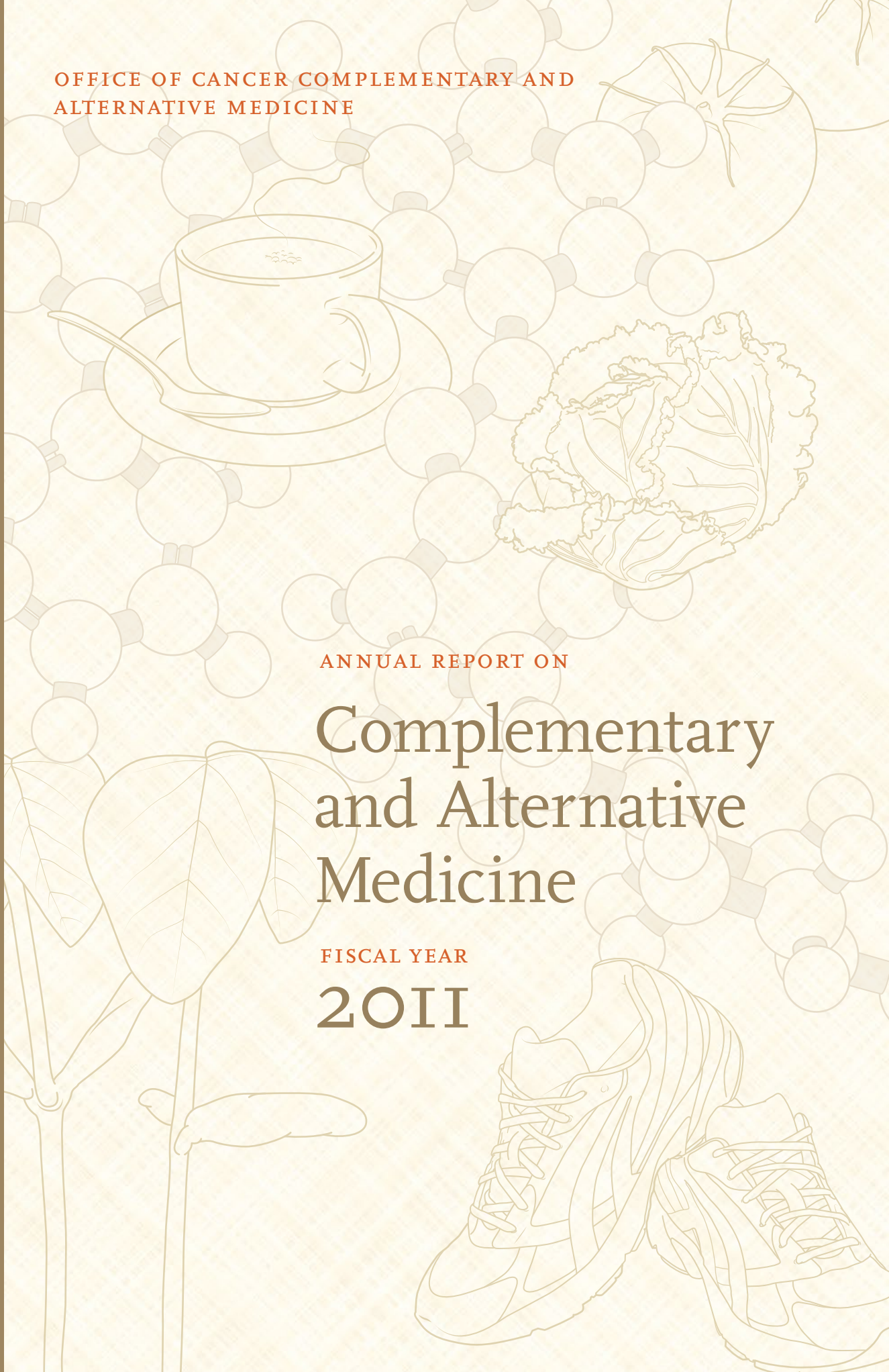
National Cancer Institute

OFFICE OF CANCER COMPLEMENTARY AND ALTERNATIVE MEDICINE



ANNUAL REPORT ON

Complementary and Alternative Medicine

FISCAL YEAR

2011

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Director's Message

The research the National Cancer Institute (NCI) supports, both in its own laboratories and at institutions worldwide, is focused on the ultimate goal of helping cancer patients. That mission – achieved through rigorous science – extends to NCI's program on complementary and alternative medicine, also known as CAM. It is with great pleasure and pride that we once again provide NCI's research partners, physicians, the advocacy community, policymakers, and cancer patients with this seventh annual review of NCI's extensive accomplishments in advancing evidence-based CAM interventions and therapies.

This report includes information about an extensive and diverse portfolio of research with projects ranging from the use of food-derived substances, diet modification and exercise for cancer prevention or treatment, to studies of the use of acupuncture to diminish side effects of standard cancer therapy.

NCI's commitment to CAM research and evidence-based clinical practice has been steadily supported, coordinated, and expanded by the Office of Cancer Complementary and Alternative Medicine (OCCAM) over the years. OCCAM's goal is to increase NCI's ability to extend the search for effective therapies into areas that show promise but which often are not thoroughly explored in conventional biomedical research.

I hope you find this report helpful and informative. I also hope that it will generate an enhanced dialogue – especially between patients and health care professionals – about the appropriate uses of CAM interventions in conjunction with conventional medicine. Cancer patients deserve credible, unbiased information about any intervention or treatment regimen that they are considering. It is our duty to conduct and support the science that makes wise and informed decisions possible.

Jeffrey D. White, M.D.
Director
Office of Cancer Complementary and Alternative Medicine
Division of Cancer Treatment and Diagnosis
National Cancer Institute

FIGURE 1: MAJOR CATEGORIES OF CAM THERAPIES

ALTERNATIVE MEDICAL SYSTEMS	
DEFINITION: Alternative medical systems are built upon complete systems of theory and practice. Often, these systems have evolved apart from and earlier than the conventional medical approach used in the United States.	EXAMPLES: Ayurveda, Homeopathy, Traditional Chinese Medicine, Tibetan Medicine
ENERGY THERAPIES	
DEFINITION: Energy therapies involve the use of energy fields. There are two types:	
Biofield therapies are intended to affect energy fields that purportedly surround and penetrate the human body. The existence of such fields has not yet been scientifically proven.	EXAMPLES: Qi gong, Reiki, Therapeutic touch
Electromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating current or direct current fields.	EXAMPLES: Pulsed electromagnetic fields, Magnet therapy
EXERCISE THERAPIES	
DEFINITION: Exercise therapies include health-enhancing systems of exercise and movement.	EXAMPLES: T'ai chi, Yoga asanas
MANIPULATIVE AND BODY-BASED METHODS	
DEFINITION: Manipulative and body-based methods in CAM are based on manipulation and/or movement of one or more parts of the body.	EXAMPLES: Chiropractic, Therapeutic massage, Osteopathy, Reflexology
MIND-BODY INTERVENTIONS	
DEFINITION: Mind-body medicine uses a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms.	EXAMPLES: Meditation, Hypnosis, Art therapy, Biofeedback, Imagery, Relaxation therapy, Music therapy, Cognitive-behavioral therapy, Aromatherapy
NUTRITIONAL THERAPEUTICS	
DEFINITION: Nutritional therapeutics are an assortment of nutrients and non-nutrients, bioactive food components used as chemo-preventive agents, and specific foods or diets used as cancer prevention or treatment strategies.	EXAMPLES: Macrobiotic diet, Vegetarianism, Gerson therapy, Kelley/Gonzalez regimen, Vitamins, Soy
PHARMACOLOGICAL AND BIOLOGIC TREATMENTS	
DEFINITION: Pharmacological and biologic treatments include the off-label use of certain prescription drugs, hormones, complex natural products, vaccines, and other biological interventions not yet accepted in mainstream medicine.	EXAMPLES: Antineoplastons, Low-dose naltrexone, Immunoaugmentative therapy, Laetrile
SUB-CATEGORY: Complex Natural Products	
DEFINITION: Complex natural products are an assortment of plant samples (botanicals), extracts of crude natural substances, and un-fractionated extracts from marine organisms used for healing and treatment of disease.	EXAMPLES: Herbs and herbal extracts, Mistletoe, Mixtures of tea polyphenols
SPIRITUAL THERAPIES	
DEFINITION: Spiritual therapies are therapies that focus on deep, often religious beliefs and feelings, including a person's sense of peace, purpose, connection to others, and beliefs about the meaning of life.	EXAMPLES: Intercessory prayer, Spiritual healing

Contents

Introduction

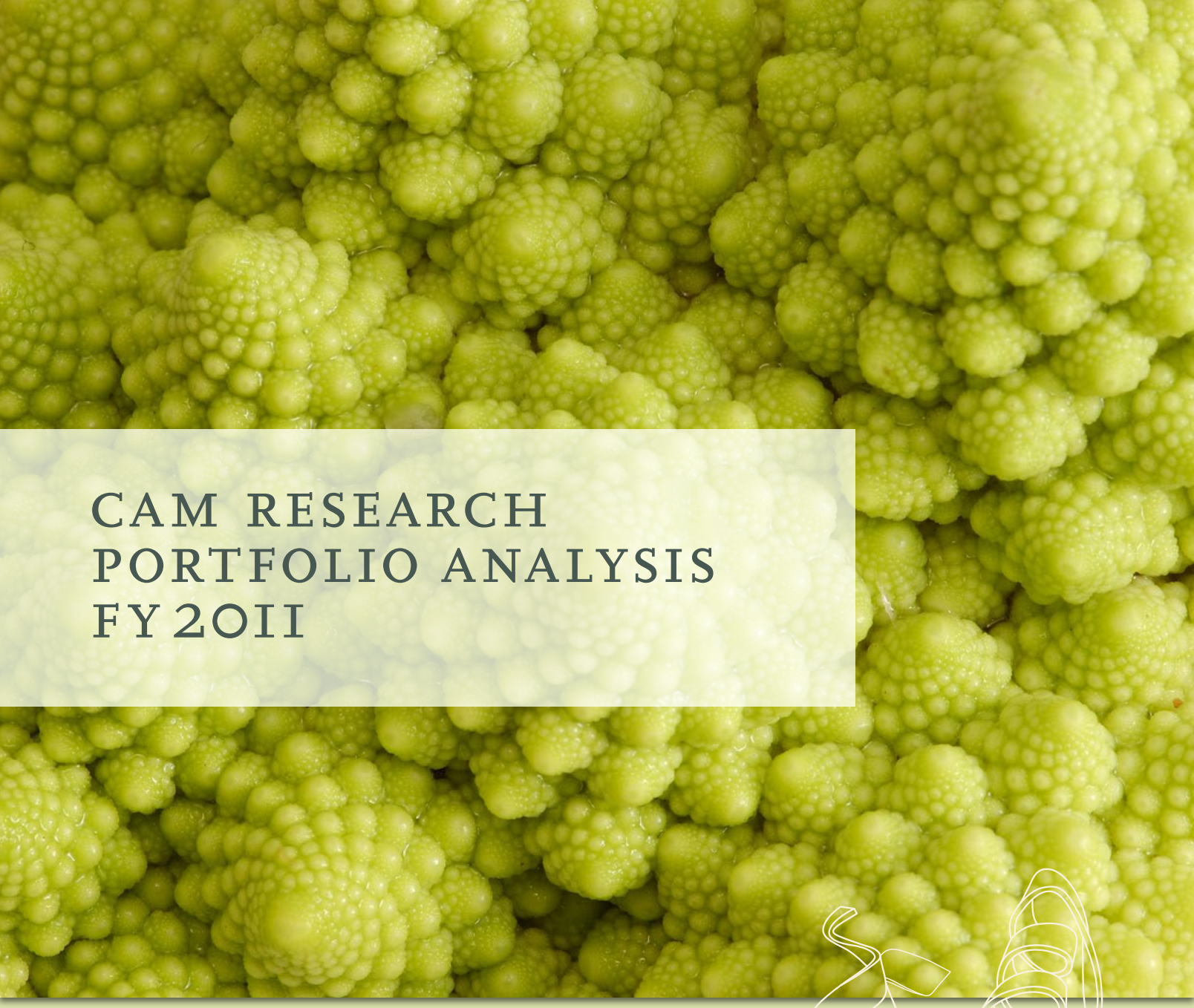
This report highlights the National Cancer Institute's initiatives and annual expenditures in complementary and alternative medicine (CAM)* research. It is intended as a way for NCI to communicate its progress in this area of medical research to all interested stakeholders including cancer researchers, CAM practitioners, health care providers, advocacy organizations, cancer patients, and the general public.

This publication provides an overview of the NCI-supported work in this field along with details on selected cancer CAM research projects. For more information on specific projects included in this report, please visit the NIH Research Portfolio Online Reporting Tools (RePORTER) database and search the grant or project number.

This report highlights projects, grants, and cooperative agreements supported by each of the Institute's extramural grant funding divisions – the Division of Cancer Biology (DCB), the Division of Cancer Control and Population Sciences (DCCPS), the Division of Cancer Prevention (DCP), and the Division of Cancer Treatment and Diagnosis (DCTD), along with projects from NCI's intramural laboratories in the Center for Cancer Research (CCR) and the Division of Cancer Epidemiology and Genetics (DCEG). These projects represent a variety of CAM categories, cancer types, research types, and grant mechanisms. Also included in the report is a breakdown of NCI's CAM research portfolio.

In FY 2011, NCI's research expenditures for CAM are an estimated $105,341,737 for the funding of 382 CAM research projects. As this report on cancer CAM indicates, we at the NCI are committed to an integrated approach to bring together all of the many resources and approaches necessary to decrease the frequency, destructiveness, and lethality of cancer. We believe that evidence-based CAM techniques, systems, and products can have an important role in reaching that worthwhile goal.

* CAM is often defined as any medical system, practice, or product that is not thought of as "western medicine" or standard medical care. Complementary medicine is used along with standard medicine, also called conventional medicine. Alternative medicine is used in place of standard treatments. CAM treatments may include dietary supplements, megadose vitamins, herbal preparations, acupuncture, massage therapy, magnet therapy, spiritual healing, and meditation. (See figure 1 on page ii for the major categories of CAM therapies.)



CAM RESEARCH PORTFOLIO ANALYSIS FY2011

The CAM Portfolio Analysis Process

How much money does NCI spend on CAM research each year? This is one of the questions most frequently posed to OCCAM. Researchers, cancer patient advocates, proponents of CAM, and Congress are interested in the answer, and OCCAM is responsible for gathering the data needed to report the total CAM expenditures budget figure each year.

It is a common misconception that OCCAM manages all of the CAM projects for NCI. The vast majority of CAM projects are managed by other programs and laboratories throughout the Institute. After the close of the fiscal year, NCI's Division of Extramural Activities (DEA) provides OCCAM with a list of funded grants and cooperative agreements coded as containing some component of CAM research. Similarly, NCI's two intramural components, the Center for Cancer Research (CCR) and the Division of Cancer Epidemiology and Genetics (DCEG), provide lists of their potentially relevant projects. Also, a list of contracts identified as potentially containing CAM research is provided. OCCAM staff review each project to confirm they are accurately classified as CAM research. Then, aspects of each project are identified allowing their placement into sub-categories based on the type of research and CAM intervention investigated.

NCI's total CAM expenditure figure includes money awarded for intramural projects (projects conducted within NIH facilities and labs), extramural grants (projects conducted outside of NIH), cooperative agreements, contracts, and supplements. It is important to note the reported figure for total NCI CAM expenditures for a fiscal year only includes projects for which NCI is the primary funder.

NCI's total CAM expenditure figure includes money awarded for intramural projects, extramural grants, cooperative agreements, contracts, and supplements

TOTAL ESTIMATED CANCER CAM RESEARCH EXPENDITURE

In FY 2011, NCI invested $105,341,737 for 382 intramural and extramural research projects relevant to CAM. For the purpose of the FY 2011 analysis, the following types of funding are included: intramural projects and extramural grants, cooperative agreements, contracts, and supplements (Figure 2).

The above numbers do not include CAM training grants (T and F awards), K (research career) or R25 (cancer education) grants. These numbers are listed separately in Figure 3.

BREAKDOWN BY RESEARCH TYPE

The accompanying pie-chart (Figure 4) shows the distribution of the projects by prevention, treatment, symptom/side effects management, epidemiology, and conferences. In FY 2011, 60.8% of cancer CAM-related research project funds went to various cancer prevention efforts, while treatment, symptom/side effects management, epidemiology, and conferences received 18.4%, 15.2%, 5.5%, and 0.03% respectively.

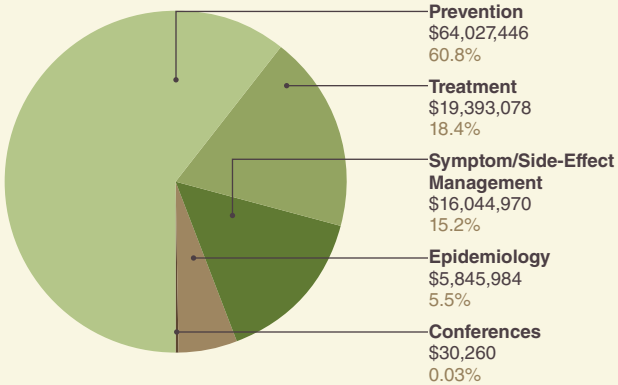
FIGURE 2: NCI CAM EXPENDITURES FY 2003–2011*

* Includes grants, cooperative agreements, intramural projects, and contracts. Grants and cooperative agreements are only included when NCI is the primary funding agency. Excludes training grants (T's, F's, K's and R25s). Total projects include all active projects in FY2011.

FIGURE 3: NCI CAM TRAINING PROJECTS 2011

Training Grant Mechanisms	Number of Grants	Total Funding
F (31,32)	4	$132,157
K (01, 05, 07, 22, 23, 24)	16	$1,434,554
R25	4	$760,861
T32	3	$472,829
TOTAL	**27**	**$2,800,401**

FIGURE 4: NCI CAM RESEARCH PROJECTS BY RESEARCH TYPE*



* Includes grants, cooperative agreements, intramural projects, and contracts. Grants and cooperative agreements are only included when NCI is the primary funding agency. Excludes training grants (T's, F's, K's and R25s). Total projects include all active projects in FY2011.

BREAKDOWN BY MAJOR CAM THERAPY CATEGORY

In FY 2011, NCI performed or supported research addressing a variety of CAM approaches (Figure 5). These CAM therapies fall into nine groups: alternative medicine systems, energy therapies, exercise therapies, manipulative and body-based methods, mind-body interventions, nutritional therapeutics, pharmacological and biologic treatments, spiritual therapies, and miscellaneous.

The largest percentage (70.1%) of CAM research funding went to projects that investigated nutritional therapeutics, which can be further broken out into subcategories of research on: foods (e.g., broccoli and berries); minerals (e.g., calcium and selenium); vitamins (e.g., vitamins C and D); bioactive food components (e.g., isoflavones and carotenoids); dietary regimens (e.g., caloric restriction and high fruits and vegetables); fats (e.g., linoleic acid and omega-3); and amino acids and proteins (e.g., N-acetyl cysteine and glycine).

Figure 6 shows the distribution of projects by the subcategories of nutritional therapeutics.

FIGURE 5: NCI CAM RESEARCH PROJECTS BY CAM CATEGORY*

A Nutritional Therapeutics	B Pharmaco-logical and Biologic Treatments	C Exercise Therapies	D Mind-Body Interventions	E Miscellaneous	F Alternative Medical Systems	G Energy Therapies	H Manipulative and Body-based Methods	I Spiritual Therapies
$73,822,107 70.1%	$11,241,945 10.7%	$7,952,892 7.6%	$4,554,383 4.3%	$3,002,474 2.9%	$2,259,428 2.1%	$1,195,143 1.1%	$755,576 0.7%	$557,790 0.5%

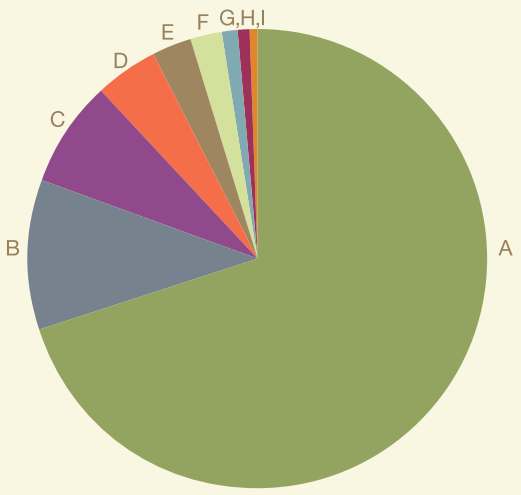
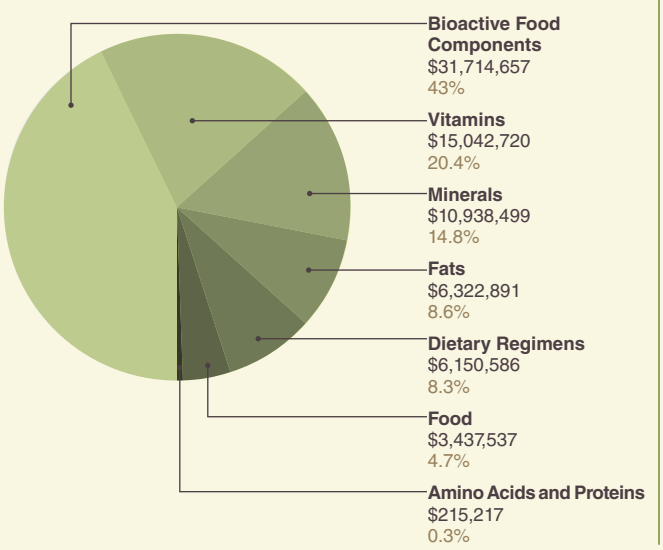


FIGURE 6: NCI CAM NUTRITIONAL THERAPEUTICS PROJECTS BY CATEGORY*



* Includes grants, cooperative agreements, intramural projects, and contracts. Grants and cooperative agreements are only included when NCI is the primary funding agency. Excludes training grants (T's, F's, K's and R25s). Total projects include all active projects in FY2011.

BREAKDOWN BY CANCER TYPE

The research projects that make up NCI's FY 2011 CAM research portfolio address 19 categories of cancer types. Among the various categories, prostate, breast, colorectal, and lung cancers received the largest amounts of cancer CAM research funding. Nearly 25% of NCI's cancer CAM research funding supported projects addressing "multiple types" of cancer.

For a complete listing of the cancer type categories and estimated funding amounts, please see Figure 7 below.

FIGURE 7: NCI CAM RESEARCH PROJECTS BY CANCER TYPE*

Bladder	$1,821,067
Brain	$503,280
Breast	$17,906,361
Cervical	$606,829
Childhood Cancer	$480,646
Colorectal	$18,868,169
Esophageal	$1,198,777
Gastric	$2,012,671
Head and Neck	$3,147,427
Hematologic	$2,089,455
Kidney	$41,578
Liver	$1,015,442
Lung	$5,980,610
Various (Multiple Types)	$25,898,621
Ovarian	$835,888
Pancreatic	$3,485,480
Prostate	$15,694,395
Skin: Non-Melanoma and Melanoma	$3,422,254
Thyroid	$332,786
Total	**$105,341,737**

* Includes grants, cooperative agreements, intramural projects, and contracts. Grants and cooperative agreements are only included when NCI is the primary funding agency. Excludes training grants (T's, F's, K's and R25s). Total projects include all active projects in FY2011.

OFFICE OF CANCER COMPLEMENTARY AND ALTERNATIVE MEDICINE (OCCAM)

NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM) is a coordinating office responsible for: identifying gaps in the science and creating corresponding funding opportunities for cancer CAM research; partnering with NCI program staff and other governmental and nongovernmental organizations to increase the testing of CAM approaches for cancer prevention, diagnosis, treatment, symptom management, and rehabilitation; developing communication products for various audiences concerning the investigation and use of these approaches; and helping to build bridges between CAM practitioners and the cancer research community.

OCCAM is part of the NCI Division of Cancer Treatment and Diagnosis (DCTD). The division's mission is to improve the lives of the American public by discovering and conducting better ways to diagnose, assess, treat, and cure cancer through stimulating, coordinating, and funding a national program of cancer research. OCCAM's programs and activities complement DCTD's mission and are enhanced by the other major programs and branches within DCTD.

OCCAM's research priorities include:

- Identifying novel therapeutics in the pharmacopeia of traditional medical systems as defined by the World Health Organization
- Research of complementary approaches to improve the therapeutic ratio of standard and investigational anti-cancer therapies
- Research on lifestyle modifications (e.g., diet, exercise, mind-body approaches) for their impact on cancer outcomes such as response to conventional cancer therapy and survival

OCCAM Programs

EXTRAMURAL RESEARCH PROGRAM

OCCAM's Extramural Research Program (ERP) staff manages a portion of NCI's CAM research portfolio, works with other program staff throughout NCI on CAM research issues, assists investigators in identifying funding opportunities, and provides guidance to applicants in the pre- and post- review periods of grant applications. The staff also coordinates programs and initiatives designed to stimulate research in cancer CAM as well as activities to develop the foundation of the science in cancer CAM research.

ERP continued to support funding opportunity announcements (FOAs) for developmental and small grant mechanisms R21 and R03, entitled "Developmental Projects in Complementary Approaches to Cancer Care and Treatment" for part of FY11. The R21 funding opportunities encouraged and supported the development of basic and clinical complementary and alternative cancer research projects (prevention, therapeutic, and palliative) through exploratory/developmental research grants. The R03 mechanism offered researchers a chance to generate data needed for conducting larger scientific studies of CAM. OCCAM continues to encourage new and young as well as veteran investigators to pursue research in areas not typically explored in studies funded by larger grant mechanisms. R21 and R03 grants provide that opportunity.

In FY11, NCI continued co-sponsoring three program announcements which specifically solicited CAM-related research:

- Biology of Manual Therapies (R01) PA-10-209 (Expires 1/8/2014)
- Biology of Manual Therapies (R21) PA-10-210 (Expires 1/8/2014)
- Limited Competition: Fogarty International Research Collaboration – Basic Biomedical (FIRCA-BB) Research Award (R03) PAR-11-037 (Expired 1/11/2012)

Highlights from OCCAM's Grant Portfolio

In FY 2011, NCI, along with the National Center for Complementary and Alternative Medicine (NCCAM) and the NIH Office of the Director, funded a P01 project grant* to investigate the effectiveness of PHY906 as a modulator of the chemotherapy drug irinotecan in the treatment of patients with metastatic colorectal cancer. PHY906 is an extract of four herbs based on a formula of traditional Chinese medicine (TCM), known as Huang Qin Tang (HQT). HQT is used as a treatment for gastrointestinal ailments, including diarrhea, nausea, and vomiting. Preclinical data suggests PHY906 can help improve the gastrointestinal side effects of irinotecan while simultaneously increasing the drug's anticancer activity.

The study, titled "Chinese Herbal Medicine as a Novel Paradigm for Cancer Chemotherapy," is led by Principal Investigator Yung-chi (Tommy) Cheng, Ph.D., of Yale University. The study has three main goals: 1) to confirm in humans that combining PHY906 with irinotecan may result in greater cancer-cell killing

abilities of the chemotherapy drug, improve treatment side effects, and increase quality of life for the patients; (2) to explore the potential mechanisms of action of PHY906 by identifying specific molecular factors of the herbal mixture and their by-products; and (3) to develop novel and appropriate statistical and computational modeling methods for use in analyzing data from clinical effectiveness studies of herbal extracts.

It is the hope of the scientists that this study may generate new methods for developing herbal or botanical medicines in combination with conventional chemotherapy for the treatment of cancer.

Further information on this project is available online, http://projectreporter.nih.gov/project_info_description.cfm?aid=8175586&icde=0.

*Project number: 1P01CA154295-01A1

OCCAM Grant Portfolio

OCCAM managed several grants in FY 2011. Additional information about each grant can be obtained by searching the project number in the NIH RePORTER database.

OCCAM Newly Funded Grants in FY 2011

- R21CA161182, Using Ketogenic Diets to Enhance Radio-Chemo-Therapy Response: A Phase I Trial, Project End 8/31/2013
- R21CA155518, Soy Isoflavones to Augment Radiotherapy of Lung Carcinoma, Project End 8/31/2013
- P01CA154295, Chinese Herbal Medicine as a Novel Paradigm for Cancer Chemotherapy, Project End 8/31/2016

CASE REVIEW AND INTRAMURAL SCIENCE PROGRAM

The mission of the Case Review and Intramural Science Program (CRISP) is to identify novel complementary and alternative (CAM) therapies for the treatment of cancer. This aim is accomplished through various program activities, such as the rigorous scientific evaluation of retrospective case reports (NCI Best Case Series Program) and round table discussions with cancer experts and CAM practitioners, with the ultimate goal of identifying those CAM interventions that have enough evidence to support NCI-initiated prospective research.

NCI Best Case Series Protocol

The NCI Best Case Series (BCS) Protocol received final approval from NCI's Special Studies Institutional Review Board in January 2011. The BCS Protocol is designed as a retrospective data analysis of patients treated with alternative cancer approaches in order to assess whether enough information exists to make a decision in favor of future NCI-initiated research. Because most alternative cancer treatments have not been formally evaluated in prospective studies, the NCI BCS Protocol strives to verify existing case report data in order to assess whether further research on the alternative treatment is warranted.

During FY 2011, 72 cases of cancer patients treated with an alternative approach were submitted to the NCI Best Case Series Program and reviewed for eligibility. Eleven of these cases met the NCI BCS criteria for further review.

COMMUNICATIONS AND OUTREACH PROGRAM

OCCAM's Communications and Outreach Program (COP) develops and disseminates information about NCI program initiatives and funding opportunities, workshops and other events, and educational materials through OCCAM's publications and web site.

This program also assesses the opinions, interests, and informational needs of cancer researchers, CAM practitioners, and cancer patients regarding CAM research through surveys, public comment sessions, and focus groups. Results from these explorations are used to guide outreach efforts to these communities.

Newsletter on NCI's CAM Activities

OCCAM's twice-yearly newsletter, *NCI CAM News*, provides the latest information on NCI-sponsored research, funding opportunities, meetings and workshops, as well as educational information on cancer and CAM. *NCI CAM News* also includes features on cancer CAM projects representing the full range of NCI's activities as well as OCCAM program updates.

The newsletter is available online: http://cam.cancer.gov/news_newsletter.html

OCCAM STAFF LIST: FY 2011

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NCI CAM CLINICAL TRIALS

Many CAM approaches are being studied via clinical trials in cancer patients. The OCCAM web site hosts a database which organizes CAM clinical trials by cancer types and types of symptoms. Clicking on an entry in the table triggers a search of the NCI's PDQ® Cancer Clinical Trials Registry, which includes approximately 8,000 clinical trials that are open and approved to accept patients. The table also archives trials that are currently closed. The Registry is available on the NCI web site at http://www.cancer.gov/clinicaltrials/search/.

There are currently (at time of publication) 79 active NCI-supported cancer CAM clinical trials. See Appendix for the complete list.

For the current list of all CAM clinical trials by cancer type and to access the CAM clinical trials table, go to http://cam.cancer.gov/cam/clinicaltrials_table.html.

Note: NCI web sites do not offer personalized medical advice to individuals about their condition or treatment, and the resources on the sites should not be used as a substitute for professional medical care.

HIGHLIGHTS FROM NCI'S CAM TRAINING PROJECTS

NCI Research in Complementary and Alternative Medicine

The highlights on the following pages are selected from the 27 CAM training projects that NCI supported during FY 2011 at laboratories and clinics throughout the United States and the world. NCI's programs allow students and professionals at all stages of their careers to develop the skills necessary to conduct basic, clinical, and cancer control research into CAM therapies and interventions.

Abstracts for the CAM training projects featured in the report can be found by searching the project or grant number in the NIH RePORTER research trials database.

Testing Vegetable Compounds to Boost Breast Cancer Survival

CENTER FOR CANCER TRAINING

The relatively minimal side effects of most dietary interventions for primary cancer prevention, as well as for prevention of cancer recurrence, make such approaches appealing to cancer researchers. Li Tang, Ph.D., an Assistant Professor of Oncology at Roswell Park Cancer Institute, has focused her career on studying the anti-cancer properties of isothiocyanates, a group of naturally occurring phytochemicals found in cruciferous vegetables such as broccoli, cauliflower, and cabbage.

As a post-doctoral researcher, Dr. Tang used both epidemiology and laboratory approaches to explore whether a diet high in cruciferous vegetables helps prevent the development of bladder cancer or its recurrence. She also sought to understand how isothiocyanates affect cancer cells on a molecular level.

In the epidemiology studies, Dr. Tang and her colleagues found a strong association between a diet high in raw cruciferous vegetables and both a reduced risk of bladder cancer and increased survival after bladder cancer treatment.

Studies from other laboratories suggested these effects may be due to the way the body processes isothiocyanates, Dr. Tang explained, noting that the active compounds from the vegetables accumulate in the urine, which is excreted from the bladder. In molecular studies*, she and her colleagues teased out some of the reasons that this accumulation could be beneficial to the bladder. They found that isothiocyanates, at the levels found in the bladder, both arrest the cell cycle in cancerous cells – stopping them from dividing – and induce apoptosis, which causes cells to die.

Dr. Tang became interested in whether the isothiocyanates could have preventive effects in other organs, where the doses would not be as high as in the bladder. In 2011, she received an NCI career development award** to extend her work to breast cancer, using both epidemiology and clinical studies.

"For bladder and breast cancer, we're looking at two different scenarios" for how the isothiocyanates may induce their anti-cancer effects, said Dr. Tang. Isothiocyanates do not accumulate in breast tissue at levels that could stop cell growth or cause cell death, but research from Dr. Tang's and other labs has shown that the isothiocyanates may change the expression of the estrogen receptor in breast cancer cells. For breast cancers that express the estrogen receptor – about two-thirds of all tumors in the breast – the receptor can help feed cancer cell growth. Therefore, blocking the estrogen receptor is a target of modern hormone therapy for breast cancer, including tamoxifen and the selective estrogen receptor down-regulator, fulvestrant.

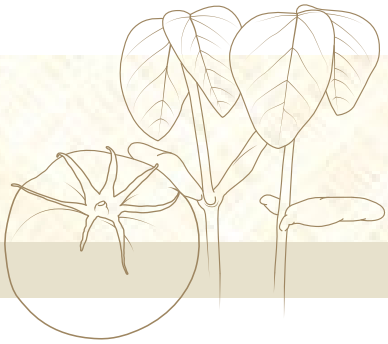
With her award, Dr. Tang is planning a randomized, pre-surgical study with 50 female breast cancer patients to see if isothiocyanates given orally – in the form of broccoli sprout extract produced at the Johns Hopkins University – can reduce expression of the estrogen receptor and change the expression of several genes that indicate breast cancer characteristics (such as aggressiveness). Because the usual time period between a biopsy for diagnosis of breast cancer and surgery is about 2 to 3 weeks, Dr. Tang and her colleagues can use that period of time – and tissue samples taken during the biopsy and surgery – for their biomarker study of isothiocyanates' effects without interfering with the standard treatment. They plan to start enrolling participants by the end of 2012.

"We want to look at these biomarker changes to see whether isothiocyanates may be used long term to modulate breast-cancer survival," explained Dr. Tang. Additional epidemiological information will be gathered through collaboration with the Pathways Study, an ongoing, prospective study of breast cancer survivors within the Kaiser Permanente Northern California Health System. This collaboration will provide information on diet, survival, and genetic profiles of breast tumors from over 3,800 women.

If their preliminary work yields positive results, Dr. Tang hopes to initiate a long-term, randomized trial testing whether an interview-based intervention can boost intake of cruciferous vegetables in breast cancer survivors, and whether that increased vegetable consumption "would have a long-term effect on breast-cancer survival."

* Tang, L., & Zhang, Y. (2004). Dietary isothiocyanates inhibit the growth of human bladder carcinoma cells. *Journal of Nutrition, 134*, 2004-10.
* Bhattacharya, A., Tang, L., Li, Y., Geng, F., Paonessa, J. D., Chen, S. C., Wong, M. K., & Zhang, Y. (2010). Inhibition of bladder cancer development by allyl isothiocyanate. *Carcinogenesis, 31*, 281-86.
** Grant number: 1K07CA148888-01A1

Tomato and Soy Combination Studied for Prostate Cancer Prevention



CENTER TO REDUCE CANCER HEALTH DISPARITIES

Krystle Zuniga, a Ph.D. candidate at University of Illinois at Urbana-Champaign (UI-UC), has always been interested in nutrition and learning how various whole foods can have an impact on cancer prevention.

Ms. Zuniga is a recipient of an NCI Ruth L. Kirschstein National Research Service Award* for Individual Pre-doctoral Fellowships to Promote Diversity in Health-Related Research (F31), which is a component of the Continuing Umbrella of Research Experiences (CURE) program at NCI. This fellowship provides Ms. Zuniga with funding support to complete her Ph.D. training in Nutritional Science at the UI-UC and to pursue her goal of becoming a translational researcher in the field of diet and cancer.

In her predoctoral training, Ms. Zuniga – under the mentoring of Steven Clinton, M.D., Ph.D., at The Ohio State University (OSU) – investigated the bioavailability of soy-based compounds, such as isoflavones, and tomato phytochemicals, such as carotenoids, in animal models. Her research on the combination of these foods in rats for prevention of prostate cancer led to Ms. Zuniga's first peer-reviewed publication**. She was also excited to work with clinical collaborators at OSU "who are trying to look at the combination of soy and tomato products in human clinical trials," she recalled. "Then we really became interested in finding the optimal combination of those foods for cancer prevention."

Ms. Zuniga is currently pursuing her interest in research to quantitatively define and understand the mechanisms by which consumption of soy or tomato products, alone or together, may reduce the risk of prostate cancer. "The objective is to investigate the effects of soy germ- and/or tomato powder-containing diets on the progression of prostate cancer in the TRAMP (Transgenic Adenocarcinoma of Mouse Prostate) model," she noted.

Based on findings from her previous animal study, Ms. Zuniga hypothesized that combining soy and tomato may not be as effective in preventing cancer as are diets that used soy or tomato alone. "We found less carotenoid accumulation in the prostate, liver, and other organs in the rats that received both tomato and soy," she said. "So we were worried there was a negative interaction of the two foods in the animals and that less of the compounds were getting into the tissues of interest and maybe making the combination less protective."

Although her current study in the TRAMP model found similarly lower levels of carotenoids in tissues from the combination diet, nonetheless, the mice who ate both soy and tomato powder did better in terms of the progression of prostate cancer, Ms. Zuniga reported, compared with mice who were fed only one of the foods, and compared to the control group who ate neither. She plans to publish her findings in the near future.

"I think it's exciting that this intervention is able to have this much of an effect in a very aggressive model of prostate cancer in mice," Ms. Zuniga noted. Because most prostate cancers in men are slow growing, "the type of effect such a dietary combination could have in humans could be pretty significant as well." The use of a whole-foods approach for cancer prevention also avoids many of the safety concerns from traditional chemoprevention by using large doses of single compounds extracted from plants and other sources, she said.

The NCI fellowship grant "has been helpful to my career," Ms. Zuniga commented. "I was really excited to get funded to do this type of project in nutrition and cancer prevention."

* Grant number: 1F31CA153804-01A1

** Zuniga K., & Erdman J. (2011). Combined consumption of soy germ and tomato powders results in altered isoflavone and carotenoid bioavailability in rats. *Journal of Agricultural and Food Chemistry, 59*, 5335-41.

HIGHLIGHTS FROM NCI'S CAM RESEARCH

Understanding the Causes and Mechanisms of Cancer

Cancer is a complex set of diseases that scientists are striving to understand from multiple perspectives. Research that improves our understanding of its causes and the mechanisms that underlie its development – from assessing cancer risk to explaining the process of metastasis – is essential to our ability to develop and apply interventions to preempt cancer initiation and progression.

Coffee Drinking Not Unhealthy and is Possibly Associated with Lower Risk of Death

DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS

Coffee is one of the most widely consumed beverages in the United States and worldwide, but the association between coffee consumption and the risk of death remains unclear, with previous studies yielding mixed results. A recent analysis by NCI researchers of data from the NIH-AARP Diet and Health Study, a large study of older adults, suggests that coffee drinking may be associated with a lower risk of death for most diseases and other causes. However, they did not find a lower risk of death by cancer among coffee drinkers.

The analysis*, by researchers from NCI's Division of Cancer Epidemiology and Genetics (DCEG), showed that people who reported that they drank coffee (whether caffeinated or decaffeinated), had a slightly lower risk of death from heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections than those who did not report drinking coffee.

The NCI researchers observed these results among study participants after adjusting for the effects of other risk factors on mortality, such as smoking and alcohol consumption. The scientists cautioned, however, that they can't be sure whether these associations mean that drinking coffee actually makes people live longer.

"A few recent studies have suggested that people [who drink coffee] have a slightly lower risk of death," explained Neal Freedman, Ph.D., M.P.H., who led the new analysis within DCEG. "Because it was a very modest effect, we wanted to look at this in a really big population cohort like NIH-AARP study, [which enabled us] to look for even modest associations between coffee drinking and different causes of death."

Dr. Freedman noted, "There has been a lot of concern that drinking coffee was not a healthy thing to do. Some people describe coffee drinking as their 'guilty pleasure.' Although we cannot infer a causal relationship between coffee drinking and lower risk of death, we believe these new results do provide some reassurance that coffee drinking does not adversely affect health."

Dr. Freedman and his colleagues examined the association between coffee drinking and risk of death in 400,000 U.S. men and women ages 50 to 71, who participated in the NIH-AARP study. Researchers collected information about coffee intake once by questionnaire at study entry in 1995–1996, and followed the participants until their date of death or December 31, 2008, whichever came first. More than 52,000 participants died during the study period.

The researchers found that the association between coffee and reduction in risk of death increased with the amount of coffee consumed. Compared with men and women who did not drink coffee, those who consumed three or more cups of coffee per day had an approximately 10% lower risk of death. In addition, the DCEG scientists found that coffee drinking was not associated with increased cancer mortality among women, but did find a slight, and only marginally statistically significant, association of heavier coffee intake with increased risk of cancer death among men.

Dr. Freedman cautioned that in the NIH-AARP study the amount of coffee consumption was assessed by self-report at only a single time point and therefore might not reflect long-term patterns of actual coffee intake by the study participants. Also, information was not available to researchers on how the coffee was prepared (espresso, boiled, or filtered). The NCI scientists consider it likely that coffee preparation methods affect the levels of different components in the coffee consumed. Dr. Freedman said that DCEG researchers hope to examine these factors in future studies.

"The mechanism by which coffee protects against risk of death – if indeed the finding reflects a causal relationship – is not clear, because coffee contains an estimated 1,000 different compounds that might potentially affect health," Dr. Freedman added.

Another recent analysis of data from the NIH-AARP study, led by Rashmi Sinha, Ph.D., also of NCI's DCEG, indicated that people who drank four or more cups of coffee (caffeinated or decaffeinated) per day had a lower risk of colon cancer

incidence**, particularly cancers of the region known as the proximal colon. DCEG researchers also recently reported an inverse association between coffee drinking and endometrial cancer*** but found no association between coffee consumption and breast cancer risk among the NIH-AARP study participants****.

* Project number: Z01CP010196
** Sinha, R., Cross, A.J., Daniel, C.R., Graubard, B.I., Wu, J.W., Hollenbeck, A.R., ... Freedman, N.D. (2012). Caffeinated and decaffeinated coffee and tea intakes and risk of colon cancer larger prospective study. *American Journal of Clinical Nutrition, 96*(2), 374-381.
*** Gunter, M.J., Schaub, J.A., Xue, X., Freedman, N.D., Gaudet, M.M., Rohan, T.E., Hollenbeck, A.R., & Sinha, R. (2012). A prospective investigation of coffee drinking and endometrial cancer incidence. *International Journal of Cancer, 131*(4), E530-536.
**** Gierach, G.L., Freedman, N.D., Andaya, A., Hollenbeck, A.R., Park, Y., Schatzkin, A., & Brinton, L.A. (2012). Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. *International Journal of Cancer, 131*(2), 452-460.

Researcher Investigates a Vitamin's Potential Dual Effect on Cancer

DIVISION OF CANCER BIOLOGY

Folate, a B vitamin, is essential for the normal functioning of the body. A shortage of folate in the diet can cause many problems, most notably birth defects such as spina bifida in children born to mothers with low levels of folate during early pregnancy.

In the 1990s, to reduce the number of children born with birth defects many countries, including the United States, mandated that flour and other grain products – such as pasta and cereal – be fortified with folate. In addition to consuming fortified foods, many people receive substantial amounts of the dietary compound through the use of vitamin supplements.

Since a low intake of folate in the diet can also increase the risk of cancer, particularly colorectal cancer, on first glance it seems that maximizing the intake of folate could only be a good thing. But Joel Mason, M.D., professor in the Friedman School of Nutrition Science and Policy at Tufts University, who has devoted his career to studying the effects of dietary folate and cancer, urges caution about this positive assessment.

"It's pretty much well accepted as a scientific fact now that habitual under-consumption of folate leads to an increased risk of cancer," Dr. Mason noted. "But interestingly, one of the things we noticed in several of our animal models is that there seemed to be a bi-modal effect of folate: if we gave inadequate amounts of folate to our animals it would increase tumor formation. On the other hand, when we gave them large quantities of folate – levels of dietary folate that were way beyond the basal requirements – we would sometimes see a promotion of cancer."

This unexpected finding is not as paradoxical as it seems, Dr. Mason said. Folate serves as an essential growth factor for dividing cells because the vitamin participates in the biochemical reaction that produces the nucleotide thymidine, one of the four building blocks of DNA, he explained. A lack of thymidine interferes with healthy DNA synthesis and appropriate cell division, Dr. Mason continued, but a flood of thymidine, as could be provided by excess folate, could potentially help fuel rapidly dividing cancer cells.

In 2007, Dr. Mason and his colleagues published a paper* hypothesizing that colorectal cancer incidence in the United States and Canada experienced a spike about a year after the introduction of mandatory folate fortification, reversing a 20-year trend of decline. "While this epidemiologic data is by no means proof of causality, it's rather interesting and provocative," said Dr. Mason.

After participating in a meeting convened by the European Food Safety Authority, which found the evidence inadequate to determine whether or not excess folate could increase the risk of cancer, Dr. Mason decided to further study the issue in a new animal model of colorectal cancer. "These types of studies can't ethically be done in humans, so [after the European meeting] there was an acknowledgment that to really determine whether this hypothetical risk is genuine in the human population it was going to require some modeling in animals," he recounted.

A colleague at Tufts, Kenneth Hung, M.D., had recently developed a new mouse model of colon cancer, called the GEM-1 mouse, which proved to be ideal for studying the effects of folate on colon cancer growth. The model has several advantages over older, more widely used models, explained Dr. Mason. One advantage is that the GEM-1 mouse develops tumors in the actual colon, also known as the large intestine. Most other mouse models of colon

cancer develop tumors in the small intestine, which has a different biology from the colon, he noted.

A second advantage is that the GEM-1 mouse develops all its tumors in the distal (lower) half of the colon, which can be reached using a micro-colonoscope created by Dr. Hung. This allows tumor growth to be measured on an ongoing basis in live animals. Finally, the mutation driving colon cancer formation in the GEM-1 mouse is only found in the cells lining the distal colon, as would be found in colon cancer in people, Dr. Mason added. Most other models contain a germline mutation — meaning it would be found in every cell of the body — which does not replicate most cases of colon cancer.

With NCI support for his ongoing experiments**, Dr. Mason is feeding mice either a diet with a regular level of folate or a diet with nine times the amount of folate required for basic body functioning, an amount easily achieved in people eating a number of fortified foods and taking vitamin supplements, he explained. With the micro-colonoscope, "we can actually watch the growth of tumors over time, and see if they have accelerated growth in those mice taking extraordinarily large amounts of folate."

As part of the experiments, some of the mice will receive the naturally occurring form of folate, and some will receive folic acid — the artificial, shelf-stable form of the vitamin used in fortification (natural folate breaks down quickly, making it unsuitable for fortification and use in supplements). This will hopefully shed some light on another unresolved question — whether folic acid rather than natural folate is the substance that can accelerate cancer growth, Dr. Mason said.

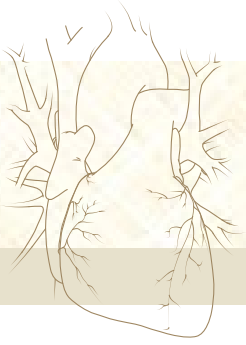
Folic acid quickly saturates the body's system that coverts it to the natural form of the vitamin. As little as half the amount found in a typical multivitamin overwhelms the system, leading to folic acid spilling into the circulation, explained Dr. Mason.

"If you insert naturally occurring forms of folate into [metabolism], it has to go through several regulatory steps that help control how much folate is getting utilized for DNA synthesis," Dr. Mason continued. "When you give folic acid, it gets inserted into folate metabolism in a way that can directly be used for the synthesis of DNA."

As part of the experiments, the researchers will be comparing the thymidine content within the lining of the colon between mice given natural and artificial folate, to see if the artificial form may be providing more material for dividing cells.

* Mason J.B., Dickstein A., Jacques P.F., Haggarty P., Selhub J., Dallal G., & Rosenberg I.H. (2007). A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: A hypothesis. *Cancer Epidemiology Biomarkers Prevention, 16*(7), 1325-9.
** Grant number: 5R21CA150118-02

Evidence Emerges for the Health Risks of Sedentary Behavior



DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS

At home, at work, and in the community, people today are moving less and sitting more than previous generations, and researchers are just beginning to understand the health risks associated with these behavior trends. Until recently, population-based research focused on the adverse effects associated with inadequate levels of exercise. But the latest evidence suggests that too much sitting – sedentary behavior – also has ill effects, and that these effects are distinct from those of too little exercise.

One researcher studying these issues is Charles Matthews, Ph.D., a physical activity epidemiologist in NCI's Division of Cancer Epidemiology and Genetics. He and his colleagues used information from the NIH-AARP Diet and Health Study, which was developed at NCI, to examine the independent effects of sedentary behavior and exercise on the risk of death due to various causes, including cancer.

The researchers found that prolonged television viewing and overall sitting time were associated with an increased risk of death (mortality) from all causes. Higher amounts of television viewing were also linked to an increased risk of death from cardiovascular disease and cancer. Compared with those who reported watching less than 1 hour of television per day, people who watched 7 or more hours per day had a 60% greater risk of dying from all causes, nearly twice the risk of death due to cardiovascular disease, and a 20% greater risk of death due to cancer.

"Our study was one of the larger studies, and one of only a handful, that has shown evidence of a link between sedentary behavior and cancer mortality," Dr. Matthews noted. Other reports from the NIH-AARP study have demonstrated links between sedentary behavior and increased risks of colon and endometrial cancer in particular, he added.

"Probably the most striking thing we saw was that even among people who reported 4 to 7 hours a week of exercise, those who also reported 5 or 6 hours per day of television viewing still had an increased likelihood of death from all causes and from cardiovascular disease compared to individuals who reported less than an hour a day of television viewing," Dr. Matthews said. In other words, "in terms of the risk for death, participating in a fair amount of exercise each week doesn't completely inoculate you against the deleterious effects of spending a lot of time in front of the television set."

The researchers followed more than 240,000 participants in the NIH-AARP Diet and Health Study, age 50–71 years old at the start of the study, for an average of 8.5 years. At the start of the study, the participants reported their average daily television or video viewing time, overall sitting time in the past year, and the average amount of leisure time per week spent in moderate to vigorous physical activity, or exercise, over the past 10 years. Examples of moderate to vigorous physical activity included walking for exercise, running or jogging, swimming laps, and heavier lawn and garden work.

Dr. Matthews explained that, in this study, prolonged time in front of the television was more strongly linked with increased mortality than overall sitting time because a single question that asks how long people spend sitting each day overall is probably not reported as accurately as a single question about a specific sitting behavior, in this case television viewing.

"Our results add to the growing evidence that the adverse effects of sedentary behavior seem to be independent of the benefits of exercise," Dr. Matthews said. The finding, he noted, "opens the door for developing new strategies to increase the overall activity level of the population by reducing sedentary time in favor of more active pursuits. To date, our primary strategy has been to encourage exercise participation."

"It's really a wake-up call to think about all of the many different places you sit during daily life and [try to] switch to an upright and active approach to doing those same activities," Dr. Matthews continued. For instance, he added, at home "you can stand up to fold laundry or cook meals. You can rearrange your computer workstation so you are able to stand [at the computer]." Taking frequent breaks to walk around the room, house, or office may also be helpful, he said.

The NCI researchers found that their results didn't change much when they adjusted for Body Mass Index (BMI), which is a measure of obesity, suggesting that factors other than obesity account for the ill effects of sedentary behavior.

Dr. Matthews and his colleagues are now analyzing information from more detailed questionnaires that were administered as part of the NIH-AARP Diet and Health Study to find out how much and what types of activity can minimize the health risks associated with sedentary behavior, including activities such as household chores, lawn and garden work, caring for children and elders, and home repairs.

Project number: Z1A CP 010197

ACCELERATING PROGRESS IN CANCER PREVENTION

Prevention is our first line of defense against cancer. Efforts to prevent cancer focus on understanding and modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting cancer-causing processes through early medical intervention.

Finding a Healthy Dietary Ratio for Prostate Cancer Prevention

DIVISION OF CANCER PREVENTION

The leading cause of mortality for the 10 percent of patients who develop recurrent or refractory (treatment resistant) prostate cancer is due to the progression of prostate cancer to androgen independence — the ability of the tumor to grow even in the absence of androgens, hormones that can stimulate the growth of prostate cancer cells. Strategies that prevent this progression are greatly needed, and early studies conducted by Linda A. deGraffenried, Ph.D., Associate Professor and Associate Chair of the Department of Nutritional Sciences at The University of Texas at Austin, demonstrate how the mammalian target of rapamycin (mTOR) — a protein regulator of cell growth — could play a role in controlling the progression of prostate cancer to androgen independence in animal models.

Several anti-cancer agents that target the mTOR pathway are currently in clinical development. "Because the mTOR pathway is regulated by growth factors and nutrients, this suggests that natural dietary interventions could also have protective effects against cancer through regulation of this pathway," said Dr. deGraffenried. "We set out to examine the impact of a variety of dietary interventions that could prove beneficial for prostate cancer patients by targeting this pathway, including omega-3 and omega-6 fatty acids*."

Omega-3 and omega-6 fatty acids are found naturally in the human diet through the consumption of cold water fish, and seeds and nuts and the oils extracted from them, respectively. In a preliminary study using an *in vitro* model of androgen suppression, Dr. deGraffenried and colleagues discovered that the balance between omega-3 and omega-6 fatty acids plays a role in affecting the progression of prostate cancer**. Specifically, the omega-3 fatty acid docosahexaenoic acid (DHA) effectively delayed the progression of prostate cancer cells to an androgen-independent state, whereas the omega-6 fatty acid arachidonic acid (AA) promoted disease progression. "Additionally, this delay in progression to hormone-refractory disease was mediated in part through inhibition of the mTOR signaling pathway," said Dr. deGraffenried.

The American Heart Association (AHA) recommends an omega-6 to omega-3 ratio of 10:1; unfortunately, those on a Western diet eat too much omega-6 and not enough omega-3. "In men consuming a Western diet, the ratio is approximately 46:1 because omega-6 levels are high in processed foods; in the Asian diet, on the other hand, the ratio is 1.3:1 because omega-3 levels are high in fish," said Dr. deGraffenried. "And if you look at the incidence of both breast and prostate cancer in the Asian population, it is very, very low."

From a dietary perspective, Dr. deGraffenried and colleagues are trying to determine the best fatty acid ratio for preventing the progression of prostate cancer in patients. Specifically, does the AHA recommendation (10:1) provide the same benefit for prostate cancer as it does for cardiac protection? Or is the Asian diet ratio (1.3:1) required for maximal protection?

Early *in vivo* data suggest that the AHA recommendation of 10:1 provides the same protective benefit for prostate cancer as does an Asian diet. "In addition, our data shows that (blood) serum levels serve as effective surrogate markers as they closely reflect the levels of fatty acids that are getting into the tumors," said Dr. deGraffenried.

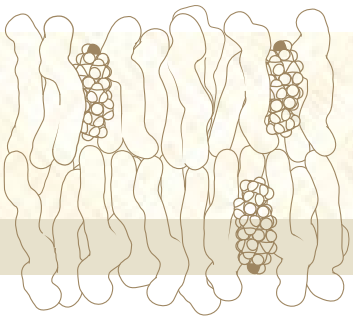
The challenge, however, is getting patients to modify their fatty acid ratio from 46:1 to 10:1 through diet alone because eating patterns are notoriously difficult to overcome. "The strategy will be to provide fatty acid supplements to patients based on their serum levels, and to adjust the supplements as needed over time to maintain the proper ratios," said Dr. deGraffenried.

NCI Division of Cancer Prevention Program Director Young Kim, Ph.D., commented, "Dr. deGraffenried's group is revealing the mechanisms by which an omega-6 to omega-3 fatty acid ratio affects the outcome in prostate cancer patients. This information will be important for the development of effective dietary intervention strategies that improve overall survival."

* Grant number: 5R01CA118962-05

** Friedrichs, W., Ruparel, S.B., Marciniak, R.A., & deGraffenried, L. (2011). Omega-3 fatty acid inhibition of prostate cancer progression to hormone independence is associated with suppression of mTOR signaling and androgen receptor expression. *Nutrition and Cancer, 63*(5), 771-777.

Complementary Strategies for Prostate Cancer Prevention and Management



DIVISION OF CANCER PREVENTION

Prostate cancer is the most common cancer diagnosis and the second deadliest cancer among men in the United States. Additionally, men living in Western countries are six times more likely to be diagnosed with prostate cancer compared to the rest of the world. This discrepancy has been in part attributed to differences in dietary intake as men in developing countries, who adopt a Western diet, experience a greater incidence of prostate cancer. It is unclear, however, whether the increased risk associated with a Western diet is due to a greater intake of fat, carbohydrates, or total calories.

With NCI funding*, Stephen J. Freedland, M.D., Associate Professor of Surgery and Pathology in the Department of Surgery at Duke University School of Medicine, has been studying the impact of both carbohydrate and fat intake on prostate cancer biology with the goal of developing novel, non-toxic complementary treatments, including dietary modification and phytopharmaceuticals (plant-based drugs), aimed at slowing prostate cancer progression. Dr. Freedland and colleagues had previously shown that mice fed a no-carbohydrate ketogenic diet (NCKD: 84% fat–0% carbohydrate–16% protein) demonstrated significantly reduced prostate tumor growth (~30%) and prolonged survival compared to mice fed a Western diet**.

"Mice consuming NCKD also had a decrease in signaling of the insulin-like growth factor (IGF) pathway, which is known to be involved in prostate cancer progress and this was confirmed in follow up studies," said Dr. Freedland. "The problem is that a zero carbohydrate diet is not feasible for humans. So the question was: how low is low? Would a low-carbohydrate diet, similar to that of the Atkins diet, provide the same protective benefits as NCKD?"

The first set of studies demonstrates that mice consuming less restrictive low-carbohydrate diets (10% to 20% kcal carbohydrates) have similar tumor growth, overall survival, and IGF signaling as mice fed NCKD***. "The results of these data are now being tested in clinical studies and approximately 30 men are already enrolled****," said Dr. Freedland. "A second study, funded by NCI*****, is set to open early next year."

The challenge is that a behavioral change such as diet is notoriously difficult to implement in both healthy individuals and sick patients, regardless of the diet being tested. Men on a Western diet typically consume 30-40% of their total caloric intake from fat and epidemiological and experimental data suggest consuming higher levels of dietary fat may negatively impact prostate cancer progression. It remains unknown, however, whether total fat or the cholesterol found in fat sources is associated with disease progression, as excess dietary fat is linked to high-serum cholesterol levels.

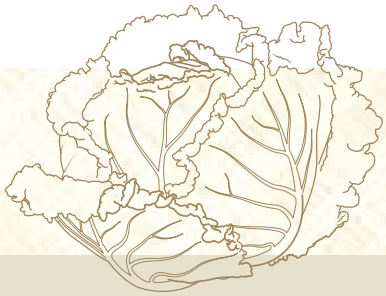
In a separate study, Dr. Freedland and colleagues searched for natural dietary interventions, including resveratrol and pomegranate that could be added to a Western diet to slow tumor growth; however, it was found that neither of these interventions had an impact. What they did find was that blocking cholesterol uptake with a cholesterol-lowering drug proved effective in slowing the growth of aggressive tumors.

In two independent studies, Dr. Freedland and colleagues demonstrated that daily treatment with the cholesterol-uptake inhibitor ezetimibe (Zetia®) delayed the rapid development of prostate cancer in animal models that mimic aggressive disease in humans. Although ezetimibe appeared to slow the growth of aggressive prostate tumors, this intervention did not impact slow-growing tumors.

NCI Division of Cancer Prevention Program Director Young Kim, Ph.D., commented, "When these mice are fed a high-fat diet that is linked to high-serum cholesterol levels (a typical Western diet), blocking cholesterol uptake significantly reduces the size of the prostate cancer. Dr. Freedland's group is providing new insight into the use of cholesterol-lowering agents as prevention for aggressive prostate cancer."

* Grant number: 5R01CA131235-05
** Freedland, S.J., Mavropoulos, J., Wang, A., Darshan, M., Demark-Wahnefried, W., Aronson, W.J., ... Issacs, W.B. (2008). Carbohydrate restriction, prostate cancer growth, and the insulin-like growth factor axis. *Prostate, 1*(68), 11-19.
** Mavropoulos, J.C., Buschemeyer, W.C. 3rd, Tewari, A.K., Rokhfeld, D., Pollak, M., Zhao, Y., ... Freedland, S.J. (2009). The effects of varying dietary carbohydrate and fat content on survival in a murine LNCaP prostate cancer xenograft model. *Cancer Prevention Research, 2*(6), 557-565.
*** Masko, E.M., Thomas, J.A. 2nd, Antonelli, J.A., Lloyd, J.C. Phillips, T.E., Poulton, S.H., ... Freedland, S.J. (2010). Low-carbohydrate diets and prostate cancer: how low is "low enough?". *Cancer Prevention Research, 3*(9), 1124-1131.
**** Clinicaltrials.gov identifier: NCT00932672
***** Grant number: 1K24CA160653-01

Plant-Based Chemoprevention Investigated for Lung Cancer



DIVISION OF CANCER PREVENTION

Despite extensive anti-smoking campaigns and a substantial drop in the number of adult smokers in the United States, lung cancer continues to be a disease that affects smokers, non-smokers, and even former smokers, years after quitting. These substantial, lingering risk factors for lung cancer in the population make developing effective chemoprevention agents – that prevent cancer from developing or progressing into detectible disease – a priority.

Fekadu Kassie, D.V.M, Ph.D., a toxicologist and assistant professor of oncology at the University of Minnesota Masonic Cancer Center, has chosen to focus his career on identifying promising compounds for testing in human lung cancer chemoprevention trials. Since 2007, his research team has been exploring the anticancer effects of a compound called indole-3-carbinol (I3C), found in cruciferous vegetables such as broccoli and cabbage.

Population-based studies have suggested that people who eat more cruciferous vegetables have a lower risk of lung cancer, and laboratory experiments with cells and animals show promising anticancer activity of I3C. These findings led Dr. Kassie, with funding from NCI*, to investigate the molecular mechanisms behind the observed effects of I3C, and to determine the dose of I3C for use in early-phase human chemoprevention trials.

The safety of I3C has been well established, explained Dr. Kassie: "No toxic or undesirable effects of these vegetables are reported in Asian countries where they're consumed at high levels. The dietary intake of I3C among populations in these countries is close to the dose found to be safe in clinical trials."

In their earlier mouse studies, administration of I3C, or a dimer of I3C that develops in the gastrointestinal tract called 3,3'-diindolylmethane (DIM), reduced the number of tobacco smoke carcinogen-induced mouse lung tumors by 60%-80%. This experimental model mimics the condition of current smokers since administration of I3C was begun during carcinogen treatment.

In addition, experiments revealed that exposure to the carcinogen resulted in changes in the expression of several proteins associated with tumor formation, including cell division and avoidance of normal, programmed cell death. According to Dr. Kassie, administering I3C along with the carcinogen blocked some of these changes.

Further mouse studies designed to mimic chemoprevention in former smokers showed that I3C also reduced the number of small lung tumors formed after carcinogen exposure by about 75% at a high dose**, Dr. Kassie noted. Additional protein expression studies suggested that I3C inhibits cell survival and division in precancerous and cancerous lung cells, he said.

Although additional tests suggested that I3C administration after precancerous cells and small tumors had already been formed could not decrease the number of these smaller tumors, it could decrease the number of these early tumors progressing to lung adenocarcinoma (a type of lung cancer)***, Dr. Kassie explained.

Dr. Kassie and his colleagues believe that their results warrant moving I3C into human studies. They are currently writing a grant to obtain funding for an early phase chemoprevention trial, which will likely use both I3C and DIM, which have similar mechanisms of action in the body.

Marjorie Perloff, M.D., program director with the NCI Division of Cancer Prevention, commented: "The studies in this grant complement the goals of the Chemopreventive Agent Development Research Group to develop new agents for cancer prevention. This trial studies a compound derived from a group of natural compounds found in cruciferous vegetables which purports to be the 'active' agent in terms of cancer prevention, and is also the source of another agent, 3,3'-diindolylmethane (DIM), which has been extensively studied for possible cancer preventive activity."

* Grant number: 5R01CA128801-04

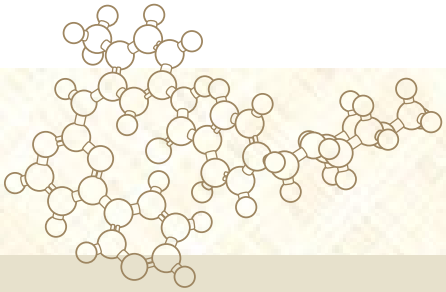
** Kassie F., Matise I., Negia M., Upadhyaya P., & Hecht S.S. (2008). Dose-dependent inhibition of tobacco smoke carcinogen-induced lung tumorigenesis in A/J mice by indole-3-carbinol. *Cancer Prevention Research, 1*(7), 568-76.

*** Qian X., Melkamu T., Upadhyaya P., & Kassie F. (2011). Indole-3-carbinol inhibited tobacco smoke carcinogen-induced lung adenocarcinoma in A/J mice when administered during the post-initiation or progression phase of lung tumorigenesis. *Cancer Letters, 311*(1), 57-65.

DEVELOPING EFFECTIVE AND EFFICIENT TREATMENTS

The development of more efficient and effective cancer treatments – that target cancer cells while leaving surrounding healthy tissue unharmed – is at the heart of NCI's research agenda. We strive to develop well-tolerated, individualized therapies that are tailored to specific features of a patient's cancer.

Antioxidant Enzymes Show Unexpected Behavior in Leukemia Cells Treated with Imatinib



DIVISION OF CANCER TREATMENT AND DIAGNOSIS

FDA approval of the targeted drug imatinib in 2001 revolutionized the treatment of chronic myelogenous leukemia (CML), changing it from a difficult-to-treat cancer with a poor prognosis to a chronic, manageable condition. A long-term, follow-up study found that CML patients treated with imatinib, who have been in remission for at least two years, have the same risk of death as their peers in the general population.

Imatinib targets a specific genetic mutation that causes almost all cases of CML. In this mutation – a type known as translocation – pieces of two different chromosomes become stuck together and produce a protein called BCR-ABL. This protein is like a switch stuck in the "on" position: it constantly signals cancer cells to divide. Imatinib stops cancer cell growth by blocking BCR-ABL.

Unfortunately, some patients eventually become resistant to imatinib, requiring a change in treatment. Alan Diamond, Ph.D., professor of pathology at the University of Illinois at Chicago, is researching whether antioxidants – substances that protect cells from the damage caused by free radicals (also called reactive oxygen species, ROS) – contribute to imatinib resistance.

With funding from NCI*, his laboratory has looked at how levels of an antioxidant enzyme, glutathione peroxidase-1 (GPx-1), change during treatment with imatinib. GPx-1 requires the trace element selenium, found naturally in many foods, to work.

Studies from Dr. Diamond's and other laboratories have found an association between lack of selenium in the diet, reduced GPx-1 activity in the body, and an increased risk of cancer. When he read a paper in 2003 that the ABL protein (part of BCR-ABL that drives CML) activates GPx-1, "my thought was that [GPx-1] is a beneficial protein, and people who have their ABL deactivated by therapy [with imatinib] might be suffering," he said.

Dr. Diamond and colleagues hypothesized that CML patients taking imatinib would have decreased GPx-1 activity, and tested this idea in blood samples taken before and during treatment from seven patients**. Instead of a decrease, "we saw the complete opposite," Dr. Diamond recalled. "The clear trend was that levels of GPx-1 were actually higher in the patients being treated."

To look closer at this unexpected finding, Dr. Diamond's research team performed a series of experiments in cultured cancer cells. They found that not only do GPx-1 levels increase in the presence of the combination of imatinib and the BCR-ABL protein, but levels of another important antioxidant enzyme, MnSOD, also rise. While GPx-1 levels approximately double in CML cells given imatinib, levels of MnSOD rise about five-fold.

Dr. Diamond is currently planning several research projects to understand how these newly discovered mechanisms regulate important antioxidant genes. The idea that more antioxidants are not always better may seem counterintuitive, but makes sense, he explained. "Years ago, we thought that antioxidants were always a good thing. [But] human epidemiology is now revealing that sometimes they're a good thing and sometimes they're a bad thing."

"The unproven model is that in the course of your lifetime antioxidants can be a very good thing," Dr. Diamond added. "They reduce the chance of carcinogenic mutations. So from birth to a certain time in your life, they're very protective. However, once you reach a certain point and cancer is starting to develop, at that point these same mechanisms can protect the cancer cells."

An added layer of complexity being studied by Dr. Diamond comes from the fact that naturally occurring genetic variations – called polymorphisms – can also alter the levels of antioxidant enzymes in cells. Extra amounts of these enzymes are not necessarily a good thing, even in normal cells. The compounds produced when these enzymes break down free radicals are not stable. If a cell doesn't have enough other antioxidant molecules from the diet to finish the break-down process, the compounds can covert back to the damaging free radicals, Dr. Diamond said.

"The increase in MnSOD antioxidant enzyme that's occurring in CML may actually be more significant than the increase in GPx-1, because a high amount of MnSOD could cause oxidative

stress," he explained. Leukemia cells experiencing oxidative stress can end up with additional mutations, some of which could contribute to resistance to drugs targeting BCR-ABL, Dr. Diamond said.

William D. Merritt, Ph.D., program director at NCI's Cancer Therapy and Evaluation Program, commented: "It is very gratifying to see how funding for this small two year discovery grant provided a novel link between resistance to a widely-used therapeutic for CML, imatinib, and antioxidants, and points to the need for further studies to explore changes in antioxidant enzymes in patients receiving this and similar therapies."

* Grant number: 5R21CA129590-03
** Terry, E. N., Gann, P. H., Molokie, R., Deininger, M., & Diamond, A. M. (2011). Changes in the activity of the GPx-1 anti-oxidant selenoenzyme in mononuclear cells following imatinib treatment. *Leukemia Research, 35*(6), 831-3.

High-Fat Diet May Enhance Cancer Patients' Response to Treatments

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

The goal of cancer treatments such as chemotherapy and radiation is to kill cancer cells while minimizing damage to healthy cells and tissues. A growing number of researchers are studying cancer cell metabolism – that is, the chemical processes in the cell that convert or use energy – as an avenue to developing new cancer treatments. They hope to selectively kill cancer cells by taking advantage of fundamental metabolic differences between cancer cells and normal cells.

With support from NCI*, Douglas Spitz, Ph.D., professor and director of the Free Radical and Radiation Biology Program at the Holden Comprehensive Cancer Center at the University of Iowa, along with his colleagues Daniel Berg, M.D. and John Buatti, M.D., hope to use a special diet to exploit metabolic differences between cancer cells and normal cells to enhance cancer patients' responses to combined chemotherapy and radiation therapy (chemo-radio-therapy).

"Radiation is believed to kill cancer cells by causing the formation of free radicals in tumor tissue, inducing a condition known as oxidative stress that can be enhanced by chemotherapy to achieve better treatment responses," Dr. Spitz noted. Oxidative stress occurs when the balance between cellular anti-oxidants and pro-oxidants – free radicals and reactive oxygen species – shifts to favor the accumulation of pro-oxidants, he explained. If left unchecked, these highly reactive pro-oxidants can damage DNA, proteins, and other biological molecules in the cell and may cause cell death.

"Tumor cells appear to have disruptions in mitochondrial oxidative metabolism that lead them to produce more superoxide and other reactive oxygen species, compared with normal cells," Dr. Spitz explained. "Oxidative metabolism is a chemical process that occurs in the mitochondria of cells in which oxygen consumption is used to make energy from food sources. Altered oxidative metabolism in cancer cell mitochondria is thought to result in chronic oxidative stress in cancer cells, relative to normal cells."

Ketogenic diets, which are high in fat and low in protein and carbohydrates, deprive cells of glucose and force them to rely more heavily on mitochondrial oxidative metabolism, Dr. Spitz said, adding that healthy cells don't appear to have the defects in mitochondrial metabolic pathways that are present in tumor cells.

Dr. Spitz is pursuing the idea that "we should be able to induce oxidative stress selectively in cancer cells by feeding patients a ketogenic diet that forces the use of mitochondrial metabolic pathways leading to the production of superoxide." The augmented level of oxidative stress in cancer cells would in turn be expected to selectively sensitize cancer cells to conventional cancer therapies that kill cells via oxidative stress in an additive fashion, he said.

To test the feasibility of this approach, Dr. Spitz and his colleagues conducted preliminary studies in mouse models of human pancreatic cancer, lung cancer, and head and neck cancer. These mice were implanted with human cancer cells and treated

with standard chemo-radio-therapy combinations used clinically with and without feeding a ketogenic diet.

"We've been able to show that if you feed tumor-bearing mice a ketogenic diet, you can inhibit tumor growth and delay the progression of disease in animals that have been treated with radiation and chemotherapy," Dr. Spitz reported. The researchers also saw an increase in chemical markers of oxidative stress in blood samples and tumor samples from animals that were fed the ketogenic diet during therapy.

"We think there might be a causal relationship between the oxidative stress and the enhanced chemo-radio-therapy responses of tumors in animals fed ketogenic diets, but we're still doing experiments to try to prove if that is true," Dr. Spitz added.

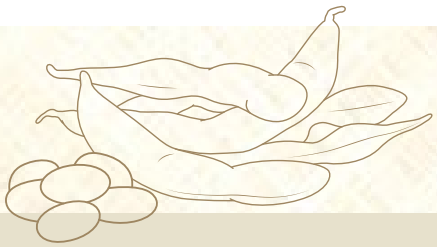
Meanwhile, in collaboration with his physician colleagues, Dr. Spitz has launched an early-phase clinical trial (phase I) in which six patients with advanced, inoperable pancreatic cancer and six patients with inoperable non-small cell lung cancer (NSCLC) will be put on a ketogenic diet for six weeks. The trial will test whether patients can safely tolerate the high-fat diet while being treated with standard chemo-radio-therapy protocols, he said. The researchers will also test blood samples from the patients for markers of oxidative stress and ketosis – a state of elevated levels of ketone bodies in the body, which would be caused from eating a ketogenic diet.

"Ketogenic diets have been used safely for more than 20 years for treating epilepsy and we're only asking people to eat it for six weeks," Dr. Spitz said. If this preliminary clinical trial shows that the ketogenic diet is safe for cancer patients, Dr. Spitz and his colleagues plan to conduct a clinical trial in a larger number of patients with pancreatic cancer and NSCLC. The goal of that trial will be to find out whether a ketogenic diet can enhance the effectiveness of standard chemo-radio-therapy in humans.

Dr. Dan Xi, the program director at OCCAM responsible for overseeing this grant, commented that "using the ketogenic diet as adjuvant approach with standard therapies in humans is very innovative. This multiple PI grant is led by a strong team with proper expertise in both basic and clinical sciences, and addresses a research area of special interest for our office and the Division of Cancer Treatment and Diagnosis, i.e., complementary approaches that augment the therapeutic index of conventional cancer therapies."

* Grant number: 1R21CA161182-01

Soy Used to Protect Normal Cells While Sensitizing Cancer Cells to Radiation



DIVISION OF CANCER TREATMENT AND DIAGNOSIS

Although radiation therapy can be a powerful treatment for lung cancer, normal lung tissue is very sensitive to radiation-induced damage. Inflammation of the lungs and the formation of scar tissue, which can occur weeks to months after treatment, pose particular risks for patients. These side effects limit the amount of radiation that can be aimed at a lung tumor, potentially decreasing the effectiveness of the therapy.

Under a grant from NCI*, Gilda Hillman, Ph.D., professor of radiation oncology at Wayne State University and the Barbara Ann Karmanos Cancer Institute in Detroit, Michigan, is studying whether natural soy isoflavones can both protect normal lung cells from radiation damage and increase the toxic effects of radiation on lung cancer cells.

Her research team first asked these questions 12 years ago, in collaboration with a colleague at Wayne State, Fazlul Sarkar, Ph.D., whose laboratory had been testing natural compounds to sensitize cancer cells to chemotherapy drugs. At that time, Dr. Hillman's research focused on combining radiation therapy with immunotherapy in several mouse models of cancer. Dr. Sarkar suggested that they try combining their areas of research to test soy isoflavones with radiation in cancer cells and in her mouse cancer models. "I tried it, and it worked!" recounted Dr. Hillman.

Since 2000, her laboratory has painstakingly teased out the details of the molecular mechanisms behind the two complementary effects observed by combining soy isoflavones and radiation: increased cancer cell death and decreased damage to normal cells.

To increase death of cancer cells, the isoflavones found in soy – including genistein, daidzein, and glycitein – seem to interfere with lung cancer cells' ability to repair the DNA damage incurred from radiation exposure, Dr. Hillman said. In their experiments, when she and her colleagues irradiated cancer cells without adding soy isoflavones, the cells rapidly activated repair pathways that fixed radiation-induced DNA damage, allowing some of the cells to live and continue dividing.

When the researchers added soy isoflavones to radiation exposure, these repair pathways were inhibited, leading to increased cancer cell death, Dr. Hillman explained. This suggests that blocking these pathways with soy isoflavones should be effective in cancer cells without causing damage to normal cells.

In fact, soy isoflavones appear to have a protective effect in normal lung tissue. In recent mouse studies from Dr. Hillman's laboratory, soy isoflavones given during and after radiation therapy reduced bleeding, inflammation, and scarring in normal lung tissue in mice treated with radiation**. At the same time, "soy increased the killing of tumor cells induced by radiation, thus playing a differential role in tumor versus normal cells," she said.

Dr. Hillman and her colleagues are currently planning a trial for lung cancer patients, looking at the combination of radiation therapy, chemotherapy with the drugs cisplatin and etoposide or pemetrexed, and soy. Patients will continue to take soy for 6 months after treatment, "since studies in our lab have shown that the effects of soy are better if you continue it after the end of radiation therapy," explained Dr. Hillman. The researchers hope to start the trial after securing a reliable, tested supply of soy isoflavone tablets that meet their standards for proof of safety.

NCI Program Director Dan Xi, Ph.D. commented, "This project addresses an established research area of special interest for complementary approaches that enhance the effects of conventional cancer therapies. It is our hope that this study, if successful, could ultimately lead to a better therapeutic strategy for non-small cell lung cancer care."

* Grant number: 1R21CA155518-01A1

** Hillman G.G., Singh-Gupta V., Runyan L., Yunker C.K., Rakowski J.T., Sarkar F.H., Miller S., Gadgeel S.M., Sethi S., Joiner M.C., & Konski A.A. (2011). Soy isoflavones radiosensitize lung cancer while mitigating normal tissue injury. *Radiotherapy and Oncology, 101*(2),329-36.

IMPROVING THE QUALITY OF LIFE FOR CANCER PATIENTS, SURVIVORS, AND THEIR FAMILIES

Advances in our ability to detect, treat, and support cancer patients have turned this disease into one that is chronic, or readily managed, for many and curable for increasing numbers. While the ultimate goal of eliminating cancer altogether continues to be our long-term commitment, the capacity to dramatically reduce the suffering caused by cancer is within our immediate grasp.

Impact of Exercise on Ovarian Cancer Prognosis Studied

DIVISION OF CANCER CONTROL AND POPULATION SCIENCES

Studies suggesting a benefit of physical activity and exercise for people with certain cancers, particularly breast cancer, are well documented in the medical literature. However, very few studies published to date discuss the beneficial effects of exercise after a diagnosis of ovarian cancer. Melinda Irwin, Ph.D., M.P.H., an epidemiologist at the Yale University School of Public Health, is seeking to address that gap with the Women's Activity and Lifestyle Study in Connecticut (WALC).

The need for interventions to improve symptom-control and alleviate treatment side effects is critical for ovarian cancer patients, Dr. Irwin noted. "When you look at women with ovarian cancer, with the treatments they go through and the surgery and the later stage of diagnosis, their quality of life (QOL) is often significantly impaired," she said. "I believe exercise will be very beneficial for these patients."

With support from NCI*, Dr. Irwin and her colleagues aim to enroll up to 230 sedentary women diagnosed with Stage I-III ovarian cancer, who are being randomized for 6 months into either a home-based walking program or into an "attention control" group who receive weekly health education sessions over the phone with a counselor. The counselor also contacts the women in the exercise arm of the study by phone, Dr. Irwin added. The counselor helps motivate and guide them to complete 150 minutes of walking per week.

The walking program intervention used for WALC is designed to gradually build in intensity, Dr. Irwin explained. "It's not as though they're training for a marathon but we're able to get the exercise levels up to exceed the recommended amount of 150 minutes a week of brisk walking. They wear a heart-rate monitor when they exercise and put a pedometer on every day." Women in the exercise group also walk a 1-mile route every month to monitor their improvement in walking speed. "When they first start the study, it may take some women about 30 minutes to walk that mile, but at 2-3 months into it, they might be walking it in 20 minutes," she reported.

Regular exercise can be challenging for women with late-stage ovarian cancer, Dr. Irwin commented. Such patients often experience disease recurrence and need to go back on chemotherapy. "Some of them also suffer from peripheral neuropathy, so they have a fear of falling," she added. "We recommend they use the Nordic walking poles to help with balance when they need to and until that fear of falling subsides and they're more confident."

There are a number of approaches and strategies the researchers use to make it easier for women to continue in the exercise program, Dr. Irwin added, and so far, "there is never a woman who comes back from an exercise session who says she doesn't feel good."

Measuring and comparing the impact of exercise, versus the health education control group, on the patients' QOL (such as fatigue, anxiety, and depression) "is the primary endpoint in our study," Dr. Irwin continued. In addition, the researchers are conducting baseline and 6-month clinic visits for study participants to evaluate the patients' QOL and surrogate biomarkers for ovarian cancer progression, Dr. Irwin added.

"We're collecting fasting blood samples at the beginning and at the end of the study because there are some serum markers, such as leptin and insulin-like growth factors (IGFs), that we know are related to ovarian cancer that have also been shown to be related to exercise or body weight," Dr. Irwin noted. The researchers will assess any changes to these biomarkers, in both the exercise and control groups, at the end of the 6-month intervention period.

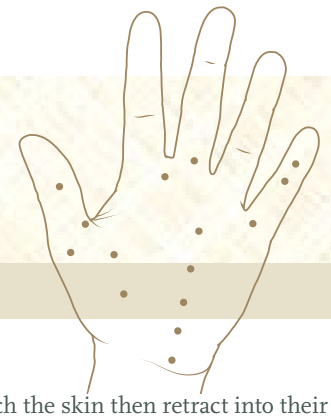
The study, which is expected to end in 2014, has been expanded to include enrollment of patients from outside of Connecticut, Dr. Irwin said. She plans to submit an abstract and possibly present preliminary findings from the study at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting. If the findings show a positive impact of exercise on ovarian cancer patients' QOL and disease biomarkers, Dr. Irwin hopes to conduct a follow-up investigation to assess its long-term (3-5 years) effects on disease progression and survival among these patients.

Currently, only about one-third of cancer centers in the United States offer some sort of exercise program to their patients and cancer survivors, Dr. Irwin commented, and often such programs are tailored for or limited to breast cancer patients. She hopes to add to the evidence base that opens up exercise interventions to more cancer patients, including women with ovarian cancer. "If we show that WALC is an effective program when done over the phone, it could easily be done and replicated nationally," she commented.

Catherine M. Alfano, Ph.D., deputy director NCI Office of Cancer Survivorship, commented: "Dr. Irwin's study addresses an important gap in NCI's grant portfolio of exercise and survivorship studies that have almost exclusively focused on women with breast cancer. This study will help us understand whether exercise can play a role in the rehabilitation of ovarian cancer survivors by alleviating persistent cancer-related symptoms and improving functional impairments and the ability to fully participate in life after cancer treatment."

* Grant number: 5R01CA138556-04

Acupuncture Studied to Prevent Radiation-Induced Chronic Dry Mouth



DIVISION OF CANCER PREVENTION

Xerostomia, or chronic severe dry mouth, is caused by reduced salivary flow and is a common side effect for many patients receiving radiotherapy for head and neck cancers. Most of the current treatments for xerostomia are palliative and offer limited benefit, but studies have begun to show promising results for the use of acupuncture in preventing and lessening xerostomia.

NCI has supported two small studies, conducted at the MD Anderson Cancer Center and the Fudan University Cancer Hospital in Shanghai, China, that investigated the feasibility and efficacy of acupuncture as a potential preventive therapy for radiation-induced chronic dry mouth. Based on promising results from the previous studies*, NCI is currently funding** two large, randomized, phase III trials that examine the effects of acupuncture for preventing or treating radiation-induced xerostomia.

Lorenzo Cohen, Ph.D., professor in the MD Anderson Departments of General Oncology and Behavioral Science and director of the cancer center's Integrative Medicine Program, is the principal investigator of the grants, which have supported all of these acupuncture studies. He said the first phase III study, already well underway, is testing the use of acupuncture in preventing xerostomia in patients undergoing radiotherapy for head and neck cancer or nasopharyngeal carcinoma.

According to Dr. Cohen, the clinical trial compares active acupuncture with the use of a placebo or "sham" version of acupuncture, as well as with a third group of patients who will receive usual medical care. Each of the three arms of the study will enroll 100 patients, divided evenly between MD Anderson and the Fudan Hospital.

Patients in the two acupuncture groups (active and sham) are treated 3 times weekly during the 7 weeks they receive radiation therapy. The comparison with sham acupuncture is important, Dr. Cohen explained, because some previous studies have found that "you often don't see any clinical differences between the two approaches although both of them are usually better than usual care alone." Both types of acupuncture treatments used in the study involve "combinations of real needles and sham needles (blunt needles that touch the skin then retract into their handles)," he explained. "This is something we're not telling our patients in the study so that we can keep them 'blinded' about which acupuncture treatment they're receiving."

The study is evaluating the patients' self-reported outcomes based on a xerostomia questionnaire, which assesses severity of dry mouth symptoms and their interference with quality of life. In addition, Dr. Cohen and his colleagues are measuring saliva flow rates using standardized sialometry collection techniques. "We'll also be looking at the constituents of the saliva, such as pH, buffering capacity, viscosity, and the different proteins that are in the saliva," he noted. Patient assessments occur at baseline, mid- and immediately post- radiation treatment, as well as at 3, 6, and 12 months following treatment.

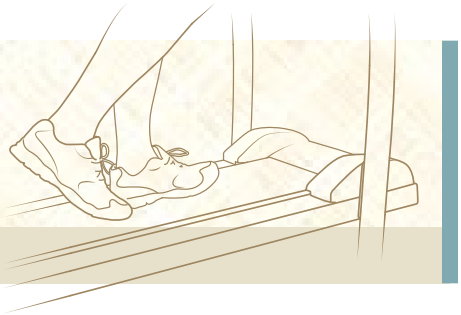
The second major research study of acupuncture (active and sham) and xerostomia will start later in 2012 in over a dozen institutions around the United States that are part of the NCI's Community Clinical Oncology Program (CCOP) network. The study will examine the effects of acupuncture to reduce the severity of radiation-induced xerostomia in patients with chronic xerostomia who have already completed radiotherapy for head and neck cancer.

"I'm hoping – if these two large, well-designed clinical trials confirm our earlier positive findings – that the use of acupuncture for the prevention and treatment of xerostomia will become the standard of care for this debilitating problem," Dr. Cohen commented. He added that he hopes these studies will also clear the way for health insurance coverage of the treatment. However, he noted, if the studies show that active and sham acupuncture produce equivalent results and are both better than usual care, that will open up areas of additional research to determine the reasons for those similarities.

* Meng, Z., Garcia, M. K., Hu, C., Chiang, J., Chambers, M., Rosenthal, D. I., & Cohen L. (2012). Randomized controlled trial of acupuncture for prevention of radiation-induced xerostomia among patients with nasopharyngeal carcinoma. *Cancer, 118*(13), 3337-44.

** Grant numbers: 5R01CA148707-02, 1R01CA160880-01A1

Exercise Study for Metastatic Breast Cancer Patients May Offer Benefits



DIVISION OF CANCER PREVENTION

There is growing recognition and acceptance of the beneficial role of exercise following a breast cancer diagnosis. Studies have suggested that exercise improves symptom control and may be associated with reductions in cancer-related and overall death rates in women with breast cancer. NCI is currently supporting a pilot research study* in women with metastatic breast cancer (MBC) as a first step in determining the feasibility of launching large-scale clinical trials investigating the effects of exercise on breast cancer outcomes.

Lee Jones, Ph.D., Associate Professor and Scientific Director of the Duke University Center for Cancer Survivorship, who is the principal investigator of the study, commented, "There are a lot of research studies that look at the role of exercise in women with early stage breast cancer, but few studies have looked at the role of exercise in patients with metastatic disease."

Jones and his team are conducting a randomized phase II clinical trial in women with MBC. Half of the patients will participate in a treadmill walking program, while the remainder of patients will be in a control group, doing only low-intensity stretching exercises.

The study focuses on the safety and feasibility of exercise training as opposed to the potential role of exercise to improve disease outcomes in women with metastatic disease. Before addressing these types of questions, it is first of crucial importance to determine if exercising by these individuals is safe or possible "because MBC is a totally different clinical scenario than those with early-stage disease," Dr. Jones noted. Women with MBC face many additional challenges from advanced disease and its treatments, including drug toxicities, infections, and hospitalizations, he added. "We have to be on our toes because their situations can change week-to-week."

Dr. Jones reported they have enrolled about 30 women into the study so far and have identified two distinct groups of MBC patients. "There is a group who essentially do very well with exercise," he said. "And then there is another group who really want to exercise but they're just not able to because of toxicity, disease progression, and other factors. I believe this study is going to be extremely informative in terms of working out the characteristics of individuals with advanced disease who may be able to tolerate and benefit from an exercise program."

"That is a simple question but it's an important first step towards moving ahead with larger clinical trials to really get to some of the biology of what's going on," Dr. Jones continued. "It's not just what can we do to help these patients feel better as they go through all these treatments, but can we also impact clinical and disease outcomes in these patients?"

If the pilot study shows promising results for exercise in MBC patients in terms of program adherence, adverse events, and safety profile, "that would bode well for future study in a more select population," Dr. Jones noted. "I think exercise is definitely going to be complementary to standard care for these patients in the future."

* Grant number: 5R21CA143254-02

APPENDIX

NCI-supported Clinical Trials in CAM Research

An NCI-supported clinical trial meets one or more of the following criteria: the protocol (1) has been reviewed and approved by NCI's CTEP Protocol Review Committee or by an approved NCI-designated Cancer Center Protocol Review and Monitoring System and/or (2) receives support through an NCI grant, contract, or cooperative agreement.

Title	Phase	Type	Status	Age	Sponsor	Protocol IDs
Pediatric/Adolescent						
Phase III Randomized Study of Glutamic Acid in Reducing Vincristine-Related Peripheral Neurotoxicity in Young Patients Undergoing Vincristine-Containing Treatment for Wilms' Tumor, Rhabdomyosarcoma, Acute Lymphoblastic Leukemia, or Non-Hodgkin's Lymphoma	Phase III	Supportive care, Treatment	Active	3 to 20	NCI	SCUSF-0402, HLMCC-0402, NCT00369564, ACCL 0731
Acupuncture Point Stimulation for Treatment of Chemotherapy Nausea and Vomiting	No phase specified	Supportive care	Active	8 to 21	NCI, Other	PEDSVAR0016, NCI-2011-03653, NCT01492569
Pilot Study of Educational and Promotional Materials Development For Use In Promoting Physical Activity In Community-Based After-School Programs By Multiethnic, Urban Adolescents	No phase specified	Educational/ Counseling/Training, Prevention	Active	11 to 14	NCI	MSUHNS-0003669, FWA00005270, NCT00301158
Adult						
Bladder						
Green Tea Extract in Treating Patients With Nonmetastatic Bladder Cancer	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	18 and over	NCI, Other	CDR0000594276, WCCC-UWI06-8-01, H2007-0250, 07-1270-03, UWI06-8-01, CO06810, NCT00666562
Brain						
Phase II Randomized Study of Adjuvant Boswellia serrata and Standard Treatment Versus Standard Treatment Alone in Patients With Newly Diagnosed or Recurrent High-Grade Gliomas	Phase II	Treatment	Active	18 and over	NCI	CASE-CCF-7348, CCF-7348, NCT00243022, CASE1304200
Yoga Therapy in Treating Patients With Malignant Brain Tumors	No phase specified	Educational/ Counseling/ Training, Supportive care	Approved-not yet active	18 and over	NCI, Other	CCCWFU 98410, NCI-2010-02044, NCT01234805
Breast						
Diindolylmethane in Treating Patients With Breast Cancer	Phase III, Phase II	Biomarker/ Laboratory analysis, Diagnostic, Treatment	Active	19 and over	NCI, Other	10-0366-04, NCI-2011-00710, NCT01391689
Oral Curcumin for Radiation Dermatitis	Phase III, Phase II	Biomarker/ Laboratory analysis, Supportive care, Treatment	Active, not recruiting	21 and over	NCI	URCC 10054, URCC 09005, NCT01246973

Title	Phase	Type	Status	Age	Sponsor	Protocol IDs
Phase III Randomized Study of Cranial Microcurrent Electrical Stimulation in Reducing Chemotherapy-Related Symptoms in Women With Stage I-IIIA Breast Cancer Receiving Adjuvant Chemotherapy	Phase III	Biomarker/ Laboratory analysis, Supportive care	Active	Adult	NCI	MCV-MCC-11995, MCC-11995, NCT00902330
Phase III Randomized Study of Omega-3-Fatty Acid in Treating Aromatase Inhibitor-Induced Musculoskeletal Pain and Stiffness in Patients With Stage I, II, or IIIA Breast Cancer	Phase III	Biomarker/ Laboratory analysis, Supportive care	Active	Not specified	NCI	SWOG-S0927, S0927, NCT01385137
Phase III Randomized Study of Acupuncture Versus Sham Acupuncture Versus Waiting List for Joint Symptoms Related to Aromatase Inhibitors in Patients With Stage I-III Breast Cancer	Phase III	Biomarker/ Laboratory analysis, Supportive care	Approved-not yet active	Postmeno-pausal	NCI	SWOG-S1200, S1200, NCT01535066
Menopause and Meditation for Breast Cancer Survivors	Phase II, Phase I	Supportive care	Active	30 to 70	NCI, Other	1R21CA106336-01A1, NCT00156416
Phase II Randomized Study of High-Dose Cholecalciferol in Premenopausal Women at High-Risk for Breast Cancer	Phase II	Biomarker/ Laboratory analysis, Prevention	Active	18 to 50	NCI	SWOG-S0812, S0812, NCT01097278
Broccoli Sprout Extract in Treating Women Who Have Had a Mammogram and Breast Biopsy	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	21 and over	NCI, Other	CDR0000634111, R21CA132236, P30CA069533, OHSU-4702, eIRB 4702, OHSU-LAY-01, NCT00843167
Alkaline Water in Reducing Skin Toxicity in Women With Breast Cancer Undergoing Radiation Therapy	Phase II	Supportive care, Treatment	Active	18 and over	NCI, Other	CASE2109, NCI-2010-01233, NCT01487954
Study of CoQ10 During One Cycle of Doxorubicin Treatment for Breast Cancer	Phase I	Supportive care, Treatment	Active	21 and over	NCI, Other	AAAD8521, NCT00976131
Cook for Your Life	No phase specified	Behavioral study, Biomarker/ Laboratory analysis, Educational/ Counseling/Training	Active	21 and over	NCI, Other	AAAE9701, 1R21CA152903-01, NCT01414062
Randomized Study of Vitamin D and Breast Cancer Biomarkers in Female Patients	No phase specified	Biomarker/ Laboratory analysis, Prevention	Active	55 and under	NCI	CALGB-70806, CALGB 70806, NCT01224678
Soy Isoflavones Supplementation in Treating Women at High Risk For or With Breast Cancer	No phase specified	Diagnostic, Prevention, Treatment	Active	30 to 75	NCI, Other	1B-10-6, NCI-2010-01847, NCT01219075
Effects of Tibetan Yoga on Fatigue and Sleep in Cancer	No phase specified	Supportive care	Active	18 and over	NCI, Other	2005-0035, NCT00507923
Randomized Study of Magnesium Oxide in Postmenopausal Women With Hot Flashes and a History of Breast Cancer	No phase specified	Supportive care	Active	18 and over	NCI	NCCTG-N10C2, N10C2, NCT01439945

Title	Phase	Type	Status	Age	Sponsor	Protocol IDs
Home-Based Symptom Management Via Reflexology for Breast Cancer Patients	No phase specified	Supportive care	Active	21 and over	NCI, Other	1R01CA157459-01, NCT01582971
Randomized Study of Education With or Without Exercise and Counseling in Preventing Lymphedema in Women With Stage I-III Breast Cancer Who Are Undergoing Axillary Lymph Node Dissection	No phase specified	Supportive care, Treatment	Active	18 and over	NCI	CALGB-70305, CALGB 70305, NCT00376597
Phase II Pilot Study of Magnesium Oxide in Treating Menopausal Hot Flashes in Women With Cancer	Phase II	Supportive care	Active	18 and over	NCI	MCV-MCC-12062, MCC-12062, NCT01008904
Venlafaxine and Hypnosis or Focused Attention In Treating Patients With Hot Flashes	No phase specified	Supportive care	Active	18 and over	NCI, Other	MC09C7, NCI-2009-01303, 09-003233, NCT01000623
Acupressure for Persistent Cancer Related Fatigue	Phase III, Phase II	Supportive care	Active	18 to 75	NCI, Other	CA151445, NCT01281904
Cancer Survivors						
Phase II Randomized Study of Green Tea Catechin Extract in Patients at High-Risk for Recurrent Colonic Neoplasia	Phase II	Biomarker/ Laboratory analysis, Prevention	Approved-not yet active	40 and over	NCI	MAYO-MC084C, MC084C, R01-CA-132991
Phase II Randomized Study of Two Home-Based Interventions for Sleep-Wake Disturbances in Cancer Survivors	Phase II	Supportive care	Active	18 and over	NCI	NCCTG-N07C4, N07C4, NCT00993928
Randomized Pilot Study of Hypnosis in Controlling Hot Flashes in Women Who are Breast Cancer Survivors	No phase specified	Supportive care	Active	Over 18	NCI	S-WHITE-8165, NCT00094133
L-Arginine Supplements in Treating Women Who Are Cancer Survivors	No phase specified	Supportive care	Active	Adult	NCI, Other	CDR0000532277, CCCWFU-05-04-01, CCCWFU-97106, WFU 05-04-01, NCT00459134
Cervix						
Folic Acid Clinical Trial for the Prevention of Cervical Cancer	Phase II	Biomarker/ Laboratory analysis, Prevention	Active	19 and over	NCI	UAB-F060511015, F060511015, UAB-IRB0000196, NCT00703196
Mindfulness-Based Stress Reduction or General Health Education in Improving Immune Response to Human Papilloma Virus in Patients With Cervical Dysplasia	No phase specified	Behavioral study, Biomarker/ Laboratory analysis, Educational/ Counseling/Training	Active	18 and over	NCI	FCCC-06851, 06-851, NCT00653146
Randomized Study of Magnetic Acupressure in Reducing Pain in Cancer Patients Undergoing Bone Marrow Aspiration and Biopsy	No phase specified	Diagnostic, Supportive care	Active	18 and over	NCI	JHOC-J07103, J07103, JHOC-NA_00013389, NCT00670917
Colon/Rectum						
Phase III Study of the Effect of Vitamin E and/or Selenium on Adenomatous Colorectal Polyps in Men Enrolled on SELECT Trial SWOG-S0000	Phase III	Natural history/ Epidemiology, Prevention	Active	50 and over	NCI	SWOG-S0000D, S0000D, NCT00706121

Title	Phase	Type	Status	Age	Sponsor	Protocol IDs
Selenium for Prevention of Adenomatous Colorectal Polyps	Phase III	Prevention	Active	40 to 80	NCI, Other	CDR0000353185, P30CA023074, UARIZ-00-0430-01, UARIZ-HSC-00142, P01CA041108, 00-0430-01, NCT00078897
Cholecalciferol(25-[OH]-Vitamin D) in Treating Patients With Colorectal Cancer	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	18 and over	NCI, Other	CASE2210, NCI-2011-01280, NCT01403103
Polyphenon E in Treating Patients With High-Risk of Colorectal Cancer	Phase II	Biomarker/ Laboratory analysis, Treatment	Approved-not yet active	40 and over	NCI, Other	MC084C, NCI-2012-00058, NCT01606124
Phase II Randomized Study of Acupuncture in Reducing Postoperative Ileus in Patients Who Have Undergone Segmental or Subtotal Colectomy for Colorectal Cancer	Phase II	Supportive care	Active	Over 18	NCI	MSKCC-06145, NCT00425412
Phase I/II Randomized Study of Inositol for the Prevention of Colorectal Cancer in Patients With Colitis-Associated Dysplasia	Phase I	Biomarker/ Laboratory analysis, Prevention	Active	18 and over	NCI	NU-NWU09-13-02, NWU09-13-02, NCT01111292
Vitamin E Supplements in Treating Patients Undergoing Surgery for Colorectal Cancer	Phase I	Biomarker/ Laboratory analysis, Treatment	Active	18 and over	NCI, Other	120901, CDR0000642446, IRB#0220090065, CINJ-120901, NCT00905918
Doctor-Recommended Home-Based Exercise Program or Relaxation Training in Improving Physical Functioning and Controlling Symptoms in Patients With Stage IV or Recurrent Colon Cancer That Cannot Be Removed By Surgery	No phase specified	Behavioral study, Supportive care	Active	18 and over	NCI	MDA-2009-0288, 2009-0288, NCT00985400
Head/Neck						
Phase III Randomized Study of Lactobacillus brevis CD2 Lozenges Versus Placebo in the Prevention of Acute Oral Mucositis in Patients With Squamous Cell Carcinoma of the Head and Neck Receiving Concurrent Radiotherapy and Chemotherapy	Phase III	Biomarker/ Laboratory analysis, Supportive care, Treatment	Approved-not yet active	18 and over	NCI	NCCTG-N11C5, N11C5, NCT01545687
Acupuncture in Treating Dry Mouth Caused By Radiation Therapy in Patients with Head and Neck Cancer	Phase III	Supportive care	Approved-not yet active	Not specified	NCI	MDA-04-01, MDA-04-01, MDA 04-01, NCT01141231
Xerostomia Acupuncture Trial	Phase III	Supportive care	Active	18 and over	NCI, Other	2010-0584, NCT01266044
Phase II Randomized Chemoprevention Study of Bowman-Birk Inhibitor Concentrate in Patients With Oral Leukoplakia	Phase II	Biomarker/ Laboratory analysis, Prevention, Treatment	Active	18 and over	NCI	UCIRVINE-UCI-98-34, UCIRVINE-UCI-1998-521, NCT00330382, U01-CA-72294
Curcumin Biomarker Trial in Head and Neck Cancer	No phase specified	Biomarker/ Laboratory analysis, Treatment	Active	18 to 90	NCI, Other	H08-081, 1R21CA137545-01A2, FWCC, NCT01160302

Title	Phase	Type	Status	Age	Sponsor	Protocol IDs
Lung						
Exercise and Lung Cancer Trial	Phase III	Behavioral study	Active	21 to 80	NCI, Other	00018255, 1R01CA138624-01A1, NCT01068210
Phase II Randomized Study of Inositol for the Prevention of Lung Cancer in Current or Former Smokers With Bronchial Dysplasia	Phase II	Biomarker/ Laboratory analysis, Prevention	Active	45 to 79	NCI	MAYO-MAY06-8-01, MAY06-8-01, NCT00783705
Calcitriol in Preventing Lung Cancer in Smokers and Former Smokers at High Risk of Lung Cancer	Phase I	Biomarker/ Laboratory analysis, Prevention	Active	40 to 79	NCI, Other	CDR0000596506, P30CA016056, RPCI-I-90206, I 90205, NCT00690924
Oleandrin (Nerium Oleander Extract) in Combination With Carboplatin and Docetaxel in Patients With Advanced Non-Small Cell Lung Cancer	Phase I	Biomarker/ Laboratory analysis, Supportive care	Approved-not yet active	18 and over	NCI	MDA-2011-0147, 2011-0147, NCT01562301
Flaxseed Supplementation in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer Undergoing Chemoradiotherapy and Radiation Therapy	Phase I	Biomarker/ Laboratory analysis, Treatment	Active	18 and over	NCI	UPCC-03309, UPCC 03309, IRB# 806733, NCT00955942
Multiple						
Phase III Randomized Study of Live Freeze-dried Lactic Acid Bacteria Probiotic (VSL#3®) Versus Placebo in the Prevention of Acute Enteritis in Patients With Cancer Receiving Concurrent Chemotherapy and Pelvic Radiation Therapy	Phase III	Supportive care, Treatment	Approved-not yet active	18 and over	NCI	NCCTG-N10CB, N10CB, NCT01473290
Probiotic Supplementation in Preventing Treatment-Related Diarrhea in Patients With Cancer Undergoing Chemotherapy	Phase II	Biomarker/ Laboratory analysis, Supportive care	Approved-not yet active	18 and over	NCI, Other	VAR0084, NCI-2012-01127, NCT01644097
Yoga-Based Cancer Rehabilitation Program	No phase specified	Behavioral study, Supportive care	Active	18 and over	NCI, Other	#2000-007, NCI R03 CA88598-01A1, NCT00179348
Mindfulness Relaxation Compared With Relaxing Music and Standard Symptom Management Education in Treating Patients Who Are Undergoing Chemotherapy for Newly Diagnosed Solid Tumors	No phase specified	Educational/ Counseling/ Training, Supportive care	Active	18 and over	NCI	MDA-CCC-0106, MDA-CCC-01-06, 2004-0024, NCT00086762
Healing Touch or Guided Imagery In Treating Pain, Fatigue, Nausea, and Anxiety in Patients Undergoing Chemotherapy	No phase specified	Supportive care	Active	18 and over	NCI, Other	CCCWFU 97511, NCI-2012-00164, NCT01553578
No Specific Cancer Type/Healthy Volunteer						
Phase III Randomized Study of a Psychoeducation, Paced Respiration, and Relaxation Intervention for Caregivers of Patients Undergoing Bone Marrow Transplantation	Phase III	Biomarker/ Laboratory analysis, Educational/ Counseling/Training, Supportive care	Active	18 and over	NCI	UCHSC-080303, 08-0303, NCT00833898
Vitamin D and Omega-3 Trial (VITAL)	Phase III	Prevention	Active	60 and over	NCI, Other	2009P-001217, NCT01169259

Title	Phase	Type	Status	Age	Sponsor	Protocol IDs
Exercise or Relaxation for Smoking Cessation	No phase specified	Behavioral study	Active	50 and over	NCI, Other	09-097-2, 1RO1 DA024872-01A1, NCT00921388
Patient-Directed Lifestyle Change and Health Promotion Program or Usual Care in Low-Income, Uninsured Participants in Los Angeles County, California	No phase specified	Behavioral study, Educational/ Counseling/Training, Health services research	Active	18 and over	NCI, Other	CDR0000561559, UCLA-G-060801501A, G06-08-015-01, NCT00521209
Randomized Study of Lycopene in Preventing Prostate Cancer in Healthy Participants	No phase specified	Biomarker/ Laboratory analysis, Prevention	Active	18 and over	NCI	UIC-2004-0217, NCT00322114
Studying the Effect of Freeze-Dried Table Grape Powder on Blood Estrogen Levels in Postmenopausal Women	No phase specified	Biomarker/ Laboratory analysis, Prevention	Active	18 and over	NCI, Other	CDR0000581219, P30CA015083, MC0536, 06-002061, MAYO-MC0536, NCT00611104
Cruciferous Vegetable Intake and Histone Status in Screening Colonoscopy Patients	No phase specified	Biomarker/ Laboratory analysis, Prevention, Screening	Active	50 to 75	NCI, Other	P01 CA090890, NCT01344330
Spiritual Care in Improving Quality of Life of Patients, Caregivers, and Hospital Staff	No phase specified	Supportive care	Active	18 and over	NCI, Other	11110, NCI-2011-02730, NCT01432431
Pancreas						
Vitamin E d-Tocotrienol Administered to Subjects With Resectable Pancreatic Exocrine Neoplasia	Phase I	Treatment	Active	18 and over	NCI, Other	MCC-15630, 1R01CA129227-01A1, NCT00985777
Prostate						
Phase II/III Randomized Study of Adjuvant Soy Protein Isolate in Preventing Recurrence in Patients Who Have Undergone Radical Prostatectomy for Stage II Prostate Cancer	Phase III, Phase II	Biomarker/ Laboratory analysis, Treatment	Active	40 to 75	NCI	UIC-2006-0706, 2006-0706, NCT00765479
Selenium in Preventing Prostate Cancer	Phase III	Biomarker/ Laboratory analysis, Prevention	Approved-not yet active	Under 80	NCI, Other	CDR0000654651, R01CA077789, P30CA023074, UARIZ-99-0045-01, 99-0045-01, NCT00978718
Improving Continence and Quality of Life in Prostate Cancer Patients	Phase III	Health services research, Supportive care	Active	21 and over	NCI, Other	1R01CA127493-01A2, NCT01365182
Effects of Tomato-Soy Juice on Biomarkers in Patients With Prostate Cancer Undergoing Prostatectomy	Phase II, Phase I	Biomarker/ Laboratory analysis, Treatment	Active	Any age	NCI, Other	CDR0000642377, OSU-2007C0026, 2007C0026, NCT01009736
Vitamin D and Soy Supplements in Treating Patients With Recurrent Prostate Cancer	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	Over 18	NCI, Other	CDR0000554969, P30CA012197, CCCWFU-85106, CCCWFU-IRB00000371, NCT00499408
Green Tea or Water in Treating Patients With Prostate Cancer Undergoing Surgery	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	40 to 75	NCI, Other	CDR0000596162, R01CA116242, P30CA016042, UCLA-061109702, 06-11-097-02, NCT00685516

Title	Phase	Type	Status	Age	Sponsor	Protocol IDs
Selenium in Treating Patients With Prostate Cancer	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	Under 85	NCI, Other	CDR0000614471, R01CA079080, P30CA023074, UARIZ-97-0395, UARIZ-HSC-97-57, DAMD17-98-1-8580, 97-0395-01, Watchful Waiting, NCT00752739
Diindolylmethane in Treating Patients With Stage I or Stage II Prostate Cancer Undergoing Radical Prostatectomy	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	18 and over	NCI, Other	CDR0000641168, P30CA022453, WSU-2007-128, 2007-128, NCT00888654
Genistein in Treating Patients With Prostate Cancer	Phase II	Biomarker/ Laboratory analysis, Treatment	Active	18 and over	NCI, Other	NCI 09U2, NCI-2010-00941, STU00019487, P50CA090386, NCT01126879
Study of Polyphenon E in Men With High-grade Prostatic Intraepithelial Neoplasia	Phase II	Prevention	Active	30 to 80	NCI, Other	MCC-15008, R01 CA12060-01A1, NCT00596011
L-Arginine Supplementation With or Without Enzyme Inhibitors In Treating Erectile Function and Quality of Life of Prostate Cancer Survivors Previously Treated With Radiation Therapy	Phase II	Supportive care	Active	18 and over	NCI, Other	cccwfu 98110, WFU-08-08-09, NCT01105130
Chemoprevention of Prostate Cancer, HDAC Inhibition and DNA Methylation	No phase specified	Biomarker/ Laboratory analysis, Prevention	Active	21 and over	NCI	Portland VA-09-0607, 2096, 6232, NCT01265953
Polyunsaturated Fatty Acids in Treating Patients With Prostate Cancer Undergoing Prostate Biopsy and/or Surgery	No phase specified	Biomarker/ Laboratory analysis, Treatment	Active	18 and over	NCI, Other	CDR0000538993, DFCI-03116, 03-116, NCT00458549
Skin						
Pilot Trial to Evaluate the Effect of Vitamin D on Melanocyte Biomarkers	No phase specified	Biomarker/ Laboratory analysis, Prevention	Approved-not yet active	18 to 75	NCI, Other	SKIN0010, SU-10272011-8570, NCT01477463

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