCI, and the American Association for Cancer Research. The Cancer Survival and Survivorship Task Force has developed plans for a similar expert think tank on energy balance and prognosis in individuals with cancer, to be held in October 2009.

Future Evaluation Activities

As described in the strategic plan for evaluation, subsequent years will see an ascendancy of the more traditional measures of scientific productivity, as TREC reaches the end of its 5-year funding period and the TREC epidemiology and intervention projects produce their primary outcomes. However, process evaluation will continue as well. Questions of high interest to the Evaluation Working Group are (1) whether we can document that the research performed by TREC is not just quantitatively greater but qualitatively different from research produced by non-transdisciplinary investigators and (2) whether transdisciplinary research is a cost-effective way of accelerating the pace of scientific discovery and the adoption of changes that positively affect the health of this nation's citizens. Answering these questions will require comparisons of the research done in TREC to that undertaken by single or small groups of investigators working on R01 grants or as members of non-initiative-based centers and teams (e.g., recipients of NIH R01 grants focusing on obesity, energetics, and cancer). We have initiated discussions on identifying appropriate comparison research groups and plan to develop evaluation methods for comparing TREC to these groups. We will also rely on external experts and advisors as an additional source of evaluation input, particularly in regard to the qualitative importance and impact of TREC-generated research, training, and translation to practice. The findings from these future evaluation endeavors will inform the next level of research and the optimal design to support such research.

Conclusions

Evaluation of TREC is an ongoing, multi-method, highly collaborative set of activities conducted at multiple levels, ranging from the individual scientists and TREC Centers to the entire TREC initiative. The metrics being applied give us far more substantial, objective, and rigorously obtained data than most other research initiatives and provide information not only to the TREC Centers and NCI but also to the field of the science of transdisciplinary science.

References

1. Hall KJ, Stokols D, Moser RP, Taylor BK, Thornquist MD, Nebeling LC, Ehret CC, Barnett MJ, McTiernan A, Berger NA, Goran MI, Jeffery RW. The collaboration readiness of transdisciplinary research teams and Centers: Findings from the National Cancer Institute's TREC year-one evaluation study. *Am J Prev Med.* 2008;35(2S):S161-72.

2. Rosenfield PL. The potential of transdisciplinary research for sustaining and extending linkages between the health and social sciences. *Soc Sci Med.* 1992;35(11):1343-57.

8

TREC Collaborations: Working Groups and Task Forces

Upon the initiation of the TREC initiative, NCI met with leaders from the awarded Centers to form the Steering Committee and to prioritize key research areas relevant to cross-site collaboration. Nine Working Groups were formed, made up of scientists from all the TREC sites. The Working Groups provide a source of expertise to all TREC partners and advise the TREC Steering Committee on protocol, policy, and scientific issues.

As time has passed, the nature and focus of these Working Groups have grown to meet the research challenges and opportunities that have evolved. The following reports summarize the breadth and scope of activities that have developed as a result, and in support, of these transdisciplinary partnerships. These Working Groups have been in the forefront of TREC research collaborations. In addition, they have developed and provided a wide variety of training opportunities and scientific workshops. The Working Groups are a key part of the dynamic, transdisciplinary approach to state-of-the-science research that has evolved during the past 3 years.

MOLECULAR PATHWAYS WORKING GROUP

Description and Mission

The Molecular Pathways Working Group is chaired by Dr Cornelia Ulrich of the Fred Hutchinson Cancer Research Center. The mission of this group is to:

- Foster scientific discussion of molecular pathways related to energetics and cancer.
- Foster scientific collaboration, within and beyond TREC, to investigate molecular pathways related to energetics and cancer.
- Foster new ideas for TREC-related research.

Productivity

The Working Group achieves its goals through activities such as:

- Regular conference calls.
- Webinars about the investigators' molecular pathway research, as part of the conference calls (see Table 1).
- Development of cross-Center proposals.
- Identification of non-TREC investigators with expertise of value to TREC and inclusion of these investigators in TREC activities (e.g., recommendations to the Steering Committee for guest speakers at TREC conferences).

TABLE 1: Webinars Sponsored by the Molecular Pathways Working Group

Seminar Title	Date	Presenter
DNA Oxidation and Cancer Risk Assessment	Mar 10, 2006	Henry Thompson, CSU
Biomarkers of Intake: The Fatty Acids Story	Nov 6, 2006	Irena King, FHCRC
Prostaglandin Synthesis, or "the COX Pathway," and Colorectal Neoplasia	Jan 8, 2007	Cornelia Ulrich, FHCRC
Obesity, Insulin Resistance, and Disease Risk: Ethnic Differences During Growth	Mar 6, 2007	Michael Goran, USC
The Price of Surviving Cancer: Effects of Chemotherapy and Radiation on Vascular Health	May 22, 2007	Donald Dengel, UMN
NHLBI Workshop on Oxidative Stress/Inflammation and Heart, Lung, Blood, and Sleep Disorders	July 1, 2007	Russ Tracy, CWRU/UVM
Modified Macronutrient Diets in the Treatment of Obesity	Nov 16, 2007	Scott Weigle, UW
Prostaglandin Synthesis and Colorectal Carcinogenesis	Planned 2009	Li Li, CWRU
Energy Balance and Apoptosis	Planned 2009	David Hockenbery, FHCRC

CSU, Colorado State University; FHCRC, Fred Hutchinson Cancer Research Center; USC, University of Southern California; UMN, University of Minnesota; CWRU, Case Western Reserve University; UVM, University of Vermont; UW, University of Washington; NHLBI, National Heart, Lung, and Blood Institute

The Working Group is chaired by Cornelia Ulrich, Fred Hutchinson Cancer Research Center. Other members of the Working Group are listed below.

- Fred Hutchinson Cancer Research Center: Kristin Campbell, Rachel Ceballos, Irena King, Mario Kratz, Johanna Lampe, Karen Makar, Anne McTiernan, Marian Neuhouser, Henry Thompson
- University of Minnesota: Andrea Arikawa, Karen Foster-Schubert, Mindy Kurzer, Kathryn Schmitz
- University of Southern California: Richard Bergman, Leslie Bernstein, Michael Goran, Howard Kaufman, Christian Roberts
- Case Western Reserve University: Li Li, Sanford Markowitz, Nora Nock, Thomas Nosek, Sanjay Patel
- NCI: Sharon Ross

Scientific Progress

Since its inception, the Molecular Pathways Working Group has been successful in achieving its goals, to foster scientific interaction and collaboration on the topics of energy balance and cancer. The webinars were a key mechanism for acquainting scientists working on different aspects of energy balance and cancer with those from other sites, as well as with outside experts. These seminars were well-attended by investigators and trainees from all sites and generated substantial discussion.

The Working Group facilitated the development of several cross-Center proposals:

- A cross-Center proposal has been funded for work between Drs Sanford Markowitz and Li Li (Case Western Reserve University) and Drs Cornelia Ulrich, Karen Makar, Irena King, and John Potter (Fred Hutchinson Cancer Research Center). The goals of this interdisciplinary research are to study prostaglandin synthesis and inflammation in relation to genetics, obesity, and colon cancer.
- The Working Group has brought forward several developmental proposals related to adipose tissue biology. Investigators from Case Western Reserve University, Fred Hutchinson Cancer Research Center, and the University of Southern California are collaborating on a cross-Center project entitled The Effect of Sleep Apnea on Adipose Gene Expression (PIs: Sanjay Patel, Karen Foster-Schubert, and Christian Roberts).
- Three within-Center developmental projects from the Fred Hutchinson Cancer Research Center are the Fat and Inflammation Study (PI: Mario Kratz), Effect of Exercise and Caloric Restriction on Adipose Tissue Biomarker Specimen Collection Pilot (PI: Cornelia Ulrich), and Impact of Diet and Physical Activity on the Number and Type of Macrophages in Subcutaneous Abdominal Adipose Tissue (PI: Mario Kratz).

Under the umbrella of the Molecular Pathways Working Group, the Adipose Biology Working Group has been formed. This Working Group is also characterized by regular conference calls (see Table 2), exchange of methodologies, cross-training of scientists (e.g., a researcher from Case Western Reserve University has observed tissue biopsy procedures developed at the Fred Hutchinson Cancer Research Center), and National Institutes of Health (NIH) funding (PI: C Ulrich, R21 CA131676, Effect of Exercise and Weight Loss on Adipose Tissue Biology). Thus, the Working Group has also successfully facilitated the development of new scientific directions to be pursued within TREC.

Future Plans

There are two speakers scheduled during the 2009 webinar series (see future topics in Table 1). One of the speakers, Dr David Hockenbery, will present results from his TREC project on apoptosis that may stimulate additional research collaborations.

TABLE 2: Interinstitutional Conference Calls on Adipose Biology Science and Developmental Proposals

Date	Event
July 19, 2007	Call with FHCRC, USC, Case Western, University of Minnesota
Oct 3, 2007	Call with FHCRC, USC, Case Western, University of Minnesota
Jan 30, 2008	Call with FHCRC, USC, Case Western
May 7, 2008	Meeting during TREC Scientific Meeting
Aug 6, 2008	Call with FHCRC and Case Western

FHCRC, Fred Hutchinson Cancer Research Center; USC, University of Southern California

BIOMARKERS WORKING GROUP

Description and Mission

The TREC Biomarkers Working Group, chaired by Dr Kathryn Schmitz, University of Pennsylvania, was formed in February 2006. The first task of the Working Group was to develop a mission statement, as shown below.

The purpose of the Biomarkers, Specimens, Laboratory Methods Working Group (hereafter known as the Biomarkers Working Group) is to define common methods and identify existing and new collaborative opportunities in this area. The Working Group's responsibilities include:

- Identifying protocols and methods common to all four TREC Centers and informing the Steering Committee so that decisions can be made regarding collaborative opportunities.
- Identifying new opportunities in sample collection, processing, and assay methods through discussion with thought leaders, review of the literature, and consultation with outside experts.
- Advising on sample collection and assay methods within the TREC program.
- Engaging in outreach to broaden the TREC investigator base.

Productivity

During its first year, this group reviewed methods used by all TREC projects, developed a list of eight recommendations regarding possible areas for coordinating efforts, and presented these recommendations to the TREC Steering Committee. Further, the group developed a TREC blood collection and processing form that was approved by the Steering Committee. The group has also been the source of cross-Center developmental project ideas.

A primary discussion point for the group was the multiple possible approaches to assuring comparable results for assays and using economies of scale to assist with individual projects. To facilitate progress in this area, the TREC Coordination Center requested and obtained TREC Steering Committee approval to allocate some of its developmental funds to support biomarker collaboration leadership. Since September 2007, the activities of the Biomarkers Working Group have been facilitated by Dr Schmitz as part of her activities as a TREC Coordination Center investigator. For information about investigation into a possible quality assurance/quality control program for laboratory assays in TREC, refer to Chapter 6.

NUTRITION ASSESSMENT WORKING GROUP

Description and Mission

The Nutrition Assessment Working Group includes TREC investigators and trainees who are active and/or interested in research on the measurement of dietary intake and nutrition. Such research spans observational and experimental research at the individual or community/group level. The Working Group is interested in many problems on the topic of assessing dietary intake, including choice of instrument, new instruments, modification of existing instruments, and development and sharing of ideas related to our TREC research projects and to related ongoing or new research. The leaders of the Working Group are Mark Pereira, PhD, University of Minnesota, Working Group Chair; Jaimie Davis, PhD, University of Southern California, Co-Chair; and Past Chairs Carolyn Ievers-Landis, PhD, Case Western Reserve University, and Marian Neuhouser, PhD, Fred Hutchinson Cancer Research Center.

The Nutrition Assessment Working Group has been established to be responsible for five thematic areas across TREC Centers:

1. Establish and utilize common measures of nutrition assessment.
2. Create new measures of nutrition assessment.
3. Advise new projects.
4. Learn about new nutrition assessment technologies.
5. Serve as a liaison across TREC.

The Working Group's responsibilities include:

- Identifying commonalities and differences in dietary measures across studies and identifying the best nutritional assessment to meet the needs of the TREC study populations, budget, and logistics.
- Seeking new measures of collecting and assessing dietary intakes and behaviors.
- Identifying and advising on new developmental projects involving diet and nutrition.
- Remaining current with state-of-the-art measures of evolving characteristics of diet relevant to TREC (e.g., glycemic index and glycemic load, home-shelf measures, neighborhood exposures to food and availability) and learning about new technologies for collecting these measures (web based, automated, hand held, etc.).
- Collaborating and ensuring currency with diet-related issues with other relevant Working Groups and advising the TREC Steering Committee on developments in dietary assessment.
- Identifying opportunities for collaboration and developmental studies across sites.

Productivity

Webinars

Over the past 14 months, the TREC Nutrition Assessment Working Group has hosted four webinars (Table 3). The speakers have included expert scientists from a range of disciplines related to nutrition and obesity assessment. The webinars were well-attended by TREC investigators from within and outside the Working Group, including several NIH scientists.

Catalogue of Nutrition Assessment

The Working Group has compiled tables of nutrition assessment tools being used across the various TREC projects across all the sites. The catalogue includes 39 nutritional assessment methods across eight TREC projects. It is meant to be a useful resource for investigators when they are considering new or alternative ways to assess diet/nutrition in their current or future research. The catalogue is available on the Nutrition Assessment Working Group section of the TREC website.

TABLE 3: Webinars Sponsored by the Nutrition Assessment Working Group

Seminar Title	Date	Presenter
Measuring the Foodscape with Geographic Information Systems	May 15, 2007	Ann Forsyth, UMN
The Importance of Childhood Height in Pediatric Obesity Assessment	Jan 15, 2008	Steven Stovitz, UMN
Measuring Household Food Purchase Behavior: Receipt Collection and Coding	Mar 18, 2008	Scott Shimotsu, UMN
Wireless Approaches to Health Behavior: Measurement or Intervention?	Sept 16, 2008	Kevin Patrick, UCSD

UMN, University of Minnesota; UCSD, University of California, San Diego

Presentations and Abstracts

The following presentations are from the 2007 Annual Meeting of the International Society of Behavioral Nutrition and Physical Activity. *The abstracts were published in the Journal of Behavioral Nutrition and Physical Activity* in 2007.

- Moe S, et al. Psychometric testing of measures to assess the social-ecological environment of obesity.
- Fulkerson J, et al. The development and validation of a home food inventory that assesses foods implicated in the obesity epidemic.
- Shimotsu S, et al. The home food environment: Food receipts and household inventories.
- Sirard J, et al. Reliability and validity of a physical activity and media equipment inventory.
- Nebeling L, et al. The NCI Transdisciplinary Research on Energetics and Cancer (TREC) Center initiative: An innovative approach in team science.
- Beresford S, et al. Recruiting small blue collar worksites for behavior change trial.
- Pereira M, Nelson M, Lytle L. Adolescent fast food and convenience food eating behaviors in relation to body mass index (BMI).

Symposia

Working Group members have been part of the following symposia:

- NCI Transdisciplinary Research on the Energetics of Cancer. 2007 Annual Meeting of the International Society of Behavioral Nutrition and Physical Activity (see preceding section).
- 2009 Annual Meeting of Experimental Biology, New Orleans, LA. Obesity and Cancer: The Transdisciplinary Research on Energetics and Cancer (TREC) Centers Initiative. Presenters/ authors: L Nebeling, H Thompson, J Nadeau, L Lytle, J Davis.

Manuscripts

Working Group members have prepared the following manuscripts:

- Davis JN, Nelson MC, Ventura EE, Lytle LA, Goran MI. A brief dietary screener: Appropriate for overweight Latino adolescents? *J Am Diet Assoc*. In press.

- Nelson MC, Lytle LA, Pasch KE. Improving literacy around energy-related issues: The need for a better understanding of the concepts behind energy intake and expenditure among adolescents and their parents. *J Am Diet Assoc.* In press.
- Nelson MC, Lytle LA. Development and evaluation of a brief screener to estimate fast food and beverage consumption among adolescents. *J Am Diet Assoc.* In press.
- Fulkerson JA, Nelson MC, Lytle L, Moe S, Heitzler C, Pasch KE. The validation of a home food inventory. *Int J Behav Nutr Phys Act.* 2008;5(1):55.

Research Projects

Working Group members have been involved in developing and conducting the following single-site and cross-site developmental projects:

Single-Site Developmental Projects

- Validation of Internet-Based Dietary Assessment (VIDA). PI: Mark Pereira, University of Minnesota. To address the need to develop more valid and cost-efficient tools for assessing energy balance and dietary intake, this project has resulted in the creation of an Internet-based past-day dietary recall. The instrument was validated in 62 adults, and results are expected by October 2008.
- Meals and Grazing Study (MAG). PI: Marian Neuhouser, Fred Hutchinson Cancer Research Center.
- Neighborhood and Home Food Environment Study. PI: Scott Shimotsu, University of Minnesota.

Cross-Site Developmental Projects

- Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-ethnic Sample of Children: A Transdisciplinary Cross-Site Developmental Project. PIs: Mark Pereira, University of Minnesota, and Donna Spruijt-Metz, University of Southern California.
- Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations. PIs: Melissa Nelson, University of Minnesota, and Jaimie Davis, University of Southern California. This project has developed a novel, much-needed instrument for assessing dietary intake in populations of minority adolescents. Two manuscripts have already been completed from this project (see Manuscripts above).
- The Effects of Information in the Media on Antecedents of Weight Control. PIs: Carolyn Ievers-Landis, Case Western Reserve University, and Marco Yzer, University of Minnesota.

PHYSICAL ACTIVITY, SLEEP, AND ENVIRONMENTAL MEASUREMENT WORKING GROUP

Description and Mission

The purpose of the Physical Activity, Sleep, and Environmental Measurement (PASE-M) Working Group is to identify state-of-the-art technology and measures for (1) physical activity and sedentary behaviors (observation, self-report, and objective); (2) sleep (all measurement forms); and (3) Global Positioning System (GPS) locational technology and available geographic information systems (GIS) databases. The PASE-M Working Group updates TREC researchers on uses of extant methodologies and informs TREC researchers on emerging technologies and applications. Donna Spruijt-Metz (University of Southern California) has chaired the Working Group since its inception. David Berrigan (NCI) co-chaired the Working Group until September 2008, at which time Audie Atienza (NCI) assumed the co-chair position. There are currently 28 Working Group members.

The responsibilities of the PASE-M include:

- Proposing common data elements, measures/instruments, and procedures/methods for the above-mentioned technologies and measures for the various TREC projects, as well as developing a manual of procedures for data collection for common measures.
- Keeping all members up to date on current literature covering the purview of the Working Group.
- Identifying measures for different forms of physical activity (such as walking) and identifying the most appropriate assessment measures for specific interventions (i.e., the measure that will be most sensitive to change given the specific intervention type).
- Developing appropriate methodological studies to compare measures as well as validation studies of existing measures (i.e., validation in specific populations, across various measures).
- Developing a grid of measures by type of physical activity, sensitivity to change, and specific population.
- Identifying collaborations that are appropriate for pooling data and using common measures given research populations and questions across sites.
- Assessing the generalizability of measures and technologies, as well as exploring new hypotheses and site-specific differences and identifying and proposing cross-Center developmental projects.
- Developing a pool of equipment/assessment tools and a database of relevant literature for access by TREC members.

Productivity

Progress

The PASE-M Working Group was originally formed, in January 2006, as the Physical Activity Assessment Working Group. Its central mandates were to (1) identify state-of-the-art physical activity and sleep measures appropriate for study populations and research questions and (2) ensure harmonization of measures across the TREC Centers, to facilitate pooling of data for joint analyses. A major accomplishment of the Working Group in its first year was to ensure harmonization of measures among relevant research projects. The harmonization of physical activity and sleep measures was finalized in 2006.

Through a series of conference calls with TREC members and outside experts at the inception of TREC, consensus was reached across all main projects on (1) accelerometers (the brand to be used) and (2) questionnaires for youth and adults.

During the first year of TREC, the Working Group assembled a toolkit that includes (1) a grid of all measures of physical activity and sleep (objective and subjective) across all projects; (2) PDF files of validation articles for all measures; (3) all questionnaire measures; and (4) protocols for data collection. The toolkit was made available to all TREC members on the TREC website at the end of 2006.

In January 2007, the TREC Environment and Psychosocial Working Group split into two separate groups. The environment part of the group was subsumed by the Physical Activity Assessment Working Group. Subsequently, the Physical Activity Assessment Working Group was renamed the Physical Activity, Sleep, and Environmental Measurement Working Group to more accurately capture the modified focus of the Working Group. This approach to environmental aspects of energetics has generated new and exciting synergies.

One of the key accomplishments of the restructured Working Group was the group authorship of a book chapter on the measurement of physical activity, sleep, and environment, published in the second edition of the prestigious *Handbook of Assessment Methods for Eating Behaviors and Weight-Related Problems: Measures, Theory, and Research.*

PASE-M Working Group members have contributed to a variety conferences and have produced 20 presentations and abstracts directly related to Working Group activities. Working Group members have published or submitted 10 papers directly related to the group's activities. Nine grant applications have either emanated from or been directly influenced by the Working Group. The group has also sponsored a number of training activities, including regular conference calls, webinars to update Working Group members on the latest TREC findings and research methodologies, special interest forums (i.e., on accelerometry and GIS), and Working Group breakout sessions at annual meetings.

Presentations and Abstracts

- Sirard JR, Nelson MC, Lytle LA. Physical activity and media equipment in the home environment. Presented at the TREC Investigators Meeting, February 2006, Pasadena, CA.
- Sirard JR, Nelson MC, Lytle LA. Physical activity and media equipment in the home environment. Invited lecture at the Obesity Research Group Weekly Meeting, Division of Epidemiology and Community Health, University of Minnesota School of Public Health, February 2006.
- Sirard JR, Nelson MC, Pereira MA, Lytle LA. Reliability and validity of a physical activity and media equipment inventory. Presented at the International Society of Behavioral Nutrition and Physical Activity Annual Meeting, June 2007, Oslo, Norway.
- Sirard JR, Nelson MC, Pereira MA, Lytle LA. Reliability and validity of a physical activity and media equipment inventory. Presented at the American College of Sports Medicine Annual Meeting, June 2007, Denver, CO.
- Sirard JR. Physical activity and media in the home environment. Invited lecture to the Energy Balance Research Group, Division of Epidemiology and Community Health, University of Minnesota School of Public Health, September 2007.

- Belcher BR, Anderson D, Hsu Y-W, McKenzie T, Spruijt-Metz D. Incorporating the effect of non-exercise activity thermogenesis (NEAT) in an observational measure of physical activity. Poster presentation at the Fourth TREC Centers Scientific Meeting, Pasadena, CA, May 1, 2007, and poster presentation at the North American Association for the Study of Obesity Annual Meeting, October 20-24, 2007, New Orleans, LA.
- Spruijt-Metz D, Belcher B, Davis J, Anderson D, Lane CL, Chou C-P, Salter D, Hsu Y-W, Neuhouser M, Richey JM, McKenzie T, Weigensberg MJ. Acute effects of high sugar/low fiber (HS) versus low sugar/high fiber (LS) breakfasts on glucose, leptin, and physical activity in preadolescent overweight Latinas. Poster presentation at the North American Association for the Study of Obesity Annual Meeting, October 20-24, 2007, New Orleans, LA.
- Redline S. An introduction to the use of sleep measurements in research. Presented at the TREC Scientific Meeting, May 6-7, 2008, Seattle, WA.
- Berrigan D. Physical activity measurement. Presented at the TREC Scientific Meeting, May 6-7, 2008, Seattle, WA.
- Berhane K, Jerrett M, Chang CC, Wolch J, Gilliland F, McConnell R. Influence of the built environment on development of obesity during childhood. Abstract to appear in October 2008 supplement to *Obesity*. Accepted for presentation at the 2008 meeting of the Obesity Society (formerly the North American Association for the Study of Obesity), Phoenix, AZ.
- Byrd-Williams C, Belcher B, Ventura E, Davis J, Spruijt-Metz D, Lane CJ, Toledo-Corral C, Goran M. Effect of nutrition and strength training intervention on habitual physical activity in overweight Latino adolescents Accepted for presentation at the 2008 meeting of the Obesity Society (formerly the North American Association for the Study of Obesity), Phoenix, AZ.
- Davis J, Tung A, Spruijt-Metz D, Chak SS, Ventura E, Byrd-Williams C, Alexander K, Lane CH, Weigensberg M, Goran MI. Randomized controlled trial of circuit training to improve risk factors for type 2 diabetes in overweight Latino girls. Accepted for presentation at the 2008 meeting of the Obesity Society (formerly the North American Association for the Study of Obesity), Phoenix, AZ.
- Hsu YW, Nguyen-Rodriguez S, Chou CP, McClain A, Belcher B, Spruijt-Metz D. Influences of social support, perceived barriers, and negative meanings of physical activity on physical activity in middle school students. Accepted for presentation at the 2008 meeting of the Obesity Society (formerly the North American Association for the Study of Obesity), Phoenix, AZ.
- Spruijt-Metz D, Hsu YW, Belcher B, McClain A, Nguyen-Rodgriguez S, Davis J, Lane CJ, Ader M, Goran M, Weigensberg M. Differences in physical inactivity between Tanner stages 1 and 2 in Latina (L) and African American (AA) girls: Relationships to insulin secretion and sensitivity, body composition and negative life events. Accepted for presentation at the 2008 meeting of the Obesity Society (formerly the North American Association for the Study of Obesity), Phoenix, AZ.
- Berhane K, Jerrett M, Chang C, Wolch J, Gilliland F, Reynolds K, McConnell R. A prospective longitudinal study on the role of road connectivity, population density, access to food in the development of obesity in children aged 10-18 years. Abstract submitted to the Active Living Research Conference, February 2009, San Diego, CA. Paper in preparation.

- Berhane K, Jerrett M, Chang CC, Wolch J, Reynolds K, Wilson J, Gilliland F, McConnell R. Street connectivity, population density and food access around the home and the development of obesity in a prospective cohort study of children aged 10-18 years. Abstract submitted to the Active Living Research Conference, February 2009, San Diego, CA. Paper in preparation.
- Berhane K, Jerrett M, Roger CC, Gilliland F, Wolch J, Reynolds K, McConnell R. Chronic health conditions, the built environment and the development of obesity in children aged 10-18 years: A longitudinal cohort study. Abstract submitted to the Active Living Research Conference, February 2009, San Diego, CA. Paper in preparation.
- Jerrett M, Chang CC, McConnell R, Wolch J, Reynolds K, Wilson J, Gilliland F, Lurmann F, Berhane K. Automobile traffic around the home and the development of obesity in children aged 10-18 years: A longitudinal cohort study. Abstract submitted to the Active Living Research Conference, February 2009, San Diego, CA. Paper in preparation.
- Wolch J, Chang CC, Jerrett M, McConnell R, Reynolds K, Berhane K. Childhood obesity and proximity to urban parks and recreational resources: A longitudinal study. Abstract submitted to the Active Living Research Conference, February 2009, San Diego, CA. Paper in preparation.
- Wolch J, Joassart-Marcelli P, Dunton G, Newell J, Jerrett M. Factors predicting the capacity of Los Angeles City-Region recreation. Abstract submitted to the Active Living Research Conference, February 2009, San Diego, CA. Paper in preparation.

Manuscripts Generated as a Working Group

- Spruijt-Metz D, Berrigan D, Kelly LA, McConnell R, Dueker D, Lindsey G, Atienza AA, Nguyen-Rodriguez ST, Irwin ML, Wolch J, Jerrett M, Tatalovich T, Redline S. Measures of physical activity and exercise. In Allison DB, Baskin ML, eds. *Handbook of Assessment Methods for Eating Behaviors and Weight-Related Problems: Measures, Theory, and Research* (2nd ed). Thousand Oaks, CA: Sage P ublications, Inc. In press.

Manuscripts Related to or Informed by Working Group Activities

- Johnson NJ, Kirchner HL, Storfer-Isser A, Cartar L, Ancoli-Israel S, Emancipator JL, Kibler AM, Redline S. Sleep estimation using wrist actigraphy in adolescents with and without sleep disordered breathing: A comparison of three data modes. *Sleep.* 2007;30(7):899-905.
- Shankardass K, McConnell RS, Milam J, Berhane K, Tatalovich Z, Wilson JP, Jerrett M. The association between contextual socioeconomic factors and prevalent asthma in a cohort of Southern California school children. *Soc Sci Med.* 2007;65:1792-806.
- Berhane K, Molitor N-T. A Bayesian approach to functional based multi-level modeling of longitudinal data: With applications to environmental epidemiology. *Biostatistics.* 2008 Mar 18. [Epub ahead of print.]
- Sirard JR, Nelson MC, Pereira MA, Lytle, LA. Reliability and validity of a physical activity and media equipment inventory. *Int J Behav Nutr Phys Act.* 2008;5:24. doi: 10.1186/1479-5868-5-24. http://www.ijbnpa.org/content/pdf/1479-5868-5-24.pdf.
- Spruijt-Metz D, Nguyen-Michel ST, Chou C-P, Goran MI, Huang T-K. Reducing sedentary behavior in minority girls via a theory-based, tailored classroom intervention. *Int J Pediatr Obes.*

- Dunton G, Kaplan J, Wolch J, Jerrett M, Reynolds K. Urban built environment correlates of childhood obesity. *Int J Behav Nutr Phys Act.* Manuscript submitted.
- Nock NL, Li L, Larkin EK, Patel SR, Redline S. Evidence for "Syndrome Z": A hierarchical five-factor model of the metabolic syndrome using sleep disturbance measures. *Sleep.* Manuscript submitted.
- Spruijt-Metz D, Belcher B, Anderson D, Lane CJ, Chou C-P, Salter D, Davis JN, Hsu Y-W, Neuhouser ML, Richey JM, McKenzie TL, Goran MI, Weigensberg M. Food, adolescence, mood and exercise: Results of an acute feeding study in overweight Latina adolescents. *J Am Diet Assoc.* Manuscript submitted.
- Wolch J, Spruijt-Metz D, Byrne J, Jerrett M, Chou C-P, Tatalovich Z, Weaver S, Wang L, Fulton W, Reynolds K. Proximity and perceived safety as determinants of urban trail use: Findings from a three-city study. *Soc Sci Med.* Manuscript submitted.

Research Projects and Grant Proposals

Single-Site Developmental Projects

- Efficacy of Sleep Extension in Conjunction with Pediatric Obesity Intervention. Investigators: L Heinberg (PI), C Ievers-Landis, S Redline, D Spruijt-Metz.
- Physical Activity and Media in the Home Environment. PI: J Sirard.
- Translation of a Novel Resistance Training Intervention to a Home Environment for Overweight Hispanic Youth. PI: L Kelly.
- Combining Strength and Cardiovascular Exercise (Circuit Training) to Reduce Obesity and Associated Diseases in Overweight Latina Youth. PI: J Davis (mentors: D Spruijt-Metz and M Goran).

Cross-Site Developmental Projects

- Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-ethnic Sample of Children: A Transdisciplinary Cross-Site Developmental Project. PIs: D Spruijt-Metz, University of Southern California, and M Pereira, University of Minnesota.

External Grant Proposals Generated

- Cell Phone-Based Activity and Diet Monitoring System. Consultant: J Sirard. Funded by the US Department of Agriculture.
- Effectiveness of Social Mobile Networked Games. Investigators: M Gotsis, T Valente, and D Spruijt-Metz. Funded by the Robert Wood Johnson Foundation.
- Circuit Training and Motivational Interviewing to Reduce Type 2 Diabetes in Youth. PI: J Davis (mentors: M Goran and D Spruijt-Metz). Funded by the National Institute of Diabetes and Digestive and Kidney Diseases.
- Circuit Training to Lower Breast Cancer Risk in Latina Teens. PI: J Davis (mentors: D Spruijt-Metz and M Goran M). Funded by the California Breast Cancer Research Program.
- Violence, Sleep, and Behavioral/Health Outcomes in Children. PI: J Spillsbury. Funded by the National Center for Research Resources, NIH.
- Places to Play: The Shifting Emotional Geographies of Minorities Growing Up. Investigators: D Spruijt-Metz, J Wolch, J Jerrett, J Mills, A Curtis, A Loukaitou-Sideris, S Narayanan. Submitted to the Robert Wood Johnson Foundation.
- Social and Physical Environments in the Eating and Activity in Teens Study. PI: J Sirard. Submitted to the Robert Wood Johnson Foundation.

- Social Networks, the Environment, and Physical Activity in Adolescents. PI: J Sirard. Submitted for NIH R21 award.
- Mobile Device Biomonitoring to Prevent and Treat Obesity in Underserved Minority Youth. Investigators: D Spruijt-Metz, M Annavaram, S Narayanan, G Sukhatme, M Urbashi, N Medvidovic, G Ragusa. Submitted to NIH.

Training

Accelerometry Special Interest Group

To tackle analyses of accelerometry data across the TREC Centers, three conference calls were initiated with national experts on accelerometry data analyses to hammer out conventions and finalize SAS coding. Two TREC trainees, Britni Belcher and Courtney Byrd-Williams, were extensively involved in this special interest group. Through her involvement in the Working Group, Britni Belcher has developed a close working relationship with David Berrigan, who is mentoring her on her thesis.

TREC Trainee Involvement in the Working Group

PASE-M has TREC trainee members from almost every Center. TREC trainees were central to the development of the toolkit described above. Through their involvement in the Working Group, TREC trainees have asked new research questions and been able to seek expertise on measurement for new grants or current papers.

Webinars

The Working Group has sponsored four webinars, which are shown in Table 4.

Conference Meetings and Monthly Conference Calls

The Working Group holds face-to-face meetings at each TREC Scientific Meeting and makes presentations on issues of measurement at TREC Scientific Meetings.

Web Resources

Working Group activity has motivated the creation of physical activity-related web resources such as:

- http://riskfactor.cancer.gov/tools/nhanes_pam/.
- http://appliedresearch.cancer.gov/tools/paq/.

TABLE 4: Webinars Sponsored by the PASE-M Working Group

Seminar Title	Date	Presenter
Accelo-calorimetry: A New Approach to Measure Activity Energy Expenditure in Humans	Apr 10, 2007	Kong Chen, NIDDK
Using Geographic Information Systems to Measure Foodscape	May 15, 2007	Anne Forsyth, UMN
Recent Results and Efforts to Improve Standardized Survey Questions Concerning Physical Activity	Jan 28, 2008	David Berrigan, NCI
Measurement of Sleep in Clinical Research and Its Relevance to TREC	Sept 22, 2008	Susan Redline, CWRU

NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NCI, National Cancer Institute; CWRU, Case Western Reserve University

Future Directions

The Working Group anticipates the following future activities:

- Collection and distribution of SAS, Stata, and SPSS code for analyses of 3-day physical activity recall, accelerometry, modifiable activity questionnaire, and sleep variables; discussion of the challenges of analyzing physical activity and sleep data.
- Integration of qualitative and quantitative physical activity data.
- Integration of activity and environmental data.
- Assessment of the impact of environmental variation on intervention results.
- Generation of energy balance questions concerning physical activity, environment, and sleep that can be addressed by combining data sets across sites.
- Exploration of total body sensing technology.
- Examination of ethical issues associated with the use of modern measurement technology (GPS, total body sensing).

PSYCHOSOCIAL AND OTHER BEHAVIOR WORKING GROUP

Description and Mission

The TREC Psychosocial and Other Behavior Working Group was formed in 2007 and is thus a relatively new Working Group. It includes TREC investigators and trainees who are active and/or interested in research regarding psychosocial measurement and relationships between psychosocial health and risk factors and health outcomes. Psychosocial information is typically measured at the individual level but is related to health outcomes and related behaviors at the individual, family, and community levels. The Working Group is interested in issues related to measurement of psychosocial indicators, including how to choose behavioral theories and related instruments that are the best match for the needs of diverse populations, modification of existing instruments, and development of new instruments. The Working Group also spends time sharing ideas related to our TREC research projects in order to spur ideas for new research. The current active members (past year) of the Working Group are Jayne A Fulkerson, PhD (University of Minnesota, Chair); Donna Spruijt-Metz, PhD (University of Southern California, Co-Chair); Amy Yaroch, Linda Nebeling, and Frank Perna (NCI); Leslie Lytle, Scott Shimotsu, and Maureen O'Dougherty (University of Minnesota); Rachel Ceballos and Lisa Cadmus (Fred Hutchinson Cancer Research Center); Carolyn Ievers-Landis (Case Western Reserve University); and Selena Rodriguez, Ketan Shankardass, and Kim Reynolds (University of Southern California). Leslie Lytle and Amy Yaroch were the original chair and co-chair, respectively.

Because energy balance, obesity, and some cancers are tightly related to human behavior, successful interventions to prevent and treat related diseases depend on an in-depth understanding of human behavior. The TREC Psychosocial and Other Behavior Working Group brings together a core group of TREC researchers interested in psychosocial indicators to share information in order to maximize the quality of the psychosocial variables/indicators used in our research, to ground current and future interventions in theory that is relevant to the targeted behaviors and populations, and to extend important psychosocial indicators into traditional bench science. The following goals have been identified for the Working Group:

- Sharing psychosocial surveys, conceptual models, and summaries that include source of questions, constructs being tapped, and psychometric properties of scales.
- Giving input on other behaviors that are being studied that do not belong to a Working Group (e.g., smoking, alcohol, drugs, unsafe sex).
- Providing review/consultation for investigators developing new psychosocial measures/scales.
- Helping expand the framing of psychosocial theories and constructs to include a more cultural and social perspective.
- Providing dialogue that may lead to pooled analysis of psychosocial constructs across sites.
- Providing a forum for examining statistical methods that might be useful in analyzing psychosocial constructs, such as mediation analysis, structural equation modeling, growth curve analysis, and latent class analysis.

It is our expectation that dialogue will stimulate new research ideas about important psychosocial precursors and contributors to the risk of obesity and cancer. We hope that the psychosocial research conducted in TREC will advance the field by developing psychometrically sound psychosocial measures and enhance our ability to test hypotheses related to obesity and cancer risk.

Productivity

Webinars/Discussions

The Working Group has sponsored the webinars shown in Table 5.

Presentations and Abstracts

The following paper and poster presentations were made at the Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity in Banff, AB, Canada, in May 2008.

- Fulkerson JA, Rydell S, Kubik MY, Lytle L, Boutelle KN, Story M, Neumark-Sztainer D, Dudovitz B, Garwick A. Healthy Home Offerings Via the Mealtime Environment (HOME): Feasibility, acceptability, and initial results of a developmental study (paper).
- Arcan C, Kubik MY, Fulkerson JA, Story M. Associations between food access and eating opportunities during the school day and dietary practices of alternative high school students (poster).
- Kubik MY, Fulkerson JA, Sirard J, Story M, Arcan C. Prevalence and correlates of overweight among students attending alternative high schools (poster).
- Pasch KE, Nelson MC, Fulkerson JA, Moe SG, Hearst MO, Lytle LA. The influence of parent's negative weight-related messages on youth's weight satisfaction and dieting behavior (paper).

TABLE 5: Webinars Sponsored by the Psychosocial and Other Behaviors Working Group

Seminar Title	Date	Presenter
Primer on Psychometrics: Overview of Reliability and Validity with Psychometric Measures	May 14, 2007	Leslie Lytle, UMN
Tutorial on Mediation and Moderation Analyses and the Use of Structural Equation Modeling	Jul 9, 2007	Jayne Fulkerson, UMN
Presentation of the Impact of Indicators of the Social Environment on Health Using Children's Health Study Data	Oct 2007	Ketan Shankardass, USC

UMN, University of Minnesota; USC, University of Southern California.

The following paper and poster presentations were made at the Sixth Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity in Oslo, Norway, in June 2007.

- Moe S, Nelson M, Fulkerson JA, Pasch K, Lytle L. Psychometric testing of measures to assess the social-ecological environment of obesity (paper presented as part of the NCI-TREC symposium).
- Fulkerson JA, Kubik MY, Story M, Lytle L. Are nutritional and other benefits of family meals apparent for at-risk youth attending alternative high schools? (poster).

Manuscripts

- Nguyen-Rodriguez ST, Chou C-P, Unger JB, Spruijt-Metz D. BMI as a moderator of perceived stress and emotional eating in adolescents. *Eat Behav.* 2008;9:238-46.
- Spruijt-Metz D, Nguyen-Michel ST, Chou C-P, Goran MI, Huang T-K. Reducing sedentary behavior in minority girls via a theory-based, tailored classroom intervention. *Int J Pediatr Obes.* In press.
- Wichianson J, Bughi S, Unger JB, Spruijt-Metz D, Nguyen-Rodriguez ST. Perceived stress, night eating and coping in college students. *Stress Health.* In press.
- Hearst MO, Pasch K, Fulkerson JA, Lytle LA. Does weight status influence weight-related beliefs and the consumption of sugar sweetened beverages and fast food purchases in adolescents? *Health Educ.* In press.
- Kubik MY, Davey C, Fulkerson J, Sirard J, Story M, Arcan C. Alternative high school students: Prevalence and correlates of overweight. *Am J Health Behav.* In press.
- Valente TW, Fujimoto K, Chou C-P, Spruijt-Metz D. Friendship affiliations and adiposity: A social network analysis of adolescent friendships and weight status. *Pediatrics.* Submitted.
- O'Dougherty M, Kurzer M, Schmitz KH. Rethinking women's motivations for physical activity: Findings from a mixed methods study. Anticipated submission to *Social Sci Med.* In progress.
- O'Dougherty M, Kurzer M, Schmitz KH. Social environments and networks for young women's physical activity. Anticipated submission to *Am J Health Promot.* In progress.

The Working Group has also developed process paper ideas:

- Cohen's stress scale is the most common measure across sites, although many studies address stress/depression as a construct.
- Qualitative paper regarding why people choose their measures.
- Integration with Biomarkers Working Group to ask new questions.
- Collaboration with the Nutrition Assessment Working Group and the Physical Activity, Sleep, and Environmental Measurement Working Group to discuss the use of psychosocial measures in analyses related to nutrition and physical activity.

Research Projects

The Working Group has developed one single-site developmental project and no cross-site developmental projects.

- Informing Measurement Strategies to Assess Relevant Food Environments Among Young Adults. Investigators: Melissa Nelson (PI), Leslie Lytle, Mark Pereira, and Jayne Fulkerson, University of Minnesota. As part of this project, a survey is being developed to assess psychosocial constructs regarding young adults' perceptions of their food environment, including self-efficacy for meal preparation and shopping, behavioral intentions, and outcome expectations.

Other Products

The Working Group has also developed a psychosocial constructs table that indicates measures, psychometric properties, and sources for all psychosocial constructs measured in all TREC studies (across sites). In addition, there is a sharing of TREC psychosocial materials on the website, including reliability findings and surveys (University of Minnesota) and surveys, reference lists, and scale construction summaries (University of Southern California).

CANCER SURVIVAL AND SURVIVORSHIP TASK FORCE

Description and Mission

The Task Force's mission is to focus on energy balance (i.e., nutrition, physical activity, and body composition) and cancer survival and survivorship. Given that most of the TREC projects focus on preventing cancer, activities associated with this Task Force focus on the time period after cancer diagnosis. The activities of the Task Force include, but are not limited to:

- Conducting developmental projects on energy balance and cancer survival/survivorship.
- Publishing papers focusing on the time period following cancer diagnosis.
- Organizing and hosting a TREC-NCI conference on energy balance and cancer survival and survivorship.

Productivity

Developmental Projects

Dr Anne McTiernan received funding to analyze certain serum hormones (C-reactive protein, tumor necrosis factor-β, interleukin-6, adiponectin) from an existing prospective cohort study of breast cancer survivors, the Health, Eating, Activity, and Lifestyle (HEAL) Study. Once assays are complete, Dr McTiernan and colleagues will examine the cross-sectional associations between these hormones and energy balance, as well as the longitudinal associations between these hormones and disease-free survival.

Dr Kathryn Schmitz has received funding to conduct a developmental study, Balance of Energy in Chemotherapy (BALANCE): A TREC Coordination Center Developmental Project. BALANCE is an observational study of 60 women during chemotherapy for breast cancer. The objectives are (1) to measure changes in energy balance factors (body composition, physical activity energy expenditure, dietary intake and supplement use, and sleep) that occur during multiple cycles of doxorubicin- or taxol/taxotere-based chemotherapy in a population of 60 breast cancer patients and (2) to examine the association between changes in absolute neutrophil counts and changes in these energy balance factors during chemotherapy in these patients. Further understanding of modifiable energy balance factors associated with chemotherapy toxicities could result in interventions to reduce toxicities and enable delivery of chemotherapy doses at the most efficacious timing. This work could lead to the development of innovative therapeutic interventions to improve short- and long-term cancer treatment outcomes.

Manuscripts

A major focus of this Task Force is to conduct secondary data analyses of existing epidemiological studies that may have data on weight, physical activity, diet, and biomarkers and prognosis in cancer survivors. These studies fall into two broad categories: (1) breast cancer patient cohorts and (2) cases derived from case-control or cohort

studies of breast cancer incidence. Studies in the first category generally have collected detailed data on treatment and have detailed data on stage and tumor characteristics; studies in the second category generally do not have detailed data on treatment, stage, and tumor characteristics. The following types of existing studies may present opportunities for secondary analyses:

- Cohorts of cancer patients with detailed data on weight, diet, and physical activity, such as the HEAL Study. Also, a number of the Task Force members are part of the Breast Cancer Consortium that was recently organized to pool data from various studies involving breast cancer survivors. We will approach the consortium about conducting secondary analyses.
- Cohort or case-control studies that now have sufficient follow-up that they can examine survival among cases relative to baseline exposure data, for example, the Women's Health Initiative (WHI). Drs Melinda Irwin and Anne McTiernan approached Rowan Chlebowski (co-investigator on WHI) to write a paper examining the association between physical activity after diagnosis and breast cancer survival among WHI participants with an incident breast cancer. Dr Chlebowski agreed to be a part of the paper. Dr Irwin submitted a proposal to the WHI Steering Committee and received approval to write the paper. Ten WHI investigators have asked to participate. We expect to complete data analyses and manuscript submission by spring 2009.

Other opportunities for secondary data analyses include energy balance trials with cancer survivors in which additional biomarkers might be explored relative to specific interventions. For example:

- The Seattle TREC Center developmental study testing the effect of yoga on weight and quality of life, in which blood (serum, plasma, DNA) has been collected and stored for future availability for assays.
- Dr Melinda Irwin's and Dr Kathryn Schmitz's trials of the effects of exercise on biomarkers in breast cancer survivors, in which blood has been collected and stored for future availability for assays.
- NCI-funded treatment trials that may have collected data on weight and height and so could be used to examine whether treatment outcomes vary by BMI.

Conference

The Task Force is organizing a joint NCI-TREC conference entitled Energy Balance and Cancer Prognosis and Survivorship, with Drs Melinda Irwin and Nathan Berger as committee chairs. The NCI-TREC conference is a joint partnership planned with a research group outside of TREC. We are planning a 2-day conference, scheduled for October 6-9, 2009, at Fred Hutchinson Cancer Research Center in Seattle, WA. The primary goal of this transdiciplinary conference will be to examine, at the molecular, animal, clinical, and epidemiological level, the relationship between energy balance and cancer prognosis and survivorship. An increasing number of observational studies suggest that men and women who are physically active after a colon or breast cancer diagnosis have an approximately 50% reduced risk of death compared to inactive men and women. Furthermore, animal studies show a favorable effect of energy balance on cancer progression. Also, obesity has recently been associated with patterns of gene expression associated with poorer prognosis. These are just a few of the topics to be discussed in more detail at the NCI-TREC conference. Below we highlight some additional sessions/topics to be discussed:

- Clinical and epidemiological evidence that energy balance affects cancer prognosis.
- The impact of cancer diagnosis and therapy on energy balance.

- Clinical trials to date: Mechanistic analysis of what worked and what did not work and why.
- Molecular, animal, and genetic research on energy balance and prognosis.
- Mediators, mechanisms, modifiers, and surrogate markers of prognosis.
- Energy balance and long-term and late effects (e.g., cardiovascular disease, lymphedema, pain).
- The neurophysiologic and psychosocial impact of alterations in energy balance on prognosis.
- Design and targets for future studies.

This 2-day conference, in October 2009, will include approximately eight sessions in total (2-3 hours per session with two to three major speakers per session, several discussants, and plenty of question-and-answer time). The program committee includes experts in energy balance and cancer such as Drs Melinda Irwin (TREC), Kathryn Schmitz (TREC), Leslie Bernstein (TREC), Jeffrey Meyerhardt, and Julia Rowland, as well as experts in molecular and clinical epidemiology, including Drs Nathan Berger (TREC) and Cornelia Ulrich. Scientists at NCI and the four TREC Research Centers, as well as the TREC Coordination Center, will be involved (i.e., as attendees, speakers, and discussants), along with non-TREC scientists who are experts in the field of energy balance, cancer prognosis, and survivorship to participate as speakers and/or attendees.

The Cancer Survival and Survivorship Task Force anticipates 150 conference participants, including speakers. The Task Force expect that this conference will stimulate focused but wide-ranging discussion among experts in these fields, resulting in an agenda to guide future research in energy balance and cancer survival/survivorship. The Task Force also expects that the conference proceedings will be published in a high-impact, peer-reviewed medical journal (e.g., *Cancer Epidemiology Biomarkers and Prevention*).

Future Task Force Activities

We would like to create a network of investigators (junior and senior, within and outside of TREC) to share similar research interests and receive mentoring in energy balance and cancer survival/survivorship. This network may also lead to future collaborations.

In the next year, we also plan to conduct at least two webinars focusing on energy balance and cancer survival and survivorship.

TRAINING TASK FORCE

Description and Mission

The TREC Training Task Force is designed to support the development of the next generation of transdisciplinary scientists (junior faculty, fellows, and students). This Task Force was established to complement and expand on the training activities and conferences led by the individual TREC Research Centers. This Task Force was formed to enhance educational activities and opportunities within the scope of TREC projects. Group activities are planned to enable new investigators across TREC to network and learn about each other's research interests. The Working Group is led by Michael Goran, PhD (chair), and Jaimie Davis, PhD (co-chair), of the University of Southern California. Other members are Courtney Byrd-Williams and Emily Ventura (University of Southern California); Andrea Arikawa and Melissa Nelson (University of Minnesota); Carolyn Ehret, Cim Eldestin, and Peter Campbell (Fred Hutchinson Cancer Research Center); Nora Nock, Leslie Heinberg, and Ralph

O'Brien (Case Western Reserve University); and Linda Nebeling (NCI).

The purpose of the TREC Training Task Force is to enhance the training and development of trainees from the TREC Centers by assisting with networking and communication tools, providing workshops and travel opportunities, fostering engagement of trainees in the TREC initiative, and promoting meaningful collaboration across geographically separate sites to promote transdisciplinary research.

Productivity

Trainee Supplemental Workshops at Annual TREC Conferences

The purpose is to provide supplemental training workshops at the annual TREC conferences, to train TREC trainees on a desired skill or research technique. To date, the following workshops have been hosted:

- At the Minnesota TREC conference in October 2007, a workshop on GIS basics mapping was held. This workshop covered the following: type of data that can be used in GIS, how various measurements are established using GIS, various applications of GIS in public health, and advanced GIS techniques/illustrations.
- At the Seattle TREC conference in May 2008, a workshop on structural equation modeling (SEM) was held. This workshop included a formal overview of SEM, covering sample size and data requirements, measurement models, structural models, and model fit.
- At the CASE TREC conference in May 2009, a workshop on "omics" is scheduled to cover metabolomics, proteonomics, and genomics.

TREC Knowledge & Education Expansion Project (KEEP)

The TREC Coordination Center has established the Knowledge & Education Expansion Project (KEEP) for each TREC Research Center. KEEP provides $5,000 annually to each Center to allow trainees access to support for educational opportunities. The individuals below were granted the KEEP funds from each site:

Case Western Reserve University

- Katarina Greer – To attend the 6th TREC Centers Scientific Meeting in Seattle, WA.
- Sanjay Patel – To attend the 6th TREC Centers Scientific Meeting in Seattle, WA, and visit Dr Richard Pratley's laboratory at the University of Vermont.
- Cheryl Thompson – To attend the 6th TREC Centers Scientific Meeting in Seattle, WA.

Fred Hutchinson Cancer Research Center

- Kristin Campbell –To attend the American College of Sports Medicine Annual Meeting in Indianapolis, IN.
- Meredith Hullar – To attend Experimental Biology in San Diego, CA.
- Alyson Littman – To attend the International Society for Behavioral Nutrition and Physical Activity Annual Meeting in Banff, AB, Canada.
- Elizabeth Poole – To attend the American Association for Cancer Research special conference "Candidate Pathways, Whole Genome Scans: Reconciling Results, Looking into the Future," in Carefree, AZ.

University of Minnesota

- Andrea Arikawa – To attend the 6th TREC Centers Scientific Meeting in Seattle, WA.
- Melissa Nelson – To attend the International Society for Behavioral Nutrition and Physical Activity Annual Meeting, in Banff, AB, Canada.

- Maureen O'Dougherty – To attend the annual meeting of Active Living Research in Washington, DC.
- Steven Stovitz – To attend the American College of Sports Medicine Annual Meeting in Indianapolis, IN.

University of Southern California

- Courtney Byrd-Williams/Britni Belcher – To participate in online training provided by the SAS Institute to improve techniques for manipulating the SAS code used to reduce accelerometry data, in Pasadena, CA, April 22-25, 2008.
- Rebecca Cherry – To attend Digestive Disease Week in San Diego, CA, May 18-21, 2008.
- Chih-Chieh (Roger) Chang – To attend "Generalized Linear Mixed Model: Theory and Applications: Continuing Education" at the Joint Statistical Meetings in Denver, CO, August 3-7, 2008.
- Emily Ventura – For a 2-day visit at Fred Hutchinson Cancer Research Center, to meet with Marian Neuhouser and her staff regarding her study on glycemic load and obesity effects on cancer biomarkers, in Seattle, WA, May 8-9, 2008.
- Jaimie Davis – To attend the 6th TREC Centers Scientific Meeting in Seattle, WA.
- Claudia Toledo – To attend the 3rd International Symposium: Integrated Biomarkers in Cardiovascular Diseases in Seattle, WA, July 9-11, 2008.
- Courtney Byrd-Williams – To attend the 6th TREC Centers Scientific Meeting in Seattle, WA.

New Investigator Travel Awards

NCI has provided travel funds for new investigators across the TREC initiative to support their attendance and participation at the biannual TREC Scientific Meeting. Awards are shown below.

May 2007: Pasadena, CA
Dr Rachel Ceballos
Dr Liz Klein
Dr Nora Nock

October 2007: Minneapolis, MN
Dr Lisa Cadmus
Dr Courtney Gray-McGuire
Dr Emily Ventura

May 2008: Seattle, WA
Dr Britni Belcher
Dr Nora Nock
Dr Melissa Nelson

October 2008: Bethesda, MD
Dr David Buchner
Dr Sebastien Bouret
Dr Mario Kratz
Dr Darin Erickson

Presentations/Symposiums

Abstract/Poster Sessions

- Greer K, Olowe K, Brenner L, Miller L, Bednarchick B, Kondru A, Grady W, Li L, Chak A. Insulin resistance as a risk factor for Barrett's esophagus. TREC poster 2008.
- Thompson CL, Larkin EK, Auker K, Negrey J, Berger NB, Redline S, Li L. Relation of sleep apnea and duration of sleep to colon adenoma risk. TREC poster 2008.
- Byrd-Williams CE, Belcher BR, Ventura EE, Davis JN, Spruijt-Metz D, Toledo-Coral C, Lane CJ, Goran MI. Effect of nutrition and strength training intervention on habitual physical activity in overweight Latino youth. TREC poster 2008 and North American Association for the Study of Obesity poster 2008.

- Ventura EE, Davis JN, Byrd CE, Alexander KE, McClain A, Lane CJ, Spruijt-Metz D, Weigensberg M, Goran MI. Improvements in insulin secretion and visceral fat in response to low-sugar, high-fiber dietary intervention in overweight Latino adolescents. TREC poster 2008 and North American Association for the Study of Obesity poster 2008.
- Nelson MC, Pasch K, Lust K, Story M, Ehlinger E. Understanding the complex context of emerging adult weight behaviors: A latent class analysis of risk behaviors and lifestyle characteristics. International Society of Behavioral Nutrition and Physical Activity poster.
- O'Dougherty M, Kaufman B, Arikawa A, Schmitz K, Kurzer M. Physical activity on your own time: Findings from a mixed methods study. TREC poster.
- Littman AJ, Doody DR, Biggs ML, Weiss NS, Schwartz SM. Physical activity in adolescence and testicular germ cell cancer risk. International Society of Behavioral Nutrition and Physical Activity poster 2008.
- Littman AJ, Forsberg CW, Koepsell TD. Obesity prevalence among veterans using Veterans Affairs medical facilities. International Society of Behavioral Nutrition and Physical Activity poster 2008.

Oral Presentations Stemming from TREC Research

- Patel S, Foster-Schubert K. Trans-Center collaboration: The Adipose Biology Group.
- Davis J, Goran M, SANO LA Team. Main outcomes from USC Project 1 – Obesity-Related Metabolic Risk for Cancer: Ethnicity and Response to Exercise in Minority Youth.

AACR-TREC-NCI THINK TANK CONFERENCE: ENERGY BALANCE AND CANCER: MECHANISMS AND MEDIATORS

Description and Mission

As part of a strategic planning process during summer 2006, TREC participants identified research on markers and mediators connecting energy balance to cancer as a critical area for discussion, deliberation, and information development. A Task Force was established, consisting of approximately 30 TREC members and representatives from NCI. The Task Force included men, women, and minorities from all the TREC Centers, with Nathan A Berger, John Potter, Kathryn Schmitz, and Cornelia Ulrich as the Task Force leaders. The Task Force identified a think tank conference venue as the most robust approach to make progress, probe the role, and set a research agenda for defining and understanding markers and mediators. The American Association for Cancer Research (AACR) and NCI were enlisted as cosponsors. Six high-priority areas were identified for review and discussion:

1. Insulin, growth factors, insulin resistance, and their relation to cancer.
2. Prostaglandins, eicosanoids, and cancer.
3. Inflammatory, stress factors, and cancer.
4. Adipokines, fat tissue products, and cancer.
5. Hormonal mediators of adiposity and their relation to cancer.
6. Markers for clinical investigation and intervention.

The consequent AACR-TREC-NCI think tank conference, entitled Energy Balance and Cancer: Mechanisms and Mediators, was held in Lansdowne, VA, on February 24-26, 2008.

The 154 total conference attendees included 36 presenters and/or discussants. Of those attending, 43% represented cancer centers, 38% represented universities and medical schools, and 14% represented government. Forty-five percent of participants self-identified as transdisciplinary scientists, 12% as basic scientists, and 6% as clinical practitioners. The conference was rated as outstanding by 49% of participants and as very good by 33%. Based on the unique format and success of this conference, a second TREC-NCI Conference on Energy Balance and Cancer to Improve Cancer Prognosis and Survivorship is being planned for 2009.

The conference generated a series of research priority recommendations in the field of energy balance and cancer, some of which are listed below.

Priorities in insulin and related growth factor research:

- Develop better serum markers of nutrition status, insulin, insulin-like growth factor (IGF)-1, etc., that are independent of daily fluctuation and reflect overall status.
- Develop better assays for free IGFs, IGF binding proteins, and tissue receptors, suitable for large population studies.
- Conduct mechanistic studies to understand the links between biomarkers and downstream effects on energy consumption.
- Study cancer prevention and control effects of agents targeted at improving hyperinsulinemia.
- Analyze the influences of race, ethnicity, and age on biomarkers and their relation to cancer.

Priorities in prostaglandin and eicosanoid research:

- Identify targets and inhibitors in the prostaglandin pathway for the prevention and treatment of tumors in skin, colon, breast, and pancreas.
- Extend studies from animal models to clinical trials.
- Investigate pathway interactions:
  - Prostaglandin E (PGE), epidermal growth factor (EGF), and IGF
  - PGE inhibitors and epidermal growth factor receptor-tyrosine kinase inhibitor
  - PGE inhibitors and aromatase inhibitors
- Study the impact of dietary changes on arachidonic acid metabolism, fatty acid metabolism, gene expression, oxidative stress, and inflammatory mediators.
- Examine the effects of quantity and type of exercise on arachidonic acid metabolism.

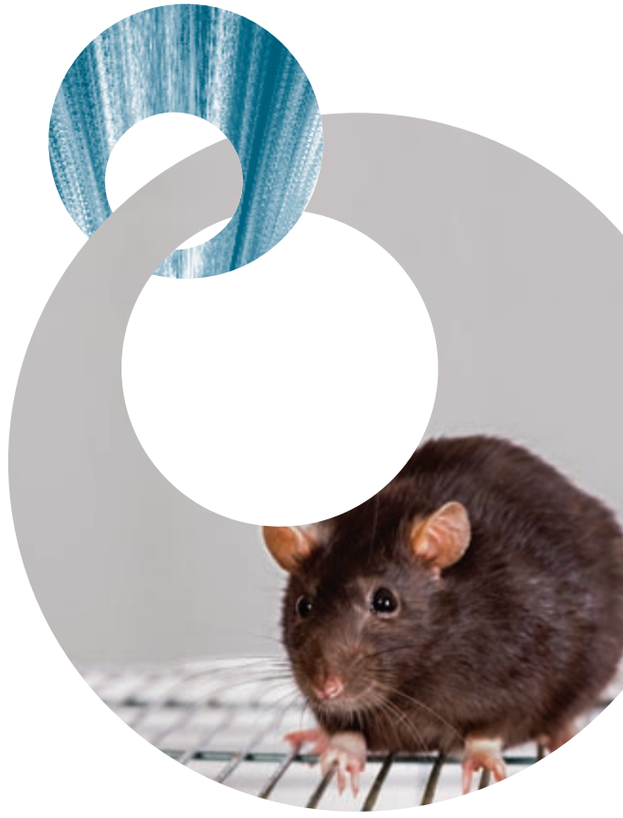
Priorities in physical activity and sex hormone research:

- Determine independent and combined effects of physical activity and weight change on circulating biomarkers and sex hormones in pre- and postmenopausal women:
  - In women of different racial/ethnic groups
  - In women at increased risk for breast cancer (BRCA1, BRCA2)
  - In women with ductal carcinoma in situ/lobular carcinoma in situ
- Determine dose response of physical activity on:
  - Circulating sex hormones
  - Sex hormones in susceptible targets, breast, uterus, and prostate

- Clarify mechanisms by which obesity and physical activity at different life changes (childhood, adolescence, adulthood, pre- and postmenopause) alter reproductive hormones and adipokines.
- Determine optimal amounts and types of physical activity to optimize beneficial effects to reduce cancer incidence and mortality.

Priorities in markers for clinical investigation:

- More research is needed on the effects of handling biological specimens before they can be incorporated into large population-based trials.
- Research is needed to identify racial/ethnic differences and to explore mechanisms responsible for these differences.
- Phase III trials are needed to validate the association between exposure, mediators, and disease relationship.
- Phase III trials need disease endpoints because costs of errors can be high, multiple pathways influence carcinogenesis, and benefits in one pathway may easily be outweighed by actions in others.



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TREC Collaborations: Developmental Research

The TREC initiative takes maximum advantage of new research opportunities by carrying out developmental research projects that facilitate new collaborations and promote the pursuit of challenging ideas.

In addition to state-of-the-art research, a TREC Center must plan for and provide funds to support developmental projects that bridge disciplines within the Center, as well as projects involving collaboration across TREC sites. These developmental projects should provide career development opportunities for new and established investigators who wish to pursue active research careers in transdisciplinary nutrition, physical activity, weight, and energy balance. These projects involve collaborations among scientists within one or more TREC Centers, or with scientists outside the TREC initiative. These developmental projects enable the TREC investigators to integrate new and innovative technologies and/or methodologies into the TREC infrastructure. To enhance efforts across sites, diminish duplication, and maximize the use of common measures, the TREC Steering Committee and Coordination Center are responsible for leading the determination of priorities for project support.

A unique opportunity within the TREC initiative has been the availability of resources to support developmental projects. Each TREC Center has designated resources that are directed to support new research opportunities and cross-Center collaborations as they arise. This chapter provides a summary of the developmental projects supported by TREC. The chapter is subdivided by TREC Center, and a table is provided within each section that lists the Center's developmental projects. Descriptions of selected projects are provided as well.

CASE WESTERN RESERVE UNIVERSITY TREC CENTER

TABLE 1: CASE Developmental Projects Funded Through TREC

YEAR 1

Case Western Reserve University

134 Metabolomic Studies of Mice Susceptible to Obesity and/or Colon Cancer (PI: Henri Brunengraber)

135 Regulation of Obesity and Endoplasmic Reticulum Stress by Salicylates (PI: Bryan Williams)

YEAR 2

Cross-Center

160 Autonomic and Metabolic Dysfunction in Obese Children with Sleep-Disordered Breathing (Co-PIs: Michael CK Khoo, University of Southern California; Susan Redline, Case Western Reserve University)

164 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (Co-PIs: Sanford Markowitz and Li Li, Case Western Reserve University; Cornelia Ulrich, Fred Hutchinson Cancer Research Center)

Case Western Reserve University

166 Genetic Dissection of Insulin Resistance in Insulin-like Growth Factor-1 in Cancer and Metabolic Function (PI: Courtney Gray-McGuire)

167 Efficacy of Sleep Extension in Conjunction with Pediatric Obesity Intervention (PI: Leslie Heinberg)

168 Voltage-Dependent Anion Channel Control of Cancer Cell Energetics (PI: Anna-Liisa Nieminen)

169 Improving Energy Balance Assessment Using Biomarkers and Genetic Determinants of Resting Metabolic Rate (PI: Nora Nock)

170 The Role of the *Ski* Proto-oncogene in the Control of Energy Metabolism (PI: Ed Stavnezer)

YEAR 3

Cross-Center

184 Obesity-Associated Molecular Changes in Barrett's Esophagus (Co-PIs: Amitabh Chak, Case Western Reserve University; William Grady, Fred Hutchinson Cancer Research Center) [Chak funded in Year 2]

207 The Effect of Sleep Apnea on Adipose Gene Expression (Co-PIs: Sanjay Patel, Case Western Reserve University; Karen Foster-Schubert, Fred Hutchinson Cancer Research Center; Christian Roberts, University of Southern California)

226 The Effects of Information in the Media on Antecedents of Weight Control (Co-PIs: Marco Yzer, University of Minnesota; Carolyn Ievers-Landis, Case Western Reserve University)

Case Western Reserve University

201 The Role of Genetic Backgrounds in Varying Susceptibility to Obesity and Tumorigenesis in Intestine Using a Proteomics Approach (PI: Jinsook Chang)

203 Role of a Novel Muscle Phosphatase (mtmr14) in Muscle Function, Obesity, and Cancer (PI: Thomas Nosek)

210 Investigating the Relationship Between Exercise, Physical Activity, and Cancer with PEPCK-C^{mus} Mouse Models (PI: Marco Cabrera)

211 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (PI: Sanford Markowitz)

TABLE 1: CASE Developmental Projects Funded Through TREC – Continued

212 Gut Microbes, Host Genetics and Diet, Metabolic Disease, and Cancer Susceptibility (PI: Joseph Nadeau)

213 Retinol Binding Protein-4 (RBP4): A Novel Biomarker for Colon Neoplasia (PI: Cheryl Thompson)

214 Functionally Define the Role of P85α Met326Il3 Single Nucleotide Polymorphism in Colon Cancer (PI: Zhenghe John Wang)

234 PEPCK-C^{mus} Mice to Study the Relationship Between Exercise, Aging, and Cancer (PI: Richard Hanson)

YEAR 4

Cross-Center

233 Effect of Physical Activity on Melatonin Levels in Previously Sedentary Men and Women (Co-PIs: Catherine Duggan, Fred Hutchinson Cancer Research Center; Sanjay Patel, Case Western Reserve University)

Case Western Reserve University

235 Mitochondrial Function in Obesity and Hepatocellular Carcinoma (PI: Charles Hoppel)

236 Maternal Obesity and Fetal Patterning of Breast Cancer Risk (PI: Ruth Keri)

237 Effect of Weight Loss on Oxidative Stress and Inflammation Markers and Gut Microbial Ecology (PI: Li Li)

238 Role of Leptin and High-Fat Diet in Development of Breast Cancer in Mice (PI: Ofer Reizes)

239 FOXP1, Obesity, and Gastrointestinal Cancer (PI: Can Shi)

240 Physical Activity and Tumor Incidence in Azoxymethane-Treated PEPCK-C^{mus} Mice (PI: James Swain)

241 Effect of Obesity and Insulin Resistance on the Activation of ^{IR}S1, AKT, and mTOR and the Development of Colon Adenomas (PI: Cheryl Thompson)

242 A Prospective Pilot Study of Endometrial Neoplasia Screening in Morbidly Obese Women (PI: Vivian Von Grueningen)

Genetic Dissection of Insulin Resistance in IGF-1 in Cancer and Metabolic Function

Courtney Gray-McGuire (PI) and Susan Redline

CASE WESTERN RESERVE UNIVERSITY

Purpose

There is little dispute that metabolic function is influenced by both genetic and environmental factors. Similarly, there is little dispute of the evidence linking growth factor levels to both obesity and cancer. Therefore, better understanding of the role of the insulin-like growth factor (IGF)-1, IGF binding protein (IGFBP)-1, and IGFBP-3 genes in controlling the levels of circulating IGF-1 and other related biomarkers is important. Specifically, this project aims to identify the genetic polymorphisms associated with obesity and therefore to help characterize the complex pathways leading to both metabolic dysfunction and cancer. Further, by genotyping genes within the same pathway, we can better assess the joint action of these factors.

This project has the following three aims:

1. To identify a subset of families in which linkage for insulin resistance has been established.
2. To genotype single nucleotide polymorphisms (SNPs) in and around IGF-1, a candidate gene for both cancer and metabolic function, as well as a candidate linkage region for insulin resistance.
3. To assess the association between insulin resistance and variations in levels of IGF-1, including and accounting for the effects of demographics, other factors influencing insulin resistance, and growth factor levels.

Methods

IGF-1 enzyme-linked immunosorbent assays (ELISAs) were run for all study participants, and SNPs have been obtained for the IGF, IGFBP-1, and IGFBP-3 genes. Using a subset of 500 individuals from the Cleveland Family Study, we performed an association analysis, utilizing multiple regression of both nuclear and extended pedigrees, accounting for the correlation between family members and adjusting for body mass index (BMI), age, and sex.

Results

Significant familial correlations for a series of obesity- and age-adjusted metabolic biomarkers were found that were not seen in a sample of half-siblings, supporting a genetic rather than environmental mechanism. We also found significant evidence of linkage between fasting insulin and the IGF-1 region (12q22-24; LOD = 3.2) in European Americans and IGFBP-1/IGFBP-3 (7p14-12) and fasting glucose (LOD = 8.0) in African Americans. The association analysis for participants in the Cleveland Family Study found significant association between SNPs in these genes and multiple biomarkers, the most significant of which was adiponectin ($p = 2 \times 10^{-22}$ and $p = 7 \times 10^{-13}$ in African Americans and European Americans, respectively). Evidence of association with circulating levels of IGF was also found, but at a much lesser threshold of significance ($p = 3 \times 10^{-3}$). Multivariate modeling of these traits is underway, as are the final assays for circulating IGFBP levels.

Conclusions

Significant variation within both African American and European American families suggests that genetic variants in or very near the IGF-1 gene and its binding proteins may influence glucose homeostasis and other aspects of metabolic function implicated in obesity and cancer. These results support the importance of better understanding the interplay between obesity and cancer as it applies to the IGF pathway.

Efficacy of Sleep Extension in Conjunction with Pediatric Obesity Intervention

Carolyn Ievers-Landis (PI), Leslie J Heinberg, and Susan Redline

CASE WESTERN RESERVE UNIVERSITY

Purpose

Prospective studies have found short sleep duration to be a risk factor for obesity among children and adults. Irregular sleep schedules have been related to obesity among adults, and adolescents experience sleep schedule inconsistency in the form of weekend oversleep and irregular sleep. Irregular sleep is a potentially modifiable risk factor for obesity, but improving sleep hygiene among adolescents has not yet been evaluated as a potential treatment modality. The goal of this investigation was to determine the feasibility of a sleep intervention among obese adolescents, to improve sleep duration and regularity.

The specific aims of the project were as follows:

1. To identify optimal approaches for achieving sleep extension in overweight youth. Specifically:
   - To solicit, through a series of focus groups, opinions from children (ages 7-12), adolescents (ages 13-18), and their parents on barriers and solutions to the adoption of healthy sleep habits, the feasibility of sleep extension strategies, and the acceptability of components of the hypothesized sleep extension intervention.
   - To use feedback from the focus groups to refine the proposed three-session sleep extension intervention, which includes psycho-education, motivational interviewing, sleep hygiene, and cognitive-behavioral skill development.
2. To conduct a preliminary, uncontrolled, 2-month trial with 12 youth who had completed the Healthy Kids/Healthy Weight weight management intervention and who reported average sleep times of at least 30 minutes below age-specific recommendations, to evaluate the efficacy of the focus group-modified sleep extension intervention and to assess the feasibility of obtaining complete information on key outcome or process measures.

   Outcomes included the following:
   - Mean daily self-reported sleep duration, physical activity, and fatigue.
   - Sleep duration (mean and coefficient of variation), as measured by actigraphy.
   - BMI z-score change at the postintervention and 3-month post-baseline assessments.
   - Mean daily macronutrient composition.
   - Fasting leptin, ghrelin, insulin, and glucose levels.
3. To determine a likely effect size for the intervention so that a larger scale randomized efficacy R21 or R01 trial with adequate power can be developed based on these results.

Methods and Results

A manualized approach for improving sleep was developed based on cognitive behavioral principles (e.g., self-monitoring, problem solving, and goal setting) and motivational interviewing strategies to increase the desire to change. Participants included six adolescents (ages 12-15) and their parents, and the intervention consisted of three 1-hour group sessions. Parents rated the intervention as highly satisfactory (M = 6.55, SD = 0.3, on a 7-point scale), and attendance at all sessions was 100%. Assessments were conducted at baseline and 4 weeks later at post-intervention, with objective measurement via 7 days of actigraphy of estimated wake/sleep time and physical activity. Food preferences were assessed with a Likert scale. From baseline to post-intervention, weekend oversleep decreased (from 38.08 to -19.80 minutes/night), with an improvement in five of the six subjects. Improvements were also observed for increases in weekday daytime activity and decreases in weekday naps and fat cravings. No significant changes were observed for sleep duration (8:24 to 8:08 hours:minutes). Additionally, BMI z-scores were stable (2.44 to 2.45).

Conclusions

The findings are significant in pinpointing the vital role of regular wake-up times for energy regulation in adolescents through improvements in physical activity. In addition, the finding at baseline of a significant relationship between BMI z-scores and the regularity of wake-up times is important because of the lack of research in this area. The published literature includes research on the relationship between regularizing sleep-wake schedules and a reduction in daytime sleepiness for young adults, as well as research on increased napping, food intake, weight gain, and decreased

physical activity among late-shift vs. day-shift adult workers, but we could locate no published research regarding these relationships for regularizing wake-up times with samples of adolescents.

This developmental project demonstrates the acceptability of this intervention and suggests its potential utility as a means for improving sleep schedule consistency. Continued follow-up and extension with a larger sample will be needed to determine the intervention's effectiveness for short- and long-term improvements in sleep.

Improving Energy Balance Assessment Using Biomarkers and Genetic Determinants of Resting Metabolic Rate

Nora L Nock (PI), Cheryl Thompson, Aimee Patrick-Melin, Marc Cook, Sarah Plummer, Graham Casey, Nathan A Berger, Robert C Elston, John P Kirwan, and Li Li

CASE WESTERN RESERVE UNIVERSITY

Purpose

This study is looking at biomarkers and genetic determinants of resting metabolic rate (RMR) and body composition to provide a better understanding of the role that these factors play in the development of colon polyps and to provide an improved overall model for energy balance using the multivariate statistical framework of structural equation modeling (SEM). This project has the following specific aims:

1. To measure RMR and body composition using indirect calorimetry and dual-energy x-ray absorption (DEXA), respectively.
2. To evaluate candidate genes in energy balance homeostasis regulation and skeletal muscle metabolism on colon polyps and on the interim quantitative phenotypes of RMR, fat mass, and fat-free mass, which we hypothesize are more proximally related to these phenotypes than to colon polyps.
3. To exploit the multivariate statistical framework of SEM by developing a novel model for evaluating the effect of energy balance on colon polyps that simultaneously models all components of energy balance (RMR, physical activity, diet-induced thermogenesis, dietary intake) and the relevant genetic and demographic factors in a hierarchy that better reflects their biological roles.

Methods

We extend our previously developed approach [Nock et al., *BMC Proc.* 2007;1 (suppl 1):S118], which models genes as latent (not directly observable) constructs described by multiple, measurable SNPs within each gene using the multivariate statistical framework of SEM, to hierarchically model multiple putative genetic, environmental, and behavioral factors involved in energy imbalance in subjects from a colon polyp case-control study (CASE TREC Center Project 2, PI: Li Li).

Results

Aim 1

We found that RMR (kcal/day), when adjusted for age, race, gender, height, and weight, was not associated with colon polyps in the total population ($p = 0.13$) or in males ($p = 0.89$); however, an inverse association in females was marginally significant ($p = 0.08$). When examining volume of oxygen consumed in milliliters per kilogram of total body mass per minute ($V0_2$ mL/kg^{-1} min^{-1}), another measure of energy expenditure, we found a marginal inverse association with polyps in the total study population ($p = 0.08$) and among females ($p = 0.07$). In terms of body composition, percentage total body fat mass was positively associated with colon polyps (OR = 1.05; 95% CI =1.01-1.10; $p = 0.04$), and percentage fat in trunkal (OR = 1.04; 95% CI = 1.01-1.07; $p = 0.05$), android (OR = 1.03; 95% CI = 1.01-1.06; $p = 0.04$), and arm (OR = 1.08; 95% CI = 1.03-1.14;

p = 0.004) regions was associated with increased colon polyp risk. When we stratified by gender, percentage arm fat remained statistically significant in females only (OR = 1.12; 95% CI = 1.03-1.21; p = 0.01).

Aims 2 and 3

Obesity is most likely manifested by the complex interplay between multiple genetic, environmental, and behavioral factors. Thus, statistical models for obesity should aim to reflect its underlying complex pathophysiology to enable a better understanding of how the individual components of energy (dietary) intake and expenditure collectively contribute to chronic positive energy imbalance and how this imbalance, in turn, contributes to various disease states while considering genetic and behavioral profiles. We extend our previously developed approach, which models genes as latent (not directly observable) constructs described by multiple variants (SNPs) within each gene, using the multivariate statistical framework of SEM to hierarchically model multiple putative genetic, environmental, and behavioral factors involved in energy imbalance in subjects from a colon polyp case-control study (Case TREC Center Project 2). We found that modeling constructs for the leptin receptor gene (LEPR; defined by SNPs rs9939609, rs1421085, and rs8044769) and the fat mass-and-obesity-associated gene (FTO; defined by SNPs rs1137100, rs1137101, rs1805096, and rs6588147) with dietary intake, physical activity, sleep, and demographic (age, race, gender) variables increased the strength of the association between the FTO gene and obesity (as defined by BMI and waist circumference) constructs (β_{std} = -0.13; SE = 0.06; p = 0.03), compared to that observed in a reduced model with only the aforementioned gene constructs and demographic variables (β_{std} = -0.05; SE = 0.03; p = 0.08). In the full model, the LEPR construct was also inversely associated with the physical activity construct (defined by leisure, recreational, household, and occupational expenditure measures) (β_{std} = -0.15; SE = 0.04; p = 0.01), and the FTO was marginally associated with "bad" dietary fat (as defined by saturated and transfat intake) (β_{std} = 0.06; SE = 0.03; p = 0.10). No association between the obesity construct and colon polyps was observed in either model. Although these multivariate results were generally consistent with conventional multivariable regression methods, interestingly, when removing the FTO construct, we observed a marginal association between the LEPR and obesity constructs (β_{std} = 0.24; SE = 0.14; p = 0.09). Genotyping of additional candidate genes is underway, and additional multivariable and multivariate modeling will be completed in the next few months.

Conclusions

This is a study looking at biomarkers and genetic determinants of RMR and body composition to provide better insight into the role these factors play on the development of colon polyps and to provide an improved overall model for energy balance using the multivariate statistical framework of structural equation modeling. Our findings illustrate the importance of accounting for the influence of multiple relevant genes and non-genetic factors in the same model, which is a major strength, in addition to exploiting the high correlation between multiple variants in the same gene, of our latent gene construct approach. In particular, we found that variation in the FTO gene is more important than variation in the LEPR gene (as measured by these SNPs) in this study population, particularly in the presence of diet, physical activity, and sleep factors. This finding would not have been revealed using conventional regression approaches because of problems with model instability/multicolinearity.

Obesity-Associated Molecular Changes in Barrett's Esophagus

Amitabh Chak[1] (Co-PI), William Grady[2] (Co-PI), Dawn Dawson,[1] Joseph Willis,[1] and Li Li[1]

[1]CASE WESTERN RESERVE UNIVERSITY AND

[2]FRED HUTCHINSON CANCER RESEARCH CENTER

Purpose

This research project, which represents the collaborative effort of gastrointestinal endoscopists, pathologists, and molecular biologists at Case Western Reserve University and the Fred Hutchinson Cancer Research Center, is providing novel insights into the mechanisms by which obesity and Western diet are contributing to the rapidly increasing incidence of Barrett's esophagus and esophageal adenocarcinoma. The three primary aims of this project are shown below:

1. To compare the insulin resistance index in Barrett's esophagus with that of control patients.
2. To immunohistochemically assay activated insulin-like growth factor-1 receptor (IGF-1R) and its downstream mediators in Barrett's epithelium.
3. To assay aberrant methylation of CDKN2A, TIMP-3, IGFBP3, RIZ-1, and REPRIMO in Barrett's epithelium and esophageal adenocarcinoma.

Research on the first two aims is being conducted at Case Western Reserve University, and research on aim 3 is being conducted at Fred Hutchinson Cancer Research Center.

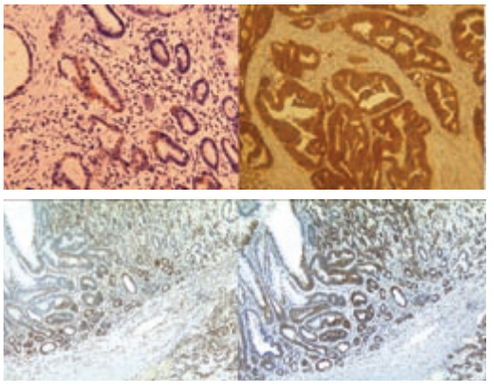
Methods

Barrett's esophagus patients (n = 71) were recruited from a tertiary care institution and compared with control patients with gastroesophageal reflux disease (GERD) (n = 104). Anthropomorphic measurements, fasting glucose, insulin, IGF, and IGF binding protein (IGFBP) concentrations were measured at enrollment. Paraffin sections of biopsies were immunostained for molecular mediators of the insulin/IGF pathway. Central adiposity was defined as a waist-to-hip ratio of > 0.9 in males and > 0.85 in females. Patients with Homeostasis Model Assessment (HOMA-IR) scores of > 3.8 were considered insulin resistant.

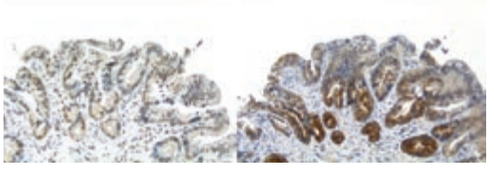
Results

Central adiposity was strongly related to insulin resistance (OR = 4.25; CI = 1.37, 13.2). Compared to the GERD controls, central adiposity did not increase the risk of Barrett's esophagus (adjusted OR = 1.08; CI = 0.60, 1.99). Having a BMI

FIGURE 1: Immunohistochemical Assessment of IGF-1R and Downstream Mediators in Barrett's Epithelium



A – Immunostains demonstrating phosphorylated IGF-1R (top left), total IGF-1R (top right), phosphorylated AKT (bottom left), and phosphorylated mTOR (bottom right) in Barrett's esophagus.



B – Immunostains demonstrating phosphorylated AKT (left) and phosphorylated mTOR (right) in paraffin sections from endoscopic mucosal biopsies.

of > 30 increased the risk of Barrett's esophagus in females only (OR = 2.02; CI = 1.04, 3.95). Mean HOMA-IR scores among Barrett's esophagus/control patients were 2.74+/-2.7 and 2.1+/-1.9, respectively. There were no differences in the proportion of patients with insulin resistance between the Barrett's esophagus cases and the GERD controls (p = 0.42).

After adjustment for age and BMI, the risk of Barrett's esophagus increased with decreasing serum concentrations of IGF-2 and IGFBP-3 (p < 0.001), up to odds ratios of 9.45 (95% CI = 3.8, 23.5) and 6.6 (95% CI = 2.8, 15.6), respectively, for the lowest quartiles. There were no significant differences in IGF-1, IGFBP-1, and the molar ratio of IGF-1/IGFBP-3.

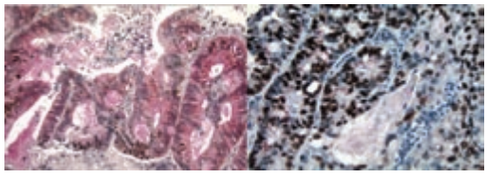
Immunostaining of phosphorylated AKT, phosphorylated mTOR, phosphorylated IGF-1R, and Ki-67 was performed on paraffin specimens from 19 Barrett's esophagus cases. Immunostaining of phos-AKT and phos-mTOR was correlated with cellular proliferation as assessed by Ki-67 immunostaining. All three patients with insulin resistance (HOMA-IR > 3.8) and the six patients with HOMA-IR scores of > 3 showed positive immunostaining with phos-AKT and phos-mTOR, whereas four of the six patients with HOMA-IR scores of < 2 showed no immunostaining (see Figure 1).

Since antibodies against phos-IGF-1R were found to be nonspecific and cross-reacted with epidermal growth factor receptor and platelet-derived growth factor receptor, we decided to develop an immunoassay for phosphorylated insulin receptor substrate-1 (see Figure 2).

Conclusions

Although insulin resistance was associated with central adiposity in this study, insulin resistance did not increase the risk of Barrett's esophagus. High levels of IGFBP-3 may be protective against the development of Barrett's esophagus, possibly by decreasing the bioavailability of IGF-1. High levels of IGF-2 also appear to be protective against the development of Barrett's esophagus, and this mechanism needs to be further investigated. Preliminary immunohistochemistry studies demonstrate activation of the insulin/IGF pathway in individuals with insulin resistance.

FIGURE 2: Immunohistochemical Comparison of Esophageal and Colorectal Malignancies



Immunostains of esophageal and colorectal malignancies with phosphorylated insulin receptor substrate-1.

This TREC project has resulted in a successfully funded R21 grant, which will enable continued research examining the association of insulin and IGF levels with activation of the insulin/IGF pathway at the tissue level. This project will also explore components of the Western diet that increase activation of this pathway. Future research will identify the effects of dietary interventions and IGF-1 inhibitors on the development of Barrett's esophagus and esophageal carcinogenesis.

The Role of Genetic Backgrounds in Varying Susceptibility to Obesity and Tumorigenesis in Intestine Using a Proteomics Approach

Jinsook Chang (PI)

CASE WESTERN RESERVE UNIVERSITY

Purpose

This project aims to identify pathways that are linked in obesity and cancer by examining specific intestinal cell populations of villus and crypt in genetically defined mice.

The first aim of this project is to utilize state-of-the-art two-dimensional gel electrophoresis (2-D DIGE) for quantitation with a combination of matrix-assisted laser desorption ionization (MALDI) and electrospray ionization (ESI) mass spectrometry for target identification to study the effects of knockout of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) on protein expression and post-translational modifications in the colon and small intestinal villus and crypt epithelial cells of FVB mice.

The second aim of this project is to determine underlying pathways and molecular mechanisms that are induced by knockout of 15-PGDH in the FVB genetic background on the expression of approximately 500 proteins in the colon and the crypt of the small intestine, using an antibody array chip.

The evidence that chronic use of cyclo-oxygenase 2 (COX-2) inhibitors, which are initiators of prostaglandin synthesis, reduces the risk of colon cancer suggests the importance of the prostaglandin pathway in colon cancer. Recent studies indicated that 15-PGDH, an enzyme responsible for the initial step of prostaglandin degradation, was markedly down-regulated in human colonic neoplasm, highlighting the oncogenic potential of the prostaglandin pathway. Furthermore, in a 15-PGDH knockout mouse model, azoxymethane-induced colon tumors were dramatically increased compared to the effect of the carcinogen in age-matched, wild-type controls, illustrating the colon cancer-suppressor nature of 15-PGDH.

Methods

To further elucidate the cancer-suppression mechanisms of 15-PGDH, we analyzed the proteomic changes induced by knockout of 15-PGDH in the FVB genetic background. Small intestinal epithelial cells were fractionated into two distinct cell types, villus and crypt. Proteomes of control and knockout samples were compared using a protein antibody array and the 2D-DIGE technique.

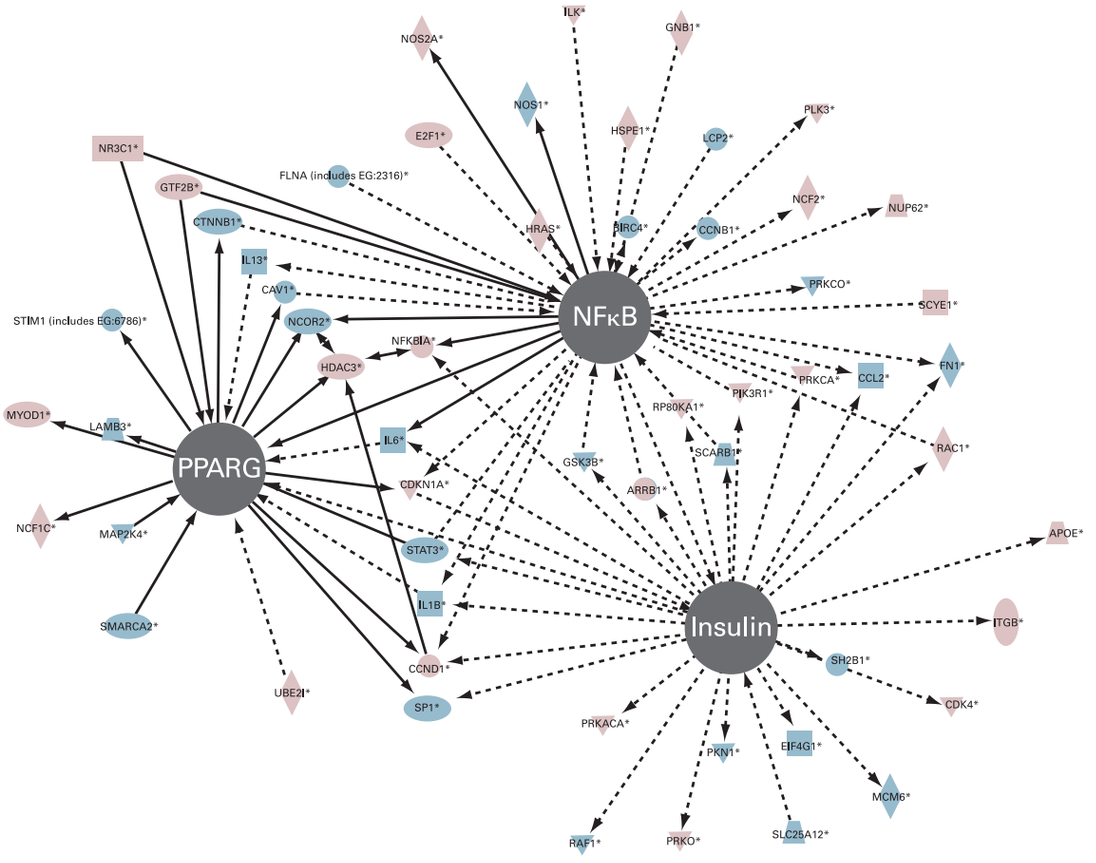
To identify important regulatory factors that may be induced by reduced activity of 15-PGDH, we performed a network analysis to identify putative regulators of the differentially expressed proteins.

Results

2D-DIGE analysis showed that a total of 27 spots were differentially expressed in either villus (21 spots) or crypt (9 spots) fractions. Four protein spots identified are sucrose isomaltase (SI) and scinderin. An additional protein, cytokeratin 8 (CK8), and villin 2 changed consistently, but not significantly, likely due to post-translational modifications (PTMs). Our initial liquid chromatography/mass spectrometry/mass spectrometry analysis of CK8 identified several novel PTM sites, including five acetylation sites, two novel methylation sites, and one novel phosphorylation site. Among the above five proteins, SI is a known prognostic marker for colorectal carcinoma, and the other proteins were previously shown to be associated with cancer development. We will identify the rest of the protein spots that show statistically significant changes to provide an improved understanding of the molecular mechanism mediating the effect of prostaglandins.

Proteomic analysis (approximately 500 proteins) of crypt cells from 15-PDGH knockout and control mice using an antibody array showed that 171 proteins changed (83 decreased, 88 increased) by 20% or more and that 85 proteins (52 decreased, 33 increased) changed by 30% or more in crypt cells of 15-PGDH knockout mice, compared to 1 change in control mice. Proteins changed in the crypt cells from 15-PGDH knockout mice were significantly enriched for those involved in cell communication, cell cycle, cell death, metabolic process, cancer, organelle organization and

FIGURE 3: Protein Network Changes in Intestinal Crypt Cells in 15-PGDH Knockout Mice



The network was generated by the shortest paths algorithm of Ingenuity software, using the list of differentially expressed proteins identified by protein antibody array analysis. Nodes represent individual proteins; the functional classes of the proteins are represented by different shapes of the nodes, and the change of fold in knockout compared to control mice is represented by color (blue, decreased; pink, increased). The edges define the relationships of the nodes; the arrowheads indicate the direction of the interaction.

The network analysis to identify important regulatory factors that may be induced by reduced activity of 15-PGDH identified a number of highly enriched hubs, including transcription factors (Myc, SP1, and NFκB), signaling molecules (ITGB1, Akt, Ras, and calmodulin), nuclear receptors (NR3C1 and PPARG), and hormones (insulin and PDGF). The network generated with the shortest path through NFκB, PPARG, and insulin shows that target proteins that changed in 15-PGDH knockout mice, as shown using an antibody array, implying the importance of the NFκB, PPARG, and insulin proteins for understanding the molecular mechanism induced by knockout of 15-PGDH (Figure 3). In addition, this network analysis reveals interesting target proteins (NCOR2, HDAC3, IL-6, CDKN1A, STAT3, IL-1B, and CCND1) that changed in 15-PDGH knockout mice and that interact with

all of the NFκB, PPARG, and insulin proteins. It is worth emphasizing that the known or novel acetylation sites of CK8, as determined by 2D-DIGE and mass spectrometry analysis, may be related to the HDAC3 expression change in 15-PGDH knockout mice.

Conclusions

These preliminary data demonstrate that proteomic analysis using a protein antibody array and/or 2D-DIGE in intestinal epithelial cells is a very powerful tool to understand proteins and the pathways involved in metabolism, cytoskeleton assembly, cell proliferation, signal transduction, and cell death in the intestine and to understand how the knockout of 15-PGDH affects the cellular regulatory system at the proteome level. Since our hypotheses relate to the linkage between diet (and villus function) and tumorigenicity (and the function of the crypt, with its stem cell-like properties), it is clear that our methodologies are well-suited to identify the specifics of the dysregulation of normal processes. Furthermore, the network analysis provides us with important putative regulators related to differentially regulated proteins that we are able to confirm by other methods, such as Western blot or immunohistochemistry.

Functionally Define the Role of P85α Met326Ile Single Nucleotide Polymorphism in Colon Cancer

Zhenghe Wang (PI) and Li Li

CASE WESTERN RESERVE UNIVERSITY

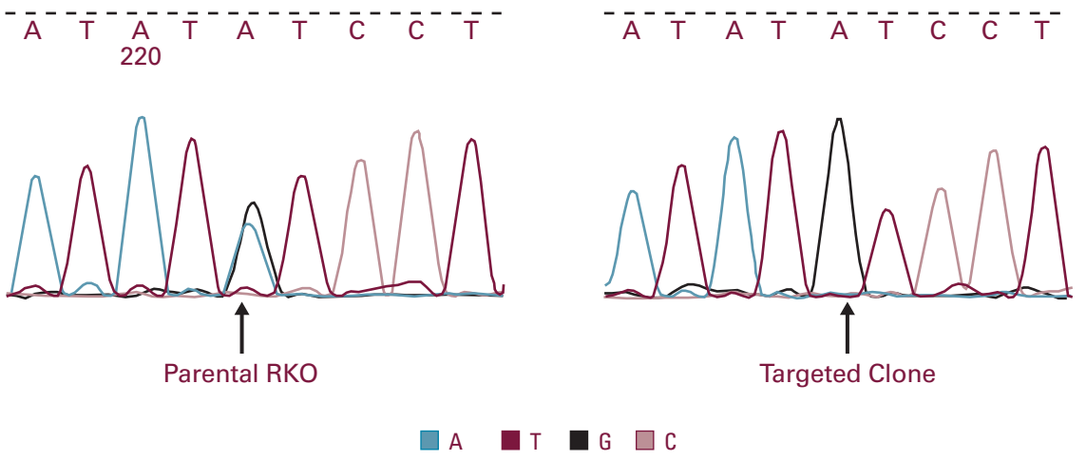
Purpose

Our developmental grant aims at determining the functional role of the p85α Met326Ile variant, which has been shown to affect insulin signaling, glucose homeostasis, and, more recently, colorectal tumorigenesis. Insulin signaling plays a pivotal role in glucose homeostasis, and the PI3-kinase, which consists of the p85 regulatory subunit and the p110 catalytic subunit, is a key signaling transducer in the insulin signaling pathway. Both epidemiologic and experimental studies demonstrated that the p85α Met326Ile allele alters glucose metabolism in human cells. First, homozygous carriers of the p85α Ile326 allele show significant reduction in whole-body glucose effectiveness and decreased rates of clearance of an intravenous glucose load in comparison with wild-type and heterozygous carriers (Hansen T, et al., *Diabetes.* 46:484). Second, the level of triglyceride accumulation in p85α knockout adipocytes reconstituted with the Ile326 allele was only 73% of that in the wild-type p85α reconstituted cells (Almind K, et al., *Proc Natl Acad Sci.* 99:2124). Thus, the p85α Met326Ile clearly plays a role in insulin resistance resulting from long-term energy imbalance. Furthermore, in a recent population-based epidemiologic study, Dr Li Li (co-PI of this project) and colleagues found that the p85α Met326Ile allele is associated with a twofold increase in risk of colon cancer. However, it remains to be determined how this genetic variant might affect PI3-kinase-regulated cell signaling and colorectal tumorigenesis. The ongoing studies funded by the TREC developmental grant will provide mechanistic understandings of how the alteration of glucose homeostasis and energy imbalance might promote oncogenic growth of colorectal cancer cells.

This project has the following specific aims:

1. To genetically engineer isogenic colorectal cancer cell lines expressing either the p85α Met326 allele or the p85α Ile326 allele.
   a. To screen for diploid colorectal cancer cell lines that are heterozygous for the p85α 326 Met/Ile.
   b. To genetically engineer isogenic colorectal cancer cell lines expressing either the p85α Met326 allele or the p85α Ile326 allele.
2. To compare the effect of the p85α Met326 and p85α Ile326 alleles on the downstream signaling of the PI3-kinase pathway and oncogenic growth of colorectal cancer cells.

FIGURE 4: Engineering RKO Colon Cancer Cells Expressing Only the p85α 326 Met Allele



Methods and Results

As planned in Aim 1a, we screened five human colorectal cancer cell lines and identified that RKO is heterozygous for the p85α 326 Met/Ile allele.

As planned in Aim 1b, we have targeted RKO cells to generate a clone expressing only the p85α Met326 allele (Figure 4). We found that the RKO cells harbor two copies of the Met 326 allele during the gene targeting process. We have obtained several targeted clones that are now harboring one Met326 allele and one Ile326 allele. We are doing a second round of targeting to generate clones expressing only the Ile allele.

We will obtain RKO cells expressing only the p85α Ile326 allele and proceed with the studies proposed in Aim 2.

PEPCK-C^{mus} Mice to Study the Relationship Between Exercise, Aging, and Cancer

Richard Hanson[1] (PI), Nathan A Berger,[1] Parvin Hakimi,[1] Gemma Casadesus,[1] James Swain,[1] Russell Tracy,[2] and Meghan M Cotter[1]

[1]CASE WESTERN RESERVE UNIVERSITY AND
[2]UNIVERSITY OF VERMONT

Purpose

Preliminary studies suggest that PEPCK-C^{mus} transgenic mice live longer than controls. These mice make an excellent animal model to determine the effect of exercise on age, carcinogenesis, cancer prognosis, and survival. This project has the following specific aims:

1. To extend preliminary observations on aging by using an increased number of PEPCK-C^{mus} mice and control animals to unequivocally determine the effect of the over-expression of PEPCK-C in skeletal muscle on the median and maximum life span of the PEPCK-C^{mus} mice. Concurrent studies will be conducted to determine aging and neoplastic behavior in tissues and physiologic parameters.

2. To characterize, in blood from PEPCK-C^{mus} mice and controls every 3 months, the levels and fluxes of adipokines and hormones that are involved in appetite regulation and adipose tissue signaling and that may serve as mediators connecting energy balance to cancer.

3. To perform a detailed pathological analysis to determine the incidence and types of cancer that develop in tissues from PEPCK-C^{mus} mice, compared with control animals, at the time of their death. In addition, we will conduct studies to determine how these mice respond to genetic, carcinogen-induced, and transplantable tumors.

Methods and Results

Initial studies demonstrated that overexpression of the gene for the cytosolic form of phosphoenol-pyruvate carboxykinase in skeletal muscle of PEPCK-C^{mus} transgenic mice results in a phenotype in which mice are more active than wild-type mice. They show greatly increased activity, exercise capacity, and endurance. They show greater food intake and have reduced weight and markedly decreased fat, as measured by magnetic resonance imaging. Their fertility is increased and prolonged to older age, and they have increased bone density and strength. The transgenic mice look better and live longer (3-4 years) than their wild-type counterparts. Despite their longevity compared to wild-type mice, the transgenic mice have shown no propensity to develop spontaneous malignancies and no tumors have been detected by serial CT scans of older animals. Metabolically, the PEPCK-C^{mus} transgenic mice have higher levels of muscle triglycerides, significantly more mitochondria, and decreased respiratory quotients during rest and exercise.

In collaboration with Dr Russell Tracy (University of Vermont), Director of the TREC Bioassay Core Facilities, the concentrations of cytokines, adipokines, and hormones were measured in the serum of transgenic and age-matched control mice. Our initial results suggest that serum concentrations of insulin, IGF-1, leptin, and adiponectin are decreased in the PEPCK-C^{mus} mice, whereas plasminogen activator inhibitor-1 is increased.

When PEPCK-C^{mus} mice are bred to contain the APCmin gene, rendering them susceptible to colon tumors, the transgenic mice retain their increased level of activity, they develop fewer intestinal tumors, the tumors occur later, and the mice live significantly longer than do APCmin mice on a wild-type background. Studies are in progress to determine the impact of the increased activity-exercise phenotype on the development and prognosis of transplantable azoxymethane- and methyl nitrosourea-induced tumors.

Conclusions

The PEPCK-C^{mus} transgenic mice, with the high-activity and exercise lifestyle, appear to be free of spontaneous tumors and are relatively resistant to genetically determined intestinal tumors. These mice provide a robust experimental model for evaluating the mechanisms that define this effect of exercise and energy balance on cancer and for targeting a reduction in cytokine and hormone levels that may be critical in determining their mechanism of action.

SEATTLE TREC CENTER

TABLE 2: Seattle Developmental Projects Funded Through TREC

YEAR 1

Seattle

136 Fitness, Fatness, and Cancer Biomarkers in Youth (closed) (PI: Glen Duncan)

137 Development of a Serum-Based Marker of Apoptosis and Assessment of Responses to Dietary and Exercise Interventions (PI: David Hockenbery)

138 The Gut Microbiota as a Cancer Biomarker Influenced by Glycemic Load and Obesity (PI: Meredith Hullar)

139 Characterization of Diet- and Exercise-Dependent Metabolic Phenotypes: Evaluating Responses to Interventions (PI: Terry Kavanagh)

140 Ancillary Data and Sample Collection in Seattle TREC Project 3, the CARB Study (PI: Johanna Lampe)

141 Effect of a 12-Month Exercise Intervention on Inflammatory Markers in Men and Women (PI: Anne McTiernan)

142 Effect of Exercise and Caloric Restriction on Adipose Tissue Biomarker Specimen Collection Pilot (PI: Cornelia Ulrich)

143 Obesity, Menopausal Status, and Mammary Carcinogenesis: Model and Mechanisms (PI: Zongjian Zhu)

YEAR 2

Cross-Center

162 Pediatric Primary Care Obesity Prevention (Co-PIs: Rona Levy, Fred Hutchinson Cancer Research Center; Nancy Sherwood, University of Minnesota)

164 Prostaglandin Genetics, Gene and Dietary Fat Interactions, and Risk of Colon Neoplasia (Co-PIs: Sanford Markowitz and Li Li, Case Western Reserve University; Cornelia Ulrich, Fred Hutchinson Cancer Research Center)

Seattle

171 Energy Balance, Polychlorinated Biphenyl (PCB) Exposure, and Possible Toxicologic Effects (PI: Anneclaire DeRoos)

172 Family-Based Physical Activity Intervention for Preschool-Age Cancer Survivors (PI: Debra Friedman)

173 A Twin Study of the Role of Gut Bacteria in Obesity and Inflammation (PI: Johanna Lampe)

174 Effect of Yoga on Weight, Fatigue, and Quality of Life in Breast Cancer Patients (PI: Anne McTiernan)

YEAR 3

Cross-Center

184 Obesity-Associated Molecular Changes in Barrett's Esophagus (Co-PIs: Amitabh Chak, Case Western Reserve University; William Grady, Fred Hutchinson Cancer Research Center) [Chak funded in Year 2]

207 Effects of a 6-Month Diet and Exercise Randomized Intervention Trial Among Overweight and Obese Postmenopausal Women on Adipose Gene Expression (Co-PIs: Karen Foster-Schubert, Fred Hutchinson Cancer Research Center; Sanjay Patel, Case Western Reserve University; Christian Roberts, University of Southern California)

TABLE 2: Seattle Developmental Projects Funded Through TREC – Continued

208 Insulin Resistance and Breast Cancer Prognosis (Co-PIs: Anne McTiernan, Fred Hutchinson Cancer Research Center; Leslie Bernstein, University of Southern California)

Seattle

217 The Impact of Diet and Physical Activity on the Number and Type of Macrophages in Subcutaneous Abdominal Adipose Tissue (PI: Mario Kratz)

218 The Meals and Grazing Study (MAG) (PI: Marian Neuhouser)

227 Successful Weight Loss Maintenance Following a Year-Long, Randomized Diet and Exercise Intervention (PI: Karen Foster-Schubert)

228 Eating and Weight-Related Behaviors Associated with Weight Loss Success Among Postmenopausal Sedentary Overweight Women (PI: Anne McTiernan)

YEAR 4

Cross-Center

233 Effect of Physical Activity on Melatonin Levels in Previously Sedentary Men and Women (Co-PIs: Catherine Duggan, Fred Hutchinson Cancer Research Center; Sanjay Patel, Case Western Reserve University)

Seattle

229 Quantitation of the Metabolically Active Gut Microbial Community in a Twin Study of Inflammation and Obesity (PI: Meredith Hullar)

230 The Fat and Inflammation Study (PI: Mario Kratz)

231 Effects of Yoga on Insulin, Glucose, and Other Metabolic Hormones in Breast Cancer Survivors (PI: Alyson Littman)

232 Modulation of Mammary Carcinogenesis by Glycemic Index: A Mechanism-Based Metabolomics Approach (PI: Elizabeth Ryan)

The Gut Microbiota as a Cancer Biomarker Influenced by Glycemic Load and Obesity

Meredith AJ Hullar (PI), Karina Stepaniants, Fei Li, and Johanna W Lampe

FRED HUTCHINSON CANCER RESEARCH CENTER

Introduction

Diet affects the amount and types of bacteria present in the gut. Microbial community composition (MCC) and activity may influence host obesity through gut microbial metabolism of dietary constituents. In contrast to current DNA sequence-based approaches, ribosomal RNA (16S rRNA) identifies the physiologically active members of the gut bacterial community that are involved in dietary metabolism.

Pediatric Primary Care Obesity Prevention

Rona L Levy[1] (Co-PI), Nancy E Sherwood[2] (Co-PI), and Shelby L Langer[1]

[1]UNIVERSITY OF WASHINGTON AND
[2]HEALTHPARTNERS RESEARCH FOUNDATION

This project is a cross-Center developmental project between the Seattle and Minnesota TREC Centers. A detailed description of the project is provided in the Minnesota section of this chapter.

Energy Balance, Polychlorinated Biphenyl (PCB) Exposure, and Possible Toxicologic Effects

Anneclaire J De Roos (PI)

FRED HUTCHINSON CANCER RESEARCH CENTER

Introduction

Polychlorinated biphenyls (PCBs) have been implicated as potential carcinogens, and they remain a public health concern despite ceasing production, because of bioaccumulation in the food chain and their presence in adipose tissue of virtually every person. These organochlorines find a stable reservoir in fat; however, they are excreted to the bloodstream with lipid mobilization during times of negative energy balance. This process of organochlorine mobilization exposes cells and tissues to increased concentrations of PCBs, thereby creating a window for enhanced toxicologic effects.

Purpose

Our TREC developmental project aimed to (1) evaluate relationships between energy balance and plasma PCBs among postmenopausal women who participated in a 12-month exercise intervention trial and (2) investigate immunotoxic effects of PCB exposures.

Methods and Results

Using the TREC developmental project funding in addition to funding from the National Institute of Environmental Health Sciences (R03 ES015787), we measured PCBs in plasma samples from 94 women in the trial (39 women randomized to the exercise intervention and 55 randomized to stretching), both before and after the intervention. We correlated total PCBs and specific PCB congeners to aspects of energy balance, including the intervention, total weight loss, and total fat loss.

Effect of Yoga on Weight, Fatigue, and Quality of Life in Breast Cancer Patients

Alyson J Littman, Lisa Cadmus, Cornelia M Ulrich, Bonnie A McGregor, and Anne McTiernan (PI)

FRED HUTCHINSON CANCER RESEARCH CENTER

Introduction

Obesity is common in breast cancer survivors; research suggests that excess body weight and weight gain following diagnosis are associated with poorer survival and increased recurrence risk compared with normal weight women. Increased physical activity has recently been linked to improved prognosis. Yoga, a type of physical activity with mind-body components, has been associated with reduced weight gain in persons without cancer but has not been tested in breast cancer patients with respect to effects on weight loss or maintenance. Fatigue and reduced health-related quality of life (QOL) are also common in women with breast cancer, and preliminary studies suggest that yoga might improve both.

Purpose

The aim of this developmental study is to evaluate the feasibility of a 6-month yoga intervention in stage 0 to IIIA breast cancer survivors and to obtain preliminary estimates of the effect of yoga on fatigue, QOL, and weight.

Methods and Results

We enrolled and randomized 63 women (32 to the intervention and 31 to the control group) to a 6-month viniyoga intervention (one class per week, 4 days of home practice) or wait list control. Follow-up assessments were completed in November 2008. Fifty-five women have completed the study and returned for 6-month follow-up visits. At baseline, the groups were balanced in terms of age (Group 1 mean = 60.6 years; Group 2 mean = 58.2 years), breast cancer stage (Group 1 = 34.8% stage II-III; Group 2 = 23.1% stage II-III), BMI (Group 1 mean = 29.5 kg/m^2; Group 2 mean = 29.6 kg/m^2), fatigue, and overall QOL scores.

Conclusions

This developmental study has demonstrated an excellent ability to recruit and retain women for an intensive yoga intervention. This study will yield important information about the feasibility of conducting a yoga intervention in breast cancer survivors and will provide preliminary estimates of efficacy that will inform future studies and grant submissions. Submission of manuscripts is expected beginning in spring 2009.

Effects of a 6-Month Diet and Exercise Randomized Intervention Trial Among Overweight and Obese Postmenopausal Women on Adipose Gene Expression

Karen Foster-Schubert[1] (Co-PI), Christian Roberts[2] (Co-PI), Sanjay Patel[3] (Co-PI), Cornelia Ulrich,[1] Kristin Campbell,[1] Karen Makar,[1] Mario Kratz,[1] and Anne McTiernan[1]

[1]FRED HUTCHINSON CANCER RESEARCH CENTER,
[2]UNIVERSITY OF SOUTHERN CALIFORNIA, AND
[3]CASE WESTERN RESERVE UNIVERSITY

and

The Impact of Diet and Physical Activity on the Number and Type of Macrophages in Subcutaneous Abdominal Adipose Tissue

Mario Kratz (PI), Cornelia Ulrich, Kristin Campbell, Karen Makar, Karen Foster-Schubert, Anne McTiernan, and Scott D Weigle

FRED HUTCHINSON CANCER RESEARCH CENTER

Introduction

Adipose tissue inflammation is increasingly recognized as a link between obesity and associated conditions such as type 2 diabetes mellitus, cardiovascular disease, and certain types of cancer. Experiments performed largely in rodent models suggest that resident tissue macrophages play a prominent role in this inflammatory process. To study the relationship between adipose tissue macrophage infiltration, inflammation, and disease-specific endpoints such as insulin resistance or biomarkers of systemic inflammation in humans, we currently collaborate on two developmental projects. These involve subcutaneous adipose tissue biopsies from overweight and obese women at baseline and after the completion of a 6-month intervention involving either a hypocaloric diet, moderate-intensity physical activity, both, or neither.

Purpose

The goal of our projects is to assess changes in the number and phenotype of adipose tissue macrophages and to explore changes in whole tissue gene expression in response to the diet and/or exercise interventions.

Methods

To date, we have collected baseline tissue samples from 49 women. Per biopsy, we have collected 926 ± 790 mg (mean ± SD) of adipose tissue (range = 90-3,859 mg). About 150 mg of tissue was flash-frozen for analyses of gene expression, which will be performed in series once all samples have been collected. The remaining adipose tissue was subjected to collagenase digestion followed by flow cytometry of the stroma vascular cells, which were stained for tissue macrophage surface markers. In the healthy overweight/obese women, we identified 89 ± 52 cells as macrophages (defined as CD14+CD206+ cells, range = 31-204) in each milligram of adipose tissue.

Insulin Resistance and Breast Cancer Prognosis

Anne McTiernan[1](Co-PI), Catherine Duggan,[1] Cornelia Ulrich,[1] Marian Neuhouser,[1] Leslie Bernstein[2] (Co-PI), Rachel Ballard-Barbash,[3] Kathryn Schmitz,[4] and Melinda Irwin[5]

[1]FRED HUTCHINSON CANCER RESEARCH CENTER, [2]UNIVERSITY OF SOUTHERN CALIFORNIA, [3]APPLIED RESEARCH PROGRAM, NCI, [4]UNIVERSITY OF PENNSYLVANIA, AND [5]YALE UNIVERSITY

Introduction

Obesity and overweight are associated with increased risk of recurrence and death in breast cancer survivors. The exact mechanisms are unknown, but we hypothesize that obesity-associated alterations in components of insulin resistance, particularly hyperinsulinemia, acute and chronic hyperglycemia, and insulin resistance markers, such as adiponectin, play a role in breast cancer recurrence and progression.

The Health, Eating, Activity, and Lifestyle (HEAL) Study is a population-based, multicenter, multiethnic prospective study of 1,183 breast cancer survivors recruited through SEER registries in Western Washington, Los Angeles County, and New Mexico. HEAL has entered its 10th year of follow-up.

Purpose

Our aim is to clarify the associations related to overweight and insulin resistance with breast cancer prognosis. We hypothesize that adiponectin, whose levels are inversely associated with BMI and breast cancer risk, will be positively associated with disease-free and overall survival. We expect that insulin levels and markers of insulin resistance will be negatively associated with disease-free and overall survival. We will also examine associations between these analytes and pathological variables at diagnosis and other biomarkers that have previously been measured in this cohort, such as serum sex steroid hormones and markers of inflammation such as C-reactive protein.

UNIVERSITY OF MINNESOTA TREC CENTER

TABLE 3: Minnesota Developmental Projects Funded Through TREC

YEAR 1

University of Minnesota

144 Biological Determinants of Obesity in Teens (PI: Donald Dengel)

145 Social, Cultural and Contextual Dimensions of Young Women's Physical Activity (PI: Maureen O'Dougherty)

146 Validation of Internet-Based Dietary Assessment (PI: Mark Pereira)

147 Effects of Exercise on Breast Cancer Biomarkers in Nipple Aspirate Fluid (closed) (PI: Andrea Plate)

148 Physical Activity and Media in the Home Environment (PI: John Sirard)

YEAR 2

Cross-Center

161 Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-ethnic Sample of Children: A Transdisciplinary Cross-Site Developmental Project (Co-PIs: Mark Pereira, University of Minnesota; Donna Spruijt-Metz, University of Southern California)

162 Pediatric Primary Care Obesity Prevention (Co-PIs: Rona Levy, Fred Hutchinson Cancer Research Center; Nancy Sherwood, University of Minnesota)

165 Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations (Co-PIs: Melissa Nelson, University of Minnesota; Jaimie Davis, University of Southern California)

University of Minnesota

175 Identifying Novel Roles of Lipocalin 2 in Insulin Action and Glucose Metabolism (PI: Xiaoli Chen)

176 Hypothalamic Acyl-CoA Metabolism and Food Intake Regulation (PI: Douglas Mashek)

177 Obesity, Elevated Blood Pressure, and Insulin Resistance Among American Indian School-children: Identifying Family- and Environment-Level Determinants (PI: Melissa Nelson)

178 ZEB1 and the Development of Obesity (PI: Michel Sanders)

180 Comparing Childhood Weight-for-Age to Body Mass Index in the Prediction of Adolescent Obesity and Chronic Disease Risk Factors (PI: Steven Stovitz)

181 GIRK4: A New Obesity Gene? (PI: Kevin Wickman)

YEAR 3

Cross-Center

215 The Interaction of Childhood Height and BMI on the Prediction of Adiposity and Insulin Resistance (Co-PIs: Steven Stovitz, University of Minnesota; Louise Kelly, University of Southern California)

226 The Effects of Information in the Media on Antecedents of Weight Control (Co-PIs: Marco Yzer, University of Minnesota; Carolyn Ievers-Landis, Case Western Reserve University)

TABLE 3: Minnesota Developmental Projects Funded Through TREC – Continued

University of Minnesota

199 Changes in Inflammatory Markers of Young Women Following Exercise (PI: Andrea Arikawa)

200 The Neighborhood and Home Food Environment Study (PI: Scott Shimotsu)

YEAR 4

University of Minnesota

243 Perinatal Influences on Infant Adiposity: The Minnesota Infant Nutrition, Neurodevelopment, and Obesity (MINNOwS) Study (PI: Ellen Demerath)

244 Obesity Prevention for Overweight Children by Targeting Parent Behaviors, the Home Environment and Family Functioning (PI: Simone French)

245 Weight Loss and Biological Parameters in Obese Breast Cancer Survivors (PI: Mindy Kurzer)

246 Informing Measurement Strategies to Assess Relevant Food Environments Among Young Adults (PI: Melissa Nelson)

Biological Determinants of Obesity in Teens

Donald Dengel (PI)

UNIVERSITY OF MINNESOTA

Purpose

The rapid rise in the number of children and adolescents who are overweight or obese is one of the greatest health problems confronting the United States. The purpose of this study is to examine a series of biological markers of glucose and lipid metabolism and inflammation and oxidative stress in youth (ages 15-18) from diverse economic and racial/ethnic backgrounds who are participating in the University of Minnesota TREC project titled Etiology of Adolescent Obesity.

Methods

Of the total sample of 349 participants, 188 adolescents (ages 10-16 years) agreed to collection of a fasting blood sample and measurements of obesity (weight, percentage fat) and blood pressure. A metabolic syndrome (MetS) cluster score was derived by calculating the sum of the sample-specific z-scores from the following components of the MetS: percentage body fat, fasting glucose, high-density lipoprotein cholesterol (negative), triglyceride, and systolic blood pressure. Geographic information systems (GIS) technology was used to calculate the distance to and density of built environmental features. Spearman correlation was used to identify significant ($p < 0.05$) relationships between the built environment and the MetS. Statistically significant correlations were added to linear regression models, adjusted for pubertal status, age, and sex.

Results

Of the 28 environmental features, only 2 were significantly correlated to the MetS: distance to food retail (rho = -0.1730, p = 0.02) and distance to convenience/ gas stations (rho = -0.1634, p = 0.03). A trend was observed for percentage of land use dedicated to parks (rho = -0.1320, p = 0.07) and density of retail food outlets (rho = 0.1302, p = 0.08). Multivariate linear regression models revealed significant associations between an increased distance to convenience stores and retail food and the MetS ($\beta = 0.0002$, $p = 0.04$).

Conclusions

The results of this study suggest a role for the built environment in the development of the MetS. Further research studies are needed to determine the contribution of the built environment to the development of cardiovascular and metabolic diseases.

We are also analyzing the baseline data to examine relationships between the home and school environments and the biological markers of glucose and lipid metabolism and inflammation and oxidative stress. We will begin the second phase of blood draws in this population starting in November 2008. At the completion of the second blood draw, serum samples will be assayed for interleukin-6, tumor necrosis factor-β, IGF-1, IGFBP-1, F2-isoprostanes, leptin, adiponectin, and C-reactive protein in the Cytokine Reference Laboratory at the University of Minnesota. We will explore these biomarkers of inflammation and oxidative stress and their relationship to the built environment.

Social, Cultural, and Contextual Dimensions of Young Women's Physical Activity (WISER–PS)

Maureen O'Dougherty (PI)

UNIVERSITY OF MINNESOTA

Purpose

According to national prevalence data, just one-third of women ages 18 to 24 report obtaining recommended levels of leisure time physical activity. Among women ages 25 to 34, nearly half do not participate in moderate or vigorous activity. To better understand women's physical activity in early adulthood, this study examined the social, cultural, and contextual factors shaping the ways young adult women incorporate physical activity into their daily lives.

Methods

Sixty women ages 18 to 30 were recruited into the study after finishing a controlled clinical trial in which half were randomized into an aerobic exercise intervention and half served as controls. This study asked participants to keep a record of their physical activity during 12 randomly assigned weeks over 6 months and to complete a 7-day travel diary and two interviews.

Results

Forty-six women completed the study; full data were obtained for 42 participants. All forms of cardio activity together comprised the majority (61%) of all recorded forms of physical activity. The single most common activities were walking for transportation (24% of all recorded physical activity), household/child care (21%), recreational walking (15%), indoor cardio activity (15%), and shopping (14%). For the group as a whole, the mean number of pedometer steps was 7,877 per day (SD = 2,182). The group mean of moderate to vigorous activity was 113 minutes per week (SD = 99). Latent class, transition, and qualitative analysis are underway to interpret the wide range of physical activity forms, frequency, and intensity among the women in the sample. Analysis of travel diaries will examine destinations for active transport and other environments frequented in daily life. Analysis of interviews will assess the social meanings and motivations for various forms of physical activity among participants.

Pediatric Primary Care Obesity Prevention

Nancy E Sherwood[1] (Co-PI), and Rona L Levy[2] (Co-PI)

[1]HEALTHPARTNERS RESEARCH FOUNDATION AND
[2]UNIVERSITY OF WASHINGTON

Purpose

Although childhood obesity is a serious and increasing health problem and is considered a risk factor for multiple conditions, including cancer, systematic research on methods for preventing or treating childhood obesity, particularly within primary care settings, has been limited. The purpose of this developmental project was to demonstrate the feasibility of a low-cost intervention for obesity prevention among children in two primary care settings: Group Health Cooperative in Seattle and HealthPartners in Minneapolis.

Methods
All participants received a physician-delivered message plus three follow-up telephone counseling calls. Participants randomly assigned to the experimental condition received content on healthy eating and exercise (HE) or home safety (HS) information. We collected data on BMI, adherence, and behaviors related to children's eating and exercise levels at baseline and 3 months.

Results
We exceeded our recruitment goals by randomizing 88 families across both sites. The average age and BMI percentile of children was 6.5 years and 89th percentile. Given the relatively small sample size and short duration of the developmental project, we did not expect to observe significant treatment group differences in body weight or BMI percentile; nevertheless, 3-month data were promising. Mean weight change for children in the HE group, adjusted for baseline body weight, was -0.55 pounds (SE = 0.78), in comparison to +1.05 pounds (SE = 0.81) for children in the HS condition ($p < 0.16$). Mean BMI percentile change for the HE group children, adjusted for baseline BMI percentile, was -4.36 (SE = 2.05), in comparison to -3.23 (SE = 2.15) for the HS group children ($p < 0.70$). HE group parents were more likely to report enrolling their children in sports (32.4% vs. 8.1%, $p < 0.03$) and that it is extremely important to be actively involved in their child's sporting events (63.9% vs. 41.7%, $p < 0.03$).

Conclusions
These developmental project results suggest that a primary care-based obesity prevention program integrating brief physician counseling and follow-up telephone counseling by health behavior specialists is feasible and potentially efficacious. The next step is to evaluate program efficacy with a larger number of families over a longer follow-up period.

Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations

Melissa C Nelson[1] (Co-PI), Jaimie N Davis[2] (Co-PI), Emily E Ventura,[2] and Leslie A Lytle[1]

[1]UNIVERSITY OF MINNESOTA AND [2]UNIVERSITY OF SOUTHERN CALIFORNIA

Purpose
Sweetened beverage and fast food intake have been identified as important targets for obesity prevention. However, there are few brief dietary assessment tools available to evaluate these behaviors among adolescents. The objective of this research was to examine the reliability and validity of a 22-item dietary screener assessing adolescent consumption of specific caloric and non-caloric beverages (9 items) and fast food (13 items) in samples of primarily Caucasian adolescents, as well as overweight Latina adolescents.

Methods
In the Minneapolis/St. Paul metropolitan region, the screener was administered to adolescents (ages 11-18 years). One subsample of adolescents completed the screener twice, to assess the test-retest reliability of the screener (n = 33, primarily Caucasian). Another adolescent subsample completed the screener along with three 24-hour dietary recalls, to assess criterion validity (n = 59 Caucasian youth).

In addition, 35 adolescent Latinas (ages 14-17) at risk for overweight (BMI ≥ 85th percentile) were recruited from East Los Angeles and completed the screener twice, approximately 7 to 14 days apart. Dietary intake was also assessed using 3-day diet records. Spearman correlation and simple Kappas were employed for test-retest assessment and comparisons between the screener and the records/recalls.

Results
Within the Caucasian sample, agreement between the two administrations of the screener was substantial, with most items yielding Spearman correlations and Kappa statistics that were > 0.60. When compared to the "gold standard" dietary recall data, findings indicate that the validity of the screener items assessing adolescents' intake of regular soda, sports drinks, milk, and water was fair. However, the differential assessment periods captured by the two methods (i.e., 1 month for the screener vs. 3 days for the recalls) posed challenges in analysis and made it impossible to assess the validity of some screener items.

Among the Latina sample, although test-retest assessment yielded a mean Spearman or Kappa statistic of 0.49 (with 17 of the 21 responses being significant, $p < 0.05$), validity was much lower and yielded a Kappa statistic of only 0.08 with no significant responses.

Conclusions
Overall, while these screener items largely represent reliable measures with fair validity for Caucasian populations, our findings highlight the challenges inherent in the validation of brief dietary assessment tools. Although this screener appeared to be a valid and reliable measure for assessing beverage and fast food consumption in a primarily Caucasian population of adolescents, it does not appear to be appropriate for a population of overweight Latina adolescents.

Comparing Childhood Weight-for-Age to BMI in the Prediction of Adolescent Obesity and Chronic Disease Risk Factors

Steven D Stovitz (PI), Mark A Pereira, Gabriela Vazquez, Leslie A Lytle, and John H Himes

UNIVERSITY OF MINNESOTA

Purpose
The purpose of this study was to examine the interaction of childhood height and childhood BMI in the prediction of young adult BMI.

Methods
The 2,802 subjects in this study were from the Child and Adolescent Trial for Cardiovascular Health (CATCH). The subjects' height and weight were measured in 3rd grade (mean age = 8.7 years) and again in 12th grade (mean age = 18.3 years). The associations and interactions between height (cm) and BMI (kg/m^2) were assessed using mixed linear regression models with adult BMI as the dependent variable.

Results
We found a significant interaction between childhood height and childhood BMI in the prediction of adult BMI ($p < 0.0001$). Stratification by Centers for Disease Control and Prevention (CDC) reference quintiles revealed that a positive association between childhood height and adult BMI existed only for those subjects in the top quintile of childhood BMI, within whom predicted adult BMI ranged from 27.5 kg/m^2 (95% CI = 26.4-28.6 kg/m^2) for those in the shortest height quintile to 30.2 kg/m^2 (95% CI = 29.7-30.6 kg/m^2) for those in the tallest height quintile. Among children with high BMI levels, those who were taller, as compared to those who were shorter, had significantly higher young adult BMI levels. This pattern seems primarily due to the positive association of childhood height and childhood BMI.

Conclusions
Clinicians should recognize the risk of excess body weight in young adulthood for all children who have a high BMI and pay special attention to those who are tall, because their childhood height will not protect them from subsequent weight gain and elevated BMI.

UNIVERSITY OF SOUTHERN CALIFORNIA (USC) TREC CENTER

TABLE 4: USC Developmental Projects Funded Through TREC

YEAR 1

University of Southern California

149 Combining Strength and Cardiovascular Exercise (Circuit Training) to Reduce Obesity and Associated Diseases in Overweight Latina Youth (PI: Jaimie Davis)

150 Hip Hop 2 Health (HH2H) (PI: Lester Jones)

151 Colon Cancer-Related Epigenetic Changes in Obesity (PI: Howard Kaufman)

152 SportBrain™ Pedometer and GPS Logging Technology: Better Tools for Evaluating Physical Activity in Children and an Application to the Impact of Neighborhood Land Use and Children's Commuting Time (PI: Rob McConnell)

153 Exploring the Link Between Obesity and Poor Prognosis of Childhood Acute Lymphoblastic Leukemia Using a Murine Model (PI: Steve Mittleman)

154 Ola No Ke Kino (The Body Enjoys Health!) (PI: Victor Pang)

155 Food for Thought: A Community-Wide Strategic Summit for Reducing Overweight/Obesity Among Latino and African American Families (PI: Michael Ruble)

156 Functional Brain Responses After Satiety in Normal Weight and Overweight Adolescent Girls (PI: Dawna Salter-Venzon)

157 "Kid Healthy" Steps to Healthy Living (PI: Jackie Teichmann)

158 Social Network Influences on Diet and Physical Activity (PI: Thomas Valente)

YEAR 2

Cross-Center

160 Autonomic and Metabolic Dysfunction in Obese Children with Sleep-Disordered Breathing (Co-PIs: Michael CK Khoo, University of Southern California; Susan Redline, Case Western Reserve University)

161 Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-ethnic Sample of Children: A Transdisciplinary Cross-Site Developmental Project (Co-PIs: Mark Pereira, University of Minnesota; Donna Spruijt-Metz, University of Southern California)

165 Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations (Co-PIs: Melissa Nelson, University of Minnesota; Jaimie Davis, University of Southern California)

University of Southern California

182 Translation of a Novel Resistance Training Intervention to a Home Environment for Overweight Hispanic Youth (PI: Louise Kelly)

183 Global Gene Expression in White Blood Cells from Hispanic and African American Adolescents (PI: Christian Roberts)

YEAR 3

Cross-Center

207 The Effect of Ethnicity on Lipomic Profile and Adipokines: Relation to Adipose Tissue Morphology and mRNA Expression (Co-PIs: Christian Roberts, University of Southern California; Sanjay Patel, Case Western

TABLE 4: USC Developmental Projects Funded Through TREC – Continued

Reserve University; Karen Foster-Schubert, Fred Hutchinson Cancer Research Center)

208 Insulin Resistance and Breast Cancer Prognosis (Co-PIs: Anne McTiernan, Fred Hutchinson Cancer Research Center; Leslie Bernstein, University of Southern California)

215 The Interaction of Childhood Height and BMI on the Prediction of Adiposity and Insulin Resistance (Co-PIs: Steven Stovitz, University of Minnesota; Louise Kelly, University of Southern California)

University of Southern California

221 Impact of Gestational Diabetes Mellitus on Fetal and Postnatal Hypothalamic Development (PI: Sebastien Bouret)

222 Fine-Mapping of *FTO* and *TCF2* in African Americans (PI: Christopher Haiman)

223 Investigating the Relationships Between Obesity and Leukemia Relapse (PI: Steven Mittelman)

224 Rapid and Non-invasive Quantitation of Abdominal Fat Distribution Using Magnetic Resonance Imaging (PI: Krishna Nayak)

YEAR 4

Cross-Center

None funded

University of Southern California

247 Effect of Insulin Resistance on the Brain and the Implications for Weight Regulation (PI: Tanja Adam)

248 Roles of Sex Hormones in Obesity and Breast Cancer (PI: Shiuan Chen)

249 The Role of Energy Sensor AMPK in Liver Cancer Development (PI: Bangyan Stiles)

Combining Strength and Cardiovascular Exercise (Circuit Training) to Reduce Obesity and Associated Disease Risk in Overweight Latina Youth

Jaimie Davis (PI)

UNIVERSITY OF SOUTHERN CALIFORNIA

Purpose

The purpose of this developmental project was to examine whether adding aerobic exercise to a strength training program would optimize improvements in adiposity and metabolic outcomes related to glucose regulation in overweight Latino youth.

Methods

The study was conducted with overweight Latina adolescents as a supplement to USC TREC Center Project 1 (PI: M Goran). In a 16-week randomized trial, 41 overweight Latina girls (15.2 ± 1.1 years) were randomly assigned to one of four groups: (1) control (n = 7); (2) nutrition education once a week (n = 10); (3) nutrition education once a week plus strength training twice a week (n = 9); and (4) nutrition education once a week plus combined aerobic and strength training (CAST) twice a week (n = 15). The following were measured pre- and postintervention: body weight, anthropometry and body composition by dual energy x-ray absorptiometry (DEXA), and glucose/insulin indices by oral and intravenous glucose tolerance tests on separate days.

Results

There were significant overall intervention effects for all adiposity-related measures (weight, BMI, BMI z-scores, and DEXA total body fat), with a

decrease of ~3% in the group receiving CAST compared to a 3% increase in the group receiving strength training ($p \leq 0.05$). There was also a significant intervention effect for fasting glucose, with the nutrition education group increasing by 3% in comparison to a 4% improvement in the group receiving CAST ($p \leq 0.05$). All other parameters of insulin and glucose regulation were not significantly different by intervention group.

Conclusions

This developmental project demonstrates that the combination of aerobic and strength training is more effective than nutrition education alone or nutrition education plus strength training for reducing multiple adiposity outcomes as well as fasting glucose concentration in overweight Latina girls. These main outcomes have been submitted for publication. The PI of this developmental project has been very successful in securing additional funding, including a KO1 award from the National Institute of Diabetes and Digestive and Kidney Diseases and a grant from the California Breast Cancer Research Fund.

Impact of Gestational Diabetes Mellitus on Fetal and Postnatal Hypothalamic Development

Sebastian Bouret (PI)

CHILDREN'S HOSPITAL OF LOS ANGELES

Purpose

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, and the offspring of mothers with GDM have a much greater risk of developing obesity and diabetes later in life. Despite these observations, the biological processes mediating this disturbance in metabolic programming and energy balance regulation are not well understood. In the present study, we explored the consequences of GDM for the development of hypothalamic neural circuits involved in regulating energy balance.

Methods

We used a mouse model of GDM induced by streptozotocin (STZ) injections, leading to persistent hyperglycemia throughout gestation and lactation. Hypothalamic leptin signaling was evaluated from the number of pSTAT3-immunoreactive neurons in the arcuate nucleus of pups derived from diabetic or control dams on postnatal day 10 (P10), 45 minutes after intraperitoneal injection with leptin; this method is based on the fact that STAT3 is a key intracellular signaling pathway of the leptin receptor.

Results

Preliminary findings indicate that induction of diabetes during gestation is associated with changes in offspring growth, as revealed by a significant increase in pre- and postweaning body weight curves in the offspring of STZ-treated dams compared with control mice. Mice born to diabetic dams also had increased fasting glucose and increased food intake during adult life. These impairments in metabolic regulation were associated with changes in hypothalamic leptin signaling during postnatal development. The results also indicate that leptin treatment causes marked increases in pSTAT3 staining in the arcuate nucleus of control pups on P10. However, the same leptin treatment results in significantly fewer pSTAT3-immunoreactive cells in the arcuate nucleus of P10 pups born to STZ-treated dams. A quantitative analysis of this experimental material revealed that the number of pSTAT3-immunoreactive cells in the arcuate nucleus of pups born to diabetic dams was reduced by more than 30% compared with control mice.

Conclusions

These results suggest that leptin signaling in arcuate neurons is impaired during postnatal development in the offspring of STZ-treated dams relative to control animals. We are currently examining whether these changes in leptin sensitivity during a critical period of brain development also affect

formation of hypothalamic neural projections. In summary, these data show that GDM has long-term consequences for energy metabolism and affects the sensitivity of hypothalamic neurons to leptin during critical periods of development.

Fine-Mapping of *FTO* and *TCF2* in African Americans

Christopher Haiman (PI)

UNIVERSITY OF SOUTHERN CALIFORNIA

Purpose

The goal of this developmental project is to conduct fine-mapping in African American men and women from a large multi-ethnic cohort (MEC) to localize disease variants in genes with established roles in type 2 diabetes, obesity, and cancer.

Methods and Results

In Aim 1 of the developmental project, we are fine-mapping the obesity gene, *FTO*, to identify the causal variant underlying the association of this region with adult and childhood obesity in European populations. Genetic variation in *FTO* has also been associated with obesity, and, in a meta-analysis of 13 cohorts (38,759 subjects), a common variant (rs9939609; minor allele frequency = 39%) was significantly associated with BMI (~0.36 kg/m^2 increase per allele; p = 3 x 10^{-35}). In 15,826 participants from the MEC, we have examined the association between rs8050136, a SNP in perfect linkage with rs9936909 (r_2 = 1.0) in *FTO*, and BMI. In age- and gender-adjusted analyses, we observed a statistically significant positive association in all populations, except in African Americans (p for heterogeneity of effects across population = 0.01; Table 5).

We have therefore initiated fine-mapping of this locus, selecting tagging SNPs that capture common alleles in the HapMap Yoruban and CEPH populations. We have estimated the size of the targeted linkage disequilibrium (LD) block at the *FTO* locus to be ~49 kb and that ~34 tagging SNPs will be required to tag all common variation in this region in the HapMap populations with an $r^2 \geq 0.9$. To date, we have genotyped 10 tag SNPs in a panel of > 2,700 African Americans from the MEC. A nominally significant association was noted with variant rs7206790, which is linked with rs9939609 in European Americans but not in African Americans (r_2 = 0.47 in the CEU population and r_2 = 0.02 in the YRI population). Further genotyping of tag SNPs is underway. In addition, we are collaborating with Dr Joel Hirschhorn (Harvard University), who has also initiated fine-mapping of the *FTO* gene in other African American cohorts, including the Jackson Heart Study. We propose to pool data from both efforts to allow for the largest and most comprehensive analysis of common variation at this locus in relation to obesity in African Americans.

TABLE 5: Association Between Variation in *FTO* and BMI in Multi-ethnic Cohort

	AA	JA	LA	NH	WH	All Populations
n	4,402	2,929	4,884	1,001	2,610	15,826
Percent change in BMI per allele	+0.26	+0.99	+2.05	+2.45	+1.87	+1.31
P-value	0.49	0.031	<0.0001	0.026	0.0004	<0.0001

AA, African American; JA, Japanese American; LA, Latino American; NH, Native Hawaiian; WH, White

In Aim 2 of the developmental project, we are fine-mapping the *TCF2* locus to localize the risk alleles for prostate cancer and type 2 diabetes. In genome-wide association studies of prostate cancer conducted in European Whites, multiple highly correlated variants (rs7501939 and rs757210) have been identified in the *TCF2* (HNF1β) gene that confer risk of prostate cancer (OR = 1.19; 95% CI = 1.12-1.26; $p = 1.4 \times 10^{-11}$). One of these variants (rs757210) was previously shown to be inversely associated with risk for type 2 diabetes. In an attempt to replicate these findings with prostate cancer, we genotyped these two variants in a large nested case-control study of prostate cancer in the MEC (2,788 cases and 2,613 controls). These SNPs were found to be positively associated with increased risk of prostate cancer in Whites, Latinos, Japanese, and Native Hawaiians (OR = 1.18; 95% CI = 1.08-1.32; $p = 4.4 \times 10^{-4}$) but not among African Americans (824 cases and 620 controls; OR = 0.95; 95% CI = 0.82-1.10; p = 0.49). We have since genotyped all SNPs in HapMap (~25) across this gene, including the 5' region. No significant associations were noted in African Americans; however, additional unlinked variants (with rs757210) in adjacent LD blocks were nominally associated with risk in Japanese and European Americans ($p < 0.01$). We have recently sequenced across these candidate LD block regions (> 65 kb) in a multiethnic panel of subjects from the MEC (16 of each African, Japanese, and European Americans). Through this effort we have identified > 350 SNPs, which we are now genotyping in MEC samples to assemble a complete data set of common alleles at this locus. Over the next few months, we will continue with association testing to reveal the full spectrum of common alleles that contribute to prostate cancer risk (and diabetes) in this region.

Investigating the Relationships Between Obesity and Leukemia Relapse

Steven Mittelman (PI)

CHILDREN'S HOSPITAL OF LOS ANGELES

Purpose

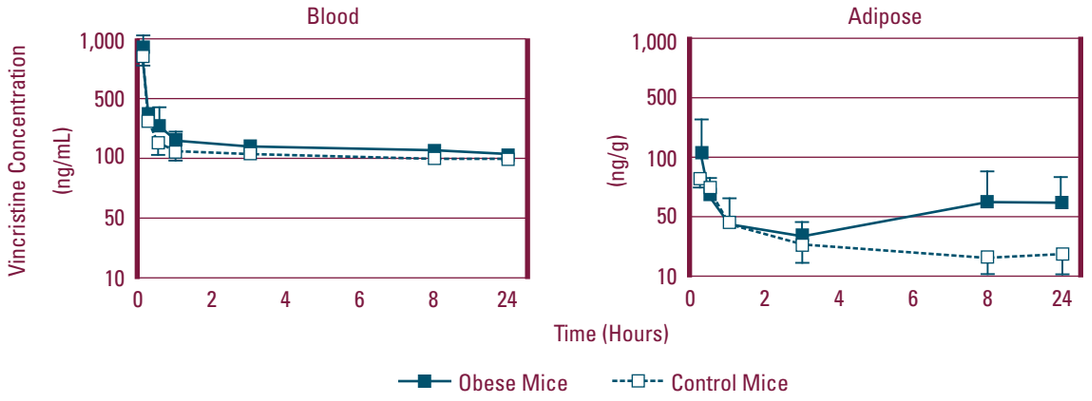
Previous studies have shown that children who are obese at the time they are diagnosed with acute lymphoblastic leukemia have a 50% increased risk of relapse compared to their lean counterparts. The purpose of this developmental study was to develop mouse and tissue culture models to investigate the mechanism(s) by which increased body fat might lead to leukemia relapse.

Methods and Results

This developmental study demonstrated that leukemia cells in diet-induced obese mice were resistant to at least two commonly used chemotherapies, vincristine and nilotinib. A novel tissue co-culture method was developed in which adipocytes are grown together with leukemia cells. With this method, we showed that adipocytes engender treatment resistance to leukemia cells against a multitude of chemotherapies with independent mechanisms of action (vincristine, dexamethasone, daunorubicin, L-asparaginase, and nilotinib). Using transwells with porous membranes, we further showed that this protection did not depend on cell-cell contact.

Using the tissue co-culture system, we also showed that vincristine accumulates in adipocytes. However, the media concentration of vincristine was not affected in this system, demonstrating that this accumulation was not the only mechanism by which adipocytes cause leukemia drug resistance. This finding was also confirmed in the diet-induced mouse model. As shown in Figure 5, vincristine was shown to accumulate in adipose tissue, but, when mice were dosed by body weight, blood concentrations were actually higher over the first 24 hours in the obese mice.

FIGURE 5: Blood and Adipose Vincristine Concentrations in Mice



Blood and adipose vincristine concentration after a 0.5 mg/kg intravenous injection in obese (closed squares, solid lines) and control (open squares, dashed lines) mice.

Conclusions

These findings suggest that obesity alters the pharmacokinetics of vincristine and important first-line chemotherapy, but that there are other mechanisms responsible for adipocyte-derived chemotherapy resistance.

Rapid and Non-invasive Quantitation of Abdominal Fat Distribution Using Magnetic Resonance Imaging

Krishna Nayak (PI)

UNIVERSITY OF SOUTHERN CALIFORNIA

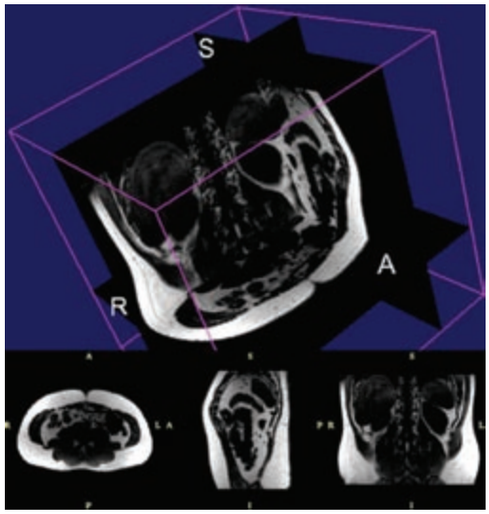
Purpose

The objective of this developmental project was to develop, optimize, and evaluate a new magnetic resonance imaging (MRI)-based approach that could potentially quantify fat mass in adipose tissue and organs of interest. The underlying hypothesis is that MRI can provide more flexible, accurate, and three-dimensional measurements of fat distribution than current techniques (e.g., DEXA, nuclear magnetic resonance spectroscopy) and that this may prove valuable for the study of energetics and obesity.

Methods and Results

This innovative approach utilizes the latest developments in MRI technology, including (1) iterative decomposition using echo-asymmetry in the least-squares sense (IDEAL), an optimal fat-water signal separation technique that utilizes knowledge of the 1H spectra in lipid and water, and (2) 3-Tesla (3T) MRI systems and abdominal receiver coil arrays that provide additional means of accelerating data collection. Using this approach, we have shown that the IDEAL-spoiled gradient echo (SPGR) MRI pulse sequence could be implemented in a fashion that covers the entire abdomen of an average-sized adult with 4 x 4 x 5 mm^3 isotropic resolution within 24 seconds (suitable for a prolonged breath-hold) while achieving an acceptable signal-to-noise ratio on a 3T MRI scanner (Figure 6). Fat and lean signals can be robustly separated from this data, resulting in fat-signal fraction mapping (not to be confused with fat mass or fat volume mapping).

FIGURE 6: MRI Images of 3D Fat Signal Maps



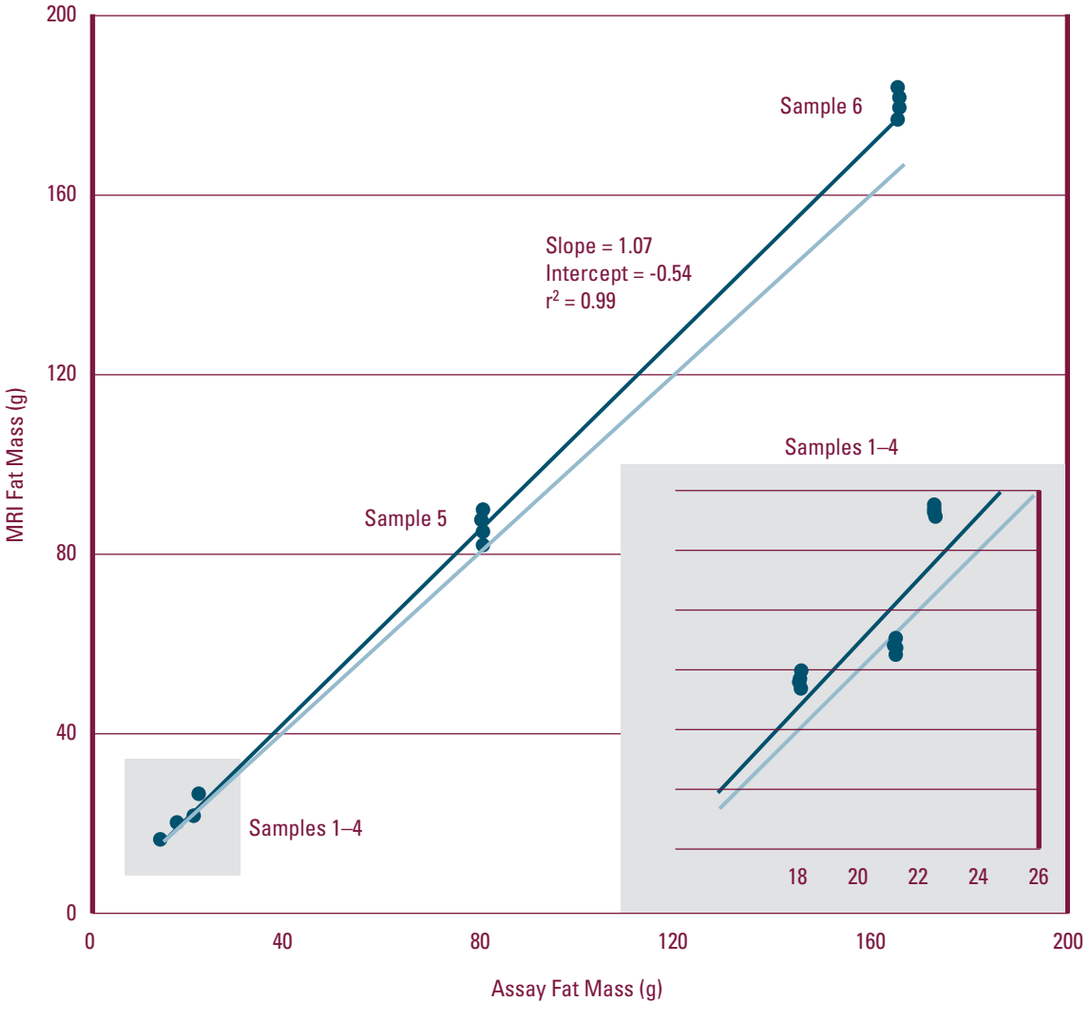
3D fat signal maps obtained in a single 24-second breath-hold. The acquisition also produces water signal maps (not shown) that allow the computation of fat signal fraction on a voxel-by-voxel basis.

Another key finding was that fat mass can be derived from IDEAL-SPGR MRI data using an adipose tissue signal reference. When applied to ex vivo tissue specimens, this approach produced fat mass measurements that were in excellent agreement with a lipid assay and had an average difference of 7% (Figure 7). In phantoms containing homogeneous mixtures of fat and lean tissue, MRI fat mass measurements also showed an excellent linear correlation with the true underlying fat content.

Conclusions

Together these findings suggest that it is feasible to quantitatively image 3D fat mass distribution in the adult abdomen within one or a few short breath-holds. Next steps include validation studies in whole animals (likely swine), the exploration of more specific biomarkers that may be detected with this non-invasive imaging technique (brown versus white adipose tissue, fat cell size, etc.), and the development of efficient 3D abdominal segmentation methods to facilitate use in clinical studies.

FIGURE 7: Comparison of Fat Mass Measurements by MRI and Lipid Assay



Experiments in ex vivo tissue specimens show a strong correlation between fat mass measured by non-invasive MRI and by lipid assay.

TREC COORDINATION CENTER

TABLE 6: Coordination Center Developmental Projects Funded Through TREC

YEAR 1

Coordination Center

159 Specimen Tracking System for the Seattle TREC Center (PI: Mark Thornquist)

YEAR 2

Cross-Center

220 Scientific Support: Conference Calls (PI: Mark Thornquist)

YEAR 3

Cross-Center

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Balance of Energy in Chemotherapy (BALANCE)

Kathryn Schmitz (PI) and Rebecca Speck (Co-investigator/study coordinator)

Introduction

There is a need to understand the association of modifiable energy balance factors with toxicities experienced during chemotherapy treatment for breast cancer. Findings could lead to the development of innovative therapeutic interventions that reduce toxicities and enable delivery of chemotherapy doses at the most efficacious timing, improving short- and long-term cancer treatment outcomes.

Purpose

Body composition, physical activity, diet, and sleep have each been observed to independently alter immune function and are each associated with alterations in metabolism. It is hypothesized that interindividual variability in each of these energy balance factors will change duringchemotherapy and will be correlated to changes in immune parameters.

This project has the following specific aims:

1. To examine the association between changes in absolute neutrophil counts (ANC) and changes in energy balance factors (body composition, physical activity energy expenditure, dietary intake and supplement use, and sleep) during multiple cycles of doxorubicin- or taxol/taxotere-based chemotherapy in 60 breast cancer patients.
2. To measure the changes in energy balance factors (body composition, physical activity energy expenditure, dietary intake and supplement use, and sleep) that occur during multiple cycles of doxorubicin- or taxol/taxotere-based chemotherapy in a population of 60 breast cancer patients.

Methods

BALANCE is an observational study of 60 women during adjuvant chemotherapy for breast cancer.

BALANCE is the dissertation project of Rebecca Speck, predoctoral mentee of PI Kathryn Schmitz in clinical epidemiology at the University of Pennsylvania. The project has received additional funding from a predoctoral US Department of Defense Breast Cancer Research Training Grant. All regulatory approvals are in place, and the anticipated start for patient recruitment, screening, and enrollment is September 2008.

References

The TREC initiative has generated a wide range of collaborations, both within and across Centers, as well as with outside institutions. To that end, the listing of TREC publications will include publications directly supported by TREC as well as those stimulated by TREC collaborations, as defined below.

TREC-supported publications include the following:

- Publications describing TREC-funded project data (i.e., the TREC grant number is cited in the manuscript).
- Publications involving TREC investigators receiving TREC funds for salary support, including reviews, data from other energy balance-related work, and other scholarly work, whether or not the TREC grant number is cited in the manuscript.

TREC-stimulated publications include the following:

- Publications describing research not directly supported by TREC funds, but affiliated through TREC connections, partnerships, scientific collaborations, etc. (However, if any component is TREC supported, it will be listed as TREC supported.)
- Publications that result from TREC conferences, workshops, seminars, etc., but that are not directly supported by TREC funds.

The above guidelines also apply to the listing of TREC presentations.

Case Western Reserve TREC

Publications

1. Anderson B, Storfer-Isser A, Taylor HG, Rosen CL, Redline S. Associations of executive function with sleepiness and sleep duration in adolescents. *Pediatrics.* In revision.
2. Barber TD, McManus K, Yuen KW, Reis M, Parmigiani G, Shen D, Barrett I, Nouhi Y, Spencer F, Markowitz SD, Velculescu VE, Kinzler KW, Vogelstein B, Lengauer C, Hieter P. Chromatid cohesion defects may underlie chromosome instability in human colorectal cancers. *Proc Natl Acad Sci USA.* 2008;105(9):3443-8.
3. Biswas S, Trobridge P, Romero-Gallo J, Billheimer D, Myeroff L, Willson JKV, Markowitz SD, Grady W. Mutational inactivation of TGFBR2 in microsatellite unstable colon cancer arises from the cooperation of genomic instability and the clonal outgrowth of transforming growth factor ß resistant cells. *Genes Chromosomes Cancer.* 2008;47:95-106.
4. Chak A, Falk D, Grady WG, Kinnard M, Barnholtz-Sloan J, Mittal S, King JF, Willis J, Kondru A, Brock W, Elston RC. Epidemiology of cancers in Barrett's esophagus. *Gut.* Submitted.
5. Chen W-D, Han ZJ, Skoletsky J, Olson J, Sah J, Myeroff L, Platzer P, Lu S, Dawson D, Willis J, Pretlow TP, Lutterbaugh J, Katuri L, Willson JKV, Rao JS, Shuber A, Markowitz SD. Detection in fecal DNA of colon cancer-specific methylation of the nonexpressed vimentin gene. *J Natl Cancer Inst.* 2005;97:1124-32.
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7. Daley D, Morgan W, Lewis S, Willis J, Elston RC, Markowitz SD, Wiesner GL. Is TGFBR1*6A a susceptibility allele for nonsyndromic familial colorectal neoplasia? *Cancer Epidemiol Biomarkers Prev.* 2007;16(5):892-4.
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10. Grady WM, Willis JE, Trobridge P, Romero-Gallo J, Munoz N, Olechnowicz J, Ferguson K, Gautam S, Markowitz SD. Proliferation and Cdk4 expression in microsatellite unstable colon cancers with TGFBR2 mutations. *Int J Cancer.* 2006;118(3): 600-8.

11. Guo C, Sah JF, Beard L, Willson JK, Markowitz SD, Guda K. The noncoding RNA, miR-126, suppresses the growth of neoplastic cells by targeting phosphatidylinositol 3-kinase signaling and is frequently lost in colon cancers. *Genes Chromosomes Cancer.* 2008;47(11):939-46.

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13. Hakimi P, Yang J, Casadesus G, Massillon D, Tolentino-Silva F, Nye CK, Cabrera ME, Hagen DR, Utter CB, Baghdy Y, Johnson DH, Wilson DL, Kirwan JP, Kalhan SC, Hanson RW. Overexpression of the cytosolic form of phosphoenolpyruvate carboxykinase (GTP) in skeletal muscle repatterns energy metabolism in the mouse. *J Biol Chem.* 2007; 282(45):32844-55.

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16. Heinberg LJ, Kutchman E, Lawhun S, Seabrook R, Cuttler L, Horwitz S. Is parent involvement an important predictor of success in pediatric obesity treatment? *Int J Ped Obes.* Under review.

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Presentations

1. Berger NA. *Energetics and cancer: Impact of obesity on cancer.* Presented at Cancer Center Grand Rounds, Cleveland, OH, 2006.

2. Berger NA. *The link between nutrition and cancer: Does it matter what we eat?* Presented in Independence, OH, 2006.

3. Berger NA. *Obesity and cancer: A public health crisis.* Presented at the Third International Shanghai-Case Symposium on Community Health-Family Medicine Research, Shanghai, China, 2007.

4. Berger NA. *Aging, cancer and energy balance.* Presented to the American Federation for Aging Research, National Institute on Aging, New York, NY, 2008.

5. Berger NA. *Poly (ADP-ribose) polymerase function and activities.* Presented to the American Association for Cancer Research, San Diego, CA, 2008.

6. Cabrera M. *Effects of exercise on tumor development in APCmin mouse model of colon cancer. Metabolomics study.* Presented at the Fourth Annual International Conference of the Metabolomics Society, Boston, MA, 2008; and the TREC Centers Scientific Meeting, Bethesda, MD, 2008.

7. Chak A. *Genetics and imaging of high-grade dysplasia.* Mark Blue Memorial Lecture, presented at the Cleveland Clinic, Cleveland, OH, 2006.

8. Chak A. *Barrett's esophagus: Clinical and genetic implications.* Presented at the International Symposium on Gastrointestinal Cancers, Osaka, Japan, 2007.

9. Chak A. *Familial Barrett's esophagus.* Presented at Grand Rounds, Brown University, Providence, RI, 2008.

10. Chak A. *Genetics of Barrett's esophagus and cancers.* Presented in Richmond, VA, 2008.

11. Chak A. *Insulin/IGF-1 in BE.* Presented at a Research Seminar, Brown University, Providence, RI, 2008.

12. Chak A. *What is the influence of stage migration on the expected survival of esophageal cancer patients?* Presented at the Ninth World Congress of the World Organization for Specialized Studies of Diseases of the Esophagus (OESO), Monaco, 2008.

13. Chak A. *What is the role of genetic predisposition in the development of Barrett's esophagus?* Presented at the Ninth World Congress of the World Organization for Specialized Studies of Diseases of the Esophagus (OESO), Monaco, 2008.

14. Hanson R. Cardiac Research Center Lecture, presented at Case Western Reserve University School of Medicine, Cleveland, OH, 2007.

15. Hanson R. *Exercise, aging, and cancer.* Presented to the Department of Cell Biology, Cleveland Clinic Foundation, Cleveland, OH, 2007.

16. Hanson R. *Exercise, aging, and cancer.* Presented to the Department of Pathobiology, Cleveland Clinic Foundation, Cleveland, OH, 2007.

17. Hanson R. Howard Mason Lecture. Presented at Oregon Health and Science University, 2007.

18. Hanson R. *Metabolic effects of exercise.* Robert Kohn Memorial Lecture, presented at the Case Western Reserve University School of Medicine, 2007.

19. Hanson R. *Metabolism master class.* Presented at Oregon Health and Science University, 2007.

20. Hanson R. *Metabolism in medical education.* American Medical and Graduate School Chairs of Meeting, 2007.

21. Hanson R. *Metabolism in medicine.* Presented at the Aultman Institute, Canton OH, 2007.

22. Hanson R. *Muscle PEPCK-C and exercise performance.* Discovery Lecture, presented at Vanderbilt University, 2007.

23. Hanson R. *PEPCK-C^{mus} mouse and metabolic effect of exercise.* LaVall Henderson Memorial Lecture, presented at the University of Minnesota, 2007.

24. Hanson R. *Muscle PEPCK-C and exercise performance.* Presented at the Annual Meeting of the American Diabetes Association, 2008.

25. Hanson R. *Neonatal adaptations to glucose metabolism.* Presented at MetroHealth Medical Center, Cleveland, OH, 2008.

26. Heinberg L. *Fighting the rising tide of pediatric obesity.* Invited presentation at Case Conversations on Children in Research and Policy, Schubert Center, Cleveland, OH, 2006.

27. Heinberg L. *Body image in men: Assessing and treating the overlooked.* Chair and moderator, International Conference for Eating Disorders, Baltimore, MD, 2007.

28. Heinberg L. *Preliminary findings from a pediatric obesity program: Energy balance, sleep, and psychosocial factors.* Invited Continuing Medical Education presentation at the Transdisciplinary Research on Energetics and Cancer Series, Case Comprehensive Cancer Center, Cleveland, OH, 2007.

29. Heinberg L. *Empower and engage: Getting families involved in obesity interventions.* Invited Continuing Medical Education presentation at the Transdisciplinary Research on Energetics and Cancer Series, Case Comprehensive Cancer Center, Cleveland, OH, 2008.

30. Heinberg LJ, Kutchman E, Lawhun S, Laheta J, Uli N, Cuttler L. *Predictors of eating disordered symptoms in a treatment-seeking overweight pediatric population.* Presented at the Annual Meeting of the North American Association for the Study of Obesity, Boston, MA, 2006.

31. Heinberg LJ, Rosen C, Cuttler L, Kutchman E, Lawhun S, Laheta J, Uli N, Redline S. *Effect of sleep duration on BMI and treatment completion in a pediatric weight management program.* Presented at the Annual Meeting of the North American Association for the Study of Obesity, Boston, MA, 2006.

32. Ievers-Landis C. *Weight control and sleep enhancement intervention for young children who are overweight.* Presented at a TREC seminar, Cleveland, OH, 2007.

33. Ievers-Landis CE, Heinberg L, Donovan LM, Gorovoy SB, Varkula L, Bhatnagar K, Rosen C, Redline S. *Feasibility of a sleep intervention for adolescents who are obese.* Presented at the TREC Centers Scientific Meeting, Bethesda, MD, 2008.

34. Ievers-Landis CE, Storfer-Isser A, Rosen C, Johnson NL, Redline S. *Relationship of sleep parameters, child psychological functioning and parenting stress to overweight status among preadolescent children.* Presented at the TREC Centers Scientific Meeting, Minneapolis, MN, 2007.

35. Keri R. *Functional genomics of breast development and cancer.* Presented to the Department of Reproductive Biology, Cornell University College of Veterinary Medicine, Ithaca, NY, 2008.

36. Kutchman E, Hazen R, Heinberg LJ. *Degree of unfitness in overweight children ages 7-13 participating in a 12-week multidisciplinary intervention program.* Presented at the Annual Meeting of the North American Association for the Study of Obesity, Boston, MA, 2006.

37. Li L. *Translating scientific evidence into community disease prevention.* Presented at the First Case-Shanghai Symposium on Community-Based Disease Prevention Research, Shanghai, China, 2005.

38. Li L. *A life course approach to chronic disease epidemiology and prevention.* Presented at the Third International Shanghai-Case Symposium on Community Health-Family Medicine Research, Shanghai, China, 2007.

39. Li L, Plummer S, Thompson CL, Tucker TC, Casey G. *Association between phosphatidylinositol 3-kinase p85α regulatory subunit Met326Ile polymorphism and colon cancer risk.* Presented to the International Genetic Epidemiology Society, 2006.

40. Markowitz S. *Colon cancer: New genes and new pathways.* Presented at Colorectal Cancer: Molecular Pathways and Therapies, American Association for Cancer Research Special Conference, Dana Point, CA, 2005.

41. Markowitz S. *Genetic lessons from human colon cancer.* Presented at Hematology-Oncology Grand Rounds, Beth-Israel Deaconess Medical Center, Boston, MA, 2005.

42. Markowitz S. *Molecular opportunities for colon cancer prevention.* Presented at Frontiers in Cancer Prevention, American Association for Cancer Research Special Conference, Baltimore, MD, 2005.

43. Markowitz S. *Genetic lessons from colon cancer.* Invited presentation at the Third Annual Tumor Progression and Therapeutic Resistance Conference, Baltimore, MD, 2006.

44. Markowitz S. *Genetic lessons from colon cancer.* Presented at the Vanderbilt Cancer Center, Nashville, TN, 2006.

45. Markowitz S. *Genetic pathways to colon cancer.* Invited presentation at the 97th Annual Meeting of the American Association for Cancer Research, Washington, DC, 2006.

46. Markowitz S. *Genetic targets in human colon cancer.* Presented at Genentech, Inc., South San Francisco, CA, 2006.

47. Markowitz S. *Genetic targets in human colon cancer.* Seminar presented at the University of Chicago Cancer Center, Chicago, IL, 2006.

48. Markowitz S. *New concepts in organ site research: From genotype to treatment in colorectal cancer.* Presented at the 97th Annual Meeting of the American Association for Cancer Research (Co-Chair), Washington, DC, 2006.

49. Markowitz S. *New genetic targets in colon cancer prevention.* Invited presentation at Frontiers in Cancer Prevention, American Association for Cancer Research Special Conference, Boston, MA, 2006.

50. Markowitz S. *Genetic lessons from colon cancer.* Presented at GI Grand Rounds, MD Anderson Cancer Center, Houston, TX, 2007.

51. Markowitz S. *Genetic lessons from colon cancer.* Presented as part of the Cell Biology Seminar Series, Cleveland Clinic Lerner School of Medicine, 2007.

52. Markowitz S. *Genetic lessons from colon cancer.* Presented as part of the National Human Genome Research Institute Seminar Series, Bethesda, MD, 2007.

53. Markowitz S. *Genetic lessons from colon cancer.* Annual Postdoctoral Fellow Invited Visiting Speaker, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX, 2007.

54. Markowitz S. *Genetic lessons from colon cancer.* Presented as part of the Montefiore Hospital Department of Medical Oncology Seminar Series, Bronx, NY, 2007.

55. Markowitz S. *Genetic lessons from colon cancer.* Presented at Department of Medicine Grand Rounds, Memorial Sloan-Kettering Cancer Center, New York, NY, 2007.

56. Markowitz S. *Genetic lessons from colon cancer.* Presented as part of the Center for Molecular Medicine Seminar Series, University of Connecticut School of Medicine, Farmington, CT, 2007.

57. Markowitz S. *Genetic lessons from colon cancer.* Presented at Department of Medicine Grand Rounds, MD Anderson Cancer Center, Houston, TX, 2007.

58. Markowitz S. *Genetic pathways to colon cancer.* Seminar presented at Vanderbilt University Cancer Center, Nashville, TN, 2007.

59. Markowitz S. *Genetic pathways to colon cancer.* Presented at the MD Anderson Symposium on Cancer Prevention, Houston, TX, 2007.

60. Markowitz S. *Genetic pathways to colon cancer.* Presented at Genentech, Inc., South San Francisco, CA, 2007.

61. Markowitz S. *How TGF-β is nature's celecoxib for preventing colon cancer.* Presented at Advances in Colon Cancer Research, American Association for Cancer Research Special Conference, Cambridge, MA, 2007.

62. Markowitz S. *Molecular advances in colon cancer: Moving to the bedside.* Invited presentation at the 98th Annual Meeting of the American Association for Cancer Research, Los Angeles, CA, 2007.

63. Markowitz S. *New genetic pathways to colon cancer.* Presented at Current Challenges in the Understanding and Management of Colon Cancer, 38th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, Japan, 2007.

64. Markowitz S. *TGF-β: The genome's aspirin for colon cancer prevention.* Presented at the Annual Meeting of the Polyp Prevention Study Group, Chicago, IL, 2007.

65. Markowitz S. *Early detection of colon cancer using methylated fecal DNA.* Presented at Molecular Diagnostics in Cancer Therapeutic Development, American Association for Cancer Research Special Conference, Philadelphia, PA, 2008.

66. Markowitz S. *Genes, fatty acids, and colon cancer.* Presented at the Fred Hutchinson Cancer Research Center, Seattle, WA, 2008.

67. Markowitz S. *Genetic targets in colon cancer.* Presented at Genentech, Inc., South San Francisco, CA, 2008.

68. Markowitz S. Keynote address at the Cleveland Clinic Colorectal Cancer Summit, Cleveland, OH, 2008.

69. Markowitz S. *15-PGDH: Nature's NSAID for colon cancer prevention.* Invited presentation at the 99th Annual Meeting of the American Association for Cancer Research, San Diego, CA, 2008.

70. Nadeau J. *All about epistasis–Genetics through Bette Davis eyes.* Presented to the Department of Epidemiology and Biostatistics, Case Western Reserve University, 2007.

71. Nadeau J. *Atomos and kosmos: The genetics and systems biology of metabolic diseases.* Presented to the Department of Genetics, Case Western Reserve University, Cleveland, OH, 2007.

72. Nadeau J. *Atomos and kosmos: The genetics and systems biology of metabolic diseases.* Presented to the Department of Genetics, University of Wisconsin, Madison, WI, 2007.

73. Nadeau J. *Atomos and kosmos: The genetics and systems biology of metabolic diseases.* Presented at the Alcohol Research Center, Cleveland Clinic Research Foundation, Cleveland, OH, 2007.

74. Nadeau J. *Bugs, guts, and fat: Systems analysis of the metabolic axis of evil.* Keynote speech presented at the Fifth Asian Pacific Bioinformatics Conference, Hong Kong, 2007.

75. Nadeau J. *Epistasis and the genetic and systems control of complex traits.* Presented at Regeneron, New York, 2007.

76. Nadeau J. *The genetic architecture and systems properties of complex traits.* Presented at the 21st International Mammalian Genome Conference, Kyoto, Japan, 2007.

77. Nadeau J. *Genetic architecture and systems properties of metabolic traits in chromosome substitution strains.* Presented at Discovery Strategies Conference: Metabolic Disease and Type 2 Diabetes, Jackson Laboratory, Bar Harbor, ME, 2007.

78. Nadeau J. *Genetics of health.* Presented at Foundations of Research and Scholarship, Case Western Reserve University School of Medicine, Cleveland, OH, 2007.

79. Nadeau J. *Genetics of health and disease.* Presented at the Systems Medicine Workshop, National Institutes of Health, Bethesda, MD, 2007.

80. Nadeau J. *Genetics and systems biology of metabolic diseases.* Dahlem Colloquium Lecture, presented at the Max Planck Institute for Molecular Genetics, Berlin, Germany, 2007.

81. Nadeau J. *Metabolic diseases: Simple traits, modifier genes, and systems biology.* Presented at the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007.

82. Nadeau J. *Modifier genes: Simple traits and complex systems, in sickness and in health.* Presented at the Fifth Pathways, Networks, and Systems Conference, Porto Heli, Greece, 2007.

83. Nadeau J. *Modifier genes and the systems biology of health and disease.* Presented to the Department of Genetics, Washington University School of Medicine, St. Louis, MO, 2007.

84. Nadeau J. *Systems medicine: Integrating genetic variation and phenotypic diversity.* Keynote address to the National Genome Research Network, Heidelberg, Germany, 2007.

85. Nadeau J. *Consomic mouse strains–Discovering diabetes genes.* Presented at the 68th Annual Conference of the American Diabetes Association, San Francisco, CA, 2008.

86. Nadeau J. *Deconstructing complex traits.* Presented at the 49th Annual Short Course on Medical and Experimental Mammalian Genetics, Bar Harbor, ME, 2008.

87. Nadeau J. *Diet-induced metabolic disease and cancers in genetically-predisposed mice.* Presented at the TREC Centers Scientific Meeting, Bethesda, MD, 2008.

88. Nadeau J. *Diet-induced metabolic disease and cancers in genetically-predisposed mice.* Presented at the Maine Medical Center Research Institute Research Seminar, Portland, ME, 2008.

89. Nadeau J. *Diet-induced metabolic disease and cancers in genetically predisposed mice.* Keynote address presented at the Annual Conference of the Ohio Physiological Society, Toledo, OH, 2008.

90. Nadeau J. *Diet-induced metabolic disease and cancers in genetically predisposed mice.* Presented at the Institute for Systems Biology, Seattle, WA, 2008.

91. Nadeau J. *Fractal genetics and systems: The architecture of diet-induced metabolic disease.* Presented at the 20th International Genetics Congress, Berlin, Germany, 2008.

92. Nadeau J. *Genetic architecture of complex traits in chromosome substitution strains.* Plenary talk at Pathological and Physiological Regulation of Cardiac Hypertrophy, Keystone Symposium, Copper Mountain, CO, 2008.

93. Nadeau J. *Genetic architecture and systems properties of complex traits.* Presented at the First International Conference on Functional Annotation of the Mammalian Genome, Rottach-Egern, Germany, 2008.

94. Nadeau J. *The genetic architecture of diet-induced obesity.* Presented at the Fifth International Conference on Innate Immunity, Chania, Greece, 2008.

95. Nadeau J. *Genetic and dietary control of susceptibility to obesity, NASH, and liver cancer.* Presented at the TREC Centers Scientific Meeting, Fred Hutchinson Cancer Research Center, Seattle, WA, 2008.

96. Nadeau J. *Systems biology approaches for studying the genetic basis for complex conditions.* Invited presentation at the 54th Annual Meeting of the Orthopaedic Research Society, San Francisco, CA, 2008.

97. Nosek T. *The cellular basis of muscle fatigue.* Presented to the Muscle Biology Group, University of Missouri at Kansas City, MO, 2008.

98. Nosek T. *Role of MIP and PI(3,5)P2 on muscle fatigue, disease, and aging.* Presented at Pulmonary Medicine Grand Rounds, Case Western Reserve University, 2008.

99. Patel S. *The association of ACE polymorphisms with sleep apnea and hypertension.* Presented at the American Thoracic Society Annual Meeting, San Francisco, CA, 2007.

100. Patel S. *The effects of sleep deprivation on medical professionals.* Presented at the Department of Medicine Fellowship Conference, University Hospitals of Cleveland, OH, 2007.

101. Patel S. *Health effects of sleep deprivation in women.* Presented at the Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, 2007.

102. Patel S. *Intermediate phenotypes in sleep apnea.* Presented at the Sleep Disorders Program Research Conference, Brigham and Women's Hospital, Boston, MA, 2007.

103. Patel S. *Introduction to epidemiology and statistics.* Presented at the Pulmonary Fellows Conference, Pulmonary Division, University Hospitals of Cleveland, OH, 2007.

104. Patel S. *Obstructive sleep apnea.* Presented at the Ambulatory Medicine Nursing CNA Conference, University Hospitals of Cleveland, OH, 2007.

105. Patel S. *Oximetry and capnography.* Presented at the Pulmonary Fellows Conference, Pulmonary Division, University Hospitals of Cleveland, OH, 2007.

106. Patel S. *Sleep duration as a novel risk factor for disease.* Presented at the Case Cardiovascular Research Institute Seminar Series, University Hospitals of Cleveland, OH, 2007.

107. Patel S. *The basics of sleep and sleep disorders.* Presented at the T35 Minority Training Grant Research Conference, Case Western Reserve University School of Medicine, Cleveland, OH, 2008.

108. Patel S. *Genetics of sleep disorders.* Presented at the SLEEP Annual Meeting, Baltimore, MD, 2008.

109. Patel S. *Introduction to epidemiology and statistics.* Presented at the Pulmonary Fellows Conference, Pulmonary Division, University Hospitals of Cleveland, OH, 2008.

110. Patel S. *Obstructive sleep apnea.* Presented at the Sleep Medicine Fellows Conference, Pulmonary Division, University Hospitals of Cleveland, OH, 2008.

111. Patel S. *Oximetry and capnography.* Presented at the Pulmonary Fellows Conference, Pulmonary Division, University Hospitals of Cleveland, OH, 2008.

112. Patel S. *Quantifying genetic overlap between OSA and obesity.* Presented at the Annual Meeting of the American Thoracic Society, Toronto, Ontario, Canada, 2008.

113. Patel S. *Sleep deprivation as a novel risk factor for obesity.* Presented at the TREC Centers Scientific Meeting, Case Western Reserve University School of Medicine, Cleveland, OH, 2008.

114. Patel S. *Sleep and society: Towards a research agenda on the social determinants of sleep.* Presented at the SLEEP Annual Meeting, Baltimore, MD, 2008.

115. Patel S. *Update on Adipose Biology Collaborative.* Presented at the TREC Centers Scientific Meeting, Fred Hutchinson Cancer Research Center, Seattle, WA, 2008.

116. Redline S. *Evolving epidemiology of pediatric sleep apnea and implications of the obesity epidemic.* Postgraduate course presented at the Annual Meeting of the American Thoracic Society, San Francisco, CA, 2007.

117. Redline S. *Associations between sleep disorders and cardiovascular disease in adolescents.* Presented at the 26th Annual Conference on Sleep Disorders in Infancy and Childhood, Annenberg Center for Health Sciences, Palm Springs, CA, 2008.

118. Redline S. *The health impact of insufficient sleep in adolescents.* Presented at Harvard College, Cambridge, MA, 2008.

119. Redline S. *Measurement of sleep in clinical research and its relevance to TREC.* Presented to the TREC Physical Activity, Sleep, and Environmental Measurement Working Group, 2008.

120. Redline S. *Obesity and sleep disorders.* Presented at the Shanghai Conference on Community Health and Harmonious Society, Shanghai, China, 2008.

121. Redline S. *Pediatric obesity and sleep-disordered breathing.* Presented at the Annual Meeting of the American Thoracic Society, Toronto, Ontario, Canada, 2008.

122. Redline S. *Weekly Sleep and Epidemiology Research Seminar for Young Investigators.* Presented at Case Western Reserve University, Cleveland, OH, 2008.

123. Redline S, Ievers-Landis CE, Patel S, Stone K. *Sleep and circadian rhythm disturbances as risk factors for obesity.* Presented at the TREC Centers Scientific Meeting, Bethesda, MD, 2008.

124. Shi C, Sakuma M, Mooroka T, Liscoe A, Gao H, Croce KJ, Sharma A, Kaplan D, Greaves DR, Wang Y, Simon DI. *Downregulation of the forkhead transcription factor Foxp1 is required for monocyte differentiation and macrophage function.* Presented at the Cardiovascular Division Annual Scientific Seminar Retreat, Case Western Reserve University, Cleveland, OH, 2008.

125. Stavnezer E. *Multiple activities of the Ski oncogene.* Presented to the Biochemistry Department, University of Medicine and Dentistry of New Jersey, 2006.

126. Stavnezer E. *The reverse Warburg effect: Stimulation of mitochondrial oxidative metabolism by the Ski oncogene.* Presented at Case Western Reserve University, 2006.

127. Stavnezer E. *An enigma wrapped in a paradox: Ski induces oncogenesis, differentiation, oxidative metabolism.* Presented at Cleveland State University, 2007.

128. Stavnezer E. *Ski reprograms cellular energetics.* Presented at Case Western Reserve University, 2008.

129. Stellato T. *Bariatric surgery: A partial solution to a global health problem.* Presented at the Third International Shanghai-Case Symposium on Community Health-Family Medicine Research, Shanghai, China, 2007.

130. Thompson C. *Phosphatidylinositol 3-kinase subunit genetic polymorphisms and colon cancer risk.* Presented at the TREC Centers Scientific Meeting, Minneapolis, MN, 2007.

131. Thompson C. *Genetic variation and risk of type II diabetes and obesity.* TREC Seminar, 2008.

132. Thompson C. *Retinol binding protein-4 and colon neoplasia.* TREC Seminar, 2008.

133. Thompson CL, Gray-McGuire C. *Importance of population substructure characterization in linkage studies of admixed populations.* Presented to the American Society of Human Genetics, San Diego, CA, 2007.

134. Thompson CL, Klein BEK, Klein R, Capriotti J, Leontiev D, Lee KE, Iyengar SK. *The 10q26 region and age-related macular degeneration.* Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, 2007.

135. Thompson CL, Larkin EK, Auker K, Negrey J, Berger NA, Redline S, Li L. *Relation of sleep apnea and duration of sleep to colon adenoma risk.* Presented at the TREC Centers Scientific Meeting, Seattle, WA, 2008.

136. Thompson CL, O'Leary V, Huang H, Auker K, Kirwan J, Li L. *Retinol-binding protein 4, central obesity, and colon adenomas.* Presented at the TREC Centers Scientific Meeting, Pasadena, CA, 2007.

137. Thompson CL, Plummer SJ, Tucker TC, Casey G, Li L. *Does colon cancer share common genetic susceptibility loci with diabetes and obesity?* Presented at the TREC Centers Scientific Meeting, Bethesda, MD, 2008.

138. Thompson CL, Plummer S, Tucker TC, Casey G, Li L. *No association between UDP-glucuronosyltransferase 1 genetic polymorphisms or interaction with non-steroidal anti-inflammatory drug use and colon cancer.* Presented to the International Genetic Epidemiology Society, 2006.

139. von Gruenigen V. *Advances in cancer survivorship.* Presented at the Ireland Cancer Center, National Cancer Leadership Council, 2008.

140. von Gruenigen V. *Be your own health care advocate: Gynecologic cancers.* Presented to ABB, Inc., 2008.

141. von Gruenigen V. *Endometrial cancer: Prevention and control.* Presented at University Hospitals Case Medical Center, Mentor Satellite, 2008.

142. von Gruenigen V. *Endometrial cancer survivorship.* Presented as part of the Ireland Cancer Center Online Continuing Medical Education Program, 2008.

143. von Gruenigen V. *Endometrial cancer survivorship: Quality of life and lifestyle.* Presented to the Gynecologic Cancer Foundation, Oklahoma City, OK, 2008.

144. Yuan C, Yan M, Markowitz SD, Chance M, Chang J. *Proteomic changes induced by knock-out of a colon cancer suppressor, 15-PGDH.* Presented at the 56th Conference of the American Society for Mass Spectrometry, Denver, CO, 2008.

Seattle TREC Center

Publications

1. Abrahamson P, King I, Bess Sorensen B, Potter J, Lampe J, Yasui Y, Ulrich C, McTiernan A. No effect of exercise on colon mucosal prostaglandin concentrations: A 12-month randomized controlled trial. *Cancer Epid Biomarkers Prev.* 2007;16(11): 2351-6.

2. Abrahamson PE, Tworoger SS, Aiello EJ, Bernstein L, Ulrich CM, Gilliland FD, Stancyk FZ, Baumgartner R, Baumgartner K, Sorensen B, Ballard-Barbash R, McTiernan A. Association between CYP17, CYP1B1, COMT, and SHBG polymorphisms and serum sex hormones in postmenopausal breast cancer survivors. *Breast Cancer Res Treat.* 2007;105(1):45-54.

3. Aiello EJ, Yasui Y, Tworoger SS, Ulrich CM, Potter JD, Bowen D, Irwin M, Stanczyk F, McTiernan A. Associations among circulating sex hormones, insulin-like growth factor, lipids, and breast density in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2005; 14(6):1411-7.

4. Alfano CM, McGregor BA, Kuniyuki A, Reeve BB, Bowen DJ, Baumgartner KB, Bernstein L, Ballard-Barbash R, Malone K, Ganz PA, McTiernan A. Psychometric properties of a tool for measuring hormone-related symptoms in breast cancer survivors. *PsychoOncology.* 2006;15(11):985-1000.

5. Alfano CM, McGregor BA, Kuniyuki A, Reeve B, Bowen DJ, Smith AW, Baumgartner K, Bernstein L, Ballard-Barbash R, Malone K, Ganz P, McTiernan A. Psychometric evaluation of the Brief Cancer Impact Assessment among breast cancer survivors. *Oncology.* 2006;70:190-202.

6. Alfano CM, Smith AW, Irwin ML, Bowen DJ, Sorensen B, Reeve BB, Meeske KA, Bernstein L, Baumgartner KB, Ballard-Barbash R, Malone KE, McTiernan A. Physical activity, long-term symptoms, and physical health-related quality of life among breast cancer survivors: A prospective analysis. *J Cancer Surviv.* 2007;1:116-28.

7. Barnett A, McGinley JM, Brick L, Hester L, Thompson HJ. Utilization of high resolution digital image acquisition to investigate mammary carcinogenesis in the rat. *Breast Cancer Res.*

8. Bowen DJ, Fesinmeyer MD, Yasui Y, Tworoger SS, Ulrich CM, Irwin ML, Rudolph RE, LaCroix KL, Schwartz RR, McTiernan A. Effects of physical activity on quality of life in sedentary middle aged women. *Int J Nutr Phys Act Behav.* 2006;3:34.

9. Boynton A, Neuhouser ML, Sorensen B, McTiernan A, Ulrich CM. Predictors of diet quality among postmenopausal women. *J Am Diet Assoc.* 2008; 108(1):125-30.

10. Boynton A, Neuhouser ML, Wener MH, Wood B, Sorensen B, Chen-Levy Z, Kirk EA, Yasui Y, LaCroix K, McTiernan A, Ulrich CM. Associations between healthy eating patterns and immune function or inflammation in overweight or obese postmenopausal women. *Am J Clin Nutr.* 2007;86(5):1445-55.

11. Campbell KL, Campbell PT, Ulrich CM, Wener MW, Alfano CM, Foster-Schubert KE, Rudolph RE, Potter JD, McTiernan A. Effect of a 12-month randomized controlled trial of exercise on C-reactive protein among men and women. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(7):1714-8.

12. Campbell KL, Makar KW, Kratz M, Foster-Schubert KE, McTiernan A, Ulrich CM. A pilot project of sampling subcutaneous adipose tissue to examine biomarkers of cancer risk. *Cancer Prev Res.* In press.

13. Campbell KL, McTiernan A. Exercise and biomarkers for cancer prevention studies. *J Nutr.* 2007;137(1):161S-9S.

14. Campbell KL, McTiernan A, Li SS, Sorensen BE, Yasui Y, Lampe JW, King IB, Ulrich CM, Rudolph RE, Irwin ML, Surawicz C, Ayub K, Potter JD, Lampe PD. Effect of a 12-month exercise intervention on apoptotic regulating proteins Bax and Bcl-2 in colon crypts: A randomized controlled trial. *Cancer Epid Biomarkers Prev.* 2007;16(9):1767-74.

15. Campbell PT, Wener MH, Sorensen B, Wood B, Chen-Levy Z, Potter JD, McTiernan A, Ulrich CM. Effect of exercise on in vitro immune function: A 12-month randomized, controlled trial among postmenopausal women. *J Appl Physiol.* 2008;104(6):1648-55.

16. Cauley J, Margolis K, McTiernan A, Vitolins M, Furberg C, Bauer D, LaCroix A, Chlebowski R. HMG co-A reductase inhibitor (statin) use and the risk of breast cancer in the Women's Health Initiative Observational Study. *J Natl Cancer Inst.* 2006;98:700-7.

17. Cheblowski R, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, Nolan NC, Paskett ED, McTiernan A, Hubbell FA, Adams-Campbell LL, Prentice R. Ethnicity and breast cancer: Factors influencing differences in incidence and outcome. *J Natl Cancer Inst.* 2005;97:439-48.

18. Chia VM, Newcomb PA, Lampe JW, White EJ, Mandelson MT, McTiernan A, Potter JD. Leptin concentrations, leptin receptor polymorphisms, and colorectal adenoma risk. *Cancer Epidemiol Biomarkers Prev.* 2007;16:2697-703.

19. Chubak J, McTiernan A, Sorensen B, Wener MH, Yasui Y, Velasquez M, Wood B, Rajan KB, Wetmore CM, Potter JD, Ulrich CM. Moderate-intensity exercise reduces the incidence of colds among postmenopausal women. *Am J Med.* 2006;119(11):937-42.

20. Chubak J, Tworoger SS, Yasui Y, Ulrich CM, Stanczyk FZ, McTiernan A. Associations between reproductive and menstrual factors and postmenopausal androgen concentrations. *J Womens Health (Larchmt).* 2005; 14:704-12.

21. Chubak J, Ulrich CM, Tworoger SS, Sorensen B, Yasui Y, Irwin ML, Stanczyk FZ, Potter JD, McTiernan A. Effect of exercise on bone density and lean mass in postmenopausal women. *Med Sci Sports Exerc.* 2006;38(7):1236-44.

22. Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, Grant B, McTiernan A, Rock CL, Thompson C, Gansler T, Andrews KS. The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Survivors. *CA Cancer J Clin.* 2006;56(6):323-53.

23. Duffy C, Assaf AL, Cyr M, Burkholder G, Coccio L, Rohan T, McTiernan A, Paskett E, Lane D, Chetty VK. Alcohol and folate intake and breast cancer risk in the WHI Observational Study. *Breast Cancer Res Treat.* In press.

24. Fan J, McKean-Cowdin R, Bernstein L, Stanczyk FZ, Ballard-Barbash R, McTiernan A, Baumgartner R, Gilliland F. An association between a common variant (G972R) in the IRS-1 gene and sex hormone levels in post-menopausal breast cancer survivors. *Breast Cancer Res Treat.* 2006;99(3):323-31.

25. Foster-Schubert KE, McTiernan A, Frayo RS, Schwartz RS, Rajan KB, Yasui Y, Tworoger SS, Cummings DE. Human plasma ghrelin levels increase during a one-year exercise program. *J Clin Endocrinol Metab.* 2005; 90(2):820-5.

26. Frank LL, Rajan KB, Yasui Y, Tworoger SS, Ulrich CM, McTiernan A. Effects of physical activity on metabolic risk variables in overweight postmenopausal women: A randomized clinical trial. *Obes Res.* 2005;13:615-25.

27. Hall KL, Stokols D, Moser RP, Taylor BK, Thornquist M, Nebeling L, Ehret C, Barnett M, McTiernan A, Berger NA, Goran M, Jeffery R. The collaboration readiness of transdisciplinary research teams and centers: Findings from the National Cancer Institute TREC year-one evaluation study. *Am J Prev Med.* 2008; 35(2 Suppl):S161-72.

28. Hawk ET, Greenwood A, Gritz ER, McTiernan A, Sellers T, Hursting SD, Leischow S, Grad O, for the Translational Research Working Group. The Translational Research Working Group developmental pathway for lifestyle alterations. *Clin Cancer Res.* 2008;14:5707-13.

29. Hawkins V, Foster-Schubert K, Chubak J, Sorensen B, Ulrich CM, Stancyzk FZ, Plymate S, Stanford J, White E, Potter JD, McTiernan A. Effect of exercise on serum sex hormones in men: A 12-month randomized clinical trial. *Med Sci Sports Exerc.* 2008;40(2):223-33.

30. Irwin ML, Aiello E, McTiernan A, Baumgartner R, Baumgartner KB, Bernstein L, Gilliland F, Ballard-Barbash R. Pre-diagnosis physical activity and mammographic density in breast cancer survivors. *Breast Cancer Res Treat.* 2006;95(2):171-8.

31. Irwin ML, Aiello E, McTiernan A, Bernstein L, Gilliland F, Baumgartner RN, Baumgartner KB, Ballard-Barbash R. Physical activity, body mass index and mammographic density in post-menopausal breast cancer survivors. *J Clin Oncol.* 2007;25(9):1061-6.

32. Irwin ML, McTiernan A, Baumgartner R, Baumgartner K, Bernstein L, Gilliland FD, Ballard-Barbash R. Changes in body fat and weight after a breast cancer diagnosis: Influence of demographic, prognostic and lifestyle factors. *J Clin Oncol.* 2005;23(4):774-82.

33. Irwin M, McTiernan A, Bernstein L, Gilliland F, Baumgartner R, Baumgartner K, Ballard-Barbash R. Relationship of obesity and physical activity with c-peptide, leptin, and insulin-like growth factors in breast cancer survivors. *Cancer Epidemiol Biomarkers Prev.* 2005;14(12):2881-8.

34. Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, Baumgartner RN, Baumgartner KB, Bernstein L. Association of pre- and post-diagnosis physical activity with mortality in breast cancer survivors: The Health Eating Activity and Lifestyle (HEAL) Study. *J Clin Oncol.* 2008;26:3958-64.

35. Jiang W, McGinley JM, Zhu Z, Thompson HJ. Targeting mitochondrial dysfunction for the prevention of mammary carcinogenesis. *Cancer Epidemiol Biomarkers Prev.* In preparation.

36. Jiang W, Zhu Z, Thompson HJ. Dietary energy restriction modulates the activity of AMP-activated protein kinase, Akt, and mammalian target of rapamycin in mammary carcinomas, mammary gland, and liver. *Cancer Res.* 2008;68(13):5492-9.

37. Jiang W, Zhu Z, Thompson HJ. Association of myokine production during wheel running with tissue levels of interleukin-6 and the carcinogenic response in the mammary gland. *J Appl Physiol.* In preparation.

38. Jiang W, Zhu Z, Thompson HJ. Pathways of cell death induction in mammary carcinomas by wheel running: Apoptosis versus autophagy. *Carcinogenesis.* In preparation.

39. Kushi LH, Byers T, Doyle C, Bandera EV, McCullough M, McTiernan A, Gansler T, Andrews KS, Thun MJ. American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin.* 2006;56(5):254-81.

40. Littman AJ, Vittielo MV, Foster-Schubert K, Ulrich CM, Tworoger SS, Potter JD, Weigle DS, McTiernan A. Sleep, ghrelin, leptin, and changes in body weight during a 1-year moderate-intensity physical activity intervention. *Int J Obesity.* 2007; 31(3):466-75.

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66. Thompson HJ. Oxidative DNA damage and cancer risk assessment. *J Nutr.* 2006;136:2693S-4S.

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72. Thompson HJ, Jiang W, Zhu Z. AMP-activated protein kinase, protein kinase B and mammalian target of rapamycin: An integrated signaling network responsive to energy balance. *J Nutr.* In preparation.

73. Thompson HJ, McGinley JM, Jiang W, Zhu Z. Autophagy and the prevention of mammary carcinogenesis by dietary energy restriction. *Cancer Res.* In preparation.

74. Thompson HJ, McGinley JN, Zhu Z, Jiang W. Effect of physical activity on plasma concentrations of sex steroid hormones and on the estrogen and progesterone status of induced mammary carcinomas. *Cancer Lett.* Under review.

75. Thompson HJ, Neuhouser M, Lampe J, Zhu Z, Jiang W. Glycemic load: Its impact on carcinogenesis and candidate mechanisms. *J Natl Cancer Inst.* In preparation.

76. Thompson HJ, Neil ES, Sells JL, McGinley JN, Jiang W, Zhu Z. Effects of the duration of vigorous physical activity on mammary carcinogenesis: Evidence of a hormetic response. *Carcinogenesis.* Under revision.

77. Thompson HJ, Zhu Z, Jiang W. How does physical activity inhibit mammary carcinogenesis independent of its effects on energy balance. *IUBMB Life.* In press.

78. Thompson HJ, Zhu Z, Jiang W. Methyl-nitrosourea induced mammary carcinogenesis: A model for mTOR network mediated breast cancer. *J Breast Cancer Res.* In preparation.

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84. Wayne S, Neuhouser ML, Ulrich CM, Koprowski C, Wiggins C, Baumgartner KB, Bernstein L, Baumgartner RN, Gilliland FD, McTiernan A, Ballard-Barbash R. Association between alcohol intake and serum sex hormones and peptides differs by tamoxifen use in breast cancer survivors. *Cancer Epidemiol Biomarkers Prev.* 2008;17(11):3224-32.

85. Weiqin J, Zongjian Z, Thompson HJ. In vitro and in vivo studies of the regulation of the AMP-activated protein kinase, protein kinase B, and mammalian target of rapamycin signaling network by energy restriction mimetic agent 2-deoxyglucose. *Mol Carcinog.* 2008.

86. Whisnant SA, Beresford SAA, Henderson JA, Patrick D, Xiao L, McTiernan A. Move and Moderate in Balance (Move'M) worksite study: Are diet, physical activity, and body mass index associated with quality of life and productivity? Submitted.

87. Williams L, Ulrich CM, Larson T, Wener MH, Wood B, Campbell PT, Potter J, McTiernan A, De Roos AJ. Proximity to traffic in relation to inflammation and immune function among women in the Seattle area. *Environ Health Perspect.* In press.

88. Zhu Z, Jiang W, McGinley JN, Price JM, Gao B, Thompson HJ. Effects of dietary energy restriction on gene regulation in mammary epithelial cells. *Cancer Res.* 2007;67:12018-25.

89. Zhu Z, Jiang W, McGinley JN, Thompson HJ. 2-Deoxyglucose as an energy restriction mimetic agent: Effects on mammary carcinogenesis and on mammary tumor cell growth in vitro. *Cancer Res.* 2005;65:7023-30.

90. Zhu Z, Jiang W, McGinley JM, Thompson HJ. Inhibition of chemically induced mammary carcinogenesis by metformin. *Carcinogenesis.* In preparation.

91. Zhu Z, Jiang W, Sells JL, Neil ES, McGinley JN, Thompson HJ. Effect of non-motorized wheel running on mammary carcinogenesis: Circulating biomarkers, cellular processes, and molecular mechanisms in rats. *Cancer Epidemiol Biomarkers Prev.* In press.

92. Zhu Z, Jiang W, Thompson HJ. Identification of plasma biomarkers modulated by physical activity and that predict the carcinogenic response in the mammary gland. *Breast Cancer Res.* Submitted.

93. Zhu Z, Jiang W, Thompson HJ. Effects of different planes of energy nutrition on factors associated with cancer risk. *Nutr Cancer.* Revision pending decision.

94. Zhu Z, Jiang W, Thompson HJ. Reduction in plasma cytokines associated with wheel running intensity and duration. *Cancer Lett.* In preparation.

Presentations

1. Beresford S. *The role of human epidemiological studies in identifying hazards from chemical contaminants in food.* Invited presentation at Challenges in Managing Food-Derived Risk, Institute of Medicine: Food Forum/Food and Nutrition Board Workshop, December 2005.

2. Beresford S. *WHI Dietary Modification Trial: Colorectal cancer.* Presented at the WHI Legacy to Future Generations of Women Conference, Bethesda, MD, February 2006.

3. Beresford S. *WHI Dietary Modification Trial: Colorectal cancer and other endpoints.* Presented at the 79th Annual Meeting of the American Epidemiological Society, Berkeley, CA, March 2006.

4. Beresford S. *The PACE Study: Promoting Activity and Changes in Eating.* Presented at the Fifth Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Boston, MA, July 2006.

5. Beresford S. *The Women's Health Initiative: Main results.* Invited presentation to the Network of Perinatal Health Centres of the Buenos Aires Metropolitan Area and the Clinical Effectiveness Institute of the University of Buenos Aires, Argentina, August 2006.

6. Beresford S. *The Women's Health Initiative dietary results and clinical outcomes: Colorectal cancer and cardiovascular disease.* Presented at the 89th Food and Nutrition Conference and Expo of the American Dietetic Association, Honolulu, HI, September 2006.

7. Beresford S. *Low fat eating pattern intervention and risk of colorectal cancer in postmenopausal women: The WHI randomized controlled Dietary Modification Trial.* Presented at the 134th Annual Meeting and Exposition of the American Public Health Association, Boston, MA, November 2006.

8. Beresford S. *Taking the ENVIRONMENT into account: A worksite perspective.* Invited presentation at the Cross-Interdisciplinary Science, Health Promotion, and Disease Prevention Meeting, Pasadena, CA, May 2007.

9. Beresford S. *Recruiting small blue collar worksites for behavior change trial: The Move 'M Study.* Presented at the Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Oslo, Norway, June 2007.

10. Beresford S. *Using employee advisory boards for obesity prevention in small and medium-sized businesses.* Invited presentation at the American Heart Association Scientific Sessions, New Orleans, LA, November 2007.

11. Beresford S. *Folic acid fortification: Reflections on the implementation of a public health intervention.* Presented at the 81st Annual Meeting of the American Epidemiological Society, Pittsburgh, PA, March 2008.

12. Beresford S. *Social and behavioral factors associated with life satisfaction among Japanese elders in the United States.* Invited presentation at the Asian Chinese Quality of Life Conference, Guangzhou, China, May 2008.

13. Beresford S. *Low-fat dietary pattern and health-related quality of life: The WHI randomized controlled DM trial.* Invited presentation at the 15th Annual Conference of the International Society for Quality of Life Research, Montevideo, Uruguay, October 2008.

14. Lampe JW. *Characterizing diadem-ing-metabolizing phenotypes in population-based studies.* Presented at the Second International Conference on Polyphones and Health, Davis, CA, October 4-7, 2005.

15. Lampe JW. *Inter-individual differences in photochemical metabolism and disposition.* Presented at the Fourth Annual American Association for Cancer Research International Conference on Frontiers in Cancer Prevention Research, Baltimore, MD, October 30-November 2, 2005.

16. Lampe JW. *Interindividual differences in response to cruciferous vegetable diets: Implications for cancer risk.* Presented at the 97th Annual Meeting of the American Association for Cancer Research, Washington, DC, April 1-5, 2006.

17. Lampe JW. *Vegetable diets and your cancer risk: Implications of differences in response to vegetable diets.* Seminar presented to the Clinical Nutrition Research Unit, University of Washington, Seattle, WA, April 14, 2006.

18. Lampe JW. *Diet, genetic polymorphisms, detoxification, and health risks.* Presented at the 13th International Symposium on Functional Medicine, Tampa, FL, April 19-22, 2006.

19. Lampe JW. *Exploring daidzein-metabolizing phenotypes in human studies.* Invited seminar presented at the University of Ghent, Belgium, April 27, 2006.

20. Lampe JW. *Genotypic differences in response to diet: Implications for cancer risk.* Presented at Nutrigenomics: New Perspectives and Applications, Korea Conference on Innovative Science and Technology, Muju, Korea, July 20-22, 2006.

21. Lampe JW. *Effects of vegetable and fruit supplementation: Omics in controlled feeding studies.* Presented at NuGO Week, European Nutrigenomics Organisation, Oxford, UK, September 12-15, 2006.

22. Lampe JW. *Dietary modulation of UDP-glucuronosyltransferases in humans.* Presented at Diet and Optimum Health, Portland, OR, May 16-19, 2007.

23. Lampe JW. *Evaluating effects of phytochemicals in humans: Controlled feeding studies at Fred Hutchinson Cancer Research Center.* Invited seminar presented at the University of Ghent, Belgium, May 24, 2007.

24. Lampe JW. *Lignan excretion and uterine fibroid risk in young to middle-aged women in the United States.* Presented at the International Conference on Lignans, Alkylresorcinols, and Health, Helsinki, Finland, June 7-9, 2007.

25. Lampe JW. *Dietary modulation of UDP-glucuronosyltransferases in humans: Effects of genetics.* Invited seminar for the Department of Food Science and Nutrition, University of Minnesota, St. Paul, MN, October 9, 2007.

26. Lampe JW. *Phytoestrogens: Interindividual variation in their metabolism and impact on biologic response.* Presented at the Third International Conference on Polyphenols and Health, Kyoto, Japan, November 28, 2007.

27. Lampe JW. *Dietary modulation of UDP-glucuronosyltransferases in humans: Effects of genetics.* Invited seminar for the Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, Canada, December 11, 2007.

28. Lampe JW. *Interrelationship between soy isoflavone-metabolizing phenotypes and human genetics.* Presented at the National Institutes of Health Conference on Gastrointestinal Microbiota and Advances in Prebiotic and Probiotic Research, Rockville, MD, December 11-12, 2007.

29. Lampe JW. *Should you eat your broccoli? Human variation in response to phytochemical exposure: Impact of polymorphic biotransformation enzymes.* Presented as part of the San Antonio Cancer Institute Seminar Series, San Antonio, TX, January 17, 2008.

30. Lampe JW. *Interindividual differences in response to plant-based diets: Implications for cancer risk* and *Is isoflavone metabolism the key to the efficacy of soy foods?* Presented at the Fifth International Congress on Vegetarian Nutrition, Loma Linda, CA, March 4-6, 2008.

31. Lampe JW. *Gut microbial metabolism of dietary constituents: Implications for cancer prevention.* Presented at the Experimental Biology Annual Meeting Special Conference on Functional Foods for Health Promotion: Microbes and Health, San Diego, CA, April 5, 2008.

32. Lampe JW. *View to the future: Applying nutrigenomic approaches towards understanding individual differences in diet and cancer risk.* Presented at the Experimental Biology Annual Meeting, San Diego, CA, April 5-9, 2008.

33. Lampe JW. *Vegetables and genetics: Feeding studies in cancer prevention.* Presented at the Fruit and Vegetable Summit, Paris, France, May 28-30, 2008.

34. Lampe JW. *Plasma isoflavones and fibrocystic breast conditions and breast cancer.* Presented at the Fifth International Conference on Soy and Health, Ghent, Belgium, June 2-3, 2008.

35. Lampe JW. *Dietary modulation of biotransformation enzymes in controlled feeding trials: Effects of genetics.* Alberta Heritage Foundation for Medical Research Visiting Scholar Lecture, presented to the Department of Population Health Research, Alberta Cancer Board, Calgary, Alberta, Canada, June 19, 2008.

36. McTiernan A. *Exercise and cancer prevention.* Presented at Rockefeller University, New York, NY, September 2005.

37. McTiernan A. *Open forum of breast health.* Presented at Mexico City, Mexico, October 2005.

38. McTiernan A. *Breast fitness: Exercise for breast cancer patients and survivors.* Presented at the Cancer Wellness Center, Northbrook, IL, November 2005.

39. McTiernan A. *Obesity in breast cancer patients.* Presented at the School of Breast Oncology, Atlanta GA, November 2005.

40. McTiernan A. *Insulin resistance syndrome and cancer risk.* Presented at the International Conference on Metabolic Syndrome, San Francisco, CA, November 2005.

41. McTiernan A. *Selected major findings from the OS results: Breast cancer.* Presented at the Women's Health Initiative Conference, Bethesda, MD, February 2006.

42. McTiernan A. *Intermediate endpoints in energy balance and physical activity trials.* Presented at the NCI Workshop on State of the Evidence for a Weight Control Trial to Prevent Breast Cancer, March 2006.

43. McTiernan A. *Physical activity and cancer recurrence and survival.* Presented at the Physical Activity Across the Cancer Continuum symposium, Centers for Disease Control and Prevention International Congress on Physical Activity and Public Health, Atlanta, GA, April 2006.

44. McTiernan A. *Exercise, estrogens, and breast cancer: Physical activity trials.* Presented to the American College of Sports Medicine, May 2006.

45. McTiernan A. *Exercise and nutrition in chemoprevention.* Presented at the World Cancer Research Fund/ American Institute for Cancer Research International Research Conference, Washington, DC, July 2006.

46. McTiernan A. *Exercise and cancer prevention.* Presented at the National University of Singapore, Singapore, July 2006.

47. McTiernan A. *Breast cancer prevention; Lifestyle, diet, and breast cancer;* and *Lifestyle changes may reduce the risk of recurrence.* Presented at the Fifth Annual Meeting of the Mexican Association of Breast Diseases, Leon, Mexico, August 2006.

48. McTiernan A. *WHI and breast cancer.* Presented to the Seattle Gynecological Society, Seattle, WA, September 2006.

49. McTiernan A. *Physical activity, weight control, and cancer prevention.* Presented at the Dana-Farber Cancer Center Chinning Laboratory and Harvard School of Public Health Seminar Series, October 2006.

50. McTiernan A. *Obesity in breast cancer patients.* Presented to the School of Breast Oncology, Atlanta, GA, November 2006.

51. McTiernan A. *Energy balance and cancer: Human intervention studies.* Presented to the NCI Energy Balance Working Group, Bethesda, MD, January 2007.

52. McTiernan A. *Overweight, obesity, and sedentary lifestyle in breast cancer prognosis.* Presented at Interdisciplinary Science, Health Promotion, and Disease Prevention, Pasadena, CA, May 2, 2007.

53. McTiernan A. *Transdisciplinary research to elucidate the pathways linking components of energy balance to the cancer process.* Presented at the Transatlantic Research and Innovation Symposium, Research Triangle Park, NC, May 3, 2007.

54. McTiernan A. *Obesity, physical activity, and breast cancer.* Presented to the University of Washington Clinical Nutrition Research Unit, May 11, 2007.

55. McTiernan A. *Women's Health Initiative clinical trials.* Presented at the Northwestern University Clinical Research Educational Conference, Chicago, IL, May 18, 2007.

56. McTiernan A. *Exercise and weight loss in women and men.* Presented to the Northwestern University Department of Preventive Medicine, Chicago, IL, May 18, 2007.

57. McTiernan A. *Exercise and cancer prevention* (and chair of Exercise and Cancer Prevention and Prognosis session). Presented at FASEB Energy Balance, Body Fat, and Disease, Indian Wells, CA, August 2007.

58. McTiernan A. *Overweight, obesity, physical activity, and breast cancer prevention.* Presented at MD Anderson Cancer Prevention Grand Rounds, Houston, TX, September 2007.

59. McTiernan A. *Obesity, weight loss, and physical activity for cancer patients and survivors.* Presented as part of the MD Anderson Integrative Medicine Program Lecture Series, Houston, TX, September 2007.

60. McTiernan A. *Primary prevention of breast cancer: Lifestyle changes, diet, Western lifestyle.* Presented at Breast Health Global Initiative. Budapest, Hungary, October 2007.

61. McTiernan A. *Obesity in breast cancer patients.* Presented at the School of Breast Oncology, Atlanta, GA, November 2007.

62. McTiernan A. *Breast cancer: Women at risk and new strategies for prevention.* Presented to the Practicing Clinicians Exchange, San Francisco, CA, November 2007.

63. McTiernan A. *Exercise effect on inflammation and other cancer biomarkers.* Presented to the Southeast Chapter of the American College of Sports Medicine, Birmingham, AL, February 2008.

64. McTiernan A. *Exercise and body composition change effects on sex hormones in postmenopausal women.* Presented at the American Association for Cancer Research-TREC Markers and Mediators Meeting, Virginia, February 2008.

65. McTiernan A. *Obesity in breast cancer risk and prognosis.* Presented at Case Western Reserve University, Cleveland, OH, March 2008.

66. McTiernan A. *Exercise interventions in breast cancer prevention and outcomes.* Presented in Cleveland, OH, March 2008.

67. McTiernan A. *TREC talk.* Presented at the Cancer Prevention and Research Center Retreat, Coeur d'Alene, ID, March 2008.

68. McTiernan A. *Fitness vs. fatness: Evidence from epidemiologic and intervention studies on the separate and combined effects of physical activity and obesity on cancer risk.* Presented at the International Physical Activity Meeting, Amsterdam, The Netherlands, April 2008.

69. McTiernan A. *Influence of exercise on immune function: Possible link to breast cancer.* Presented to the American College of Sports Medicine, Indianapolis, IN, May 2008.

70. McTiernan A. *Breast cancer prevention and survivorship through lifestyle and chemoprevention.* Presented at the Memorial Sloan-Kettering Cancer Center, New York, NY, September 2008.

71. McTiernan A. *Early detection, diet, physical activity, and cancer.* Presented at the Women in High Places Meeting, Riyadh, Saudi Arabia, October 2008.

72. McTiernan A. *Diet and breast cancer.* Presented at the Saudi Arabian Cancer Conference, Riyadh, Saudi Arabia, October 2008.

73. McTiernan A. *Physical activity and weight control in breast cancer prevention and prognosis.* Presented at Reducing the Risk, Advancing the Cure: New Recommendations, New Options for Primary Care Providers and Survivors, Alaska (televised from Seattle), October 2008.

74. McTiernan A. *Lessons learned from real-life lifestyle interventions.* Presented to the Obesity Society, Phoenix, AZ, October 2008.

75. McTiernan A. *Breast cancer: Weight loss and exercise.* Presented to the School of Breast Oncology, Atlanta, GA, November 2008.

76. McTiernan A. *Fitness vs. fatness in breast cancer risk and prognosis.* Presented at Frontiers of Cancer Prevention, Washington, DC, November 2008.

77. Thompson H. *Energy status and cancer risk.* Invited presentation to the Energetics and Cancer Task Force, National Institutes of Health, Washington, DC, January 18, 2007.

78. Thompson H. *Energy sensing pathways and cancer risk.* Invited presentation at the Fred Hutchinson Cancer Research Center, Seattle, WA, February 8, 2007.

79. Thompson H. *Energy balance and the development of cancer.* Invited presentation at the University of Texas at San Antonio, TX, February 15, 2007.

80. Thompson H. *Physical activity and cancer risk.* Invited presentation at the Ohio State University Cancer Center Annual Meeting, Columbus, OH, February 23, 2007.

81. Thompson H. *Energetics and cancer.* Invited lecture for the Endowed Lectureship Series, University of Texas at Austin, TX, March 20-23, 2007.

82. Thompson H. *Energy balance and breast cancer risk.* Invited platform presentation at the Annual Meeting of the American Association for Cancer Research, April 14-18, 2007.

83. Thompson H. *Exercise and breast cancer risk.* Invited symposium platform presentation at the Annual Meeting of the Society for Experimental Biology, April 28-May 2, 2007.

84. Thompson H. *Physical activity and cancer risk.* Invited platform presentation at the World Cancer Research Fund/American Institute for Cancer Research World Guidelines Launch Conference, November 2, 2007.

85. Thompson H. *Dietary energy intake, exercise, and energy sensing in the prevention of cancer.* Invited presentation for the Frontiers in Energy Sensing Workshop, National Cancer Institute, Washington, DC, March 12, 2008.

86. Thompson H. *The insider's energetics view: Exercising new options to prevent cancer.* Presented to the Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, WA, April 5, 2008.

87. Thompson H. *Glycemic load: Its impact on carcinogenesis and candidate mechanisms* and *Physical activity: Cellular and molecular leads in understanding.* Presented at the TREC Centers Scientific Meeting, Fred Hutchinson Cancer Research Center, Seattle, WA, April 6, 2008.

88. Thompson H. *Dietary energy intake, exercise, and energy sensing in the regulation of carcinogenesis.* Invited presentation at Case Western Reserve University, Cleveland, OH, April 23, 2008.

89. Thompson H. *The role of energy sensing in protecting against cancer.* Invited presentation at Pennsylvania State University, Hershey, PA, July 29, 2008.

90. Ulrich C. *Folate homeostasis: Epidemiology, genetics, and modeling.* Plenary session presentation at European Nutritional Genomics Week, Tuscany, Italy, September 2005.

91. Ulrich C. *Studies of survivorship and pharmacogenetics: Opportunities and obstacles.* Presented at the Special Conference on New Developments in the Epidemiology of Cancer Prognosis, American Association for Cancer Research, January 2006.

92. Ulrich C. *Modeling folate, one-carbon metabolism, and DNA methylation.* Presented at Environmental Health Sciences Research Day, University of Washington, Seattle, WA, May 2006.

93. Ulrich C. Colloquium speaker at the German Cancer Research Center, Heidelberg, Germany, July 2006.

94. Ulrich C. Speaker at the 10th Karlsruhe Nutrition Congress, Federal Research Centre for Nutrition and Food, Karlsruhe, Germany, October 2006.

95. Ulrich C. *Folate and colon cancer: Epi, genetics, and epigenetics.* Presented at the American Association for Cancer Research Cancer Prevention Conference, Baltimore, MD, November 2006.

96. Ulrich C. *The two faces of folate and folate genetics in colorectal cancer risk and prognosis.* Presented at the Annual Meeting of the American Association for Cancer Research, April 2007.

97. Ulrich C. *Approaching colon cancer on candidate pathways: Folate and inflammation*. Presented at Approaches to Complex Pathways in Molecular Epidemiology, American Association for Cancer Research Special Conference, May 2007.

98. Ulrich C. *Folate in cancer treatment and prognosis: A multi-omic approach.* Presented at Molecular Diagnostics in Cancer Therapeutic Development: Maximizing Opportunities for Personalized Treatment, American Association for Cancer Research Special Conference, September 2007.

99. Ulrich C. *Modeling folate, one-carbon metabolism, and DNA methylation.* Presented at Diet, Epigenetic Events, and Cancer Prevention, National Institutes of Health Special Conference, September 2007.

100. Ulrich C. *Vegetables and fruits: The controversy explored* and *Folate and colorectal cancer: Timing is everything.* Presented at the Symposium on Diet and Cancer (Masterclass), Wageningen, The Netherlands, November 2007.

101. Ulrich C. *Pharmacogenetics of NSAIDs and folate in colorectal cancer: Where to next?* Presented at a Meet-the-Expert Sunrise Session, American Association for Cancer Research Cancer Prevention Conference, Philadelphia, PA, January 2008.

102. Ulrich C. *Folate and cancer prevention.* Presented to the University of Washington, Gastrointestinal Division Journal Club, January 2008.

103. Ulrich C. *Primer on cancer biology and environmental risk factors.* Presented at Advances in Oncology for the Primary Care Clinician: Expert Updates from the Seattle Cancer Care Alliance, Seattle, WA, April 2008.

104. Ulrich C. *Epigenetics and environment: One-carbon metabolism and beyond.* Presented at the Symposium on Epigenetic Responses to the Environment and Cancer, 101st Annual Meeting of the American Association for Cancer Research, San Diego, CA, April 2008.

105. Ulrich C. *Folate and cancer prevention: Is timing everything?* Presented at Diet-Gene Interaction in Human Health and Disease, Third Asia-Pacific Nutrigenomics Conference, Melbourne, Australia, May 2008.

106. Ulrich C. *Epigenetics and environment: One carbon metabolism and beyond.* Presented to the Epigenetics Affinity Group, Fred Hutchinson Cancer Research Center, Seattle, WA, June 2008.

107. Ulrich C. *Learning from the unexpected: Folate, NSAIDs, and genetics in cancer prevention.* Presented at the NCI Cancer Prevention and Control Colloquia, Bethesda, MD, September 2008.

University of Minnesota TREC Center

Publications

1. Allison KC, Crow SJ, Reeves RR, West DS, Foreyt JP, DiLillo VG, Wadden TA, Jeffery RW, Van Dorsten B, Stunkard AJ; Eating Disorders Subgroup of Look AHEAD Research Group. Binge eating disorder and night eating syndrome in adults with type 2 diabetes mellitus. *Obesity.* 2007;15(5):1287-93.

2. Arterburn D, Ichikawa L, Ludman EJ, Operskalski B, Linde JA, Anderson E, Rohde P, Jeffery RW, Simon GE. Validity of clinical body weight measures as substitutes for missing data in a randomized trial. *Obes Res Clin Pract.* In press.

3. Arterburn D, Westbrook EO, Wiese CJ, Ludman EJ, Grossman DC, Fishman PA, Finkelstein EA, Jeffery RW, Drewnowski A. Insurance coverage and incentives for weight loss among adults with the metabolic syndrome. *Obesity.* 2008;2(1):70-6.

4. Baldwin AS, Rothman AJ, Hertel AW, Keenan NK, Jeffery RW. Longitudinal associations between people's cessation-related experiences and their satisfaction with cessation. *Psychol Health.* In press.

5. Bertoni AG, Clark JM, Feeney P, Yanovski SZ, Bantle J, Montgomery B, Safford MM, Herman WH, Haffner S; Look AHEAD Research Group. Suboptimal control of glycemia, blood pressure, and LDL cholesterol in overweight adults with diabetes: The Look AHEAD Study. *J Diabetes Complications.* 2008;22(1):1-9.

6. Davis JN, Nelson MC, Ventura EE, Lytle LA, Goran MI. A brief dietary screener: Appropriate for overweight Latino adolescents? *J Am Diet Assoc.* In press.

7. Dengel DR, Hearst MO, Harmon JH, Forsyth A, Lytle L. Does the built environment relate to the metabolic syndrome in adolescents? *Health Place.* Under review.

8. Flood A, Mitchell N, Jaeb M, Finch EA, Laqua PS, Welsh EM, Hotop A, Langer SL, Levy RL, Jeffery RW. Energy density and weight change in a long-term weight-loss trial. *Obesity.* Under review.

9. French SA, Shimotsu ST, Wall M, Gerlach A. Capturing the spectrum of household food purchasing behavior: A review. *J Am Diet Assoc.* In press.

10. Fuglestad PT, Rothman AJ, Jeffery RW. Getting there and hanging on: The effect of regulatory focus on performance in smoking and weight loss interventions. *Health Psychol.* 2008;27(3 Suppl):S260-70.

11. Fulkerson JA, Nelson MC, Lytle L, Moe S, Heitzler C, Pasch KE. The validation of a home food inventory. *Int J Behav Nutr Phys Act.* 2008; 5(1):55.

12. Gorin AA, Wing RR, Fava JL, Jakicic JM, Jeffery R, West DS, Brelje K, DiLillo VG; Look AHEAD Home Environment Research Group. Weight loss treatment influences untreated spouses and the home environment: Evidence of a ripple effect. *Int J Obes.* 2008;32:1678-84.

13. Hall KL, Stokols D, Moser RP, Taylor BK, Thornquist M, Nebeling L, Ehret C, Barnett M, McTiernan A, Berger NA, Goran M, Jeffery R. The collaboration readiness of transdisciplinary research teams and centers: Findings from the National Cancer Institute TREC year-one evaluation study. *Am J Prev Med.* 2008;35(2S): S161-72.

14. Hearst MO, Lytle L, Pasch K, Heitzler C. Inventory versus checklist approach to school vending and a la carte assessment. *J School Health.* Under review.

15. Hearst MO, Pasch KA, Fulkerson JA, Lytle L. Does weight status influence weight-related beliefs and the consumption of sugar sweetened beverages and fast food purchases in adolescents? *Health Educ J.* In press.

16. Hertel AW, Finch EA, Kelly KM, King C, Lando H, Linde JA, Jeffery RW, Rothman AJ. The impact of expectations and satisfaction on the initiation and maintenance of smoking cessation: An experimental test. *Health Psychol.* 2008;27(3 Suppl): S197-206.

17. Jeffery RW, Finch EA, Linde JA, Simon GE, Ludman EJ, Operskalski BH, Rohde P, Ichikawa L. Does clinical depression affect the accuracy of self-reported height and weight in obese women? *Obesity.* 2008;16(2): 473-5.

18. Jeffery RW, Harnack L. Evidence implicating eating as a primary driver for the obesity epidemic [invited paper]. *Diabetes.* 2007;56:2673-6.

19. Jeffery RW, Levy RL, Langer SL, Welsh EM, Flood AP, Jaeb MA, Laqua PS, Hotop AM, Finch EA. Increasing treatment variety to promote weight loss maintenance: An experimental trial. *J Am Med Assoc.* Under review.

20. Jeffery RW, Linde JA, Simon GE, Ludman EJ, Rohde P, Ichikawa LE. Reported food choices in older women in relation to BMI and depressive symptomatology. *Appetite.* In press.

21. Jeffery RW, Rydell S, Dunn CL, Harnack LJ, Levine AS, Pentel P, Baxter J, Walsh EM. Effects of portion size on chronic energy intake. *Int J Behav Nutr Phys Act.* 2007;4:27.

22. Jeffery RW, Sherwood NE. Is the obesity epidemic exaggerated? No [invited paper]. *Br Med J.* 2008; 336:245.

23. Kubik MY, Lytle LA, Farbaksh K, Moe S, Samuelson A. Food use in middle and high school fundraising: Does policy support healthy practice? Results from a survey of Minnesota school principals. *J Am Diet Assoc.* In press.

24. Linde JA, Jeffery RW, Finch EA, Simon GE, Ludman EJ, Operskalski BH, Ichikawa L, Rohde P. Relation of body mass index to depression and weighing frequency in overweight women. *Prev Med.* 2007;45:75-9.

25. Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: One-year results of the Look AHEAD trial. *Diabetes Care.* 2007;30(6):1374-83.

26. Look AHEAD Writing Group P042 Action for health in diabetes: Recruitment strategies and results for the Look AHEAD study. Under review.

27. Ludman E, Simon G, Ichikawa L, Operskalski B, Arterburn D, Rohde P, Jeffery R, Linde J, Anderson E. Does depression reduce the effectiveness of behavioral weight loss treatment? *Obesity.* Under review.

28. Nelson MC, Lytle LA. Development and evaluation of a brief screener to estimate fast food and beverage consumption among adolescents. *J Am Diet Assoc.* In press.

29. Nelson MC, Lytle LA, Pasch KE. Improving literacy around energy-related issues: The need for a better understanding of the concepts behind energy intake and expenditure among adolescents and their parents. *J Am Diet Assoc.* In press.

30. Nelson MC, Story M, Larson NI, Neumark-Sztainer D, Lytle LA. Emerging adulthood and college-aged youth: An overlooked age for weight-related behavior change. *Obesity.* 2008;16(10):2205-11.

31. O'Dougherty M, Harnack LJ, French SA, Story M, Oakes M, Jeffery RW. Nutrition labeling and value size pricing at fast food restaurants: A consumer perspective. *Am J Health Promot.* 2006;20(4):247-50.

32. Pasch KE, Hearst MO, Nelson MC, Forsyth A, Lytle LA. Alcohol outlets and youth alcohol use: Exposure in suburban area. *Health Place.* In press.

33. Perry CA, Pravetoni M, Teske JA, Aguado C, Erickson DJ, Medrano JF, Luján R, Kotz CM, Wickman K. Predisposition to late-onset obesity in GIRK4 knockout mice. *Proc Natl Acad Sci USA.* 2008;105:8148-53.

34. Ribisl PM, Land W, Jaramillo SA, Jakicic JM, Stewart KJ, Bahnson J, Bright R, Curtis JF, Crow RS, Soberman JE; Look AHEAD Research Group. Exercise capacity and cardiovascular/metabolic characteristics of overweight and obese individuals with type 2 diabetes: The Look AHEAD Clinical Trial. *Diabetes Care.* 2007; 30(10):2679-84.

35. Rohde P, Ichikawa L, Simon GE, Ludman EJ, Linde JA, Jeffery RW, Operskalski BH. Associations of child sexual and physical abuse with obesity and depression in middle-aged women. *Child Abuse Negl.* 2008;32:878-87.

36. Rydell SA, Harnack LJ, Oakes JM, Story M, Jeffery RW, French SA. Why eat at fast food restaurants: Reported reasons among frequent consumers. *J Am Diet Assoc.* In press.

37. Sherwood NE, Welsh E, Jeffery RW, VanWormer J. The Drop It At Last (DIAL) Study: Six months results of a phone-based weight loss trial. *Am J Health Promot.* In press.

38. Simon GE, Ludman EJ, Linde JA, Operskalski BH, Ichikawa L, Rohde P, Finch EA, Jeffery RW. Association between obesity and depression in middle-aged women. *Gen Hosp Psychiatry.* 2008;30:32-9.

39. Sirard JR, Nelson MC, Pereira MA, Lytle LA. Reliability and validity of a physical activity and media equipment inventory. *Int J Behav Nutr Phys Act.* 2008;5:24.

40. Stovitz SD, Pardee PE, Vazquez G, Duval S, Schwimmer JB. Musculoskeletal pain in obese children and adolescents. *Acta Paediatr.* 2008; 4:489-93.

41. Stovitz SD, Pereira MA, Vazquez G, Lytle LA, Himes JH. The interaction of childhood height and childhood BMI in the prediction of young adult BMI. *Obesity.* 2008;16(10):2336-41.

42. Stovitz SD, Schwimmer JB, Martinez, H, Story M. Pediatric obesity: The unique issues in Latino-American male youth. *Am J Prev Med.* 2008; 34(2):153-60.

43. Tate DF, Wing R, Jeffery RW, Sherwood NE. Long-term weight losses associated with prescribing higher physical activity goals: Are higher levels of physical activity protective against weight regain. *Am J Clin Nutr.* 2007; 85:954-9.

44. Templeton D, Kelly A, Steinberger J, Dengel D. Bone mineral content in overweight and normal weight children. *Pediatr Exerc Sci.* Under review.

45. Thieschafer AJ, Hughes JM, Popp KL, Wetzsteon RJ, Kaufman BC, Stovitz SD, Kurzer MS, Petit MA. Bone volumetric density, geometry, and strength in female and male collegiate runners. *Med Sci Sports Exerc.* Under review.

46. Widome R, Neumark-Stzainer D, Haines J, Hannan PJ, Story M. What do you eat when you don't have enough to eat? Eating behaviors and perceptions of food insecure youth. *Am J Pub Health.* In press.

47. Widome R, Rohde, P, Linde J, Ludman E, Jeffrey R. Relationships between depression, smoking, and obesity in middle aged women. *Am J Pub Health.* Under review.

48. Wing RR, Jakicic J, Neiberg R, Lang W, Blair SN, Cooper L, Hill JO, Johnson KC, Lewis CD; Look AHEAD Research Group. Fitness, fatness, and cardiovascular risk factors in type 2 diabetes: Look AHEAD Study. *Med Sci Sports Exerc.* 2007; 39(12):2107-16.

49. Zhang J, Wu Y, Zhang Y, Leroith D, Bernlohr DA, Chen X. The role of lipocalin 2 in the regulation of inflammation in adipocytes and macrophages. *Mol Endocrinol.* 2008; 22(6):1416-26.

Presentations

1. Arikawa A. *Women In Steady Exercise Research (WISER).* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.
2. Arikawa A. *Women In Steady Exercise Research (WISER): Update on study progress.* Presented at the TREC Centers Scientific Meeting, National Cancer Institute, Bethesda, MD, October 2008.
3. Arikawa A, O'Dougherty M, Kaufman B, Kurzer M, Schmitz K. *Exploring behavioral and body composition changes in young women after a 16-week exercise intervention.* Presented at the Sixth Annual Meeting of the International Society of Behavioral Nutrition and Physical Activity, Oslo, Norway, June 2007.
4. Baldwin AS, Rothman AJ, Hertel AW, Keenan NK, Jeffery RW. *Elucidating the factors that longitudinally relate to people's satisfaction with smoking cessation.* Presented at the 26th Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, Washington, DC, March 2007.
5. Baldwin AS, Rothman AJ, Jeffery RW. *What influences satisfaction with behavior change? An examination of the longitudinal associations between people's weight loss experiences and satisfaction.* Presented at the 29th Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, San Diego, CA, March 2008.
6. Crawford D, Ball K, Jeffery R, Salmon J, Roberts R, Timperio A. *Mismatch between perceived and objective measures of physical activity environments.* Presented at the Perceived or Objective Physical Environmental Factors: What Should We Measure? symposium, Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.
7. Dengel DR. *Super-size me: The epidemic of childhood obesity.* Invited seminar presented to Saturday Scholars, University of Minnesota, Minneapolis, MN, September 2005.
8. Dengel DR. *The price of surviving cancer: Effects of chemotherapy and radiation on vascular health.* Webinar presented to the TREC Molecular Pathways Working Group, May 2007.
9. Dengel DR. *Children: A special population.* Keynote lecture presented to the Northland Regional Chapter of the American College of Sports Medicine Annual Fall Meeting, Brookings, SD, October 2007.
10. Dengel DR. *Super sizing our kids: Problems and solutions for childhood obesity.* Invited seminar at the Medtronic Twin Cities Marathon—Target Health and Fitness Expo, Minneapolis, MN, October 2007.
11. Erickson D. *Facilitating transdisciplinary research: Applying advanced statistical methods.* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.
12. Forsyth A. *GIS measurement issues.* Invited presentation at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.
13. Forsyth, A. *The built environment, food, and physical activity: Measurement issues.* Field of Nutrition Seminar presented at Cornell University, Ithaca, NY, September 2008.
14. French SA. *Home food purchase measurement methods: Data from three countries.* Symposium presented at the Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.
15. French SA. *Family-based obesity prevention targeting television, eating, and physical activity: The Take Action Study.* Presented at the Challenges to Obesity Prevention workshop, National Institutes of Health and Nutrition, Tokyo, Japan, August 2008.
16. French SA. *Family-based obesity prevention targeting television, eating, and physical activity: The Take Action Study.* Presented at the TREC Centers Scientific Meeting, National Cancer Institute, Bethesda, MD, October 2008.
17. French SA, Shimotsu ST, Wall M, Gerlach AG. *Household receipts capture grocery and eating out food purchases.* Presented at the Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.
18. Fulkerson JA, Lytle L, Nelson M, Moe S. *The development and validation of a home food inventory that assesses foods implicated in the obesity epidemic.* Presented at the NCI-TREC Centers Initiative symposium at the Sixth Annual Meeting of the International Society of Behavioral Nutrition and Physical Activity, Oslo, Norway, June 2007.
19. Fulkerson JA, Lytle LA, Nelson M, Moe S. *The development and validation of a home food inventory that assesses foods implicated in the obesity epidemic.* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.
20. Jeffery RW. *Prevention and treatment of obesity: Cause for hope or despair.* Invited presentation at Cardiology Grand Rounds, University of Massachusetts, Logan, MA, January 2006.
21. Jeffery RW. *Environment as a modifiable risk factor for health behavior mediated disease* [presenter and symposium organizer]. Presented at Environment as a Modifiable Risk Factor for Health Behavior Mediated Disease, Second North American Congress of Epidemiology, Seattle, WA, June 2006.

22. Jeffery RW. *Obesity prevention: Can it be done and how?* Invited presentation to the President's Cancer Panel on Promoting Healthy Lifestyles to Reduce the Risk of Cancer, University of Minnesota Cancer Center, Minneapolis, MN, September 2006.

23. Jeffery RW. *Obesity prevention research at the University of Minnesota.* Presented at the Joint Scientific Symposium of the Indian Council of Medical Research and the University of Minnesota, New Delhi, India, October 2006.

24. Jeffery RW. *Community approaches to obesity treatment and prevention.* Invited presentation at Nutrition, Activity, Obesity, and Cancer, plenary session at Frontiers in Cancer Prevention Research, Fifth Annual American Association for Cancer Research International Conference, Boston, MA, November 2006.

25. Jeffery RW. *Economic incentives for weight control.* Invited seminar at the Stanford Prevention Research Center, Stanford University School of Medicine, San Francisco, CA, January 2007.

26. Jeffery RW. *Prevention and treatment of obesity.* Invited presentation at the Medtronic Technical Forum, Minneapolis, MN, June 2007.

27. Jeffery RW. *Behavior change research: TREC projects.* Presented at the NCI-TREC Initiative symposium, Annual Scientific Meeting of the Obesity Society, New Orleans, LA, October 2007.

28. Jeffery RW. *Increasing intervention variety to promote weight loss maintenance: An experimental trial.* Presented to the Energy Balance Research Group, University of Minnesota Obesity Prevention Center, Minneapolis, MN, January 2008.

29. Jeffery RW. *Maintenance: Theoretical and empirical concepts.* Presented at the Sustaining Behavior Change in Health Promotion, Diabetes Prevention and Management, and Weight Loss symposium, 29th Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, San Diego, CA, March 2008.

30. Jeffery RW. *Environmental effects on energy balance: An experiment in portion size.* Invited presentation at the Challenges to Obesity Prevention Workshop, National Institutes of Health and Nutrition, Tokyo, Japan, August 2008.

31. Jeffery RW. *Maintenance: Theoretical and empirical concepts.* Presented at the Promoting Sustained Behavior Change to Prevent Disease and Promote Health symposium, 10th International Congress of Behavioral Medicine, Tokyo, Japan, August 2008.

32. Jeffery RW, Langer SL, Welsh EM, Flood AP, Jaeb MA, Laqua PS, Hotop AM, Finch EA, Levy RL. *Effectiveness of a maintenance tailored obesity intervention.* Presented at the 10th International Congress of Behavioral Medicine, Tokyo, Japan, August 2008.

33. Jeffery RW, Langer SL, Welsh EM, Flood AP, Jaeb MA, Laqua PS, Hotop AM, Finch EA, Levy RL. *Effectiveness of a maintenance tailored obesity intervention.* Presented to the Energy Balance Research Group, University of Minnesota Obesity Prevention Center, Minneapolis, MN, October 2008.

34. Jeffery RW, Rydell S, Dunn C, Harnack L, Levine A, Pentel P, Baxter J. *Effects of portion size on chronic energy intake.* Presented at the Portion Sizes: Impact on Food Intake and Starting Point for Interventions symposium, Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.

35. Jeffery RW, Rydell S, Dunn CL, Harnack LJ, Levine AS, Walsh E. *Effects of portion size on body weight.* Presented at the TREC Centers Scientific Meeting, Fred Hutchinson Cancer Research Center, Seattle, WA, June 2006.

36. Kaufman BC, Wetzsteon RJ, Kurzer M, Stovitz SD, Prior JC, Petit MA. *Premenopausal women with short luteal phase length have reduced vBMD, but normal bone bending strength at the tibial midshaft.* Presented at the 29th Annual Meeting of the American Society for Bone and Mineral Research, Honolulu, HI, September 2007.

37. Kikuchi Y, French SA, Shimotsu ST, Suzuki N. *Development of receipt measure to evaluate food purchase behavior in Japan.* Presented at the Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.

38. Kikuchi Y, French SA, Shimotsu ST, Suzuki N. *Development of receipt measure to evaluate food purchase behavior in Japan utilizing food receipts.* Presented at the 10th International Congress of Behavioral Medicine, Tokyo, Japan, August 2008.

39. Kurzer M. *Women In Steady Exercise Research (WISER).* Presented at the TREC Centers Scientific Meeting, Case Western Reserve University, Cleveland, OH, October 2006.

40. Kurzer M. *Exercise and body weight effects on sex hormones and menstrual cycle in premenopausal women.* Presented at Energy Balance and Cancer: Mediators and Mechanisms, American Association for Cancer Research-TREC-NCI Think Tank Conference, Landsdowne, VA, February 2008.

41. Langer SL, Levy RL, Flood A, Jaeb M, Laqua P, Hoptop A, Jeffery R. *Patterns of mood and weight, and predictors of distress among participants in a long-term weight-loss trial.* Presented at the 29th Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, San Diego, CA, March 2008.

42. Levy RL, Langer S, Welsh EM, Flood AP, Jaeb MA, Laqua PS, Hotop AM, Finch EA, Jeffery RW. *Maintenance-tailored treatment improves long-term weight loss.* Presented at Digestive Diseases Week, San Diego, CA, May 2008.

43. Linde JA, Simon GE, Ludman EJ, Ichikawa L, Operskalski B, Arterburn D, Rohde P, Anderson EA, Jeffery RW. *Behavioral weight loss vs. combined weight loss/depression treatment among women with comorbid obesity and depression.* Presented at the 29th Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, San Diego, CA, March 2008.

44. Ludman EJ, Simon G, Ichikawa L, Arterburn D, Operskalski B, Linde J, Jeffery R, Rohde P, Finch E. *The effect of major depression on behavioral weight loss treatment success.* Presented at the 29th Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, San Diego, CA, March 2008.

45. Lytle LA. *Examining the obesity epidemic through youth, family, and young adults.* Presented at the TREC Centers Scientific Meeting, University of Southern California, Pasadena, CA, February 2006.

46. Lytle LA. *School and family influences on children's eating behaviors.* Presented at the Field to Plate Conference, Loire Valley, France, April 2007.

47. Lytle LA. *Reliability and validity of a physical activity and media equipment inventory.* Presented at the TREC Centers Scientific Meeting, University of Southern California, Pasadena, CA, May 2007.

48. Lytle LA. *Validation of Internet-Based Dietary Assessment (VIDA).* Presented at the TREC Centers Scientific Meeting, University of Southern California, Pasadena, CA, May 2007.

49. Lytle LA. *Examining the etiology of youth obesity.* Presented at the University of Florida, Jacksonville, FL, December 2007.

50. Lytle LA. *Examining the etiology of childhood obesity.* Department of Nutrition Seminar, Oslo, Norway, March 2008.

51. Lytle LA. *Examining the etiology of childhood obesity.* Oxford Round Table, Oxford, UK, March 2008.

52. Lytle LA. *Examining the etiology of childhood obesity.* Presented at the EMGO Institute, Medical School of Amsterdam, Amsterdam, The Netherlands, March 2008.

53. Lytle LA, Pasch K, Nelson M. *Examining the relationship between sleep and weight status in a cohort of adolescents: Results from the IDEA study.* Presented at the Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.

54. Moe S, Nelson M, Fulkerson JA, Pasch K, Lytle L. *Psychometric testing of measures to assess the social-ecological environment of obesity.* Presented at the NCI-TREC Centers Initiative symposium, Sixth Annual Meeting of the International Society of Behavioral Nutrition and Physical Activity, Oslo, Norway, June 2007.

55. Nelson M, Davis J, Ventura E, Lytle LA. *Evaluating the reliability and validity of a survey instrument of dietary behaviors among ethnically diverse youth populations.* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.

56. Nelson MC, Pasch KE, Lust K, Story M, Ehlinger E. *Understanding the complex context of emerging adult weight behaviors: A latent class analysis of risk behaviors and lifestyle characteristics.* Presented at the Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.

57. Nelson MC, Pasch KE, Lust K, Story M, Ehlinger E. *Postsecondary settings for young adult obesity prevention: Thinking beyond the 4-year college.* Presented at the Annual Scientific Meeting of the Obesity Society, Phoenix, AZ, October 2008.

58. Nelson MC, Story M. *Characterizing food environments among young adult college youth.* Presented at the TREC Centers Scientific Meeting, Fred Hutchinson Cancer Research Center, Seattle, WA, May 2008.

59. O'Dougherty M. *Women In Steady Exercise Research postscript: Social, cultural, and contextual dimensions of young women's physical activity.* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.

60. O'Dougherty M, Kaufman B, Arikawa A, Schmitz K, Kurzer M. *Physical activity on your own time: Findings from a mixed methods study with young women.* Presented at the Active Living Research Annual Conference, Washington, DC, April 2008.

61. O'Dougherty M, Kurzer M. *Design and progress of the WISER study: Exercise effects on breast cancer risk reduction in young women.* Presented at the 39th Annual Seminar of Obstetrics, Gynecology, and Women's Health, University of Minnesota, Minneapolis, MN, September 2008.

62. Parker ED, Widome R, Pereira M. *Food security and MetS among US adolescents and adults.* Presented at the 21st Annual Meeting of the Society for Epidemiologic Research, Chicago, IL, June 2008.

63. Pasch KE, Nelson MC, Fulkerson J, Moe S, Hearst M, Lytle LA. *The influence of parents' negative weight-related messages on youth's weight satisfaction and dieting behavior.* Presented at the Seventh Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity, Banff, Alberta, Canada, May 2008.

64. Saykally J, Dogan S, Cleary M, Sanders MM. *Expression of the ZEB-1 transcription factor positively correlates with adiposity.* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.

65. Saykally JS, Dogan M, Cleary M, Sanders M. *The estrogen-regulated ZEB1 transcription factor opposes adipogenesis.* Presented at Nuclear Receptors: Steroid Sisters, Keystone Symposium, Whistler, British Columbia, Canada, March 2008.

66. Saykally JN, Sandri B, Sanders MM. *The transcription factor ZEB1 opposes obesity in mice.* Presented at Obesity: Novel Aspects of the Regulation of Body Weight, Keystone Symposium, Banff, Alberta, Canada, January 2009.

67. Shimotsu ST, French SA. *Food receipts and home inventories: Innovations in measuring the home food environment.* Invited seminar at the Department of Nutrition, University of North Carolina, Chapel Hill, NC, January 2007.

68. Shimotsu ST, French SA. *Family-based obesity prevention targeting television, eating, and physical activity: The Take Action Study.* Presented to the Department of Nutrition, Keio University, Tokyo, Japan, September 2008.

69. Shimotsu ST, French SA, Gerlach AF. *A measure of the home food environment.* Presented to the Obesity Research Group, University of Minnesota, Minneapolis, MN, March 2006.

70. Shimotsu ST, French SA, Gerlach AF. *The household food environment: Receipts and household inventories.* Presented at the TREC Centers Scientific Meeting, University of Southern California, Pasadena, CA, May 2007.

71. Shimotsu ST, French SA, Gerlach AF. *The home food environment: Food receipts and household inventories.* Presented at the NCI-TREC Center Initiative symposium, Sixth Annual Meeting of the International Society of Behavioral Nutrition and Physical Activity, Oslo, Norway, June 2007.

72. Shimotsu ST, French SA, Gerlach AF. *Measuring household food purchase behavior: Receipt collection and coding.* Webinar presented to the TREC Nutrition Working Group, March 2008.

73. Shimotsu ST, French SA, Wall M, *Gerlach AF. Utility of receipt measure to evaluate household food purchase behaviors in a sample of US households.* Presented at the 10th International Congress of Behavioral Medicine, Tokyo, Japan, October 2008.

74. Sirard JR, Nelson MC, Pereira MA, Lytle LA. *Reliability and validity of a physical activity and media equipment inventory.* Presented at the NCI-TREC Center Initiative symposium, Sixth Annual Meeting of the International Society of Behavioral Nutrition and Physical Activity, Oslo, Norway, June 2007.

75. Sirard JR, Nelson MC, Pereira MA, Lytle LA. *Validity and reliability of a home environment inventory for physical activity and media equipment.* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.

76. Stovitz SD. *The importance of childhood height in pediatric obesity assessment.* Webinar presented to the TREC Nutrition Working Group, January 2008.

77. Stovitz SD. *The interaction of childhood height and BMI in the prediction of adult BMI and obesity.* Presented as part of the Division of Epidemiology and Community Health Seminar Series, University of Minnesota, Minneapolis, MN, February 2008.

78. Templeton D. *Effects of adolescent obesity and physical inactivity on vascular structure and function in young adulthood.* Presented at the 24th Pediatric Work Physiology Meeting, Tallinn, Estonia, September 2007.

79. Templeton D. *Insulin sensitivity, secretion, and glucose tolerance differences in normal-weight and overweight adolescents.* Presented at the TREC Centers Scientific Meeting, University of Minnesota, Minneapolis, MN, October 2007.

80. Templeton D. *Bone mineral content in overweight and normal weight children.* Presented at the 55th Annual Meeting of the American College of Sports Medicine, Indianapolis, IN, May 2008.

81. Thieschafer A, Hughes J, Popp K, Kaufman B, Stovitz S, Petit M. *Examining the bone-muscle relationship in male and female runners.* Presented at the 55th Annual Meeting of the American College of Sports Medicine, Indianapolis, IN, May 2008.

82. Thieschafer A, Hughes J, Popp K, Wetzsteon R, Stovitz S, Kaufman B, Kurzer M, Petit M. *Bone volumetric density, geometry, and strength in female and male collegiate runners.* Presented at the Annual Meeting of the American Society for Bone and Mineral Research, Montreal, Quebec, Canada, September 2008.

83. Widome R, Parker ED. *Food security and concentrations of C reactive protein among US adults.* Presented at the 21st Annual Meeting of the Society for Epidemiologic Research, Chicago, IL, June 2008.

University of Southern California TREC

Publications

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Presentations

1. Annavaram M, Medvidovic N, Mitra U, Narayanan S, Sukhatme G, Meng Z, Qui S, Kumar R, Thatte G, Spruijt-Metz D. *Multimodal sensing for pediatric obesity applications.* Presented at the International Workshop on Urban, Community, and Social Applications of Networked Sensing Systems, November 2008.

2. Behan JW, Avramis VI, Yun JP, Butturini A, Mittelman SD. Obesity alters the pharmacokinetics of vincristine in mice. *Blood.* 2008;112: 1636.

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7. Belcher BR, Spruijt-Metz D, Unger JB, Chou C-P, Nguyen-Rodriguez ST, Hsu Y-W, McClain AD. *Exploring the relationship among worries, emotional eating, BMI percentile, and weight-related concerns in girls.* Presented at the Obesity Society Annual Scientific Meeting, Phoenix, AZ, October 3-7, 2008.

8. Bernstein L. *Breast cancer risk reduction: Insights and opportunities.* Plenary presentation at Breast Cancer: From Gene to Cure, Amsterdam, The Netherlands, 2006.

9. Bernstein L. *The California Teachers Study: New approaches to old questions.* Presented to the Boards of Overseers and Directors, Breakthrough Breast Cancer Trust, London, UK, 2006.

10. Bernstein L. *Does physical activity influence cancer outcomes?* Presented at the New Developments in the Epidemiology of Cancer Prognosis: Traditional and Molecular Predictors of Treatment Response and Survival, American Association for Cancer Research Special Conference, Charleston, SC, 2006.

11. Bernstein L. *Focus on the host: Diet and exercise.* Presented at Current Trends in Breast Cancer, Updates from the 2005 San Antonio Breast Cancer Symposium, Greenwich, CT, 2006.

12. Bernstein L. *Impact of health behaviors on breast cancer risk.* Presented at Cancer Genetics 2006: Bridging Science and Practice, Fox Chase Cancer Center, Philadelphia, PA, 2006.

13. Bernstein L. *Insights and innovation: Results from the California Teachers Study.* Presented at the 16th Annual Cancer Surveillance Program Educational Symposium, Los Angeles, CA, 2006.

14. Bernstein L. *Lifestyle approaches to breast cancer risk reduction: Insights and opportunities—The Breakthrough Generations Lecture.* Presented at the National Cancer Research Institute Cancer Conference, Birmingham, UK, 2006.

15. Bernstein L. *Obesity and cancer risk: Etiologic insights.* Presented at the Environmental Health Sciences Center, University of North Carolina, Chapel Hill, NC, 2006.

16. Bernstein L. *Obesity, physical inactivity, and cancer risk: Etiologic insights.* Presented at Molecular Targets in Cancer Prevention, Keystone Symposium, Tahoe City, CA, 2006.

17. Bernstein L. *Physical activity and cancer: Progress and "opportunities."* Presented at Frontiers in Cancer Prevention Research, American Association for Cancer Research Special Meeting, Boston, MA, 2006.

18. Bernstein L. *Physical activity and cancer: State of the evidence.* Presented to the President's Cancer Panel, Minneapolis, MN, 2006.

19. Bernstein L. *Prospects for the prevention of breast cancer.* Meadow Brook Lecture, presented at the Southeast Michigan Center for Medical Education, Detroit, MI, 2006.

20. Bernstein L. *Pursuing lifestyle modification to lower cancer risk: The case of exercise activity.* Presented as part of the Epidemiology and Public Health Sciences Seminar Series, Wake Forest University, Winston-Salem, NC, 2006.

21. Bernstein L. *Reducing breast cancer risk: Insights and opportunities.* Presented at Grand Rounds, Karmanos Cancer Institute, Detroit, MI, 2006.

22. Bernstein L. *Adopting an active lifestyle: Why exercise may lower women's risk of breast cancer.* Presented at the Zero Breast Cancer Forum, Marin County, CA, 2007.

23. Bernstein L. *Breast cancer news: What's behind the headlines?* Presented at the National Breast Cancer Coalition Annual Advocacy Conference, Washington, DC, 2007.

24. Bernstein L. *Breast cancer prevention: Learning from the past, mentoring the future.* Prevent Cancer Foundation Award Lecture, presented at Frontiers in Cancer Prevention Research, American Association for Cancer Research, Philadelphia, PA, 2007.

25. Bernstein L. *Epidemiology and current standards in breast cancer prevention.* Presented at the Seventh Annual New Strategies in Breast Cancer Conference, Philadelphia, PA, 2007.

26. Bernstein L. *Physical activity and breast cancer: Evolution of a hypothesis.* Brinker Award Lecture presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 2007.

27. Bernstein L. *Breast cancer: What is known? What is myth? What can you do to reduce your risk?* Presented at the Eighth Annual Women's Health Conference, Pasadena, CA, 2008.

28. Bernstein L. *Can we lower breast cancer risk? Moving biology and intuition into population-based approaches.* Presented at Grand Rounds, Breast and Prevention Research Programs, Washington University, St Louis, MO, 2008.

29. Bernstein L. *Changing breast cancer risk: Novel population approaches.* Presented at Grand Rounds, School of Public Health, University of Michigan, Ann Arbor, MI, 2008.

30. Bernstein L. *Changing breast cancer risk: A population approach.* Judith P Schlager Lecture, presented at Breast Cancer: Current Controversies and New Horizons, Harvard Medical School, Boston, MA, 2008.

31. Bernstein L. *Exercise and cancer risk: Tipping the energy balance.* Presented at Cancer Center Grand Rounds, City of Hope, Duarte, CA, 2008.

32. Bernstein L. *Exercise and cancer risk: Tipping the energy balance.* Presented at the American Association for Cancer Research-TREC-National Cancer Institute Conference on Energy Balance and Cancer: Mediators and Mechanisms, Lansdowne, VA, 2008.

33. Bernstein L. *Modifiable risk factors: Physical activity and cancer.* Presented at the 99th Annual Meeting of the American Association for Cancer Research, San Diego, CA. 2008.

34. Bernstein L. *Physical activity.* Presented as part of Modifiable Risk Factors for Cancer (chair/organizer of educational session and speaker), American Association for Cancer Research Annual Meeting, San Diego, CA, 2008.

35. Bernstein L. *Physical activity present and future: Reducing breast cancer risk and mortality.* Presented at Era of Hope, US Department of Defense Breast Cancer Research Program Meeting, Baltimore, MD, 2008.

36. Bernstein L. *Restoring fitness after breast cancer.* Presented at Reclaiming Control: Life After Breast Cancer, 12th Annual Cincinnati Breast Cancer Conference, Cincinnati, OH, 2008.

37. Bouret SG. *Development of hypothalamic feeding pathways.* Seminar presented at the University of Southern California, Los Angeles, CA, 2008.

38. Bouret SG. *Developmental programming of CNS pathways that regulate metabolism.* Seminar presented at the Institute of Metabolic Science, Addenbrookes Hospital, Cambridge, UK, 2008.

39. Bouret SG. *Developmental programming of hypothalamic feeding circuits.* Symposium presented at the Programming and Epigenetic Meeting, Lille, France, 2008.

40. Bouret SG. *Impact of gestational diabetes on development of metabolic systems.* Presented at the TREC Centers Scientific Meeting, Bethesda, MD, 2008.

41. Bouret SG. *Nature versus nurture: Perinatal programming of brain pathways involved in obesity and diabetes.* Seminar presented at the Pasteur Institute, Lille, France, 2008.

42. Bouret SG. *Perinatal programming of hypothalamic neural circuits regulating energy homeostasis.* Presented at the Development, Epigenetics, and the Diabesity Epidemic symposium, New York Academy of Science, New York, NY, 2008.

43. Bouret SG. *Role of diet and metabolic hormones in perinatal programming of brain circuits regulating energy homeostasis.* Symposium at the Third World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition, Igassu, Brazil, 2008.

44. Bouret SG. *Wired for eating: Perinatal development of hypothalamic feeding circuits.* Seminar presented at King's College of London, London, UK, 2008.

45. Bouret SG. *Early life origins of obesity and diabetes: Role of brain development.* Symposium at the Third Japanese-French Frontiers of Science Symposium, Japan, 2009.

46. Bouret SG. *Early life origins of obesity: Role of hypothalamic programming.* Symposium at the 65th Nestlé Nutrition Workshop, Kuala Lumpur, Malaysia, 2009.

47. Bouret SG. *Hormonal and nutritional programming of CNS feeding pathways.* Symposium at the Experimental Biology Meeting, New Orleans, LA, 2009.

48. Bouret SG. *Wired on hormones: Developmental programming of hypothalamic feeding pathways.* Plenary lecture presented at the Ninth Meeting of the French Society of Neuroscience, Bordeaux, France, 2009.

49. Byrd-Williams CE, Belcher BR, Ventura EE, Davis JN, Spruijt-Metz D, Toledo-Corral CM, Lane CJ, Goran MI. *Effect of nutrition and strength training intervention on habitual physical activity in overweight Latino adolescents.* Poster presented at the TREC Centers Scientific Meeting, May 2008.

50. Byrd-Williams CE, Belcher BR, Ventura EE, Davis JN, Spruijt-Metz D, Toledo-Corral CM, Lane CJ, Goran MI. *Increases in objectively measured physical activity result in improvements in body composition in overweight Latino adolescents.* Poster presented at the Obesity Society Meeting, October 2008.

51. Davis JN, Goran MI, SANO LA Team. *Main outcomes from USC – Project 1.* Presented at the TREC Centers Scientific Meeting, May 2008.

52. Davis J, Kelly L, Lane CJ, Spruijt-Metz D, Weigensberg MJ, Goran M. *The effects of nutrition education with and without strength training on adiposity in overweight Latino adolescents.* Poster presented at the Obesity Society Annual Scientific Meeting, New Orleans, LA, October 20-24, 2007.

53. Davis JN, Tung A, Spruijt-Metz D, Chak SS, Ventura EE, Byrd-Williams CE, Alexander KE, Lane CJ, Weigensberg MJ, Goran MI. *Randomized control trial of circuit training to improve risk factors for type 2 diabetes in overweight Latina adolescents.* Presented at the Obesity Society Annual Scientific Meeting, Phoenix, AZ, October 3-7, 2008.

54. Davis J, Ventura E, Alexander K, Kelly L, Toledo-Corral C, Byrd-Williams C, Roberts CK, Weigensberg MJ, Spruijt-Metz D, Goran M. *The relation of sugar intake versus glycemic index on adiposity and insulin dynamics in Latino youth.* Poster presented at the Obesity Society Annual Scientific Meeting, New Orleans, LA, October 20-24, 2007.

55. Davis JN, Ventura EE, Spruijt-Metz D, Shaibi GQ, Weigensberg MJ, Watanabe RM, Goran MI. *Reductions in added sugar intake improve insulin secretions in Latina adolescents.* Presented at the Annual Scientific Meeting of the Obesity Society, Boston, MA, October 20-24, 2006.

56. Dunton GF, Reynolds KD, Spruijt-Metz D, Wolch J, Chou C-P, Jerrett M, Byrne J, Weaver S. *Reasons for urban trail use predict trail-related physical activity.* Presented at the American Public Health Association 135th Annual Meeting, Washington, DC, November 3-7, 2008.

57. Hsu Y-W, Nguyen-Rodriguez ST, Chou C-P, Lane CJ, Spruijt-Metz D. *Physical activity in Asian/Pacific Islander and Latina middle school girls.* Poster presented at the Obesity Society Annual Scientific Meeting, New Orleans, LA, October 20-24, 2007.

58. Hsu Y-W, Nguyen-Rodriguez ST, Chou C-P, McClain AD, Belcher BR, Spruijt-Metz D. *Influences of social support, perceived barriers, and negative meanings of physical activity on physical activity in middle school students.* Presented at the Obesity Society Annual Scientific Meeting, Phoenix, AZ, October 3-7, 2008.

59. Hsu Y-W, Nguyen-Rodriguez ST, Chou C-P, Lane CJ, Spruijt-Metz D. *Physical activity in Asian/Pacific Islander and Latina middle school girls.* Poster presented at the TREC Centers Scientific Meeting, Pasadena, CA, May 1, 2007.

60. Hu HH, Nayak KS. *Absolute quantification of fat mass in adipose tissue with MRI.* Presented at the International Body Composition Symposium, New York, NY, July 2008.

61. Hu HH, Sung K, Nayak KS. *Rapid proton-density weighted abdominal MRI at 3 Tesla with RF non-uniformity correction.* Presented at the International Society for Magnetic Resonance in Medicine 16th Scientific Sessions, Special Session: Unsolved Problems and Unmet Needs in MRI, Toronto, Ontario, Canada, May 2008.

62. Hu HH, Sung K, Nayak KS. *Can MRI represent an accurate quantitative tool for assessing fat distribution in obesity research?* Presented at the International Society for Magnetic Resonance in Medicine 16th Scientific Sessions, Special Session: Unsolved Problems and Unmet Needs in MRI, Toronto, Ontario, Canada, May 2008.

63. Kelly L, Davis J, Lane CJ, Weigensberg MJ, Spruijt-Metz D, Goran M. *The effects of a randomized controlled trial of nutrition education and strength training on insulin sensitivity in overweight Latino boys.* Poster presented at the Obesity Society Annual Scientific Meeting, New Orleans, LA, October 20-24, 2007.

64. Mai PL, Sullivan-Halley J, Bernstein L, California Teachers Study Investigators. *Physical activity and colon cancer risk in the California Teachers Study.* Presented at the 30th Annual Meeting of the American Society for Preventive Oncology, Bethesda, MD, 2006.

65. McClain A, Nguyen-Rodriguez S, Spruijt-Metz D, Belcher BR, Hsu YW, Ventura E, Lane CJ, Davis J, Goran M. *Motivation to eat fruits and vegetables as a predictor of sugar intake in Latino adolescent girls.* Poster presented at the Annual Scientific Meeting of the Obesity Society, Phoenix, AZ, October 3-7, 2008.

66. Michel S, Unger JB, Spruijt-Metz D. *Psychological determinants of emotional eating in adolescents.* Presented at the Society of Behavioral Medicine Annual Meeting, San Francisco, CA, March 22-25, 2006.

67. Mittelman S. *Influence of obesity on treatment of childhood cancer.* Presented at the TREC Centers Scientific Meeting, Seattle, WA, May 5, 2008.

68. Mittelman S. *Evaluating the links between obesity and leukemia relapse using mouse models.* Presented at the University of Southern California TREC Center Team Seminar, May 23, 2008.

69. Mittelman S. *Investigating the relationships between obesity and leukemia relapse.* Presented at the TREC Centers Scientific Meeting, Bethesda, MD, October 14, 2008.

70. Mittelman S. *Adipose tissue impairs the treatment of leukemia.* Presentation given at the National Institute of Child Health and Human Development Child Health Research Center Annual Retreat, Houston, TX, November 7, 2008.

71. Mumford K, Lee R, Spruijt-Metz D. *Moving to the next level: Applying trails and parks research to policy.* Presented at the Active Living Research Conference, Coronado, CA, February 22-24, 2007.

72. Pentz MA, Riggs NR, Greenberg MT, Spruijt-Metz D, Reynolds KD. *PATHWAYS: A randomized study of a school-based curriculum for childhood obesity prevention.* Presented to the Society for Prevention Research, San Francisco, CA, May 28-30, 2008.

73. Reynolds KD, Spruijt-Metz D, Wolch J, Chou C-P, Jerrett M, Byrne J, Weaver S, Fulton W, Wang L. *Urban trail use and the built environment as determinants of physical activity.* Presented to the Association for American Geographers, Boston, MA, April 15-19, 2008.

74. Reynolds K, Spruijt-Metz D, Wolch J, Chou C-P, Jerrett M, Byrne J, Weaver S, Fulton W, Wang L. *Relationship of urban trail use and the built environment with MVPA.* Presented at the American Public Health Association 135th Annual Meeting, Washington, DC, November 3-7, 2008.

75. Reynolds K, Wolch J, Byrne J, Weaver S, Chou C-P, Feng B, Spruijt-Metz D, Fulton W, Jerrett M. *Trail characteristics as correlates of urban trail use.* Invited presentation at the Active Living Research Conference, San Diego, CA, 2006.

76. Reynolds KD, Wolch J, Fulton W, Byrne J, Jerrett M, Weaver S, Spruijt-Metz D, Chou C-P. *Research on urban trail environments: Preliminary findings.* Invited presentation at the Active Living Research Conference, San Diego, CA, 2005.

77. Spruijt-Metz D. *Behavioral techniques for promoting healthy lifestyle in children and teens.* Presented at Pediatric Obesity Update from Clinic to Community, University of Southern California, Los Angeles, CA, April 1, 2006.

78. Spruijt-Metz D. *Behavioral techniques for promoting healthy lifestyles in children and teens.* Invited presentation at the Educational Conference at Providence Saint Joseph Medical Center, Los Angeles, CA, May 11, 2006.

79. Spruijt-Metz D. *The utility of behavioral theories in obesity and cancer prevention and treatment research.* Invited presentation at the TREC Centers Scientific Meeting, Pasadena, CA, May 1, 2007.

80. Spruijt-Metz D. *Pediatric obesity research: A transdisciplinary approach.* Invited presentation at the Seventh Annual American Association for Cancer Research International Conference on Frontiers in Cancer Research, Washington, DC, November 16-19, 2008.

81. Spruijt-Metz D, Belcher B, Davis J, Anderson D, Lane CL, Chou C-P, Salter D, Hsu Y-W, Neuhouser M, Richey JM, McKenzie T, Weigensberg MJ. *Acute effects of high sugar/low fiber (HS) versus low sugar/high fiber (LS) breakfasts on glucose, leptin, and physical activity in preadolescent overweight Latinas.* Poster presented at the Obesity Society Annual Scientific Meeting, New Orleans, LA, October 20-24, 2007.

82. Spruijt-Metz D, Chou C-P, Wang L, Byrne J, Wolch J, Jerrett M, Hsieh S, Myles S, Hsu Y-W, Reynolds K. *Validation of the ROUTES self-administered trail-use questionnaire.* Presented at the Active Living Research Conference, Coronado, CA, February 22-24, 2007.

83. Spruijt-Metz D, Hsu Y-W, Belcher BR, McClain AD, Nguyen-Rodriguez ST, Davis JN, Lane CJ, Ader M, Goran MI, Weigensberg MJ. *Differences in physical inactivity between Tanner stages 1 and 2 in Latina and African American girls: Relationships to insulin secretion and sensitivity, body composition, and negative life events.* Presented at the Obesity Society Annual Scientific Meeting, Phoenix, AZ, October 3-7, 2008.

84. Spruijt-Metz D, Lee R, Mumford K. *Measurement of parks and trails access, characteristics and use: Moving the field forward.* Presented at the Active Living Research Conference, Coronado, CA, February 22-24, 2007.

85. Spruijt-Metz D, Lindsey G. *Active living research common measures: Parks and trails.* Invited roundtable presentation at the Active Living Research Conference, San Diego, CA, 2006.

86. Spruijt-Metz D, Lindsey G, Troped P, Reynolds K. *Collaborative development of core trail use measures.* Oral presentation at the Active Living Research Conference, Coronado, CA, February 25-26, 2005.

87. Spruijt-Metz D, McClain AD, Nguyen-Rodriguez ST, Belcher BR, Hsu YW, Weigensberg MJ. *Insulin resistance and declining physical activity levels in African American and Latina girls.* Presented at the 11th European Association for Research on Adolescence Conference, Turin, Italy, May 7-10, 2008.

88. Spruijt-Metz D, Reynolds KD, Lindsey G, Troped P. *Development of a multi-site trail use measure.* Roundtable presentation at the Active Living Research Conference, San Diego, CA, 2005.

89. Spruijt-Metz D, Reynolds K, Lindsey G, Troped P, Wolch J, Byrne J, Myles R, Hsieh S, Xie B, Gatto N, Sallis J. *Development of a modular trail use questionnaire.* Poster presentation at the Active Living Research Conference, Coronado, CA, February 25-26, 2005.

90. Spruijt-Metz D, Reynolds K, Troped P, Lindsey G, Sallis J. *Development of a modular trail use questionnaire.* Round table discussion (leader) at the Active Living Research Conference, Coronado, CA, February 25-26, 2005.

91. Steculorum S, Bouret SG. *Impact of diabetes during gestation on development of hypothalamic metabolic systems in mice.* Presented at the 35th Annual Meeting of the French Society of Neuroendocrinology, Strasbourg, France, 2008.

92. Valente TW, Chou C-P, Kayo F, Spruijt-Metz D. *Fat and friends: Social network influences on adolescent obesity.* Presented at the 11th European Association for Research on Adolescence Conference, Turin, Italy, May 7-10, 2008.

93. Valente T, Nguyen-Rodriguez S, Chou C-P, Spruijt-Metz D. *Social network influences on weight and physical activity.* Poster presentation at the Obesity Society Annual Scientific Meeting, New Orleans, LA, October 20-24, 2007.

94. Valente T, Spruijt-Metz D, Chou C-P. *Social network influences on weight and physical activity.* Poster presentation at the TREC Centers Scientific Meeting, Pasadena, CA, May 1, 2007.

95. Ventura EE, Davis JN, Byrd-Williams CB, Alexander KE, McClain A, Lane CJ, Spruijt-Metz D, Weigensberg MJ, Goran MI. *Improvements in insulin secretion and visceral fat in response to low-sugar, high-fiber dietary intervention in overweight Latino adolescents.* Poster presentation at the Obesity Society Annual Scientific Meeting, Phoenix, AZ, October 3-7, 2008.

96. Weigensberg MJ, Avila Q, Konersman K, Hammer M, Hill M, Padilla A, Enriquez F, Sternbach D, Spruijt-Metz D. *"IMAGINE HEALTH": Development and acceptability of a novel lifestyle intervention for overweight Latino adolescents using principles of Intuitive Eating and Interactive Guided Imagery℠.* Presented at the Obesity Society Annual Scientific Meeting, Phoenix, AZ, October 3-7, 2008.

97. Weigensberg MJ, Lane CJ, Michel S, White W, Scherrer K, Winners O, Goran MI, Spruijt-Metz D. *Stress-reduction Interactive Guided Imagery℠ (IGI) acutely lowers salivary cortisol in overweight Latino adolescents.* Presented at the North American Association for the Study of Obesity Scientific Sessions, Boston, MA, October 20-24, 2006.

98. Weigensberg MJ, Spruijt-Metz D, Goran MI. *Blunted awakening cortisol response is associated with features of the metabolic syndrome in overweight Latino youth.* Presented at the American Diabetes Association 68th Scientific Meeting, San Francisco, CA, June 6-10, 2008.

99. Wolch J, Reynolds K, Spruijt-Metz D, Chou C-P, Jerrett M, Feng B, Fulton W, Byrne J, Weaver S. *Patterns of urban trail use and neighborhood correlates.* Presented at the International Congress on Physical Activity and Public Health, Atlanta, GA, April 17-20, 2006.

100. Wolch J, Tatalovich Z, Spruijt-Metz D, Byrne J, Jerrett M, Chou C-P, Weaver S, Wang L, Fulton W, Reynolds K. *Proximity and perceived safety as determinants of urban trail use: Findings from a three-city study.* Presented to the Association for American Geographers, Boston, MA, April 15-19, 2008.

101. Xie B, Chou C, Spruijt-Metz D, Gallaher P, Palmer PH, Sun P, Guo Q, Wu Q, Johnson CA. *Longitudinal analysis on general and central adiposity, socioeconomic status, and cultural variables in Chinese adolescents.* Presented at the 14th Annual Meeting of the Society for Prevention Research, San Antonio, TX, May 31-June 2, 2006.

102. Xie B, Chou C-P, Spruijt-Metz D, Palmer PH, Sun P, Gallaher P, Guo Q, Johnson CA. *Cigarette smoking is associated with unhealthy patterns of food consumption, physical activity and alcohol drinking in Chinese male adults: China Seven-City Study.* Presented at the Second East-West Conference on Tobacco and Alcohol: Culture, Environment, and Genes, University of Southern California, Alhambra, CA, April 5-6, 2005.

103. Xie B, Chou C, Spruijt-Metz D, Reynolds K, Palmer PH, Gallaher P, Sun P, Qian G, Johnson CA. *Socio-demographic and economic correlates of overweight status in Chinese adolescents.* Presented at the 2006 Annual Scientific Meeting of the Obesity Society, Boston, MA, October 20-24, 2006.

104. Xie B, Chou C, Spruijt-Metz D, Reynolds K, Palmer PH, Sun P, Gallaher P, Quo Q, Johnson CA. *Overweight status, weight perception and weight management goals and practices among female Chinese college students.* Presented at the 133rd Annual Meeting of the American Public Health Association, Philadelphia, PA, December 10-14, 2005.

105. Xie B, Unger JB, Spruijt-Metz D, Chou C-P, Johnson CA. *Combined effects of acculturation and timing of menarche on overweight, depressive symptoms and smoking experimentation in female Hispanic adolescents.* Presented at the Society for Prevention Research 16th Annual Meeting, San Francisco, CA, May 28-30, 2008.

106. Yun JP, Klemm L, Behan J, Muschen M, Mittelman SD. Obesity accelerates T-cell leukemia in a spontaneous mouse model. *Blood.* 2008;112:1909.

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