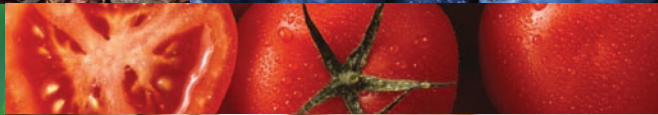


NCI's Annual Report on Complementary and Alternative Medicine

Fiscal Year 2006



Director's Message

The research the National Cancer Institute (NCI) supports, at universities across the country and in our NCI laboratories, is focused on the ultimate goal of helping cancer patients. That mission – achieved through intricate research and rigorous science – most certainly extends, as well, to NCI's study of complementary and alternative medicine, also known as CAM.

This report offers a window into NCI's accomplishments in advancing evidence-based CAM interventions and therapies, along with some perspective on our efforts to more fully understand their efficacy, because of the genetic and biological differences between patients. It is important that physicians caring for patients with cancer know which CAM therapies are compatible with standard chemotherapy methods and with medicines we use to combat the symptoms associated with treatment.

Because cancer is a disease of such complexity, CAM must be an integrated part of the larger research enterprise, touching on many other areas, including studies of basic tumor biology, drug design, nutrition, and behavioral medicine. Consequently, NCI's portfolio of CAM research is distributed throughout many of the Institute's programs.

The Office of Cancer Complementary and Alternative Medicine supports this research through its efforts to attract experienced investigators to work in this important area of science.

I hope you find this report helpful. I also hope that it will generate increased dialogue – especially between patients and their healthcare professionals – about the appropriate uses of CAM, 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 the science that makes their wise decisions possible.



John E. Niederhuber, M.D.
Director
National Cancer Institute



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FIGURE 1. Major Categories of CAM Therapies

**A. Alternative Medical Systems
(and some specific components)**

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: acupuncture, ayurveda, homeopathy, naturopathy, traditional Chinese medicine, Tibetan medicine

B. 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

C. Exercise Therapies

Examples: tai chi, yoga asanas

D. 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

E. 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, mental healing, imagery, relaxation therapy, support groups, stress management, music therapy, cognitive-behavioral therapy, dance therapy, aromatherapy.

F. Nutritional Therapeutics

Definition: An assortment of nutrients and non-nutrients, bioactive food components that are used as chemo-preventive agents, and the use of specific foods or diets as cancer prevention or treatment strategies.

Examples: dietary regimens such as macrobiotics, vegetarian, Gerson diet, Kelley/Gonzalez regimen, vitamins, dietary macronutrients, dietary supplements, soy phytoestrogens, nutrient minerals and elements (amino acids), antioxidants, glutamine, selenium, coenzyme Q10, orthomolecular medicine.

G. Pharmacological and Biologic Treatments

Definition: Off-label use of prescription drugs, hormones, complex natural products, vaccines, and other biological interventions not yet accepted in mainstream medicine.

Examples: antineoplastons, products from honey bees, mistletoe, shark cartilage, 714X, low dose naltrexone, metenkephalin, immuno-augmentation therapy, laetrile, hydrazine sulfate, melatonin.

Sub-category: Complex Natural Products

Definition: 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, mixtures of tea polyphenols, shark cartilage

H. Spiritual Therapies

Examples: intercessory prayer, spiritual healing

Introduction

Each year, Congress requests a report of NCI's annual expenditures in complementary and alternative medicine* (CAM) research. To give more meaning to the numbers provided to Congress, a more detailed account of the Institute's investment in CAM was produced for the first time last year. That report, *NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2005*, was created as a way for NCI to communicate its progress in this area of medical research, not only to Congress but also to other interested stakeholders including cancer researchers, CAM practitioners, health care providers, advocacy organizations, and the general public.

This year, the NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM) is proud to present the second such report, *NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2006*. Similar to the FY 2005 report, this publication provides an overview of the NCI-supported work in this field along with details on certain specific projects in the areas of cancer CAM relating to communication, training and conferences, and research.

This report highlights projects, grants, and

cooperative agreements supported by each of the Institute's extramural grant funding divisions – Division of Cancer Biology (DCB), Division of Cancer Control and Population Sciences (DCCPS), Division of Cancer Prevention (DCP), and Division of Cancer Treatment and Diagnosis (DCTD) along with projects from NCI's intramural laboratories – Center for Cancer Research (CCR) and 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 2006, NCI's research expenditures for CAM are an estimated \$123,076,167 for the funding of 461 CAM research projects.

As this report on cancer CAM indicates, we at the NCI are committed to an integrated approach to marshalling all of the many resources and approaches necessary to make cancer a condition that is – at worst – a manageable, chronic illness similar to most heart disease and diabetes. We believe that evidence-based CAM techniques, systems, and products can have an important role in helping us reach 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 means it 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 4 for the major categories of CAM therapies.)



The background of the slide is a close-up photograph of aloe vera leaves. The leaves are a vibrant green color and have a characteristic serrated or scalloped edge. They are arranged in a dense, overlapping pattern, with some leaves in the foreground being more prominent than others in the background. The lighting is soft, highlighting the texture of the leaves.

Office of Cancer Complementary and Alternative Medicine

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

OCCAM Programs

Research Development and Support Program

As previously noted, NCI sponsors more than 460 cancer CAM research projects, each of which are managed within the various Divisions and Centers of the Institute. The Research Development and Support Program (RDSP) staff manages a portion of this portfolio and works with other program staff throughout the NCI, assists investigators in identifying funding opportunities, and provides guidance in the pre- and post-review periods of grant application. 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.

In FY 2006, RDSP's program announcement series PAR-02-040 and PA-04-053 was one of the most productive mechanisms for attracting new CAM grants to NCI. A total of 46 of the 167 solicited CAM grants active in FY 2006 came to NCI through these two announcements. (See Figure 2) The RDSP staff also worked with staff of other NCI programs to fund new grants and supplements to existing grants.

Highlights of the RDSP Research Portfolio

In FY 2006, OCCAM began funding grants and cooperative agreements that will substantially expand NCI's support of the exploration of traditional non-Western medical systems for anti-cancer therapies.

International Center for the Evaluation of East Asian Botanicals for Cancer – Investigators at Harvard University, in collaboration with the Chinese University of Hong Kong and Hong Kong Baptist University, initiated a project to establish the first library of authenticated medicinal plants, extract each plant according to standardized protocols, fractionate the extracts using reproducible methods, and then test individual extracts as well as combinations of extracts (and fractions) systematically for their anti-cancer biological properties. Ultimately, the extracts and/or fractions from these candidate plants which demonstrate anti-cancer properties in preclinical studies will next be tested in relevant animal models. Results of animal studies will then be used to plan appropriate human clinical trials.

Through a combination of Traditional Chinese Medicine (TCM) expertise, the leveraging of biotechnology at Harvard, and substantial NCI involvement, this project will directly address many of the shortcomings of previous botanical research in this area. It will establish a future

FIGURE 2. Cancer CAM-related Grants Awarded in FY 06 by Program Announcement (PA) and Request for Applications (RFA)

AT03-002	2	CA03-004	3	CA05-013	2	PA03-041	0	PA05-027	1	PAR01-110	1	PAR04-147	0
CA01-020	1	CA03-006	1	CA99-003	1	PA03-169	0	PA05-125	1	PAR02-037	1	PAR04-155	1
CA02-003	2	CA03-007	0	ES02-009	1	PA03-053	1	PA05-141	1	PAR02-040	28	PAR04-159	0
CA02-007	2	CA03-016	0	ES05-007	1	PA04-034	1	PA06-041	2	PAR02-176	1	PAR05-156	1
CA02-008	1	CA03-018	1	OD03-008	1	PA04-053	17	PA06-120	1	PAR03-009	0	PAR06-073	1
CA02-009	2	CA04-001	1	PA00-080	0	PA04-068	0	PA96-008	1	PAR03-010	3	PAR99-167	0
CA03-001	3	CA04-002	1	PA01-015	1	PA04-099	4	PA99-163	0	PAR03-153	5	PAS02-009	0
CA03-003	8	CA04-004	5	PA02-001	0	PA04-108	2	PA99-081	1	PAR03-176	0	Unsolicited	141
CA03-004	3	CA04-008	1	PA02-124	2	PA04-146	1	PAR00-025	1	PAR04-011	0	TOTAL	195



A SCREENING OF *THE NEW MEDICINE*

On April 24, 2006, RDSP organized and hosted a screening of a portion of *The New Medicine*, a two-part documentary on mind-body medicine research produced by Middlemarch Films and Twin Cities Public Television. The screening was held for staff members from the National Center for Complementary and Alternative Medicine (NCCAM), the National Institute of Mental Health (NIMH), the Office of Behavioral and Social Sciences Research, and NCI. Dr. Margaret Chesney of NCCAM and Dr. Esther Sternberg of NIMH, both featured in the documentary, answered questions concerning the featured research studies and concepts.

model for systematically identifying medicinal plant extracts, compounds, and combinations of extracts with clinically significant anti-cancer effects. (*Grant number: 1U19CA128534-01*)

Cancer Prevention by West African Medicinal Plants – West Africa is rich in indigenous medicinal practices including knowledge of and use of botanicals with extensive anti-inflammatory effects. The overall goal of this project at the Palmetto Health System of South Carolina is to discover novel, anti-inflammatory compounds from medicinal plants native to West Africa. The broad, long-term objective is to establish a role for this unexploited source of natural products for future chemoprevention applications for colon and other cancers. (*Grant number: 1R21CA107138-01A2*)

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 Web site (www.cancer.gov/cam) and publications.

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.

- COP developed the following products in FY 2006:
- NCI Best Case Series Brochure
- OCCAM Brochure
- *NCI CAM News* – Winter 2006 and Summer 2006 issues
- *Strategies for Success: How to Write a Grant in Cancer CAM*

Practice Assessment Program

OCCAM's Practice Assessment Program (PAP) reviews retrospective and prospective data on cancer patients treated with alternative therapies. PAP manages the NCI Best Case Series (BCS) Program, which provides an opportunity for CAM practitioners to submit medical data regarding cancer CAM treatments used in their settings. Practitioners are asked to submit patient records

Cancer CAM Research Funding Directory

Securing federal funding for research is often challenging. To assist researchers in finding other funding opportunities for their cancer CAM research projects, OCCAM developed a non-NIH funding directory. This directory is updated periodically and consists of foundations, advocacy groups, non-federal government organizations, and private sector organizations that have expressed an interest in funding cancer CAM research. Contact information and specific areas of CAM interests are provided for each organization.

The directory can be viewed and downloaded from <http://www.cancer.gov/cam/attachments/occam-research-funding-directory.pdf>.

OCCAM Announcements

To support the program goal of disseminating information, OCCAM has created the e-mail distribution list OCCAM Announcements. OCCAM Announcements provides individuals who have an interest in cancer CAM with timely notifications about new funding opportunities, upcoming workshops and lectures, publications, and other resources.

To subscribe online for OCCAM Announcements, go to <http://www.cancer.gov/cam/news/occam-announcements.html>.



for evaluation by experts in clinical assessment and cancer treatment research. Results of the NCI BCS Program are used to inform decisions regarding NCI-initiated research and to share well-documented best cases with interested members of the scientific community in order to stimulate research.

In FY 2006, OCCAM released two broad agency announcements related to the NCI BCS Program. The first announcement (N01-CO-57034-48) was designed to support a contract proposal for the preparation of a best case series submission and prospective research on a CAM therapy if the submission review shows that the criteria have been fully met. A contract awarded as a result of the second announcement (N01-CO-57035-48) would provide support for prospective research (preclinical, clinical trial, or both) on specific alternative medicine approaches that have already completed the NCI BCS Program process.

More OCCAM Highlights

Traditional Chinese Medicine and Cancer Research: Fostering Collaborations; Advancing the Science

OCCAM hosted an ambitious conference titled “Traditional Chinese Medicine and Cancer Research: Fostering Collaborations; Advancing the Science,” held in April 2006 at the National Institutes of Health (NIH) campus in Bethesda, Maryland. This endeavor took six months of planning and was prompted by multiple meetings with the China Academy of Chinese Medical Sciences (CACMS), a national center for TCM research, teaching, and health care in China.

Over 150 scientists and physicians attended the conference, including more than 40 who traveled from China to participate. While the conference included posters and presentations like a standard biomedical gathering, its main purpose was to serve as an incubator for establishing new

collaborative relationships between Chinese and Western scientists, particularly NCI intramural researchers, interested in exploring TCM for cancer prevention, treatment, and palliation.

OCCAM's Participation at Major Professional Conferences

OCCAM staff members are active in both domestic and international professional conferences through presentations and engaging in dialog with cancer CAM researchers, practitioners, and patient advocacy groups. (See also Training and Conferences on pg. 17). During FY 2006, this encompassed several important meetings:

- In November 2005, Dr. Oluwadamilola Olaku presented “Survey of Researchers and Practitioners Regarding Complementary and Alternative Medicine” at the Society for Integrative Oncology in San Diego, California.
- On February 23, 2006, Dr. Jeffrey D. White presented “Clinical Research on CAM in Cancer: NCI's Perspective” at the meeting on Controversies about Complementary and Alternative Medicine (CAM) in Oncology in Brussels, Belgium.
- On April 7, 2006, Dr. Wendy B. Smith presented “Research and Funding Opportunities in Pain Medicine at NIH” at the Integrative Pain Medicine Course at Columbia University.
- On April 30, 2006, Shea Buckman, M.A. presented “Cancer CAM Information Resources” at the National Breast Cancer Coalition Fund Annual Meeting in Washington, D.C.
- In May 2006, CDR (USPHS) Colleen Lee, CRNP, AOCN® presented “NCI Best Case Series Program: Goals, Criteria, and Outcome Measures” at the North American Research Conference on Complementary Medicine in Edmonton, Canada.



OCCAM's Exhibit Program

In addition, OCCAM expanded its outreach efforts through exhibiting or sending publications to numerous professional meetings:

- American Holistic Medical Association
- American Association of Naturopathic Physicians
- Society for Integrative Oncology
- American College for the Advancement of Medicine
- American Association for Cancer Research
- Oncology Nursing Society
- American Society for Clinical Oncology
- American Association of Family Physicians

Working with Advocates

In FY 2006, OCCAM staff had several opportunities to work with representatives of the cancer patient advocacy community including the following:

- Presenting at two sessions of the National Breast Cancer Coalition Fund Annual Meeting
- Exhibiting on June 19, 2006 at the Director's Consumer Liaison Group Poster Picnic, an activity of the NCI consumer summit meeting *Listening and Learning Together: Building a Bridge of Trust*
- Working with five advocates within the NCI's Consumer Advocates in Research and Related Activities program on the review of a draft of *NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2005*
- Hosting a national question and answer forum on the NCI's Listens and Learns Web site, a pilot program designed to improve communication and collaboration between NCI, the cancer advocacy community, and the public

OCCAM Staff List: FY 2006

Jeffrey D. White, M.D.	Director, OCCAM
Wendy B. Smith, Ph.D., B.C.I.A.C.	Director, Research Development and Support Program
CDR (PHS) Colleen Lee, M.S., AOCN®	Coordinator, Practice Assessment Program
Shea Buckman, M.A.	Coordinator, Communications and Outreach Program
Tai N. Baker, M.P.H.	Communications Analyst
Christina Armstrong	Administrative Program Specialist
Ashanti Certain	Office Assistant
Dan Xi, Ph.D.	Biologist
Oluwadamilola Olaku, M.D., MRCOG	Scientific Program Analyst
Phil Tonkins, Dr.P.H.	Scientific Program Analyst
Libin Jia, M.D.	Scientific Program Director (on detail)
Karen Alladin, M.S.	CRTA Fellow
Elisabeth Beaver, M.S.	CRTA Fellow



NCI CAM Communications Programs

NCI directs communications programs that are committed to providing current and credible information resources about CAM to its stakeholders.

Providing Information Online

OCCAM's Web site serves as NCI's information hub on CAM issues at <http://www.cancer.gov/cam>. It provides a wealth of information and timely updates about the Institute's CAM research portfolio, grant opportunities, and other news.

The site includes links to NCI-produced cancer treatment, prevention, and screening summaries – called Physician Data Query (PDQ®) summaries – including certain CAM therapies as well as shorter question and answer documents (Fact Sheets). During FY 2006, NCI released the patient version PDQ summary *Aromatherapy* (<http://www.cancer.gov/cancertopics/pdq/cam/aromatherapy/patient>), bringing the total number of CAM-related summaries to 17.

Online access is also provided to NCI's PDQ Cancer Clinical Trials Registry. This registry includes approximately 4,500 abstracts of protocols that are open and approved to accept patients, including 74 clinical studies on CAM approaches for cancer (See appendix). The PDQ database is used by health professionals and patients alike and may be searched a number of ways including by diagnosis, treatment modality, locality, or a combination of these search criteria.

In FY 2006, a newly designed CAM clinical trials search table was added to the OCCAM Web

site. Similar to the search function on the NCI Web site, this new search table provides direct access to the entire list of cancer CAM clinical trials, including those clinical trials which have already closed. The new clinical trials search table also allows users to view active CAM clinical trials by either cancer type or an associated symptom.

At the present time, there are approximately 15 cancer types listed as active CAM clinical trials. Examples include:

- Bladder cancer
- Head and neck cancer
- Lung cancer
- Prostate cancer

There are active CAM clinical trials for six common symptoms:

- Anorexia
- Hot flashes
- Fatigue
- Nausea
- Pain
- Oral complications

For the complete list of CAM clinical trials by cancer type and to access the CAM clinical trials table, go to http://www.cancer.gov/cam/clinical_trials_list.html.

Note: NCI's 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.

Award for Cancer CAM Booklet

The informative booklet *Thinking About Complementary and Alternative Medicine* won the bronze National Health Information Award in 2006. Written by OCCAM, in conjunction with NCI's Office of Education and Special Initiatives and NIH's NCCAM, this publication has since been translated into both French and Italian.

Download the booklet online at <http://www.cancer.gov/cancertopics/thinking-about-CAM> or order as a print copy from NCI's Cancer Information Service (Inventory Number P042) by calling 1-800-4-CANCER (1-800-422-6237) or from NCI's Publications Locator at www.cancer.gov/publications.

Thinking About Complementary & Alternative Medicine



A guide for people with cancer



PATIENT & family EDUCATION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute
National Center for Complementary and Alternative Medicine

Producing Publications

In addition to the OCCAM Web site, various offices within NCI provide educational materials on CAM in print formats to health professionals, people affected with cancer, and consumers.

NCI's First Annual Report on CAM

OCCAM published *NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2005*, which was the first report of its kind documenting NCI's participation in and support of a wide range of CAM activities. The report highlights the contributions of communications programs, training and conferences, and cancer CAM research in addressing the NCI strategic areas to support the elimination of suffering and death due to cancer. Copies of the report can be viewed and downloaded from <http://www.cancer.gov/cam/attachments/CAMAnnualReportFY2005.pdf>.

Newsletter on NCI's CAM Activities

OCCAM also launched a biannual newsletter *NCI CAM News* to provide the latest information on NCI-sponsored research, funding opportunities, meetings and workshops, as well as educational information on cancer and CAM. The inaugural issue introduced OCCAM's programs and highlighted its activities. Subsequent issues include features on cancer CAM projects representing the full range of NCI's activities as well as OCCAM program updates. The following FY 2006 issues of *NCI CAM News* are available online:

- Winter 2006
<http://www.cancer.gov/cam/newsletter/2006-winter/home.html>
- Summer 2006
<http://www.cancer.gov/cam/newsletter/2006-summer/home.html>

CAM in the NCI Cancer Bulletin

The *NCI Cancer Bulletin* is a biweekly online newsletter designed to provide useful, timely information about cancer research to the cancer research community. OCCAM was featured in three issues of the *NCI Cancer Bulletin* during FY 2006:

- *CAM Scientist Tests Lung Cancer Herb*; February 14, 2006 (Volume 3, Number 7)
- *Conference Promotes Collaborations in Traditional Chinese Medicine Research*; April 18, 2006 (Volume 3, Number 16)
- *NCI CAM Newsletter Debuts*; April 25, 2006 (Volume 3, Number 17)

In addition, there were also several cancer CAM studies featured in the *NCI Cancer Bulletin* during FY 2006:

- *Carnitine Supplementation for Cancer-Related Fatigue*; January 3, 2006 (Volume 3, Number 1)
- *American Ginseng for Cancer-Related Fatigue*; January 24, 2006 (Volume 3, Number 4)
- *Omega-6 Fatty Acid Activates Genes Linked to Prostate Cancer Development*; February 14, 2006 (Volume 3, Number 7)
- *Saw Palmetto Fails to Improve Benign Prostate Hyperplasia*; February 14, 2006 (Volume 3, Number 7)

The NCI fact sheet "Complementary and Alternative Medicine in Cancer Treatment: Questions and Answers" was viewed 31,800 times in FY 2006. To view this publication, please visit <http://www.cancer.gov/cancertopics/factsheet/therapy/cam>.

Responding to CAM Cancer Inquiries

The Cancer Information Service (CIS) serves as NCI's link to the public by interpreting and explaining research findings in a clear and understandable manner and providing personalized responses to specific questions about cancer. Highly trained cancer information specialists are available to answer questions via phone, live online chat, mail, and e-mail about cancer treatment and clinical trials, including CAM therapies. During FY 2006, CIS responded to more than 1,600 inquiries regarding CAM approaches for cancer.

Access the CIS by calling 1-800-4-CANCER (1-800-422-6237), or by using the LiveHelp instant-messaging service at <https://cissecure.nci.nih.gov/livehelp/welcome.asp>.

CAM Surveys and Focus Groups

OCCAM's Communications and Outreach Program also assesses the opinions and interests of cancer researchers, CAM practitioners, and cancer patients regarding CAM research. OCCAM collects this information via surveys and focus groups. Results from these explorations will be used to develop programs that are most helpful for these audiences.

In FY 2006, OCCAM conducted two focus groups at the Society for Integrative Oncology 2nd International Conference in San Diego, California. A total of 23 cancer CAM researchers and CAM practitioners participated in the focus group discussions. The main objectives were to explore the experiences of cancer researchers and CAM practitioners in conducting research on CAM and identify existing obstacles and opportunities. An additional objective was to obtain information about participants' perceptions of CAM practices and the degree of involvement the participants have in cancer CAM research relative to the areas of treatment, symptom management, and/or prevention.



Training and Conferences

NCI provides an array of training support programs on aspects of CAM research including grant writing workshops and scientific conference sponsorships.

Training Opportunities at OCCAM

During FY 2006, OCCAM hosted two Cancer Research Training Award (CRTA) fellows within the office, Karen Alladin, M.S. and Elisabeth Beaver, M.S. Mentored by Dr. Jeffrey D. White, the goals for the two pre-doctoral fellows were to learn about the NIH grant process, explore approaches to building cancer CAM research, and help provide support to the OCCAM programs. Each fellow worked on a literature review project which will be submitted for publication.

In addition, OCCAM also hosted a Health Communications Intern, Tai N. Baker, MPH, who helped plan and organize a scientific conference, develop publications and other promotional materials, and managed OCCAM's Web site. Ms. Baker also participated in professional meetings and NIH-sponsored training seminars.

Awards for DCEG Fellows

The NIH Fellows Award for Research Excellence program recognizes outstanding scientific research by intramural postdoctoral fellows. In FY 2006, three DCEG fellows received awards for their CAM-related projects:

- Larissa Korde, M.D., M.P.H.: *Early life soy intake and breast cancer risk in Asian American Women*
- Kenneth F. Adams, Ph.D.: *Association between body mass and colon cancer in the NIH-AARP Diet and Health Study*
- Amanda J. Cross, Ph.D.: *Red meat intake and increase risk of colorectal cancer in the NIH-AARP Diet and Health Study*

Establishing a CAM Monthly Lecture Series at NCI

In January 2006, OCCAM introduced a new educational outreach program, the OCCAM Monthly Lecture Series. This program was developed to inform the NCI community about recent and ongoing research projects in cancer CAM. These hour-long lectures feature a fifty-minute presentation on a cancer CAM topic and allow 10 minutes for questions. The lectures are open to the public and also are archived on the OCCAM Web site.

During FY 2006, the series included lectures on:

- Ascorbic acid and tight control: unexpected consequences for cancer treatment
- Lung cancer chemoprevention using herbal agents
- Traditional medicines and the prevention of colon cancer
- Targeting inflammation by dietary agents for prevention and treatment of cancer
- Zylflamed-mediated inhibition of proliferation of human prostate cancer: preclinical pharmacology and clinical trial results

Supporting Scientific Conferences

Society of Integrative Oncology

A good example of NCI's support of scientific cancer CAM conferences is the Society of Integrative Oncology's (SIO) 2nd International Conference in San Diego, California, November 10-12, 2005. OCCAM staff participated in program development and provided conference grant support* to SIO for its conference. In addition, Dr. Oluwadamilola Olaku, an OCCAM Scientific Program Analyst, gave a presentation titled "Survey of Researchers and Practitioners Regarding Complementary and Alternative Medicine." The abstracts from the meeting are available in the December 2006 issue of the *Journal of the Society of Integrative Oncology*.

Grant number: *1R13CA126426-1

North American Research Conference on Complementary and Integrative Medicine

On May 24-27, 2006, the North American Research Conference on Complementary and Integrative Medicine, supported in part by a grant from NCI and NCCAM, was held in Edmonton, Canada. This conference presented basic and clinical research on complementary and integrative therapeutic approaches and promoted educational collaboration across multiple medical disciplines. During this meeting, researchers and health care providers examined and addressed the validity of a variety of complementary and integrative medicine approaches including massage, herbal therapies, acupuncture, dietary supplements, yoga, hypnosis, mind-body, and lifestyle approaches to patient care. The Consortium of Academic Health Centers for Integrative Medicine, which consists of 32 leading schools of medicine in the United States and Canada, sponsored the conference. OCCAM's PAP Coordinator CDR (USPHS) Colleen Lee, M.S., CRNP, AOCN®, presented "NCI Best Case Series Program: Goals, Criteria, and Outcome Measures."

Conference Presentations by NCI

NCI Deputy Director Mark Clanton, M.D., and Mary Anne Bright, director of NCI's Cancer Information Service (CIS), spoke at the *Non-Conventional Treatments for Cancer Patients: How to Provide Reliable Information* meeting in Rome, Italy on December 16, 2005. The conference was sponsored by the Associazione Italiana Malati di Cancro (AIMaC), the Italian version of NCI's CIS.

OCCAM Director Jeffrey White, M.D., gave a presentation on NCI's perspective on clinical research on CAM at a European conference on "Controversies about CAM in Cancer" which took place February 2006 in Brussels, Belgium.

Finally, the Oncology Nursing Society (ONS) sponsored its first all-day session on the Cancer CAM Primer for Oncology Nurses at ONS's 31st Annual Congress in Boston, Massachusetts in May 2006. OCCAM PAP Coordinator Commander (CDR) Colleen O. Lee was a presenter and helped develop the session. The content was tailored to nurses whose practices span the range from community settings and hospitals, to research-based facilities. Therefore, areas of expertise encompassed the care of cancer patients within acute, chronic, and supportive care settings.

As a result of the success of the ONS' Cancer CAM Primer, a cancer CAM supplement will be submitted to the Society's two peer-reviewed journals *The Oncology Nursing Forum* and *The Clinical Journal of Oncology Nursing*. In addition, a pocket guide will be published highlighting the evidence-based conventional and CAM interventions for the symptoms that were discussed in the Primer session at the ONS conference.





NCI Research in Complementary and Alternative Medicine

One of OCCAM's duties as NCI's coordinating office on CAM is to conduct an analysis of the Institute's expenditures on CAM research for each fiscal year. The analysis of both the intramural and extramural CAM research portfolios serves to: respond to Congressional inquiries on NCI's investment in this area; determine trends of funding in particular topics; refine NCI's definition of CAM; identify research gaps in the field of cancer CAM; and encourage dialog about the potential direction of future cancer CAM research. This yearly analysis is an exercise that reveals an estimated total amount of funding that goes to cancer CAM research projects and provides breakdowns according to the type of research (prevention, treatment, side effects/symptom management, and epidemiology), CAM category, and cancer type.



NCI CAM Research Portfolio Analysis: FY 2006

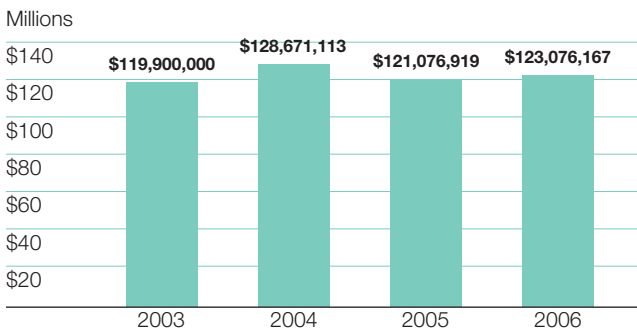
Total Estimated Cancer CAM Research Expenditure

In FY 2006, NCI invested \$123,076,167 for 461 intramural and extramural research projects of which some portion addresses CAM. For the purpose of the FY 2006 analysis, the following types of funding are included: intramural projects and extramural grants, cooperative agreements, contracts, and supplements. Training grant awards (Ts, Fs, Ks, and R25s) were excluded. (See 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 2006, 67.85% of cancer CAM-related research project funds went to various cancer prevention efforts, while treatment, symptom/side effects management, epidemiology, and conferences received 21.13%, 7.37%, 3.37%, and .28% respectively.

FIGURE 3. NCI's CAM Expenditures FY 2003-2006*



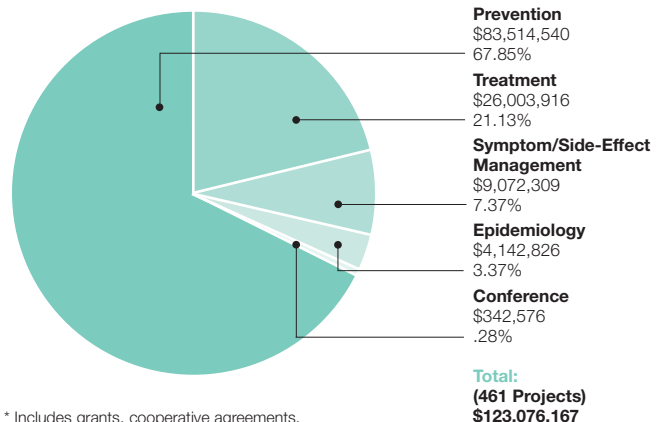
* Includes grants, cooperative agreements, intramural projects, and contracts. Regarding grants and cooperative agreements, only includes those for which NCI is the primary funding IC and excludes training grants (Ts, Fs, Ks, and R25s).

Breakdown by Major CAM Therapy Category

In FY 2006, NCI performed or supported research addressing a variety of CAM therapies (Figure 5). These CAM therapies fall into seven groups: alternative medicine systems, exercise therapies, manipulative and body-based methods, mind-body interventions, nutritional therapeutics, pharmacological and biologic treatments, and spiritual therapies. (See page 4 for definitions of CAM categories.)

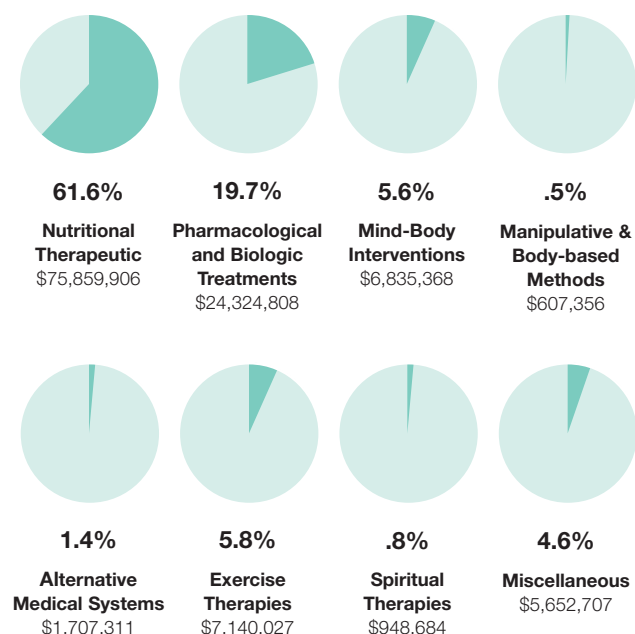
The largest percentage (61.5%) of research funding went to projects that investigated nutritional therapeutics, which can be further broken out into subcategories of research on: food (e.g., broccoli and berries); minerals (e.g., calcium and selenium); vitamins (e.g., vitamins C and D); bioactive food components (e.g., isoflavones and carotenoids); dietary regimens (e.g., caloric restriction and high fruits and vegetables); and fats (e.g., linoleic acid and omega-3). Figure 6 shows the distribution of projects by the subcategories of nutritional therapeutics.

FIGURE 4. NCI's CAM Research Projects FY 2006 by Research Type*



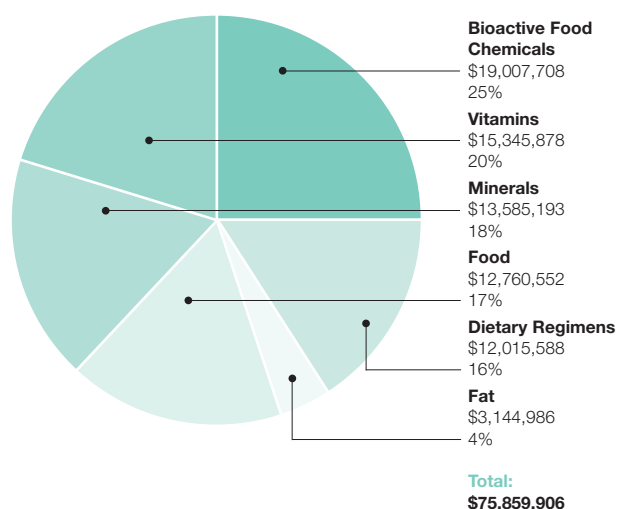
* Includes grants, cooperative agreements, intramural projects, and contracts.

FIGURE 5. NCI CAM Therapies—FY 2006*



* Includes grants, cooperative agreements, intramural projects, and contracts.

FIGURE 6. NCI's FY 2006 CAM Nutritional Therapies Projects

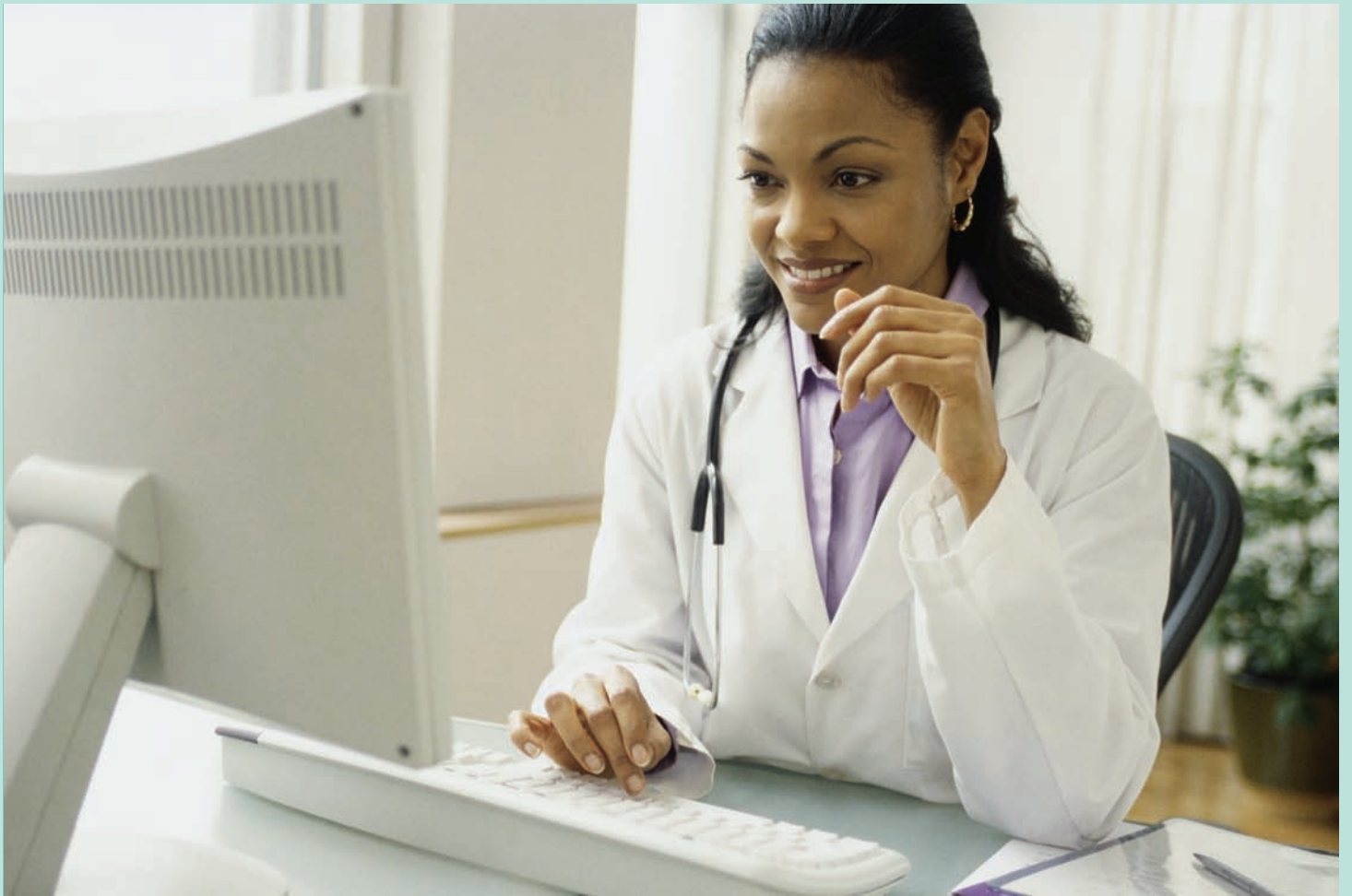


Breakdown by Cancer Type

The research projects that make up NCI's FY 2006 CAM research portfolio address 20 categories of cancer types. Among the various categories, prostate, breast, colorectal, and lung cancers received the largest amounts of cancer CAM research funding. Almost half (46%) of NCI's cancer CAM research funding was allotted for multiple types of cancer within the same project. For a complete listing of the cancer type categories and estimated funding amounts, please see Figure 7 below.

FIGURE 7. NCI CAM Research Projects FY 2006 by Cancer Type

Bladder	\$731,318
Brain	\$538,357
Breast	\$14,788,877
Cervical	\$2,645,072
Childhood Cancer	\$365,561
Colorectal	\$11,564,397
Endometrial	\$67,174
Esophageal	\$928,081
Gastric	\$337,024
Head and Neck	\$938,960
Kidney	\$539,617
Liver	\$601,364
Lung	\$6,115,562
Melanoma	\$516,509
Multiple Myeloma	\$25,721
Multiple Types	\$56,313,158
Ovarian	\$136,170
Pancreatic	\$1,269,592
Prostate	\$18,861,790
Skin. Non-Melanoma	\$5,791,863
TOTAL:	\$123,076,167



MAJOR ACCOMPLISHMENTS IN 2006

Fiscal Year 2006 saw the release of major findings which for the first time offer compelling evidence to suggest that regular physical activity in the months following treatment may decrease the risk of cancer recurrence and death from colorectal cancer. The Women's Health Initiative (WHI) Dietary Modification prevention study also showed that reducing dietary fat and increasing fruits, grains, and vegetables may reduce risk of invasive breast cancer in some women.

MAJOR ACCOMPLISHMENTS IN 2006

Studies Suggest Exercise Improves Colorectal Cancer Outcomes

Two new prospective, observational studies offer compelling evidence to suggest regular physical activity in the months after treatment may decrease the risk of recurrence and death from colorectal cancer.

In the studies, patients with early- to later-stage colorectal cancer (no distant metastases) who engaged in regular activity after diagnosis had a lower likelihood of cancer recurrence and mortality by 40% to 50% or more compared with patients who engaged in little to no activity.

Published in the July 6, 2006 issue of the *Journal of Clinical Oncology*, the studies' results showed outcomes from exercise held true regardless of physical activity levels before cancer diagnosis or other factors that predict recurrence risk, such as the number of nearby lymph nodes harboring cancer cells.

The results, said the studies' lead author, Jeffrey A. Meyerhardt, M.D., M.P.H., of the Dana-Farber Cancer Institute, may offer insight into why some colorectal cancer patients who receive standard-of-care treatments, including surgery and adjuvant chemotherapy, have recurrences, and some don't.

"One assumption has always been that it must be something about the molecular makeup of their tumor," he said. "This study implies that there are some lifestyle factors that may also have a significant effect on [treatment] outcomes."

The first study, an NCI-sponsored clinical trial led by the Cancer and Leukemia Group B cooperative group, compared two adjuvant chemotherapy regimens in 832 patients with stage III colorectal cancer.

Four and fourteen months after having their tumors surgically removed, well after adjuvant therapy was completed, participants provided details about their diet and physical activity via a self-administered questionnaire. Only data from the second questionnaire were considered in the analysis. Researchers converted the reports of physical activity (ranging from jogging to flights of stairs climbed) to metabolic equivalent task (MET) hours. For example, walking at a moderate pace

for an hour is equivalent to three MET hours.

Compared with patients who reported less than three total MET hours per week, those reporting 18 to 26.9 and 27 or more MET hours weekly had their risk of death from colorectal cancer reduced by 49% and 45%, respectively. In other words, six or more hours a week of walking at a moderate pace was associated with better outcomes.

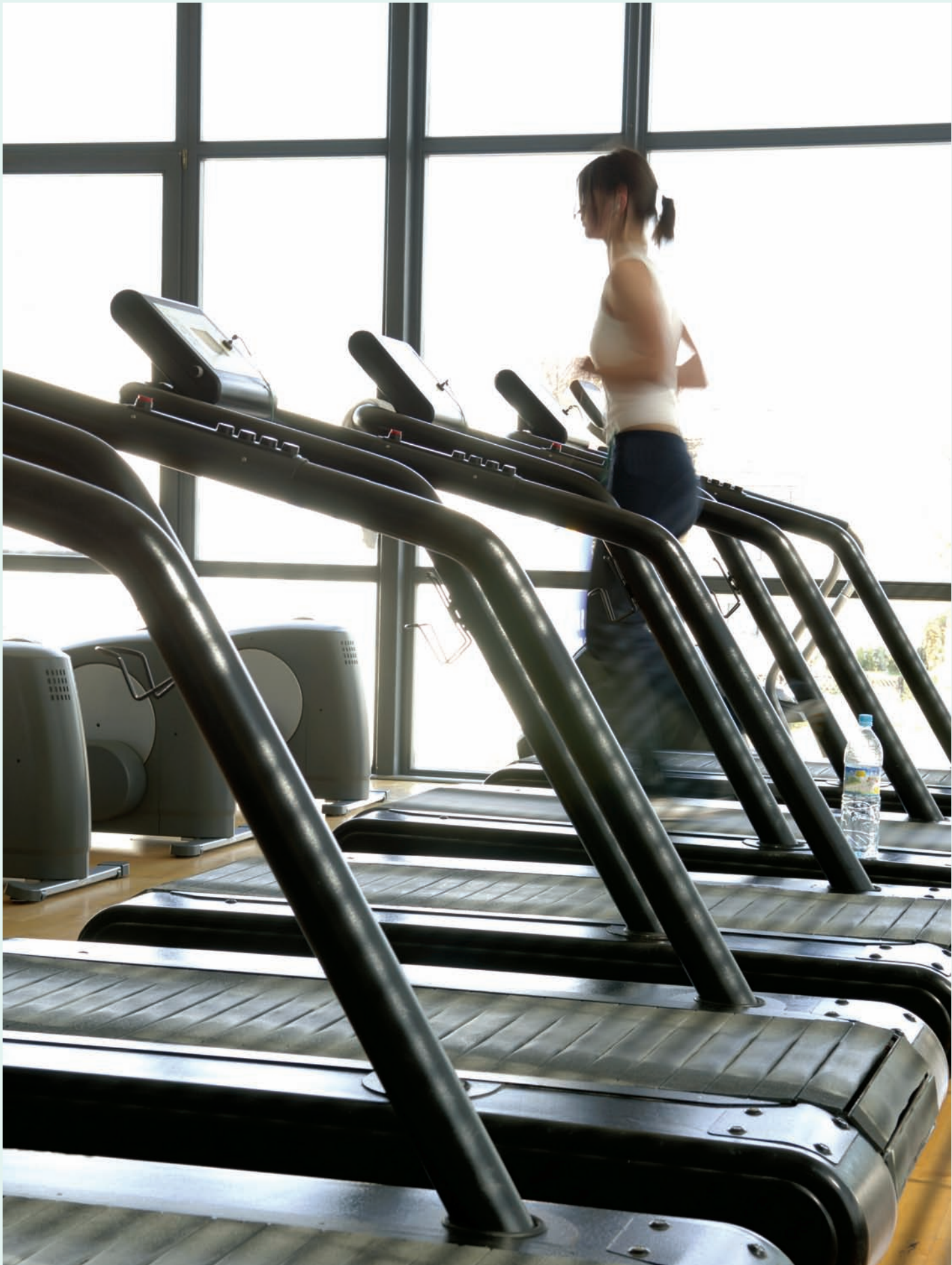
The second study followed a cohort of 573 participants in the Nurses' Health Study who, during the course of the study, were diagnosed with colorectal cancer.

Compared with participants reporting less than three MET hours of activity per week, those reporting 18 or more had their risk of death from colorectal cancer cut by 61% and their risk of death from any cause reduced by 57%.

In an accompanying editorial, Dr. Wendy Demark-Wahnefried of Duke University Medical Center noted that the risk reductions seen in these studies – as well as strikingly similar results reported last fall from a study of women with early-stage breast cancer – parallel "that of trastuzumab (Herceptin) for HER 2-positive breast cancer patients."

Julia Rowland, Ph.D., head of the NCI Office of Cancer Survivorship, said these findings add to the evidence base on physical activity and cancer outcomes. "They suggest that the time may be ripe to launch a randomized clinical trial of physical activity after cancer treatment," she continued.

In March 2006, the NCI-sponsored workshop *Feasibility of a Physical Activity, Weight Control Trial to Prevent Breast Cancer* examined the rationale for and issues related to designing a physical activity intervention in the context of a primary prevention trial and also for a trial to prevent breast cancer recurrence and death in survivors. NCI also contributed to the American Cancer Society's guidelines on "Nutrition and Physical Activity During and After Cancer Treatment" published in the November/December 2006 issue of the journal *CA*.



MAJOR ACCOMPLISHMENTS IN 2006

Low-Fat Diet May Have Small Impact on Breast Cancer in Women

Results from the Women's Health Initiative (WHI) Dietary Modification (DM) prevention study show that reducing dietary fat and increasing fruits, grains, and vegetables may reduce risk of invasive breast cancer in some women, but has no effect on invasive colorectal cancer. Although more than 19,500 postmenopausal women followed the modified diet, the overall breast cancer risk reduction of 9% was not statistically significant after an average of 8.1 years. Women whose diets were highest in fat before they entered the study, however, were 22% less likely to develop breast cancer than the comparison group.



Ross L. Prentice, Ph.D., of the Fred Hutchinson Cancer Research Center in Seattle and colleagues write that the risk reduction seen in this and other subgroups “would not be expected if the intervention had no effect on breast cancer risk.” Citing other trends in the data in favor of DM,

they note the benefit increased to 15% among women who most closely followed the dietary regimen. Also, citing the small impact of DM on breast cancer, which begins to occur after about 4 years and appears to be increasing with time, the authors note that “the health implications of a low-fat dietary pattern may take years to be fully realized.” In an accompanying editorial, Aman U. Buzdar, M.D., from the University of Texas M.D. Anderson Cancer Center said the study is another indication that breast cancer oncologists “are beginning to understand which approaches may be effective for particular subsets of patients.”

Leslie Ford, M.D., of NCI's DCP, noted that, “Breast cancer is an exceedingly complex disease. The more we learn about the molecular underpinnings of the disease, the better we will understand how a healthy eating pattern and exercise may contribute to a reduction in risk for some women.”

Regarding the colorectal study, lead author Shirley A.A. Beresford, Ph.D., of the University of Washington in Seattle and colleagues also say that the currently planned, longer follow-up studies “may reveal delayed benefit,” although, unlike the breast cancer study, “no time trends ... have been seen.”

The WHI DM study is the largest randomized controlled clinical trial of low-fat dietary interventions ever conducted. Results were published in the February 8, 2006, *Journal of the American Medical Association*.

This article was originally published in the *NCI Cancer Bulletin*, February 7, 2006, Volume 3, Number 6. (http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_020706/page5)



ADDRESSING NCI'S STRATEGIC AREAS WITH EXTRAMURAL RESEARCH

The remaining research highlights are selected from the 461 CAM research projects that NCI supports at laboratories throughout the United States and the world. These research projects are organized under the major goals of The NCI Strategic Plan for Leading the Nation. NCI's Strategic Plan can be found on the Web at <http://strategicplan.nci.nih.gov>. Abstracts for the research projects featured in the report can be found by searching the NIH Computer Retrieval of Information on Scientific Projects (CRISP) database at <http://crisp.cit.nih.gov>.

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.

UNDERSTANDING THE CAUSES AND MECHANISMS OF CANCER

Antioxidants and Chemotherapy: Help or Hindrance?

Division of Cancer Control and Population Sciences

According to recent studies, such as the Women's Healthy Eating and Living (WHEL) Study, as many as 50% to 60% of cancer patients take vitamins or other nutritional supplements during treatment, and up to 20% use supplements containing high doses of antioxidants. Traditionally, doctors have cautioned patients not to take antioxidants during chemotherapy, because many anticancer drugs kill tumor cells by forming oxygen-based compounds that damage DNA.

It is not clear, however, if antioxidants do actually interfere with the effects of chemotherapy. In fact, said Christine Ambrosone, Ph.D., chair of Epidemiology and Cancer Prevention at Roswell Park Cancer Institute, "Some preclinical and animal data have shown that when antioxidants are given with chemotherapy, they decrease toxicity so that more of a drug can be given. They also increase efficacy – the antioxidants with the chemotherapy agent work better than the chemotherapy agent alone."

"There haven't been any large studies conducted in very well-controlled environments where everybody is getting the same treatment agent and followed up carefully," Ambrosone added. "The preclinical studies evaluating effects of antioxidants given with chemotherapy have usually used very high doses, so we don't know what, if anything, happens when people take supplements at the levels commonly available."

In September 2006, Ambrosone and her colleagues received NCI funding* to begin a prospective observational study of antioxidants and chemotherapy as part of a clinical trial being conducted by the Southwest Oncology Group (SWOG). That trial will randomly assign women with invasive breast cancer to one of four chemotherapy regimens, comparing different doses, intensities, and schedules of the chemotherapy drugs cyclophosphamide, adriamycin, and paclitaxel.

For the antioxidant study, participating women will fill out a detailed questionnaire reporting the composition and dosage of any multivitamins taken regularly, as well as the use of additional supplements and other complementary and alternative treatments. The women will provide this information before starting chemotherapy, after treatment, and then yearly during follow-up for the main clinical trial.

The investigators will also look at the contribution of lifestyle factors, including physical activity, alcohol consumption, and smoking, and perform laboratory studies to determine if genetic make-up, particularly related to protection from oxidative stress, has any effect on relationships between supplement use and treatment outcomes.

While results from this study can only be applied to women given the specific chemotherapy drugs tested in the SWOG clinical trial, "almost all women treated for breast cancer are given some combination of cyclophosphamide, adriamycin, and a taxane," Ambrosone explained. "So the results would apply to a very large patient population."

Isis S. Mikhail, M.D., Dr.P.H., with NCI's DCCPS commented: "This is a very interesting study by Dr. Ambrosone that could answer a challenging question regarding the association between use of antioxidant supplements, cancer treatments outcome, and the contribution of genetic and lifestyle factors. This study fits very well with the DCCPS portfolio, and following up this group of women participating in the SWOG trial prospectively before, during, and after they start their chemotherapy regimen is an effective model and could have valuable results that can be translated to benefit many cancer patients."

*Grant number: 1R01CA116395-01A1

UNDERSTANDING THE CAUSES AND MECHANISMS OF CANCER

Calcium and Vitamin D May Help Prevent Colorectal Cancer

Division of Cancer Control and Population Sciences

Colorectal cancer causes more deaths in the United States than any other cancer except lung. Robert M. Bostick, M.D., M.P.H., a professor at Emory University in Atlanta, believes part of the reason is that we no longer eat like people did in prehistorical times. “We consume very little calcium and vitamin D by evolutionary standards,” he said. Bostick’s lab is currently studying whether those dietary components could be used to prevent adenomatous polyps, a precursor of most cases of colorectal cancer.

“We’ve made huge progress in preventing heart attacks,” explained Bostick. “By taking steps to reduce blood pressure and cholesterol, you can directly reduce risk. Treat the biomarker (high cholesterol), and you may stop the disease before it fully develops.” His lab is working on a similar approach to colorectal cancer. In an NCI-supported research study*, they recruited patients who have had adenomatous polyps surgically removed and are thus at high risk of recurrence.

Patients take pills twice a day receiving calcium, vitamin D, both, or a placebo that contains neither. Biopsies of their rectal tissue will be examined after one, three, and five years to see if any differences at the lining of the colon emerge between the various groups. In addition, patients will undergo colonoscopies three and five years after entering the study to see if they have developed any new polyps. “If we could show that calcium and/or vitamin D can treat the biomarkers and prevent these warning-sign polyps from developing, we would have a bona fide medical strategy to prevent colorectal cancer,” said Bostick.

While calcium has been shown to have a moderately protective effect in a few studies, “we need to know better how and why,” explained Bostick. Some evidence suggests that calcium’s protective effect is greater in people with fairly high storage levels of vitamin D, but the studies have usually been confounded by the fact that both dietary substances often occur together, such as in dairy products. This

new clinical trial will tease apart their separate impact by controlling for other dietary sources – many foods are fortified with vitamin D in the United States – and by checking circulating blood levels of vitamin D that can be influenced by sunlight.

“We’re trying to develop meaningful markers in the tissue by looking at a number of genes that produce the enzymes we know to be part of the pathways that metabolize the calcium and vitamin D,” Bostick said. Vitamin D is not only manufactured but also removed from the body by different genes, so they also want to measure actual blood levels, not merely intake. “It makes sense that the active vitamin D in the body is a balance between these two processes,” he noted.

The researchers also believe that the amount of proteins produced may be as important as genes simply turning on or off, and these protein levels could be influenced by other factors. “We hope to develop a fuller picture that includes genes, proteins, and blood levels of the nutrients,” Bostick said. From that picture could emerge new blood tests which would better identify people at high risk for colorectal cancer. “Since only about 6% of people get the disease and die from it, 94% of those receiving colonoscopies may not really need them,” he noted. The public health impact would be dramatic, getting those at greater risk into screening and treatment earlier, and saving money on costs and risks associated with periodic colonoscopies among low-risk individuals.

NCI’s Program Director for the study Virginia W. Hartmuller, Ph.D., R.D., commented, “Dr. Bostick’s study is important to NCI’s Diet/Nutrition Cancer Epidemiology research portfolio since he is examining whether the formation and degradation of the active form of vitamin D provides a critical focal point underlying the development of colon cancer.” She noted the NCI-sponsored meeting Vitamin D and Cancer: Current Dilemmas/Future Needs in May 2007 discussed research in this critical area.

*Grant number: 1R03CA121873-01



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.

ACCELERATING PROGRESS IN CANCER PREVENTION

Lycopene Studied for the Prevention of Lung Cancer

Division of Cancer Prevention

While observational studies have shown a protective effect against lung cancer from a diet high in fruits and vegetables, isolating specific plant compounds for use as chemopreventive agents has proven difficult. Beta carotene, and other related compounds called carotenoids, showed promise in preventing lung cancer in animal models; however, clinical trials in humans actually found an increase in lung cancer incidence in smokers given the compounds.

New carotenoid chemoprevention studies are now focused on better understanding biological activity, dose safety, and interactions with the byproducts of cigarette smoke before progressing to human trials, explained Xiang-Dong Wang, M.D., Ph.D., professor and co-leader of the Cancer Prevention Program at the Tufts University Cancer Center. He is currently studying lycopene, a major carotenoid from tomato and tomato products, in a model of lung cancer in ferrets*.

“We’re trying to answer three main questions,” said Wang. “First, what is the role of lycopene in lung cancer chemoprevention? Second, what is the optimal dose in terms of lung cancer prevention and safety? Lastly, we’re trying to understand the mechanism of how lycopene and its metabolites may help to protect against lung cancer.”

The ferret provides an excellent animal model for the study of lung cancer and of lycopene as a chemopreventive agent in humans. Ferrets and humans both absorb lycopene intact, and the tissue distribution and metabolism of the compound are also similar between the species. Most animals, including mice and rats, must be given relatively huge doses of carotenoids to observe any biological effect. The use of such megadoses in laboratory models might have caused unnecessarily high, even dangerous doses to be chosen for previous human chemoprevention trials of carotenoids, explained Wang. Ferrets exposed to cigarette smoke and lycopene

can be expected to provide a more accurate estimation of a safe dose for human trials.

Because specific metabolites have been implicated in the increased incidence of lung cancer in smokers given beta carotene, Wang and his colleagues are performing both laboratory experiments and animal testing to understand the biological activity of lycopene metabolites. Their experiments have already demonstrated that lycopene can be converted into a highly biologically active molecule called apo-10'-lycopenoic acid. Additional work from Wang's laboratory will focus on identifying biomarkers that can be used in human clinical trials to track the biological activity and the metabolism of lycopene.

Marjorie Perloff, M.D., with the NCI DCP, called Wang's research important, because it spans the spectrum from epidemiology trials in humans, back to animal research, “and, hopefully, then back again to human studies.” It is also significant, she adds, because lycopene is currently being used by consumers as a nutritional supplement, but could later be more carefully developed as a pharmaceutical agent, if that is warranted by the final results from Wang's research and from other scientific studies.

*Grant number: 1R01CA104932-01A2



Dr. Wang is currently studying lycopene, a major carotenoid from tomato and tomato products, in a model of lung cancer in ferrets.

ACCELERATING PROGRESS IN CANCER PREVENTION

Concentrated Vitamin D May Slow Prostate Cancer

Division of Cancer Biology and Office of Centers, Training and Resources

Prostate cancer is the second-leading killer of men in America. In a series of related studies, scientists have shown that vitamin D may have a significant role to play in slowing progression of the disease.

“Currently, docetaxel is the most potent chemotherapy drug we have for prostate cancer,” explained Tomasz Beer, M.D., director of Prostate Cancer Research at the Oregon Health and Science University Cancer Institute in Portland, Oregon. “We have found a promising companion agent that appears to enhance the impact of docetaxel, an activated form of vitamin D known as calcitriol. In an NCI-supported study in 2003, we showed it to be safe when given once a week at a dose that is larger than would ever be found naturally.”

While researchers continue to test that drug-supplement combination in a large, randomized, controlled trial for prostate cancer, Beer is now hard at work, under a grant from NCI*, trying to figure out exactly how calcitriol helps docetaxel kill prostate cancer cells. He is also examining what role it could potentially play as an adjunct to other treatments, possibly for other types of cancer.

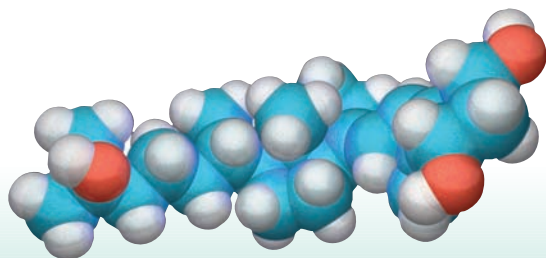
“We’ve found a promising gene, which we’re hoping might develop into a new therapeutic target,” Beer said. The gene belongs to the “homeobox” family. As a group, homeobox genes have been known as one of the main ways that growing organisms figure out how to segment themselves into different functional regions, which in turn form limbs and other structures.

Calcitriol appears to turn off one of the homeobox genes, both in patients with prostate cancer and in certain human prostate cancer cells in the lab, Beer found. As a result, the cancer cells die – a fate that applies to most normal cells in the body but which many cancers are able to avoid. Calcitriol may somehow be reversing this unnatural “immortality” of cancer cells, allowing them to die a programmed death like the rest of the body’s cells – a process that scientists call “apoptosis”.

Beer and his colleagues are conducting a series of experiments in mice that should begin to explain calcitriol’s effects on homeobox genes in prostate cancer cells**. This includes testing the gene’s impact on artificially-induced tumors, both in the prostate and elsewhere. Ultimately, they hope to demonstrate that this homeobox gene is a target that calcitriol can switch off in order to slow down or even prevent the growth of prostate cancer.

*Grant numbers: 1R21CA113380-01A1 and

**5P30CA069533



A computer-generated molecular model of calcitriol, 1,25-dihydroxycholecalciferol, the biologically active form of vitamin D, with carbon atoms shown in blue, hydrogens in white, and oxygen in red.

ACCELERATING PROGRESS IN CANCER PREVENTION

Improving Cancer Prevention Strategies Using the Biological Clock

Division of Cancer Prevention

Because the Earth revolves completely around its axis every 24 hours, it makes sense that this daily (circadian) cycle has left its imprint on the evolution of life and the biology of all living organisms. The research field of chronobiology has developed over some four decades to pursue the implications of this biological clock, particularly on medical treatments.

“We refer to it as chronotherapeutics,” said Jack Burton, M.D., an investigator in immunology and oncology at the Center for Molecular Medicine and Immunology at the Garden State Cancer Center in Belleville, New Jersey. “It involves administering treatment as a function of the body’s circadian rhythms, in an effort to make certain cancer treatments more effective and to cause fewer side effects.”

“Both laboratory and clinical research have left little doubt that the timing of treatment matters,” Burton believes. A number of studies have already shown that patients do better when their treatments are scheduled at certain times of their daily cycle.

The body’s internal “clock” may be controlled by the brain, but cells in many tissues have independent circadian rhythms as well, including, as it turns out, tumors. In earlier research, Burton and colleagues showed in a mouse model of breast cancer that more than twice the amount of the drug celecoxib (Celebrex®) is safe and well tolerated when given at a specific time of day, leading to a greater inhibition of tumor growth and less toxicity to the animal.

“The body’s internal rhythms as set by its own biological clock appear to affect all phases of treatment – surgery, radiotherapy and particularly chemotherapy, as well as the side effects that follow them,” explained Burton.

The next big area for circadian rhythm research may well be cancer prevention. Burton’s lab is building on the principles and successes of earlier work in chronotherapeutics. “Several nutritional substances have shown promise in their preventive effects on the development of various cancers in people,” he noted, including, an ingredient in the spice turmeric, vitamin D, selenium, and green tea. His first studies will test selenium and a purified extract of green tea.

“We hope to establish a robust proof of principle in animal models that will provide key preliminary data to design appropriate human studies,” Burton said. In one study, mice were injected with a prostate cancer cell line, which in several weeks produces visible tumors. “As with classical therapeutic agents, our earlier results in this model demonstrate that preventive agents also inhibit the growth of experimental prostate tumors differently according to circadian delivery times,” he reported.

The current studies use a similar mouse model to evaluate how chronobiology might influence the preventive effects of selenium and green tea*. Part of the study will test how well these preventive agents reach the prostate and other tissues. “We will collect all of these specimens into a tissue bank for use in future genomic and proteomic studies to understand the mechanisms by which these agents prevent cancer and to better understand any resulting side effects,” Burton said.

*Grant number: 1R21CA113470-01A2

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.

DEVELOPING EFFECTIVE AND EFFICIENT TREATMENTS

Ginseng Studied as Possible Breast Cancer Treatment

Division of Cancer Treatment and Diagnosis

Herbal supplements like ginseng have been in use for centuries in Asia, but U.S. researchers and government agencies have been cautious about certifying them for use in medical practice, especially for cancer. “And yet the evidence continues to mount that ginseng has anticancer properties,” said Laura Murphy, Ph.D., an associate professor in the Department of Physiology at Southern Illinois University in Carbondale.

“Ginseng is a virtual drugstore,” explained Murphy, referring to some 20 ginsenosides, bioactive phytochemicals found in the American species of ginseng root. This rich diversity is both good and bad news. Each of the ginsenosides may have its own pharmacological effect, which reflects one of the recurring dilemmas in using botanicals as medicine. When people buy unregulated dietary supplements or even whole roots, it is hard to know what combination of ginsenosides they are getting and in what strengths. In addition, Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) have different concentration profile of ginsenosides, so it is expected they would show different effects on cancer cells. Murphy’s lab has been working on this dilemma by developing reliable methods to evaluate the more important of these ginsenosides, alone and in combination.

Murphy’s current NCI-supported work* is focused on the Rg3 and Rh2 ginsenosides which are thought to be especially effective against cancer cells. She continues the effort to tease out the specific biological action for each of these ginseng components. In animal and cell studies, “we showed they slow down tumor cell progression by inducing more of the p21 protein, an important cell cycle regulator involved in cancer cell proliferation,” Murphy reported. By adding a third ginsenoside known as Rc, they developed a “3-ginsenoside cocktail” that potently inhibits the proliferation of a human breast cancer cell line known as MCF-7.

The cocktail also selectively inhibits and kills cancer versus normal mammary cells.

“We’re finding that not all ginseng components are equal,” commented Murphy. “For example, ginsenoside Rg1 completely counteracted MCF-7 cell inhibition induced by other anticancer ginsenosides. So while some of the anticancer ginsenosides work together, others appear to undermine their efficacy.” This line of research may lead to the characterization of an effective or a biologically well defined combination of ginsenoside mixtures that could be used to complement standard treatments of breast cancer. More research into the mechanism of action of ginseng’s pharmacologically active ingredients is needed.

“Complementary ginseng use has gained credibility in human studies,” Murphy noted. Research published in the April 1, 2006 *American Journal of Epidemiology* has shown that ginseng usage, along with standard treatments, increases both survival and quality of life in breast cancer patients. However, Murphy cautioned that it is premature to unequivocally recommend that patients take ginseng during cancer treatment. “Ginseng use has not been studied with the more modern chemotherapy medications, and it could potentially interfere or interact with some of them,” she added. Still, she is hopeful that “eventually ginseng may be validated for prevention as well as in the complementary treatment for some cancers.”

Yali Fu, Ph.D., of NCI’s DCTD noted, “The work done by Dr. Murphy is significant, because pure ginsenosides are being tested in cancer cells to see their effects. This is a step in the right direction for providing direct molecular evidence on the effects of ginsenosides. NCI continues to support this kind of research in its mission to find better treatment for cancer. Further studies are needed in animal models and human testing to validate the effectiveness of ginseng products.”

*Grant number: 1R21CA121074-01

DEVELOPING EFFECTIVE AND EFFICIENT TREATMENTS

Noni Juice Studied for Prevention of Breast Cancer

Division of Cancer Prevention

The development of cancer (carcinogenesis) is recognized to be a multistage process. The occurrence of DNA adducts represents an early biomarker of exposure to cancer-causing agents and the likelihood that the cancer process has been initiated. A clinical trial with *Morinda citrifolia*, better known as “noni juice” for lung cancer prevention in 340 smokers provided some interesting findings.



A Noni Flower. The Noni plant bears a fruit which can be eaten and is sometimes used for natural medicinal purposes.

After one month, noni juice significantly reduced the binding of aromatic adducts to DNA in smokers, raising the possibility that it might also reduce cancer risk. “DNA adducts are a good marker for very early carcinogenesis and cancer prevention,” said Mian-Ying Wang, M.S., M.D., who has been exploring the use of noni juice for the prevention of cancers for eight years. “If noni supplements are able to block carcinogen binding to DNA, it could prevent carcinogenesis at the initiation stage.”

“Because noni juice is a strong antioxidant and an anti-inflammatory nutritional supplement, we wanted to know if it can help prevent cancer in another model,” Wang explained. To test her hypothesis, Wang received a developmental grant from NCI to study whether noni juice can help prevent carcinogen-induced tumor formation in an animal model of breast cancer.

Her current investigations use the carcinogenic agent dimethylbenz(a) anthracene (DMBA) to induce mammary cancer*. In her studies, rats received water or water supplemented with up to 10% noni juice. Preliminary results revealed that those animals given 5% noni juice fortified water had the lowest incidence of tumor formation 5 months after exposure to DMBA.

*Grant number: 1R21CA121682-01A2

DEVELOPING EFFECTIVE AND EFFICIENT TREATMENTS

Studying the Effects of Vitamin E and Soy During Radiation for Prostate Cancer

Division of Cancer Prevention

After being diagnosed with cancer, many individuals search for information and make decisions about their lifestyles that they believe will benefit their health and their cancer treatments. Some men with prostate cancer will decide to take dietary supplements such as vitamin E and soy products containing substances called isoflavones. These supplements have antioxidant properties, and both are being studied for their potential benefits in men with prostate cancer.

Some medical oncologists are concerned that these antioxidants may actually interfere with radiation therapy for prostate cancer. They point out that radiation kills cancer cells in part by creating oxygen radicals, and antioxidants, including vitamin E and soy isoflavones, may work against the creation of the oxygen radicals.

“We know that prostate cancer patients are taking these supplements, but we don’t know whether the patients should be taking them if they are having radiotherapy,” cautioned Kathleen Shiverick, Ph.D., of the Department of Pharmacology and Therapeutics at the University of Florida, Gainesville. She has been exploring this question in cells in the laboratory.

Now her team is using NCI* funding to study the question in mice. The researchers are investigating whether vitamin E and soy isoflavones may enhance the toxicity of radiotherapy or may actually interfere with the radiotherapy in mice. A second study question is whether exposing prostate cancer cells to antioxidants after radiation therapy might slow the growth of cells that survive radiation.

In recent years, Shiverick and others have done experiments using prostate cancer cells, with encouraging results. When prostate cancer cells were exposed to physiologically relevant levels of these two antioxidants prior to radiation therapy, the antioxidants sensitized the cancer cells to the radiation. This meant that fewer cells survive the radiation. Each antioxidant—soy and vitamin E—decreased the survival of cells following radiation,

and there was an additive effect with the combination of radiation and the two antioxidants.

Interestingly, adding antioxidants to the cells that survived radiation further slowed the growth of cells. “For the cells that survived irradiation, their growth was much more inhibited,” reported Shiverick. Each antioxidant alone had a significant effect, and the two together had the dramatic effect of preventing any cells from surviving.

Dr. Shiverick cautions that an animal study cannot be designed to directly distinguish between the antioxidant, hormonal, or phytoestrogenic effects of isoflavones because of the complex interactions that occur between the host mouse and the tumor microenvironment, especially in the case of hormonally affected cancers.

“We expect that the phytoestrogenic effect will be clearly seen, because the mice are reported to be able to convert the soy isoflavone daidzein to equol, which is a more potent phytoestrogen than genistein,” says Dr. Shiverick.

Her team chose the combination of Vitamin E and soy for this study because their experiments with cultured prostate cancer cells have identified different cell-signaling mechanisms that are involved in the growth inhibitory effects of these two agents, respectively. They have found additive growth inhibitory effects of the Vitamin E/soy combination at low concentrations, as well as a marked interaction with irradiation in the cell culture model.

Completion of the mouse studies will take several years. In the meantime, many prostate cancer patients will take antioxidants without knowing how they might affect their therapies. “People like to have some degree of control over their course of treatment, and they like to think that nutritional supplements will be beneficial for them,” noted Shiverick. It is hoped that these mouse studies will begin to provide information to help answer what has become an important question to many men with prostate cancer.

*Grant number: 1R21CA102386-01A2

DEVELOPING EFFECTIVE AND EFFICIENT TREATMENTS

Disrupting a Tumor's Biological Clock to Improve Treatment Responses

Division of Cancer Prevention

Researchers often find puzzling differences in how well cancer patients respond to chemotherapy and how severely they experience side effects of those treatments. One explanation that is now being actively pursued involves a field called chronopharmacology. Chronopharmacology seeks to provide patients their drug treatments at times of the day and night during which their bodies' biological "clocks" make the target cancer cells most vulnerable and when side effects will be minimized.

Alec J. Davidson, Ph.D., who works at the Neuroscience Institute at the Morehouse College of Medicine in Atlanta, believes that "we can manipulate the body's circadian system to inhibit cancer." His lab was one of the first to show that tumors have their own circadian (24-hour) rhythms.

"All cells divide and replicate, and that process is regulated by their circadian clock," explained Davidson. "Since uncontrolled cell proliferation is the essential threat posed by carcinogenesis, we think that the internal rhythm that is timing that proliferation could perhaps be disrupted." Earlier work by his team showed that the cycles in isolated tumor cells were shortened by as much as four hours.

Currently, Davidson's NCI-sponsored research* is focused on how the livers of rats use such built-in clocks to anticipate their next meal and how researchers might be able to manipulate this system to fight hepatocellular carcinoma, cancer of the liver. "Timing plays an important role in how the liver functions," noted Davidson. Clock genes in that organ orchestrate rhythmic processes that influence digestion and elimination. "It turns out those rhythms are synchronized not by the time of

day (i.e. triggered by exposure to light), but rather by the timing of previous food intake," he added. While these digestive rhythms appear to persist in liver cancer, they are altered and respond less well to the timing signal for feeding.

"An intriguing possibility is that the altered response to feeding schedules in transformed liver tissue relates to the result that daily meal-feeding actually inhibits cancer growth," Davidson suggested. Research has shown that a restricted (low-calorie) diet "dramatically increases life span in many species, and probably that includes ours," he continued. Mouse experiments also clearly show that tumors develop less aggressively when the host is on a restricted diet.

"What is new here and most important is that the timing of food intake – not just the amount– has an impact on cancer," Davidson explained. "Since timing regulates nearly all of our body's functions, it is not surprising that the timing of food delivery is an important regulator of tumor growth."

The researchers will induce hepatocellular carcinoma and then measure how liver disease develops in response to restricted feeding, compared with rats that eat during the daytime, the nighttime, or on an irregular schedule. "We expect to see tumor growth respond to alterations in the liver's clock, induced by these artificially created feeding times," Davidson said. Such work is adding to a powerful foundation of evidence that may one day profoundly change our perception of the links between diet and cancer.

*Grant number: 1R21CA116261-01A1



IMPROVING THE QUALITY OF CANCER CARE

As interventions and technologies become more sophisticated, the cancer community must build upon research evidence to continually enhance the quality, safety, and appropriateness of care. We are working for the consistent and equitable delivery of the full range of evidence-based interventions that are safe, patient-centered, effective, timely, efficient, and equitable.

IMPROVING THE QUALITY OF CANCER CARE

Soy Protein Studied for Men at High Risk of Prostate Cancer Recurrence

Division of Cancer Prevention

Some men who have surgery for prostate cancer – involving removal of the entire prostate gland or radical prostatectomy – also undergo additional (adjuvant) treatment with radiation therapy, hormone therapy, or chemotherapy. However, most patients with radical prostatectomies don't automatically receive follow-up treatment but are followed closely after their operation. Before determining the need for additional treatment, doctors monitor whether a substance in the surgical patients' blood, prostate-specific antigen (PSA), becomes detectable, which indicates a potential recurrence.

Researchers are looking for new approaches that can be used after surgery for prostate cancer to reduce the risk of recurrence but have fewer side effects than the currently available conventional therapies. Maarten Bosland, D.V.Sc., Ph.D., professor of Pathology at the University of Illinois at Chicago and research professor of Environmental Medicine and Urology at the New York University School of Medicine, is studying soy protein isolate as a potential adjuvant therapy to prevent prostate cancer recurrence.

“Soy isoflavones have been investigated quite extensively in tissue culture, and there are clearly effects that can be interpreted as anticancer effects, such as inhibition of cell proliferation, induction of apoptosis (cell death), and inhibition of angiogenesis (tumor blood supply),” said Dr. Bosland. One specific isoflavone – genistein – inhibits the activity of a group of enzymes called protein tyrosine kinases, which play an important role in the regulation of cancer cell growth.

Under a grant from NCI*, Bosland and his colleagues are currently enrolling participants into a two-arm, randomized, placebo-controlled clinical trial of soy protein isolate for men who are at high risk for prostate cancer recurrence after radical prostatectomy. The investigators will randomly assign participants to receive either 20 grams of soy protein isolate a day or a casein-based placebo for two years or until cancer recurrence. Use of a highly sensitive test for PSA will allow for early detection of rising PSA levels, indicative of recurrence.

The investigators are also recruiting additional participants into a related pharmacology study. Men scheduled for prostate cancer surgery will take 20 grams of soy protein isolate a day for four to six weeks before their operation. The investigators will then use samples from the removed prostate tissue to measure the concentrations of soy isoflavones relative to the dose given, as well as the activity of tyrosine kinase enzymes and indicators of cell proliferation, apoptosis, and angiogenesis, explained Bosland. “That will give us a biological basis to interpret the data from the larger trial.”

If their trial shows a decreased risk of recurrence in patients taking the soy protein isolate, “this would be a non-toxic, non-burdensome additional treatment patients could get in the adjuvant setting,” said Bosland. “It's never been tested in a rigorous fashion, which is why we're doing this trial.”

Howard L. Parnes, M.D., chief of NCI's Prostate and Urologic Cancer Research Group, commented: “Completion of this trial would clearly advance the field of prostate cancer chemoprevention.”

*Grant number: 1R01CA116195-01A1

IMPROVING THE QUALITY OF CANCER CARE

Flaxseed and Curcumin for the Prevention of Radiation-Induced Lung Injury

Division of Cancer Treatment and Diagnosis

The amount of radiation that can be administered to fight a lung tumor is limited by potential damage to normal tissue, which includes inflammation and scarring. Such a condition is called pneumonopathy.

“A safe and effective biologic radioprotector would be extremely useful” in the prevention of radiation-induced pneumonopathy, said Dr. Melpo Christofidou-Solomidou, associate professor of medicine at the University of Pennsylvania. She and her colleagues are currently examining dietary supplementation with the well-known grain flaxseed or curcumin—an antioxidant agent derived from the spice turmeric—as potentially protective therapy against radiation-induced lung damage in a mouse model.*

These natural compounds may activate a cellular antioxidant pathway called Nrf2/ARE. “The Nrf2/ARE pathway is a ‘master switch’ that, when triggered by agents such as lignans, bioactive compounds of flaxseed or curcumin, initiates a cascade of downstream events that regulate the antioxidant and overall protective machinery of the cell,” explained Christofidou-Solomidou. These antioxidant effects would protect normal cells but not cancer cells, due to the different regulatory pathways active in the two types of cells.

Preliminary data from their project have been promising. In one experiment, mice fed a diet supplemented with 10% flaxseed for three to four weeks before receiving radiation therapy to the thorax did not show a decrease in early lung inflammation. However, they had significantly decreased late lung fibrosis and increased survival. An associated experiment showed that activation of the Nrf2/ARE pathway and expression of associated enzymes was increased in mice fed a 10% flaxseed diet for three weeks.

Mice fed a diet supplemented with 5% curcumin for two weeks before radiation therapy and then switched to a normal diet after treatment also had significantly less lung fibrosis after radiation therapy. Survival at four months after treatment was 45% for mice receiving curcumin supplementation compared to 23% in mice fed a normal diet.

The investigators presented this preliminary data at the Experimental Biology Annual Meeting in spring 2007. Additionally, they hope to begin a small, exploratory pilot trial of flaxseed or curcumin supplementation to prevent pneumonopathy in lung cancer patients scheduled to receive a standard three-month course of fractionated radiation therapy. The pilot study will evaluate the feasibility of a full-scale trial by determining the metabolism of the compounds in humans and demonstrating the ability to measure changes in radiation-induced toxicity in this patient population.

*Grant number: 1R21CA118111-01



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.

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

Tai Chi Chih Effects on Insomnia Studied in Breast Cancer Patients

Division of Cancer Control and Population Sciences

Many breast cancer patients and survivors suffer from chronic fatigue and insomnia which impacts their quality of life and may negatively affect their long-term survival. Given the well-known drawbacks of sleep medications, especially among older and sicker patients, there is a great need for behavioral interventions that have proven highly effective in the treatment of insomnia. However, these interventions have yet to be studied widely in cancer patients.

The ancient Chinese slow movement meditation practice of Tai Chi Chih (TCC) is a promising candidate for remedying sleep impairments, leading Michael R. Irwin, M.D., at the University of California at Los Angeles (UCLA) medical school, to initiate the first randomized, controlled clinical trial of the effects of TCC on sleep outcomes in breast cancer survivors. “There is a tremendous need for the treatment of insomnia in breast cancer survivors, given that almost 40% of patients experience this symptom,” Irwin noted.

Irwin, who is a Norman Cousins Professor for psychoneuroimmunology at UCLA, has previously studied TCC in older non-cancer patients and found that it not only improved their immune functioning, but it also helped lessen sleep impairments. “These findings were rather unexpected, because we didn’t tell the participants that we were looking at sleep effects at all,” he recalled. “When we analyzed the data, we found out that sleep did, in fact, significantly improve.”

With NCI funding*, Irwin is now conducting a study that compares the effects of TCC with a control group of cancer patients who participate in a sleep hygiene educational workshop. The patients in the TCC group take training classes twice weekly for 12 weeks where they learn 20 separate TCC exercises and movements. They are then followed for one year to determine whether they maintain their TCC practice and whether it improves their sleep.

Unlike previous TCC studies, “we look at objective measures of sleep by doing EEG (electroencephalogram) evaluations of sleep both before and after the intervention,” Irwin explained. “We also are monitoring the levels of proinflammatory cytokines. We have found that high levels of these biomarkers are associated with impairments of sleep.”

“The importance of this particular behavioral intervention is that TCC is so easily accessible for individuals, is low cost, and can be administered in the community as well as in medical care settings,” Irwin added. “For all those reasons, TCC could prove to be a very useful complement in treatment of insomnia in patients recovering from cancer.”

Enrollment for the study began early in 2007.

***Grant number: 1R01CA119159-01A1**

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

Study Will Test the Effect of Tibetan Yoga on Women with Breast Cancer

Division of Cancer Control and Population Sciences

Researchers at The University of Texas M. D. Anderson Cancer Center have received a \$2.4 million grant from NCI* to study the effects of Tibetan yoga on fatigue and sleep in women with breast cancer who are undergoing chemotherapy.

“Cancer and its treatment are associated with considerable distress, impaired quality of life, poor mental health, and reduced physical function,” explained Principal Investigator Lorenzo Cohen, Ph.D., an associate professor in the Departments of Behavioral Science and Palliative Care and Rehabilitation Medicine. “This is particularly true for women with breast cancer who receive multi-modality treatment over an extended period of time. For thousands of years, Tibetans have been employing a form of yoga that we think could help ameliorate the treatment-related morbidity that accumulates over time in cancer patients.”

Most of what is known about yoga in the West comes from the Indian tradition. For this project, Cohen and his colleagues have chosen the yoga traditions from Tibet, but they are also conducting NCI-funded studies using yogas from India (Hatha yoga) and China (Qigong). His team was the first to design pilot studies that examined the benefits of these techniques in cancer patients. They published a 2004 study in the journal *Cancer* that found the practice led to significant sleep improvements in patients with lymphoma. Another small study of Tibetan yoga also found improvements in cancer-related symptoms and intrusive thoughts in women with breast cancer.

Based on those findings, the research team will conduct a large randomized trial that will compare Tibetan yoga versus simple stretching or usual care in women who will be undergoing chemotherapy to treat their breast cancer. The study’s yoga instructor and co-investigator is Alejandro Chaoul, Ph.D., one of few individuals in the United States trained in Tibetan yoga. “Like other types of yoga, Tibetan yoga involves breathing, physical movements, and meditation, but it puts greater emphasis on meditation and visualization,” he said. The program has been closely supervised by the Tibetan yoga master Tenzin Wangyal Rinpoche to make sure the yoga will be taught as much as possible in the original tradition.

Women with breast cancer who are scheduled to undergo chemotherapy will be randomly assigned to either a Tibetan yoga group, a control group that does simple stretching exercises, or to a group that receives standard care. The participants will practice their assigned techniques for seven weeks during chemotherapy and then will have five booster sessions over the next six months.

The study will assess the physical and psychological benefits of the yoga program and will specifically examine such patient lifestyle factors as fatigue and sleep, mental health and distress. Additionally, the study will evaluate cognitive and emotional processing, social networking and interactions, coping, and other psychosocial factors, Cohen said.

Diana Jeffery, Ph.D., program director, NCI’s Office of Cancer Survivorship commented, “Approaches like yoga have the potential to help women actively participate in breast cancer recovery and may increase their sense of control as they transition into the post-treatment phase.”

*Grant number: 1R01CA105023-01A2

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

Hypnotherapy Eases Hot Flashes in Breast Cancer Survivors

Division of Cancer Control and Population Sciences

Hot flashes associated with treatment-induced menopause in breast cancer survivors can cause discomfort, depression, insomnia, and anxiety, and otherwise negatively affect quality of life for those former patients. Hormone-replacement therapy relieves many symptoms of menopause but also increases the risk of breast cancer and cardiovascular problems. Other medications used to treat hot flashes can produce unwelcome side effects in many patients.

Consequently, researchers are looking for effective nonpharmacologic treatments for hot flashes in breast cancer patients and others. Gary Elkins, Ph.D., and his team from Scott and White Hospital in Temple, Texas recently completed an NCI-funded randomized trial* of hypnosis for the treatment of hot flashes in breast cancer survivors. Hypnotherapy, which has been used successfully to treat cancer pain, uses the relaxation response, mental imagery, and power of suggestion to alter a person's perception of their physiologic state.

After a promising 16-person pilot study on hot flash symptoms, Elkins and colleagues expanded their research to a 60-person randomized trial. Breast cancer survivors experiencing an average of 10 hot flashes a day were randomly assigned either to five weeks of weekly hypnotherapy sessions, including training on self-hypnosis, or to a wait-list control group.

Preliminary findings indicated that women in the hypnotherapy group had a 60% reduction in the frequency of hot flashes and a 69% decrease in the severity of their remaining hot flashes, Elkins noted. Women in the hypnotherapy group also reported improvements in sleep and mood. No changes were observed in women in the control group.

Elkins and his team are now planning a larger, multicenter trial to confirm and clarify their data. The expanded study will use a "structured attention" control group, in which women in the control group receive therapy sessions that do not include hypnosis. In addition, data will be collected to analyze whether the reduction in perceived hot flashes is due to physiologic effects and/or psychological responses such as expectancies and hypnotizability of study participants.

Elkins has found that patients are very interested in participating in these studies. "The basic philosophy that underlies hypnotic treatment is, 'empower the patient,'" he explained. "It's not so much something that's done to the patient as a collaborative relationship between doctor and patient in which the patient learns hypnotic techniques and how to utilize self-hypnosis toward achieving better control over her own body."

*Grant number: 5R21CA100594-02



Women in the hypnotherapy group also reported improvements in sleep and mood.



NCI SCIENTISTS SPEARHEAD PIONEERING RESEARCH ON CAM

To the public, NCI is often thought of in terms of being the largest supporter of cancer research in the United States and the world. That is clearly one of NCI's most important functions. Perhaps the untold story, however, is the outstanding research being carried out by the talented scientists and clinicians in the Institute's own laboratories or intramural programs, the foundation of which occurs within NCI's Center for Cancer Research (CCR) and the Division of Cancer Epidemiology and Genetics (DCEG).

NCI's intramural researchers perform essential basic, clinical, and epidemiologic research, upon which a great deal of research by outside institutions or extramural programs are eventually based. This principle certainly applies to the area of CAM research where CCR and DCEG scientists are engaged in exciting and pioneering research that is both high risk and high impact. The intramural program also serves as the training ground for thousands of investigators launching their careers in science.

NCI SCIENTISTS SPEARHEAD PIONEERING RESEARCH ON CAM

NCI Scientists Are Using Mice to Study Selenium and Resveratrol's Role in Cancer Prevention

Center for Cancer Research

The Center for Cancer Research (CCR) at NCI has been a leader in pioneering useful “murine” models – the term used to refer to experimental studies in mice – which can help predict how humans might respond to similar treatments. Clinical studies of CAM also benefit from this research strategy. This is, in part, due to greater control over the animal test subjects, therefore making it easier to study diet prevention strategies.

Large-scale dietary intervention studies in humans take many years and are very expensive to conduct. Thus, it becomes crucial to learn as much as possible in advance about the mechanisms of action such dietary components might have, in order to refine and focus the subsequent human trials.

According to Jeffrey E. Green, M.D., head of CCR's Transgenic Oncogenesis Group, “Virtually all of our work now focused on preclinical testing is in genetically-engineered mouse (GEM) models.” During 2006, as in past years, the fruits of NCI research on GEMs are made available at no cost to cancer researchers in the broader community.

In the past, mice were often injected with a carcinogen, or cancer cells were implanted in mice with defective immune systems. Now, researchers are able to observe cancers arise and progress in a GEM with a fully-functioning endocrine and immune system. They are also able to engineer mice that are genetically predisposed to develop a number of different, specific tumor strains.

Green has recently been studying the trace element selenium, a micronutrient that makes its way from the soil into a number of grains and vegetables, which can also be used to fortify salt and thus delivered to large populations. The CCR researchers developed a strain of mouse engineered to develop a specific breast tumor. Mice that were engineered with inadequate mechanisms for incorporating selenium into proteins had

more than three times as many breast tumors, he reported. Such detailed biological information on how dietary components, such as selenium, actually influence carcinogenesis could help to refine analysis of large ongoing human trials, such as the NCI-sponsored Selenium and Vitamin E Cancer Prevention Trial (SELECT).

“The newest GEM model technologies have allowed us to build a better mouse to model cancer, no question,” Green noted. “By engineering genetic alterations that we know are relevant to human cancers, we can now model the onset and progression of cancer in a biological milieu that is much more like real human disease than any previous models.”

He and other CCR researchers are now actively pursuing studies that involve phytochemicals found in grape skins.* Resveratrol is a component of red grapes that has been shown to inhibit the growth of prostate cancer cells. Because the mouse models permit such detailed examination of the pathways involved, Green wondered if other, similar phytochemicals might provide a complementary approach to prostate cancer prevention. They are finding that extracts from the skins of muscadine grapes contain no resveratrol, yet appear to inhibit prostate cancer progression in the mice through different mechanisms.

Such work illustrates the synergy of basic and clinical cancer research. “The molecular dissection of human cancers continues to identify important genes, pathways, and networks that are crucial to tumor progression,” explained Green. “Our ability to generate new GEM models that reflect that refined view of human cancer biology should lead to identification of more and better biomarkers of cancer development, as well as meaningful responses to chemopreventive agents.”

*Project number: Z01BC005740

NCI SCIENTISTS SPEARHEAD PIONEERING RESEARCH ON CAM

NCI Researcher Investigates How Selenium Protects Against Cancer

Center for Cancer Research

Selenium is a trace element found in grains (like rice and wheat), meat, seafood, yeast, and certain vegetables and plants, especially Brazil nuts. Dolph Hatfield, Ph.D., head of the Molecular Biology of Selenium section in NCI's Center for Cancer Research (CCR), has been feeding selenium to mice for many years. He describes selenium as a unique element, "with fascinating properties and real opportunities, not only as an anticancer agent, but it also has the potential to fight viruses, delay the aging process, and combat heart disease."

However, "as a molecular biologist, I must say that we don't know enough about how selenium accomplishes these varied health benefits," cautioned Hatfield. There are also some serious divisions in the research community over which form of selenium works best and whether it might also carry some unsuspected risks.

NIH currently has nearly a dozen clinical trials planned or underway in order to develop hard evidence about selenium's protective properties. Because their cost will run to hundreds of millions of dollars, Hatfield thinks it is crucial to build a solid, explanatory, scientific foundation at the molecular level.

"Ironically," said Hatfield, "it was the Nutritional Prevention of Cancer Trial in the mid-1990s that illustrated both the promise and the perils of selenium." Researchers were looking for a protective effect against recurrent skin cancer but instead found that the risk actually increased by about 10%. "They got a pleasant surprise when they unblinded the study however," said Hatfield, "because it turned out those taking selenium had significantly fewer lung, colorectal, and prostate cancers" when compared to control subjects.



Once in the body, selenium makes its way into a number of chemically distinct selenoproteins, which are manufactured by cells to contain the selenium-containing amino acid, selenocysteine. Currently, Hatfield's lab is studying one of those selenoproteins thioredoxin reductase 1 (TR1).*

TR1 is found in abundance in many cancer cells, explained Hatfield, "and we think it may actually be driving carcinogenesis in a number of different cancers, including in the liver. Liver cancer is especially dangerous, because it presents few telltale early symptoms. If we could turn down TR1 expression, we might be able to prevent it from progressing into clinical disease."

One of the major NIH trials now underway is the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which includes more than 35,000 healthy men over age 55, and the study should begin producing results in a few years. Meanwhile, Hatfield and his co-workers are working hard to clarify which selenoproteins do what, in which people, and how these proteins can be turned on and off in cancers.

Hatfield has not been able to rule out the possibility that selenomethionine – the selenium-containing compound being tested in SELECT – may be one of the forms that potentially can also have detrimental effects on health. If so, and if the men in SELECT who receive selenium have a reduced risk of prostate cancer, then information will be gained to evaluate the risk-benefit ratio. This will allow a better assessment of the appropriateness of evaluating the use of selenomethionine for the treatment or prevention of other malignancies. Hatfield is continuing to explore this potential toxicity risk.

*Project number Z01BC005317

NCI SCIENTISTS SPEARHEAD PIONEERING RESEARCH ON CAM

NIH-AARP Diet and Health Study Examines Links Between Nutrition, Weight, and Cancer

Division of Cancer Epidemiology and Genetics

The first published results from the NIH-AARP Diet and Health Study* have begun to illuminate associations between nutritional and other lifestyle factors, including weight gain and exercise, and risks for cancer and other diseases.

The study was developed by investigators within the Nutritional Epidemiology Branch of DCEG and collaborators from AARP (formerly known as the American Association for Retired Persons). As the largest in-depth prospective cohort study of diet and cancer ever done, the NIH-AARP study monitored the health status of more than 500,000 AARP members aged 50-71 from 1995 to 2005 using mailed questionnaires, death records, and tumor registry data. The numerous analyses of the participants' health and disease status over the ensuing years began to be published in 2006 and have already resulted in more than 20 articles in major medical journals, noted Arthur Schatzkin, M.D., Dr.P.H., DCEG Principal Investigator for the NIH-AARP study.

In the August 24, 2006 issue of the *New England Journal of Medicine*, the research team reported that being overweight during midlife is linked to an increased risk of death. The analysis of nonsmokers at age 50 found that the risk of mortality among participants in the NIH-AARP study who were overweight increased by 20% to 40%, while mortality risk among obese participants increased two to threefold. Excess body weight increases the risk of heart disease, stroke, high blood pressure, pulmonary disease, and diabetes, and is believed to play a role in several cancers.

Another report, published in early 2007 in the journal *Cancer*, showed that while obese men are no more likely to actually develop prostate cancer than men of normal weight, they are more likely to die from the disease. Additional published reports have examined artificial sweetener aspartame and risk for certain cancers, the relationship between alcohol consumption and risk of head and neck cancer, and the possible role of dietary fat in the development of postmenopausal invasive breast cancer.

"I believe this study will be recognized as one of the leading studies on nutrition, energy balance, and cancer," Schatzkin noted. "Because of its size, the NIH-AARP study provides the opportunity to look at the complex interrelationships of dietary intake and other factors in development of disease."

Future plans include ongoing follow-up of the original study participants and expanding the study population to include more of the AARP membership by using a web-based dietary survey instrument. "We are very appreciative of the collaboration with AARP – without their members' participation, the study would not have been possible," Schatzkin commented. "The AARP leadership has been extremely supportive of the study by encouraging participant retention and publicizing the study in their publications and Web sites."

*Project number: Z01 CP01027-11

Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006; 355(8):763-778.

Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, Hurwitz P, Hollenbeck A, Leitzmann MF. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer*. 2007; 109(4):675-684.

NCI SCIENTISTS SPEARHEAD PIONEERING RESEARCH ON CAM

Exploring the Role of Cooked Red Meat in Cancer Risk

Division of Cancer Epidemiology and Genetics

Not many foods have been shown to be associated with cancer, but by the 1990s, researchers were beginning to link the consumption of meat – red meat in particular – to some forms of cancer. A primary culprit appears to be chemical structures known as heterocyclic amines (HCAs), which damage cells and have been shown to increase the risk of cancer.

HCAs are not present in uncooked meat but can be found abundantly in red meat that is cooked at high temperatures for long periods of time. They form when amino acids (the building blocks of proteins) react with creatine or creatinine (a chemical found in muscle) under certain cooking conditions, such as frying and barbecuing. Even meat cooked in other ways will form HCAs when cooked until “well done.” Also identified in some of these studies was a second group of carcinogens, polycyclic aromatic hydrocarbons (PAHs).



HCAs are not present in uncooked meat but can be found abundantly in red meat that is cooked at high temperatures for long periods of time.

“A lot of good work in the 1990s in cell and animal studies implicated HCAs,” said Rashmi Sinha, Ph.D., a senior investigator with NCI’s Nutritional Epidemiology Branch within DCEG. She was among the first epidemiologic researchers who realized that the most meaningful data on the link to human cancer would come through large, long-term, prospective observational studies. Sinha is currently working to develop and refine the questionnaires that such studies could use to tease out possible cancer links with certain meats and how they are prepared.*

For example, the massive NIH-AARP Diet and Health Study included a series of questions she and her colleagues developed about meat consumption and preparation in a cohort of more than 567,000 men and women between ages 50-69. Sinha expects to publish results from responses to that study in the near future (see also page 55). Another large study – the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial – has some 155,000 participants and has already begun to confirm some of the associations suggested in earlier studies. Sinha was also instrumental in tailoring PLCO food questionnaires to shed light on the same issues.

The estimates that emerged from many of the older studies vary, but Sinha believes the new epidemiological data that will emerge from these large trials will enable researchers to quantify how much the increase in cancer risk is attributable to high temperature meat preparation.

*Project number: Z01 CP01027-11

Scientific Publications

This is a selected list of some of the most important peer-reviewed scientific articles about the findings and analyses of NCI-supported CAM research studies published during FY 2006. The articles marked with an asterisk are published results of studies featured in FY 2005 CAM Annual Report. Abstracts of the articles are available online through the National Library of Medicine's "PubMed" database at www.pubmed.com.

Cancer Prevention

* Gail MH, You WC. A factorial trial including garlic supplements assesses effect in reducing pre-cancerous gastric lesions. *Journal of Nutrition*, March 2006; 136(3 Suppl): 813S-815S.

Henning SM, Niu Y, Liu Y, Lee NH, Hara Y, Thames GD, Minutti RR, Carpenter CL, Wang H, Heber D. Bioavailability and antioxidant effect of epigallocatechin gallate administered in purified form versus as green tea extract in healthy individuals. *Journal of Nutritional Biochemistry*, October 2005; 16(10):610-6.

Hu H, Jiang C, Schuster T, Li GX, Daniel PT, Lu J. Inorganic selenium sensitizes prostate cancer cells to TRAIL-induced apoptosis through superoxide/p53/Bax-mediated activation of mitochondrial pathway. *Molecular Cancer Therapeutics*, July 2006; 5(7):1873-82.

* Huang C, Li J, Song L, Zhang D, Tong Q, Ding M, Bowman L, Aziz R, Stoner GD. Black raspberry extracts inhibit benzo(a)pyrene diol-epoxide-induced activator protein 1 activation and VEGF transcription by targeting the phosphatidylinositol 3-kinase/Akt pathway. *Cancer Research*, January 2006; 66(1):581-7.

Lam S, McWilliams A, LeRiche J, MacAulay C, Wattenberg L, Szabo E. A Phase I study of myo-inositol for lung cancer chemoprevention. *Cancer Epidemiology, Biomarkers & Prevention*, August 2006; 15(8):1526-31.

* Lu H, Li J, Zhang D, Stoner GD, Huang C. Molecular mechanisms involved in chemoprevention of black raspberry extracts: from transcription factors to their target genes. *Nutrition and Cancer*, 2006; 54(1): 69-78.

Luo H, Tang L, Tang M, Billam M, Huang T, Yu J, Wei Z, Liang Y, Wang K, Zhang ZQ, Zhang L, Wang JS. Phase IIa chemoprevention trial of green tea polyphenols in high-risk individuals of liver cancer: modulation of urinary excretion of green tea polyphenols and 8-hydroxydeoxyguanosine. *Carcinogenesis*, February 2006; 27(2):262-8.

Malik A, Afaq F, Sarfaraz S, Adhami VM, Syed DN, Mukhtar H. Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. *Proceedings of the National Academy of Sciences*, October 2005; 102(41):14813-8.

Mantena SK, Meeran SM, Elmets CA, Katiyar SK. Orally administered green tea polyphenols prevent ultraviolet radiation-induced skin cancer in mice through activation of cytotoxic T cells and inhibition of angiogenesis in tumors. *Journal of Nutrition*, December 2005; 135(12):2871-7.

Reagan-Shaw S, Breur J, Ahmad N. Enhancement of UVB radiation-mediated apoptosis by sanguinarine in HaCaT human immortalized keratinocytes. *Molecular Cancer Therapeutics*, February 2006; 5(2):418-29.

Saleem M, Kweon MH, Johnson JJ, Adhami VM, Elcheva I, Khan N, Bin Hafeez B, Bhat KM, Sarfaraz S, Reagan-Shaw S, Spiegelman VS, Setaluri V, Mukhtar H. S100A4 accelerates tumorigenesis and invasion of human prostate cancer through the transcriptional regulation of matrix metalloproteinase 9. *Proceedings of the National Academy of Sciences*, October 2006; 103(40):14825-30.

Shukla S, Mishra A, Fu P, MacLennan GT, Resnick MI, Gupta S. Up-regulation of insulin-like growth factor binding protein-3 by apigenin leads to growth inhibition and apoptosis of 22Rv1 xenograft in athymic nude mice. *FASEB Journal*, December 2005; 19(14):2042-2044.

Siddiqui IA, Zaman N, Aziz MH, Reagan-Shaw SR, Sarfaraz S, Adhami VM, Ahmad N, Raisuddin S, Mukhtar H. Inhibition of CWR22Rnu1 tumor growth and PSA secretion in athymic nude mice by green and black teas. 1: *Carcinogenesis*, April 2006; 27(4):833-9.

Yun JM, Kweon MH, Kwon H, Hwang JK, Mukhtar H. Induction of apoptosis and cell cycle arrest by a chalcone panduratin A isolated from *Kaempferia pandurata* in androgen-independent human prostate cancer cells PC3 and DU145. 1: *Carcinogenesis*, July 2006; 27(7):1454-64.

Cancer Treatment

* Chen X, Murakami T, Oppenheim JJ, Howard OM. Triptolide, a constituent of immunosuppressive Chinese herbal medicine, is a potent suppressor of dendritic-cell maturation and trafficking. *Blood*, October 2005; 106(7):2409-16.

Khan N, Afaq F, Saleem M, Ahmad N, Mukhtar H. Targeting multiple signaling pathways by green tea polyphenol (-)-epigallocatechin-3-gallate. *Cancer Research*, March 2006; 66(5):2500-5.

Kijima I, Phung S, Hur G, Kwok SL, Chen S. Grape seed extract is an aromatase inhibitor and a suppressor of aromatase expression. *Cancer Research*, June 2006; 66(11):5960-7.

Saleem M, Kaur S, Kweon MH, Adhami VM, Afaq F, Mukhtar H. Lupeol, a fruit and vegetable based triterpene, induces apoptotic death of human pancreatic adenocarcinoma cells via inhibition of Ras signaling pathway. *Carcinogenesis*, November 2005; 26(11):1956-64.

Saleem M, Kweon MH, Yun JM, Adhami VM, Khan N, Syed DN, Mukhtar H. A novel dietary triterpene Lupeol induces fas-mediated apoptotic death of androgen-sensitive prostate cancer cells and inhibits tumor growth in a xenograft model. *Cancer Research*, December 2005; 65(23):11203-13.

Singh SV, Zeng Y, Xiao D, Vogel VG, Nelson JB, Dhir R, Tripathi YB. Caspase-dependent apoptosis induction by guggulsterone, a constituent of Ayurvedic medicinal plant *Commiphora mukul*, in PC-3 human prostate cancer cells is mediated by Bax and Bak. *Molecular Cancer Therapeutics*, November 2005; 4(11):1747-54.

Veluri R, Singh RP, Liu Z, Thompson JA, Agarwal R, Agarwal C. Fractionation of grape seed extract and identification of gallic acid as one of the major active constituents causing growth inhibition and apoptotic death of DU145 human prostate carcinoma cells. *Carcinogenesis*, July 2006; 27(7):1445-53.

Yamaguchi K, Liggett JL, Kim NC, Baek SJ. Anti-proliferative effect of horehound leaf and wild cherry bark extracts on human colorectal cancer cells. *Oncology Reports*, January 2006; 15(1):275-81.

Cancer Side Effects / Symptom Management

Ezzo J, Vickers A, Richardson MA, Allen C, Dibble SL, Issell B, Lao L, Pearl M, Ramirez G, Roscoe JA, Shen J, Shivnan J, Streitberger K, Treish I, Zhang G. Acupuncture-point stimulation for chemotherapy-induced nausea and vomiting. *Journal of Clinical Oncology*, October 2005; 23(28):7188-98.

Okunieff P, Xu J, Hu D, Liu W, Zhang L, Morrow G, Pentland A, Ryan JL, Ding I. Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines. *International Journal of Radiation Oncology, Biology, Physics*, July 2006; 65(3):890-8.

Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, Sloan JA, Lavasseur BI, Rao RM, Fitch TR, Rowland KM, Novotny PJ, Flynn PJ, Richelson E, Fauq AH. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. *Journal of Clinical Oncology*, June 2006; 24(18):2836-41.

Appendix

An NCI-sponsored 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.

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Pediatric Trials					
Randomized Study of Electroacupuncture for Treatment of Delayed Chemotherapy-Induced Nausea and Vomiting in Patients With Newly Diagnosed Pediatric Sarcoma, Neuroblastoma, Nasopharyngeal Carcinoma, or Germ Cell Tumors	NCCAM-02-AT-0172	Supportive care	10 to 35	NCCAM; NCI	No phase specified
Randomized Prospective Pilot Study of Acupressure in Preventing Chemotherapy-Associated Nausea and Vomiting in Pediatric Patients With Cancer	CCCWFU-02104	Supportive care	2 to 21	NCI	No phase specified
Randomized Study of Traumeel® S for the Prevention and Treatment of Mucositis in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplantation	COG-ACCL0331	Supportive care	3 to 25	NCI	No phase specified
Phase II Randomized Pilot Study of Silymarin (Milk Thistle Extract) in Patients With Acute Lymphoblastic Leukemia Receiving Hepatotoxic Chemotherapy	CPMC-IRB-14117	Supportive care	2 to 21	NCI	Phase II
Phase I Study of Beta-Glucan and Rituximab in Pediatric Patients With Relapsed or Progressive CD20-Positive Lymphoma or Leukemia or Post-Allogeneic Stem Cell Transplant-Related Lymphoproliferative Disorder	MSKCC-03095	Treatment	Under 22	NCI	Phase I

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Adult Trials					
Randomized Study of the Molecular Effects of Lycopene Versus Omega-3 Fatty Acid Nutritional Supplements in Patients With Stage I or II Prostate Cancer	UCSF-03553	Biomarker/Laboratory analysis; Treatment	Not specified	NCI	No phase specified
Phase II Randomized Study of Neoadjuvant Genistein in Patients Undergoing Surgical Resection for Bladder Cancer	WCCC-CO-04307	Biomarker/Laboratory analysis; Treatment	18 and over	NCI	Phase II
Chemoprevention Study of Broccoli Sprout Extract in Smokers	JHOC-J0427	Prevention	Over 18	NCI	No phase specified
Randomized Study of Dietary Modification Intervention Comprising Individual Counseling Versus Automated Computer-Based Counseling Versus Both Dietary Modification Interventions in Helping Healthy Women Adopt a Cancer Prevention Diet	KAISER-R01-CA098496	Prevention	30 to 70	NCI	No phase specified
Randomized Study of Fish Oil Supplements in Preventing Prostate Cancer in Patients With Prostatic Intraepithelial Neoplasia or Who Are at Risk for Developing Prostate Cancer	OHSU-CPC-04131-LX	Prevention	18 and over	NCI	No phase specified
Study of Zinc Supplements for Reduction of Cadmium Levels in Smokers	CCCWFU-98903	Prevention; Biomarker/Laboratory analysis	21 and over	NCI	No phase specified
Phase I Study of Lycopene as Chemoprevention for Prostate Cancer in Healthy Participants	UIC-2004-0217	Prevention; Biomarker/Laboratory analysis	18 and over	NCI	No phase specified
Phase I Study of Lycopene as Chemoprevention for Prostate Cancer in Healthy Participants	UIC-2004-0040	Prevention	18 to 45	NCI	Phase I
Phase I Randomized Study of Folate-Depleted Versus Folate-Supplemented Diet for the Prevention of Colorectal Cancer in Patients at High Risk for Colorectal Neoplasia	RUH-PHO-0514-0404	Prevention	40 to 72	NCI	Phase I
Phase I Study of Resveratrol in Healthy Participants	CCUM-2004-0535	Prevention	18 to 80	NCI	Phase I
Phase I Randomized Chemoprevention Study of Indole-3-carbinol in Healthy Participants	KUMC-HSC-9139	Prevention	18 to 70	NCI	Phase I

APPENDIX

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Adult Trials					
Phase I Pilot Chemoprevention Study of IH636 Grape Seed Proanthocyanidin Extract in Healthy Postmenopausal Women at High Risk of Developing Breast Cancer	CHNMC-IRB-03178	Prevention	40 to 75	NCI	Phase I
Phase I Randomized Study of Bowman Birk Inhibitor Concentrate in Healthy Male Participants	UPCC-706366	Prevention	18 to 65	NCI	Phase I
Phase IB Randomized Study of Green Tea Extract (Polyphenon E) in Preventing Esophageal Cancer in Patients With Barrett's Esophagus	MDA-03101	Prevention	18 and over	NCI	Phase I
Phase II Randomized Study of Dietary Soy in Patients With Elevated PSA Levels	CALGB-79806	Prevention	50 and over	NCI	Phase II
Phase II Randomized Chemoprevention Study of Calcitriol in Patients With High-Grade Prostatic Intraepithelial Neoplasia	CINJ-080404	Prevention	18 and over	NCI	Phase II
Phase II Randomized Study of Green Tea Extract (Polyphenon E) for the Prevention of Cervical Cancer in Patients With Human Papillomavirus (HPV) and Low-Grade Cervical Intraepithelial Neoplasia (CIN 1)	UARIZ-UAZ03-1-02	Prevention	18 and over	NCI	Phase II
Phase II Randomized Study of Genistein in Women at High Risk For Breast Cancer	NU-NWU03-1-04	Prevention	25 and older	NCI	Phase II
Phase II Randomized Study of Green Tea or Polyphenon E in Preventing Lung Cancer in Former Smokers With Chronic Obstructive Pulmonary Disease	UARIZ-HSC-0353	Prevention; Biomarker/ Laboratory analysis	40 to 80	NCI	Phase II
Phase II Randomized Chemoprevention Study of Atorvastatin Versus Oligofructose-Enriched Inulin (Raftilose Synergy 1) Versus Sulindac in Patients at Increased Risk of Developing Sporadic Colorectal Neoplasia	MAYO-030103	Prevention; Biomarker/ Laboratory analysis	40 and over	NCI	Phase II
Phase II Chemoprevention Study of Curcumin in Current Smokers With Aberrant Crypt Foci	UCIRVINE-UCI04-2-01	Prevention; Biomarker/ Laboratory analysis	40 and over	NCI	Phase II
Phase III Randomized Chemoprevention Study of Selenium in Participants With Previously Resected Stage I Non-Small Cell Lung Cancer	ECOG-5597	Prevention	18 and over	NCI	Phase III

APPENDIX

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Adult Trials					
Phase III Randomized Study of Selenium in Patients With Adenomatous Colorectal Polyps	UARIZ-HSC-00142	Prevention	40 to 80	NCI	Phase III
Phase III Randomized Study of Isoflavones in Reducing Risk Factors in Patients With Stage I or II Prostate Cancer	MCC-0002	Prevention	50 to 80	NCI	Phase III
Randomized Pilot Study of Glutamine Supplementation for the Prevention of Paclitaxel-Induced Myalgia and/or Arthralgia in Patients With Cancer	OHSU-ONC-99037-L	Supportive care	18 and over	NCI	No phase specified
Study of Acupuncture in Treating Hot Flashes in Patients With Prostate Cancer Undergoing Androgen Deprivation	OHSU-7235	Supportive care	Over 18	NCI	No phase specified
Randomized Pilot Study of Professional Massage Therapy Versus Professional Simple Presence (No Touch) Massage Therapy Followed By Caregiver Massage Therapy for Symptom Management in Patients With Locally Advanced or Metastatic Cancer	BIDMC-2003P-000299	Supportive care	18 and over	NCI	No phase specified
Randomized Study of Coenzyme Q10 to Relieve Treatment-Related Fatigue in Women With Breast Cancer	CCCWFU-97202	Supportive care	Any age	NCI	No phase specified
Randomized Study of Hypnosis, Massage Therapy, and Healing Touch in Patients Undergoing Chemotherapy for Ovarian Epithelial or Primary Peritoneal Cavity Cancer	UMN-2000NT790	Supportive care	Any age	NCI	No phase specified
Randomized Study of American Ginseng in Patients With Cancer-Related Fatigue	NCCTG-N03CA	Supportive care	18 and over	NCI	No phase specified
Pilot Study of Healing Touch in Treating Patients Receiving Chemotherapy For Acute Myeloid Leukemia or Acute Lymphocytic Leukemia	CCCWFU-02305	Supportive care	18 and over	NCI	No phase specified
Randomized Pilot Study of Hypnosis in Controlling Hot Flashes in Women Who are Breast Cancer Survivors	S-WHITE-8165	Supportive care	Over 18	NCI	No phase specified
Pilot Study of a Stress Reduction Program in Patients With Malignant Brain Tumors and Their Family Caregivers	CASE-CCF-2306-CC052	Supportive care	18 and over	NCI	No phase specified

APPENDIX

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Adult Trials					
Randomized Study of Music in Reducing Anxiety and Perceived Pain in Adult Patients Who Are Undergoing Bone Marrow Biopsy for Hematologic Cancers or Other Diseases	CCCWFU-98306	Supportive care	18 and over	NCI	No phase specified
Pilot Study of Soy-Based Meal Replacement (Almased®) as a Weight Loss Intervention in Patients With Estrogen Receptor/Progesterone Receptor-Negative Stage I-III Breast Cancer in Complete Remission	CCCWFU-98904	Supportive care; Educational/Counseling/ Training; Behavioral study	21 and over	NCI	No phase specified
Pilot Study of Restorative Yoga for Symptom Management and Stress Reduction in Women With Ovarian or Breast Cancer	CCCWFU-02403	Supportive Care: Educational/Counseling/ Training	18 and over	NCI	No phase specified
Pilot, Randomized Study of Mindfulness Relaxation Versus Relaxing Music Versus Standard Symptom Management Education in Patients With Newly Diagnosed Solid Tumors Undergoing Chemotherapy	MDA-CCC-0106	Supportive Care: Educational/Counseling/ Training	18 and over	NCI	No phase specified
Randomized Pilot Study of Low-Residue Diet for the Treatment of Diarrhea in Patients With Uterine, Cervical, or Prostate Cancer Who Are Undergoing Pelvic Radiotherapy	CASE-2Z05	Supportive Care: Educational/Counseling/ Training	20 to 80	NCI	No phase specified
Phase II Randomized Study of Soy Protein in Postmenopausal Women With Breast Disease Taking Tamoxifen and Experiencing Hot Flashes	CALGB-79805	Supportive care	Postmenopausal (20 and over)	NCI	Phase II
Phase II Randomized Pilot Study of Massage Therapy in Patients With Cancer Pain	MSKCC-03046A	Supportive care	18 and over	NCI	Phase II
Phase II Randomized Study of Ginger in Patients With Cancer and Chemotherapy-Induced Nausea and Vomiting	CCUM-0201	Supportive care	18 and over	NCI; NCCAM	Phase II
Phase II Study of Hypericum Perforatum (St. John's wort) in Postmenopausal Women With Non-Metastatic Breast Cancer Suffering From Hot Flashes	CCCWFU-98301	Supportive care	18 and over	NCI	Phase II
Phase II/III Randomized Study of Ginger for Chemotherapy-Related Nausea in Patients With Cancer	URCC-U1902	Supportive care	18 and over	NCI	Phase II; Phase III

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Adult Trials					
Phase III Randomized Study of Acupuncture Versus Standard of Care in Treating Pain and Dysfunction in Patients With Head and Neck Cancer Who Have Undergone Neck Dissection	MSKCC-03131A	Supportive care	Not specified	NCI	Phase III
Phase III Randomized Study of (Valerian) for Improving Sleep in Patients With Cancer Receiving Adjuvant Therapy	NCCTG-N01C5	Supportive care	18 and over	NCI	Phase III
Phase III Randomized Study of Creatine in Patients With Cancer-Associated Weight Loss	NCCTG-N02C4	Supportive care	18 and over	NCI	Phase III
Phase III Randomized Study of Levocarnitine (L-carnitine) for the Management of Fatigue in Cancer Patients	ECOG-E4Z02	Supportive care	18 and over	NCI	Phase III
Phase III Randomized Study of Alpha-Lipoic Acid in Preventing Platinum-Induced Peripheral Neuropathy in Cancer Patients Receiving a Cisplatin- or Oxaliplatin-Containing Chemotherapy Regimen	MDA-CCC-0327	Supportive care	Not specified	NCI	Phase III
Pilot Study to Evaluate the Influence of Garlic on the Pharmacokinetics of Docetaxel in Patients With Locally Advanced or Metastatic Breast Cancer	NCI-04-C-0084	Treatment	18 and over	NCI	No phase specified
Randomized Study of Pomegranate Juice in Patients With Rising Prostate-Specific Antigen Levels After Surgery or Radiotherapy for Localized Prostate Cancer	UCLA-0507059-01	Treatment	18 and over	NCI; Pharmaceutical/ Industry	No phase specified
Randomized Pilot Study of Isoflavones Versus Lycopene Prior to Radical Prostatectomy in Patients With Localized Prostate Cancer	MCC-0105	Treatment; Biomarker/ Laboratory analysis	45 to 80	NCI	No phase specified
Phase I Study of Gemcitabine and Mistletoe in Patients With Advanced Solid Tumors	NCCAM-02-AT-260	Treatment	18 and over	NCCAM; NCI; Other	Phase I
Phase I Study of Calcitriol and Gefitinib With or Without Dexamethasone in Patients With Advanced Solid Tumors	RPCI-RPC-0207	Treatment	18 and over	NCI; Pharmaceutical/ Industry	Phase I
Phase I Study of Nordihydroguaiaretic Acid in Patients With Nonmetastatic, Biochemically Relapsed Prostate Cancer	UCSF-035510	Treatment	Over 18	NCI	Phase I
Phase I Study of Absorption-Enhanced Diindolylmethane (BioResponse-DIM) in Patients With Nonmetastatic, Hormone-Refractory Prostate Cancer and Rising Prostate-Specific Antigen Levels	WSU-D-2979	Treatment	18 and over	NCI	Phase I

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Adult Trials					
Phase I/II Study of Arsenic Trioxide Plus Ascorbic Acid in Patients With Recurrent or Refractory Multiple Myeloma	SCCC-20010	Treatment	Over 18	NCI	Phase I; Phase II
Phase I/II Study of Green Tea Extract (Polyphenon E) in Patients With Previously Untreated Stage 0-II Chronic Lymphocytic Leukemia	MAYO-MC0419	Treatment	18 and over	NCI	Phase I; Phase II
Phase II Randomized Study of Soy Protein Isolate (Isoflavones) and Radiotherapy in Patients With Localized Prostate Cancer	WSU-D-2325	Treatment	18 and over	NCI	Phase II
Phase II Randomized Pilot Study of Calcitriol and Dexamethasone Before Radical Prostatectomy in Patients With Localized Adenocarcinoma of the Prostate	RPCI-RP-0212	Treatment	18 and over	NCI	Phase II
Phase II Study of Genistein in Patients With Localized Prostate Cancer and Planned Radical Prostatectomy	NU-00U7	Treatment	18 and over	NCI	Phase II
Phase II Randomized Prevention Study of Fat- and/or Flaxseed-Modified Diets in Patients With Newly Diagnosed Prostate Cancer	DUMC-1385-02-7R3ER	Treatment	18 and over	NCI	Phase II
Phase II Randomized Study of Fruit and Vegetable Extracts in Patients With Stage I-IVB Head and Neck Cancer	CCCWFU-0112	Treatment	18 and over	NCI	Phase II
Phase II Study of High-Dose Pulse Calcitriol, Mitoxantrone, and Prednisone in Patients With Androgen-Independent Metastatic Prostate Cancer	OHSU-8451	Treatment	18 to 100	NCI	Phase II
Phase II Study of Genistein, Gemcitabine Hydrochloride, and Erlotinib Hydrochloride in Patients With Locally Advanced or Metastatic Pancreatic Cancer	WSU-2005-006	Treatment	21 and over	NCI	Phase II
Phase II Randomized Study of Adjuvant Combined With a Low-Fat, Arachidonic Acid-Free Vegan Diet Versus a Standard Diet Alone in Patients With Newly Diagnosed Glioblastoma Multiforme	CASE-CCF-7348	Treatment	18 and over	NCI	Phase II
Phase II Pilot Study of Genistein and High-Dose Interleukin-2 in Patients With Metastatic Malignant Melanoma or Renal Clear Cell Carcinoma	NU-04V1	Treatment	18 and over	NCI; Pharmaceutical/ Industry	Phase II

PDQ Clinical Trials	Primary ID	Type of Trial	Age Range	Sponsor of Trial	Phase(s)
Adult Trials					
Phase II Randomized Study of Neoadjuvant Dietary Supplementation With Soy in Patients Undergoing Radical Prostatectomy for Localized Prostate Cancer	CCCWFU-98203	Treatment; Biomarker/ Laboratory analysis	Over 18	NCI	Phase II
Phase II Randomized Study of Soy Isoflavones Before Radical Prostatectomy in Patients With Stage I or II Adenocarcinoma of the Prostate	WSU-C-2418	Treatment; Prevention	18 and over	NCI	Phase II
Phase III Randomized Study of Induction Platinum-Based Chemotherapy and Radiotherapy With or Without AE-941 (Neovastat) in Patients With Unresectable Stage IIIA or IIIB Non-Small Cell Lung Cancer	MDA-ID-99303	Treatment	18 and over	NCI; NCCAM	Phase III

Organizational Chart

In FY 2006, OCCAM was one of 16 offices within NCI's Office of the Director.





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