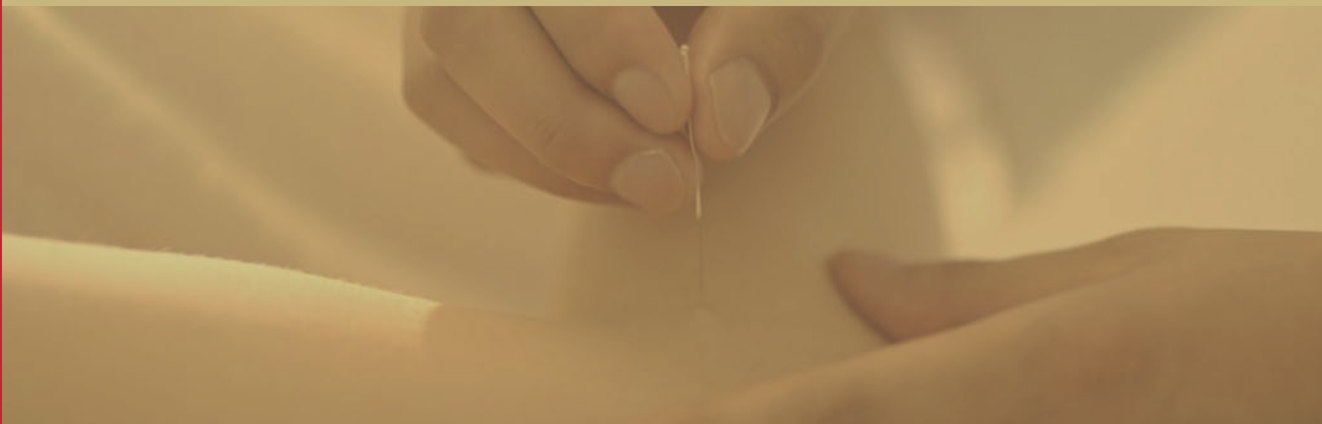




NCI's Annual Report on
**Complementary
and Alternative
Medicine:**
Fiscal Year 2005

A report published by the Office of Cancer
Complementary and Alternative Medicine



NCI's Prospective Agenda for Complementary and Alternative Medicine

Since the National Cancer Act of 1971, we have made tremendous strides in the fight against cancer. Today, that progress is evidenced by more than 10.5 million cancer survivors in the United States, and more people are living longer with cancer than ever before. Thanks to the groundbreaking work of the cancer research community, the future holds much promise for eliminating the suffering and death due to cancer in the years to come. One aspect of the research agenda that will be critical to our efforts is complementary and alternative medicine (CAM) and the potential that this area of medicine has for the prevention, diagnosis, and treatment of cancer, cancer-related symptoms, and side effects of conventional treatment.

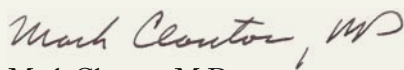
In recent years, the National Cancer Institute (NCI) has responded to the therapeutic potential of CAM by making a significant investment in the scientific evaluation of and communication about CAM therapies for cancer. In fact, this report *NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2005* outlines NCI's many accomplishments in the growing field of CAM.

I am encouraged and enthusiastic about what NCI has accomplished in advancing the evidence-base of CAM and what each of those achievements means for the future. I applaud the work of our NCI scientists and the many extramural researchers who we support through our various programs. Likewise, I value the contributions of our numerous domestic and international partners.

I hope you find this report to be helpful in outlining our scientific, training, and communication accomplishments in the past year. I also hope that the report will generate increased dialogue about CAM—especially between patients and their health care professionals—and its appropriate use in conjunction with conventional medicine. Cancer patients and survivors want and deserve to have credible, unbiased information about any treatment or compound that they are considering as part of their medical regimen and healthy lifestyle choices.

This annual report was commissioned to convey the breadth and depth of NCI's CAM activities, share the commitment of the cancer research community that I witness every day, and express the sense of hope that progress brings as we seek to eliminate suffering and death due to cancer.

Thank you for your consideration.



Mark Clanton, M.D.

Deputy Director and Deputy Director for Cancer Care Delivery Systems
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. They are of two types:

1. 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

2. 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: T'ai 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: 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, immunoenhancement therapy, laetrile, hydrazine sulfate, melatonin.

Sub-category: Complex Natural Products

Definition: An assortment of plant samples (botanicals), extracts of crude natural substances, and unfractionated 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

The National Cancer Institute's (NCI) Office of Cancer Complementary and Alternative Medicine (OCCAM) is proud to present this first *NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2005*. This unique report provides a closer look at NCI's comprehensive and exciting research portfolio into complementary and alternative medicine (CAM) approaches for cancer.

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, special teas, acupuncture, massage therapy, magnet therapy, spiritual healing, and meditation. (See Figure 1, opposite page for the major categories of CAM therapies.)

NCI has a long history of involvement in the scientific evaluation of CAM treatments for cancer. From the 1940s through the 1970s, NCI assessed information about practices then in use by cancer patients such as the Gerson regimen, Hoxsey, and the use of laetrile. In 1991, the NCI Best Case Series Program was established to formalize the evaluation of case reports of potential new cancer treatments from CAM domains. Examples of topics that came through the early years of this program include anti-neoplastons and the Kelly/Gonzalez Regimen.

In Fiscal Year (FY) 2005, NCI's research expenditures for CAM is an estimated \$121,076,919 for the funding of over 400 CAM research projects. The projects in this diverse portfolio are managed by program staff from each of the Institute's extramural grant funding divisions (Division of Cancer Biology, Division of Cancer Control and Population Sciences, Division of Cancer Prevention, and Division of Cancer Treatment and Diagnosis), and principal investigators from the intramural components (Center for Cancer Research and Division of Cancer Epidemiology and Genetics).

As this Annual Report on CAM in cancer indicates, NCI is 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.



PART I

OFFICE OF CANCER COMPLEMENTARY
AND ALTERNATIVE MEDICINE



NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM) is largely responsible for overseeing the Institute's growing research agenda in CAM related to cancer prevention, diagnosis, treatment, symptom management, and rehabilitation.

NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM) is largely responsible for overseeing the Institute's growing research agenda in CAM related to cancer prevention, diagnosis, treatment, symptom management, and rehabilitation. Established in October 1998 and directed by medical oncologist Jeffrey D. White, M.D., OCCAM also acts as NCI's link to the public, the CAM community, and cancer researchers regarding CAM and cancer. Additionally, OCCAM collaborates with other governmental and nongovernmental organizations such as the National Center for Complementary and Alternative Medicine (NCCAM) and patient advocacy groups, on cancer CAM issues.

OCCAM has been building bridges between CAM practitioners and the cancer research community by creating funding opportunities to investigate CAM approaches using scientifically rigorous research methods, working with other NCI Divisions and Centers to facilitate the testing of CAM approaches to cancer management, and helping CAM researchers overcome the challenges

unique to CAM approaches and those associated with the grant application process.

RESEARCH DEVELOPMENT AND SUPPORT PROGRAM I

Through its Research Development and Support Program (RDSP), OCCAM has expanded the funding opportunities for research in cancer CAM. RDSP staff assist investigators in identifying funding opportunities and provide assistance in the pre- and post-review periods of grant application. In addition, RDSP Director Wendy Smith, Ph.D., 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.

RDSP activities have also included the establishment of an expert panel in cancer CAM research, an invited speaker series, and a workshop to assist investigators in preparing grant applications in cancer CAM.

Examples of OCCAM Activities in FY 2005

- Awarding NCI's first grant to develop an international center of cancer CAM research (*page 9*)
- Presenting at the Best/Worst Case-International Workshop in Tromsø, Norway (See *NCI CAM News Winter 2006* issue for more information.)
- Preparing for the first Practice Outcomes Monitoring and Evaluation Systems project in Calcutta, India (*page 10*)
- Reviewing cases submitted to the NCI Best Case Series Program (*page 9*)
- Hosting the fourth Invited Speaker Series lecture (*page 17*)
- Collaborating with other federal groups to produce *Thinking About Complementary and Alternative Medicine*, a patient and family education booklet (*page 13*)
- Supplying programmatic support for Society for Integrative Oncology's 1st International Conference (*page 17*)
- Organizing and leading a cancer CAM grant writing workshop (*page 16*)
- Providing supplemental grant support to members of the Community Clinical Oncology Program (including Wake Forest University) (*page 23*)

In FY 2005, “Developmental Projects in Complementary Approaches to Cancer Care” (PA-04-053), a reissued program announcement (PA) originally initiated by RDSP, awarded 9 grants. (See Figure 2 on page 10 for the number of cancer CAM grants awarded as a result of NCI funding announcements.) This PA was released to encourage and support the development of basic and clinical complementary cancer research. Funding for exploratory/developmental projects through these R21 grants is intended to provide the basis for more extended research studies by establishing the methodological feasibility, allowing the collection of data, and strengthening the scientific rationale for future grant applications. This announcement is also intended to attract the entry of promising investigators into research of these topics.

COMMUNICATIONS AND OUTREACH PROGRAM I OCCAM’s Communications and Outreach Program, coordinated by Shea Buckman, M.A., develops and disseminates information about NCI program initiatives and funding opportunities, workshops and other events, and educational materials through OCCAM’s Web site and publications.

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

PRACTICE ASSESSMENT PROGRAM I OCCAM’s Practice Assessment Program, coordinated by Commander (U.S. Public Health Service) Colleen Lee, R.N., M.S., reviews retrospective and prospective data on cancer patients treated with alternative therapies. The best known component of the Practice Assessment Program is the NCI Best Case Series Program, which provides an opportunity for CAM practitioners to submit medical data regarding their cancer CAM treatments.

Practitioners are asked to submit patient records for evaluation by experts in clinical assessment and cancer treatment research. Results of the NCI Best Case Series Program include recommendation for NCI-initiated research and the sharing of well-documented best cases with interested members of the scientific community in order to stimulate research.

NCI Best Case Series Program Highlights

Since OCCAM’s creation in 1998, its staff has worked with CAM practitioners to identify appropriate, well-documented cases for inclusion in the

NCI’s First Grant to Develop an International Center of Cancer CAM Research

Through the R21 grant mechanism, OCCAM has awarded funding support for the development of NCI’s first international center that focuses on cancer CAM research. Originally awarded in FY 2003 and active through FY 2005, this grant has allowed the establishment of a partnership between The University of Texas M. D. Anderson Cancer Center (MDACC) and

the Cancer Hospital, Fudan University (CHFU) in Shanghai, China to investigate the potential benefits of some traditional Chinese medicine therapies for cancer patients.

During the two-year pilot study, the International Center for Traditional Chinese Medicine has studied three aspects of traditional Chinese medicine: herbal and natural treatments that target the disease

and related symptoms; acupuncture for the management of some side effects of cancer treatment; and the bio-behavioral effects of qigong and other mind/body-based interventions. The principle investigator of this grant Dr. Lorenzo Cohen has applied for and been awarded a four year U19* grant to continue and expand on the projects that started as a result of the R21.

*The R21 and U19 grants awarded to Dr. Cohen were in response to NCCAM funding announcements RFA-AT-03-002 and NOT-AT-04-008.

NCI Best Case Series (BCS) Program. Of those therapies that have been submitted, the following have completed the NCI BCS Program review and been found to warrant NCI-initiated research:

- Homeopathic therapy of cancer as practiced by Prasanta Banerji, D.Ht., (P. Banerji Homeopathic Research Foundation, Calcutta, India)
- Insulin Potentiation Therapy as practiced by Steven G. Ayre, M.D., (Burr Ridge, Illinois) and Ross Hauser, M.D., (Oak Park, Illinois).
- Macrobiotic Lifestyle Modification as taught by the Kushi Institute (Becket, Massachusetts)

In FY 2005, OCCAM prepared a broad agency announcement (N01-CO-57035-48), for release in FY 2006, to solicit contract proposals to perform research on the above mentioned therapies. A contract awarded as a result of this announcement would provide support for prospective research: pre-clinical, clinical trial, or both. http://www.cancer.gov/cam/research_funding_baa.html

POMES

Practice Outcomes Monitoring and Evaluation System (POMES) is a process for monitoring the outcomes in a small population of patients treated with an unconventional intervention as it is ordinarily administered, without altering the regimen’s delivery or outcome. The goal of a POMES project is to determine whether a phenomena observed in a retrospective case review can be seen with prospective observation of a larger population. Results from a POMES project can be used to justify an NCI-initiated clinical trial.

In FY 2005, OCCAM staff initiated the start up of the first POMES project, titled “Homeopathic treatment of lung cancer patients at the P. Banerji Homeopathic Research Foundation (PBHRF) in Calcutta, India”. PBHRF had previously presented NCI with a case series of cancer patients treated with a unique homeopathic approach, in which two patients had sustained radiographic responses of pathologically confirmed lung cancers (one complete remission, one partial remission). In addition, PBHRF also presented records of two patients with pathologically confirmed esophageal cancers: one of which had a radiographic partial remission, one stable disease, and both of whom reportedly had complete resolution of related symptoms. These patients reportedly had received only the homeopathic preparations prescribed at the clinic.

OCCAM’s review of these cases submitted by PBHRF lead to the development of a protocol for an observational study which would seek to provide an independent, prospective documentation and assessment of the outcomes that occur in 30–45 new lung cancer patients treated in the PBHRF clinic. The goal of this study is to estimate the frequency with which such responses occur and to thoroughly document all therapies received by these patients. If responses are documented in patients receiving only the homeopathic medications, the data from this study will be used to support the rationale for, and the design of pre-clinical and clinical studies to further explore this phenomenon.

Figure 2. Cancer CAM-Related Grants Awarded in FY 05 by Program Announcement (PA) and Request for Applications (RFA)

CA01-020	1	CA03-016	1	PA01-187	1	PA04-099	1	PAR03-009	1	AT01-002	1
CA02-007	2	CA03-018	1	PA02-001	2	PA96-008	2	PAR03-010	4	AT03-002	2
CA02-008	2	CA04-001	1	PA02-040	1	PA99-081	1	PAR03-153	6	OD03-008	1
CA02-009	2	CA04-002	1	PA02-124	1	PA99-163	1	PAR03-176	3	ES02-009	1
CA03-001	3	CA04-004	7	PA02-169	1	PAR00-025	9	PAR04-011	1	HS01-005	1
CA03-003	8	CA98-012	1	PA04-041	1	PAR01-110	1	PAR04-147	6	UNSOLICITED	196
CA03-004	3	CA99-003	2	PA03-169	1	PAR02-037	2	PAR04-155	1	TOTAL	351
CA03-006	1	PA00-080	1	PA04-034	1	PAR02-040	41	PAR99-167	2		
CA03-007	1	PA01-015	1	PA04-053	9	PAR02-176	8	PAS02-009	2		

PART II
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 summaries—called Physician Data Query (PDQ®) summaries—about certain CAM therapies as well as shorter question and answer documents (Fact Sheets) about some treatments. During FY 2005, NCI released 4 PDQ summaries for health professionals for the following CAM therapies, bringing the total number of these summaries to 16.

- Acupuncture (<http://www.cancer.gov/cancer-topics/pdq/cam/acupuncture>)
- Aromatherapy (<http://www.cancer.gov/cancer-topics/pdq/cam/aromatherapy>)
- Gonzalez Regimen (<http://www.cancer.gov/cancer-topics/pdq/cam/gonzalez>)
- Milk Thistle (<http://www.cancer.gov/cancer-topics/pdq/cam/milkthistle>)

In addition, health professional versions of the PDQ CAM summaries were converted into question-and-answer format summaries for patients in FY 2005. Fourteen such patient summaries are now available online.

Online access is also provided to NCI's PDQ Cancer Clinical Trials Registry. This registry currently includes approximately 4,500 abstracts of protocols that are open and approved to accept patients, including clinical studies on CAM approaches for cancer. To search for cancer CAM clinical trials, please visit http://www.cancer.gov/cam/clinicaltrials_pdq.html.

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.

***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.*

In FY 2005, the online PDQ cancer CAM treatment information summaries for health professionals were viewed 203,163 times.

PRODUCING PUBLICATIONS | In addition to the OCCAM Web site, various offices within NCI provide educational materials to health professionals and consumers in print format, including the informative booklet on *Thinking About Complementary and Alternative Medicine*, published in conjunction with the National Center for Complementary and Alternative Medicine (NCCAM). The 16-page publication was released in May 2005 and can be downloaded online at <http://www.cancer.gov/cancertopics/thinking-about-CAM>, or ordered 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.

RESPONDING TO CANCER CAM INQUIRIES | NCI's Cancer Information Service (CIS) team of cancer information specialists are also available to answer questions via phone, live online chat, mail, and e-mail about cancer treatment and clinical trials,

including CAM therapies. During FY 2005, CIS responded to more than 1,600 inquiries regarding CAM approaches for cancer.

CONDUCTING 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 and assesses information needs via surveys and focus groups. Results from these explorations will be used to develop programs that are most helpful for these audiences. In FY 2005, OCCAM conducted a total of three focus groups with cancer researchers at the Annual Meeting of the American Society of Clinical Oncology and the 1st International Conference of the Society of Integrative Oncology.

The PDQ Cancer Clinical Trials Registry contained a total of 64 (5 pediatric and 59 adult) active CAM clinical trials in FY 2005. (See the Appendix for the complete list of trials.)



PART III

TRAINING AND CONFERENCES



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

LEADING RESEARCH GRANT WRITING WORKSHOP

Although rigorous scientific investigations in CAM can and should be conducted, the development of competitive research proposals in cancer CAM and securing federal funding is often challenging. To address challenges associated with the grant application process, OCCAM staff members lead occasional technical assistance workshops such as the June 2005 meeting *Strategies for Success: How to Write a Grant in Cancer CAM*. Scientists interested in CAM research were provided opportunities to learn about Federal and private grant application processes, participate in a mock grant review, and network with representatives from funding and matchmaking organizations. This was the second such workshop hosted by OCCAM.

OCCAM has developed a companion document to the workshop that not only compiles information from existing NIH grant writing resources but also highlights some of the issues unique to CAM and CAM-related research areas. The document addresses many of the issues raised by NCI review committees and presents some of the potential solutions for applicants. The CAM grants manual was revised in June 2005 and is available for download on NCI's Web site at <http://www.cancer.gov/cam/attachments/howtowrite.pdf>.

In addition, OCCAM staff members are available to answer researchers' questions and help identify appropriate mechanisms and funding opportunities.

DEVELOPING A CANCER CAM PRACTICE-BASED RESEARCH NETWORK

On September 26, 2005, OCCAM and the Bravewell Collaboration jointly hosted a meeting on the development of Practice-Based Research Networks (PBRNs) for the cancer CAM field.

The U.S. Agency for Healthcare Research and Quality (AHRQ) defines a PBRN as an affiliated group of outpatient practices devoted principally to the primary care of patients that partner to investigate community-based practices. PBRNs may be local, regional, or national, and according to AHRQ, 140 PBRNs are registered in the United States today.

The goal of this meeting was to bring together organizations that had developed such clinical research networks to discuss their experience in this area and the feasibility of establishing PBRNs composed of health professionals who include CAM methods in their practice settings. The primary audience for the meeting included representatives of the clinical network assembled by the Bravewell Collaboration, who were planning to develop such a network that would research topics relevant to the use of CAM in the management of cancer patients.

Participants at the planning meeting identified specific challenges to CAM research within the PBRN settings, such as:

- Funding for placebos and drugs and their distribution may be a major feasibility issue for CAM clinical trials. In conventional medication studies, PBRNs rely upon pharmaceutical companies to provide the test agents. Companies that make CAM compounds (e.g., St. Johns wort, ginkgo biloba) lack the incentives of drug companies, so supplementary funding will be needed for a CAM clinical trials program.
- CAM agents present serious quality control and batch-to-batch consistency issues, since natural products vary depending on where they are grown and which strain of plant is used.

The three participating government funding organizations—NCI, AHRQ, and the National Center for Complementary and Alternative Medicine—also presented information about possible mechanisms to fund research projects which could be done by such a PBRN. As a result of this meeting, the Bravewell clinical network is forming a pilot group which will decide what types of data to collect, begin some basic data collection, and develop standardized protocols. The next phase would involve outreach to other community medical groups that have CAM practices. That expanded PBRN could conduct treatment outcomes studies and move toward clinical trials. Eventually, the CAM PBRN could become involved with other established PBRNs.

SUPPORTING SCIENTIFIC CONFERENCES I

A good example of NCI's support of scientific cancer CAM conferences is the Society of Integrative Oncology's (SIO) 1st International Conference in New York. OCCAM staff participate in program development and NCI provided conference grant support to SIO for its first ever conference. The meeting convened in November of 2004 and over 600 people attended. The abstracts from the meeting are available in the December 2005 issue of the *Journal of the Society of Integrative Oncology*.

HOSTING OCCAM'S INVITED SPEAKER SERIES I

With the goal of informing the NCI community about the variety of ongoing research in cancer and CAM, OCCAM created an Invited Speaker Series in which renowned experts present their groundbreaking research projects. During 2005, Lorenzo Cohen, Ph.D., gave a presentation titled *Traditional Chinese Medicine for Cancer: The Road to China*. Cohen reported on the initial findings of the International Center of Traditional Chinese Medicine for Cancer, which is supported by an NCI planning grant and represents a collaboration between the University of Texas M. D. Anderson Cancer Center and the Fudan University Cancer Center in China.



PART IV

NCI RESEARCH IN COMPLEMENTARY AND ALTERNATIVE MEDICINE



Figure 3. NCI's CAM Expenditures FY 2003-2005

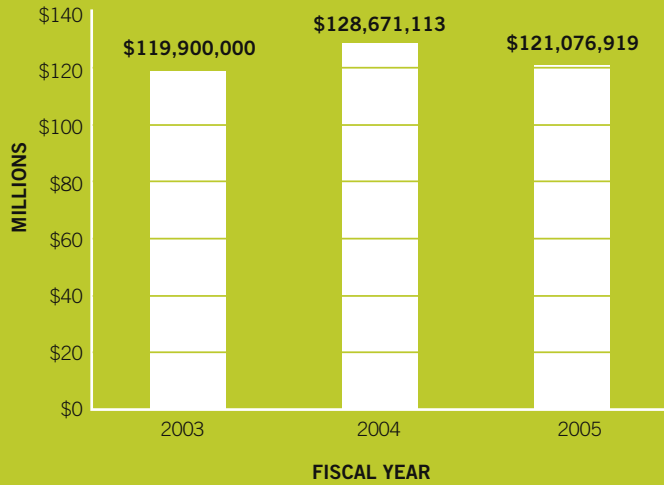
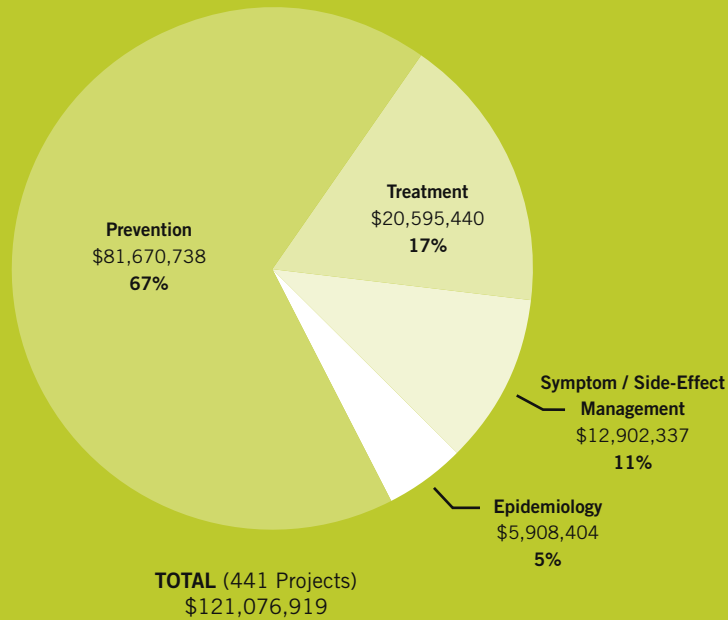


Figure 4. NCI CAM Research Projects FY 2005 by Research Type*



* Includes Grants, Cooperative Agreements, Intramural Projects, and Contracts

RESEARCH PORTFOLIO ANALYSIS

After each fiscal year comes to a close, OCCAM takes an in-depth look at NCI's CAM research expenditures. Examination of NCI's CAM portfolio is an important step in helping to identify research gaps in the field of cancer CAM and to encourage dialogue about the potential direction of future research. This yearly analysis is an exercise which reveals an estimated total amount of funding that goes to cancer CAM research projects (both intramural and extramural research) and provides breakdowns according to the type of research (prevention, treatment, side effects/symptom management, and epidemiology), CAM category, and cancer type.

TOTAL ESTIMATED CANCER CAM RESEARCH EXPENDITURE | Analysis of NCI's FY 2005 CAM research portfolio shows that the agency has funded 441 research projects of which either entirely focus or contain some portion that addresses CAM. These projects include an assortment of intramural projects and extramural grants, cooperative agreements, contracts, and supplements. The estimated total for NCI's CAM research expenditures in FY 2005 is \$121,076,919. (Figure 3)

BREAKDOWN BY RESEARCH TYPE | The accompanying figure (Figure 4) shows the distribution of the NCI's CAM research projects by: prevention, treatment, symptom/side effects management, and epidemiology. In FY 2005, 67 percent of cancer CAM-related research projects were spent on various cancer prevention efforts, while treatment, symptom/side effects management, and epidemiology received 17 percent, 11 percent, and 5 percent, respectively.

Figure 5. NCI CAM Therapies—FY 2005*

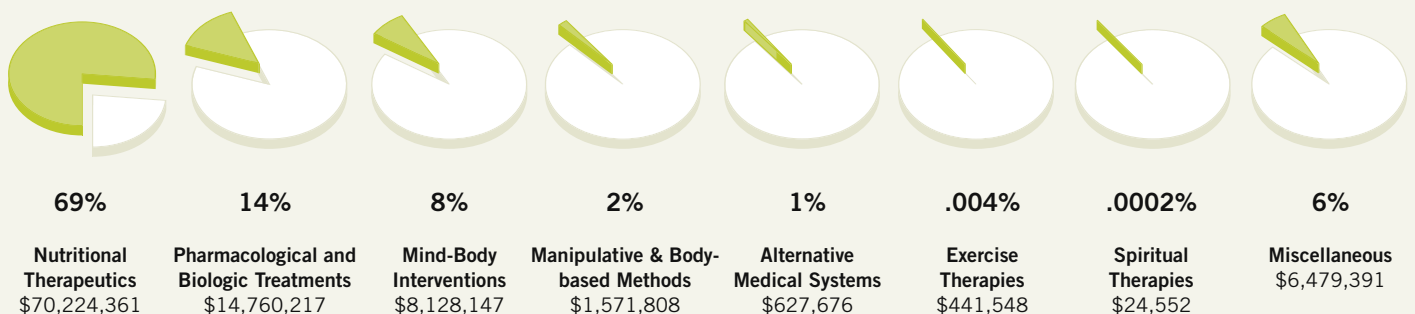
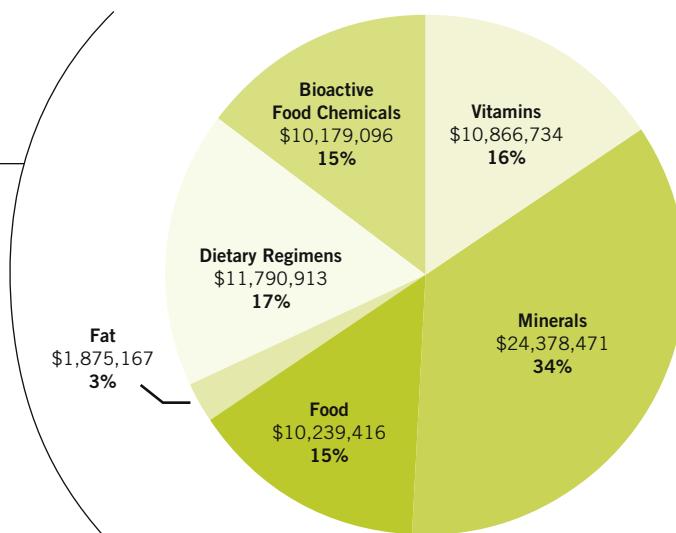


Figure 6. NCI's FY 2005 CAM Nutritional Therapies Projects

TOTAL: \$70,224,361



BREAKDOWN BY MAJOR CAM THERAPY CATEGORY I

Within the FY 2005 NCI CAM portfolio, research projects examined a wide variety of CAM therapies. These CAM therapies were categorized into eight groupings: alternative medicine systems, energy therapies, exercise therapies, manipulative and body-based methods, mind-body interventions, nutritional therapeutics, pharmacological and biologic treatments, and spiritual therapies (Figure 5). The largest percentage of research projects investigated nutritional therapeutics. Nutritional therapeutics includes 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). The accompanying pie-chart (Figure 6) shows the distribution of projects by the sub-categories.

BREAKDOWN BY CANCER TYPE I

NCI's FY 2005 research grants and cooperative agreements with CAM components can be categorized into twenty types of cancers. The largest amounts of cancer CAM research dollars spent were on prostate (\$15,332,684), breast (\$15,233,720), colorectal (\$13,370,222), and lung (\$7,774,659) cancers. Additionally, \$15,141,134 was spent on the research of CAM for nonspecified cancers and thus could not be broken down further. For more information on the remaining categories, please see Figure 7, below.

Figure 7. NCI CAM Research Projects FY 2005 by Cancer Type*

Bladder.....\$781,447	Esophageal.....\$571,021	Lung.....\$7,774,659	Prostate.....\$15,332,684
Brain.....\$424,634	Gastric.....\$250,015	Multiple Myeloma...\$203,850	Skin, Melanoma.....\$883,288
Breast.....\$15,233,720	Head and Neck....\$1,362,157	Non-Specific.....\$15,141,134	Skin, Non-Melanoma.....\$5,574,078
Cervical.....\$562,085	Kidney.....\$552,321	Ovarian.....\$145,152	TOTAL.....\$81,013,765
Colorectal.....\$13,370,222	Liver.....\$1,165,117	Pancreatic.....\$635,393	
Endometrial.....\$300,626	Leukemia.....\$484,232	Pediatric.....\$265,930	

*Excludes Cancer Center Support Grants (i.e. P30s), Special Programs of Research Excellence (SPORES, P50s), cooperative agreements that support the research bases for Community Clinical Oncology Programs (CCOPs, U10s) and their supplements.

NCI GRANT SUPPORT: THE GIFT THAT KEEPS ON GIVING

As is the case with other NCI research funding programs, NCI grants for CAM research often act as “seed money” that help institutions and organizations around the nation and the world build robust research programs in this growing field. Frequently, those same biomedical centers are then able to attract additional financial support for CAM scientific projects from other government agencies, non-profit institutions, and private industry.

Wake Forest University School of Medicine (WFUSM) provides a good example of this phenomenon. “NCI has been quite instrumental, in several ways, in the success of Wake Forest’s CAM research programs in cancer,” noted Edward G. Shaw, M.D., professor and chairman of WFUSM’s Department of Radiation Oncology.

The university hosts an NCI-designated Comprehensive Cancer Center led by Director Frank M. Torti, M.D., who has long had a great interest in the role of nutrition and CAM in cancer care. About 5 years ago, the WFUSM Cancer Center obtained a funding supplement to its NCI support grant to explore areas of CAM and cancer. The initial focus was on basic research in areas such as the potential preventive role of vitamin D for which WFUSM has established a world-renowned reputation.

“The NCI supplement support grant* received about 5 years ago catalyzed rapid growth in the evidence-based CAM research at Wake Forest Health Sciences,” said Todd Thornburg, Ph.D., director of administration at the Cancer Center. “Specifically, one area initially supported—vitamin D effects on cancer—has grown to include both the clinical trials and basic science research for this line of inquiry.” This includes studying the combination of vitamin D and soy phytoestrogens for treatment of men with prostate cancer.

Wake Forest Cancer Center is also designated as a research base for one of NCI’s Community Clinical Oncology Programs (CCOP). “The general focus of CCOP research is in symptom manage-

ment—things like fatigue, nausea, pain—and cancer prevention,” Shaw explained. “In the past few years, NCI has provided us with several ‘supplements’ to our CCOP grant specifically for doing scientifically-based, hypothesis-driven CAM clinical trials.”

Among the studies currently underway at WFUSM is a randomized study of a “nutraceutical” product called “Juice Plus”—capsules that are claimed to provide the same nutritional value as many servings of fruits and vegetables. The study will include 150 patients with head and neck cancer who have received conventional therapies who will receive either Juice Plus or placebo capsules to determine whether Juice Plus enhances patients’ immune systems which might reduce the incidence of second, primary tumors.

The Wake Forest CCOP is also testing other popular nutritional or herbal products, such as coenzyme Q10 and St. John’s wort, to relieve fatigue, hot flashes, and other side effects of cancer and conventional treatments.

The Wake Forest CAM research for cancer helped fuel WFUSM’s broader programs for “holistic and integrative medicine.” During 2005, more than 80 WFUSM faculty were pursuing academic work in this rapidly growing field, with over \$25 million in research funding and 115 peer-reviewed publications. “Overall funding for CAM research at Wake Forest has grown substantially in the last three years,” Thornburg noted.

Among the various research projects underway are investigations funded by other NIH institutes, other agencies of the U.S. Department of Health and Human Services, nonprofit foundations, and industry. “Much of this funding was the result of the success of Wake Forest’s cancer CAM program and team-building that grew from the initial supplemental grant from the NCI,” Thornburg added. “Wake Forest has found that good complementary science can lead to good complementary medicine and that can be good news for cancer patients.”

*Supplemental support was provided from OCCAM and NCCAM though grant number 5U10CA081851.

MAJOR ACCOMPLISHMENTS IN 2005

Fiscal Year 2005 saw the release of major findings which for the first time provided solid evidence that improvements in lifestyle and dietary interventions are feasible and can impact the recurrence of certain cancers.

Major Accomplishments in 2005

Low-Fat Diet May Lower Risk of Breast Cancer Recurrence

Division of Cancer Prevention

Significantly lowering dietary fat may lower the risk of recurrence of breast cancer in postmenopausal women treated for early-stage breast cancer. The findings are from the NCI-sponsored Women's Intervention Nutrition Study (WINS), the first large-scale intervention trial to examine the influence of dietary fat on breast cancer outcomes in this population.

"This could be the first randomized controlled clinical trial of a lifestyle intervention that impacts breast cancer outcomes," said study lead author Rowan T. Chlebowski, M.D., Ph.D., of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. He presented the preliminary findings for WINS at the May 2005 meeting of the American Society of Clinical Oncology.

The study included 2,437 women, aged 48 to 79, drawn from 37 U.S. medical centers. The study group was placed on a low-fat diet, averaging about 33 grams of fat daily, while a control group consumed a standard diet that included approximately 52 grams of fat per day. Each group had previously received similar treatments for early-stage breast cancer, including mastectomy or lumpectomy with radiation, and postsurgical treatment protocols with chemotherapy and/or hormonal therapy, depending on whether patients had estrogen-dependent cancers.

After 5 years, women on the low-fat diet showed a significant reduction in cancer recurrence compared with the control group: 9.8 percent vs. 12.4 percent. Women on the low-fat diet who had been previously treated for a type of breast cancer that is not estrogen-responsive (ER)—a form of the disease that is typically associated with a greater likelihood of recurrence—had a 42-percent reduced

risk of recurrence compared with those on a standard diet.

"The effect on ER-negative disease is a surprising and potentially important observation regarding breast cancer," said Dr. Peter Greenwald, director of NCI's Division of Cancer Prevention. "These data demonstrate the possible importance of considering dietary factors in cancer therapy trials."

Final results from WINS are expected to be published in 2006 or early 2007. "We also hope our results will encourage cancer researchers to look at different pathways suggested by the effectiveness of dietary interventions," said Chlebowski. "By exploring those avenues, they may identify targets for interventions by other small molecules."

Chlebowski is also hopeful that, if WINS and similar studies prove the benefits of various dietary prevention interventions for cancer, it will lead health insurers, including Medicare, to provide coverage for such approaches. "That would be a big thing," he believes. "The WINS dietary intervention would cost a patient about \$1,000 a year which they'd have to pay themselves currently." He noted that Medicare currently reimburses for dietary interventions for patients with renal disease and diabetes but not for heart disease or cancer.

Findings from the WINS study were recognized by the American Society of Clinical Oncology as a highlight at their 2005 Annual Meeting.

Major Accomplishments in 2005

WHEL Study Testing High Vegetable Diet for Breast Cancer Recurrence

Division of Cancer Prevention

In spring 2007, researchers expect to announce the long-awaited results from the Women's Healthy Eating and Living (WHEL) study, a multicenter, randomized clinical trial testing the hypothesis that a high vegetable and high fiber diet might lower the risk for recurrence and death from breast cancer.

The WHEL study, which is supported by an R01 grant from NCI, enrolled 3,088 women with early-stage invasive breast cancer between 1995 and 2000. The women were assigned to either a control group or an intensive diet intervention group who were counseled to maintain a daily diet of 5 vegetable servings, 16 ounces of vegetable juice, 3 fruit servings, 30 grams of fiber, and 15–20 percent dietary fat. The goal was to substantially increase levels of circulating carotenoids in the blood, because previous research showed that low-levels of carotenoids are associated with higher rates of breast cancer recurrence.

Although the final results will not be known until next year, WHEL has already reported spectacular success in getting women to adopt the rigorous diet, said Principal Investigator John P. Pierce, Ph.D., director of the Cancer Prevention and Control Program at the University of California, San Diego (UCSD) Cancer Center. "We've achieved major changes in behavior," he notes.

After 6 years of follow up, participants in the intervention group were eating each day, on average, about 4.5 vegetables, drinking 6 ounces of vegetable juice, and ingesting 26 grams of fiber. Even more significant, "we have doubled the circulating carotenoid levels in the blood which is much more than any other study has accomplished previously and will allow us to properly test the hypothesis," Pierce added.

The WHEL study achieved these remarkable lifestyle changes relying primarily upon telephone counseling from trained lay persons. "In designing the protocol, we asked people who they would like to talk with 18 times over the course of a year during the intensive intervention phase," Pierce recalled. Possible choices included a nutritionist, their doctor, physical therapist "or your personal chef," he said. "They always picked the latter." As a consequence of using phone counseling rather than clinic visits, "there is a considerable cost savings to our intervention," he noted.

The WHEL study took blood and other tissue samples from participants on five different occasions "so we have an outstanding biological samples database to study recurrence," Pierce explained. A supplement to the study funded a survey of WHEL participants that focused on their past and current use of various CAM modalities, including mind-body practices, energy-based therapies, and alternative medical systems, such as homeopathy and naturopathy.

The WHEL investigators are presently summarizing the responses from the interviews and will report on the frequency of use of different CAM modalities, reasons for using these modalities, and their patterns of disclosing CAM use to healthcare providers. The study has also developed one of the largest databases on nutritional supplements and will report on trends and influences on usage over time.



CAROTENOIDS, like those found in green tea, are being studied for their potential in reducing breast cancer recurrence.

Major Accomplishments in 2005

Intensive Lifestyle Changes Show Benefits for Prostate Cancer

Division of Cancer Control and Population Sciences

Patients with early, low-grade prostate cancer benefited from intensive lifestyle changes that included a “vegan” diet with lots of fruits and vegetables, moderate exercise, and stress-reducing yoga. After one year of this regimen, average levels of prostate-specific antigen (PSA)—a marker of disease progression—decreased by 4 percent in these patients while average PSA levels increased 6 percent among a control group of similar patients who didn’t follow the new lifestyle regimen, according to a small study published September 2005 in the *Journal of Urology*.

Patient recruitment for this study was limited to men who had chosen not to undergo any conventional treatment, which provided an unusual opportunity to have a nonintervention, randomized control group to avoid the confounding effects of interventions such as radiation, surgery or androgen deprivation therapy. A total of 93 volunteers with serum PSA levels of 4 to 10 ng/ml, and cancer Gleason scores less than 7, were randomly assigned to either an experimental group that was asked to make comprehensive lifestyle changes or to a usual care control group.

“The issue of diet and nutrition and supplements are of high priority to patients and their families,” noted Peter R. Carroll, M.D., chair of Urology at University of California, San Francisco (UCSF). “We’ve done additional work which has shown at

least 40 percent of men diagnosed with prostate cancer are engaged in some type of alternative therapy usually in conjunction with conventional therapy but sometimes independently.” Carroll was co-leader of the study along with UCSF Professor and noted author Dean Ornish, M.D. The study was funded by grants from NCI and other organizations.

Carroll, Ornish, and their colleagues are following up with an even closer look at the genetic changes produced by such lifestyle changes on patients’ prostate glands. He said, “The trial design we’ve chosen focuses on men similar to those in the first study. In the new study we biopsy the prostate initially, do a gene expression array on benign and malignant tissues obtained, treat them with alternative agents, re-biopsy the prostate after 3 to 4 months, and then perform another gene expression array. We want to better test the hypothesis that such therapy has a real effect on the prostate microenvironment.”

Studying the impact of diet, exercise, and stress reduction on prostate micro-environment will provide more definitive data on such interventions. The researchers are using this same approach in a separate study of lycopene, found in tomato products, and omega-3 fatty acids and their effect on prostate cancer. It can also be used to study other potential preventive agents, Carroll commented.

ADDRESSING NCI'S STRATEGIC AREAS

The remaining research highlights are selected from the over 400 CAM research projects NCI supports at laboratories throughout and 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>.

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

Milk Thistle and Prostate Cancer: Moving from Bench to Bedside

Division of Cancer Prevention

The milk thistle plant has been used to treat ailments for more than two thousand years. Over the next few years, Rajesh Agarwal, Ph.D., and his colleagues at the University of Colorado Health Sciences Center hope to learn whether a compound from the plant's seeds might help prevent prostate cancer.

The compound, silibinin, is being evaluated in a Phase II clinical trial. Participants will take the compound for 4–8 weeks prior to undergoing surgery to remove the prostate. The researchers will then determine whether the compound reaches the prostate and assess certain biological markers associated with the proliferation of cells and cell death.

“The clinical trial is very exciting for us,” said Agarwal, who has been investigating silibinin and silymarin—the crude form of silibinin—with some other compounds in cells and animals for nearly two decades. “We have succeeded in taking silibinin from the bench to the bedside in prostate cancer.”

A Phase I clinical trial is also being planned to test the compound's potential for preventing skin cancer. Based on his research, Agarwal believes silibinin may be useful against other common cancers as well, including colon and lung.

Silymarin and its main biological ingredient, silibinin, have been used in Europe for decades to

treat liver diseases. In terms of safety, silymarin and silibinin are generally well tolerated and have no toxic effects. Silymarin is sold as a dietary supplement on the Internet and in the United States and Europe.

In a project funded by NCI, Agarwal and his colleagues are now investigating the anti-tumor promoting effects of silibinin at the cellular, biochemical, and molecular levels. “Our goal is to understand the mechanisms that help protect against the development of tumors,” said Agarwal.

Agarwal also plans to conduct future studies on whether silibinin may also increase the efficacy of chemotherapy drugs and counteract some of the toxicity of these drugs.



MILK THISTLE,
silybum marianum

Understanding the Causes and Mechanisms of Cancer

Selenium and Cancer Prevention: Investigating Mechanisms of Anti-angiogenesis

Division of Cancer Prevention

During the 1990s, the results of a landmark cancer prevention trial in the United States strengthened the hypothesis that the trace mineral selenium, as a nutritional supplement, is a safe and effective preventative agent against the development of certain solid cancers, including prostate, lung, and colon. More recently, a growing body of evidence from epidemiological, ecological, and clinical studies suggests that selenium may modify the risk of these cancers.

Junxuan Lu, Ph.D., of the University of Minnesota and his colleagues have undertaken an investigation, sponsored by the NCI, of the mechanisms underlying the hypothesized effect that selenium might have on angiogenesis, the process by which blood vessels are created to supply tumors with oxygen and essential nutrients. The researchers are testing several types of mono-methylated selenium compounds that can increase the production of methylselenol, which is considered the active form of selenium for cancer chemoprevention in the body.

“We think that this type of selenium has very favorable attributes for cancer prevention,” said Lu, noting that different forms of selenium probably have different functional properties. “A lot of work by our group and collaborators in last decade has focused on identifying these different functions, and we certainly think some forms are better for cancer prevention than others.”

In recent years, his laboratory has identified a number of functions for methyl selenium in terms of regulating the blood vessel endothelial cell responses to angiogenic stimulation and controlling the production of angiogenic stimulators by the cancer cells. In addition, his laboratory and that of Clement Ip, Ph.D., of Roswell Park Cancer Institute have found that certain concentrations of methyl selenium decreases androgen and its receptor-signaling activities that are critical for prostate cancer. His group also discovered that this form of selenium may enhance the treatment efficacy of chemotherapeutic drugs.

In the NCI-funded study, Lu and his colleagues expect to validate the role of several target proteins believed to be involved in mediating the inhibition of blood vessels by methyl selenium. The results, the researchers believe, will lay the foundation for future work to investigate how methyl selenium reacts and interacts with these target proteins to bring about biochemical and cellular changes related to cancer prevention.

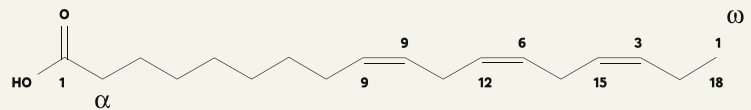
ACCELERATING PROGRESS IN CANCER PREVENTION

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.



SPANISH SARDINE, *Sardinella Aurita*

ALPHA-LINOLENIC ACID (ALA),
an essential omega-3 fatty acid



Accelerating Progress in Cancer Prevention

Fish Diet May Have Role in Preventing Prostate Cancer

Division of Cancer Prevention

Prostate cancer is far more prevalent in Northern Europe and the United States than in Asia, Alaska and Africa. Studies suggest that one reason for low incidence of prostate cancer in those regions could be the abundance of omega-3 polyunsaturated fatty acids (PUFAs) present in the fish-based diets consumed by their populations.

Jose Halperin, M.D., from the Harvard Medical School and the Dana Farber/Harvard Cancer Center, has identified how PUFAs might interfere with carcinogenesis in the prostate. Currently, the most promising candidate among the “good” fatty acids is eicosapentaenoic acid (EPA), the primary PUFA found in sea fish. Laboratory and animal studies have shown that EPA interferes with the translation process of some oncogenes and thus slows prostate cancer growth. EPA also seems to trigger the expression of some protective proteins that actually kill tumor cells.

There is every reason to hope that the protective effect of EPA also works in humans, Halperin said. Scientists at Harvard conducted a 12-year prospective population study in about 50,000 men, whose risk of metastatic prostate cancer was cut in half when they consumed fish three times a week.

Halperin is now conducting an ambitious NCI-funded study to confirm the impact of EPA on prostate cancer. He will enroll men scheduled to have

prostatectomies (removal of the prostate gland) in a prospective trial, and give them daily doses of fish oil (70 percent EPA) or placebo for several weeks before surgery. Their tumors will ultimately be analyzed for cellular evidence that the EPA has been inhibiting translation of oncogenes in the tumors, just as it does in cancer cells in the laboratory.

The patients’ blood will then be analyzed for the content of n-3 and n-6 fatty acids, and this information will be compared with biological markers that identify how translation has been affected, as well as with the clinical Gleason score used to evaluate prostate disease from biopsy tissue. Finally, he will analyze a collection of tumor tissue taken over a 10-year period, to better track translation and the progression of prostate cancer.

“This is a tremendously exciting area of cancer research which could have an enormous impact on public health,” said Halperin. “I hope our work can help increase the momentum for large clinical trials. Prostate cancer is a major disease in the West, and while we haven’t shown that fish oils prevent it altogether, they do appear to influence how it progresses. We may be looking at a natural answer for prevention and control of prostate cancer.”

Accelerating Progress in Cancer Prevention

Preventive Role of Soy Food in Endometrial Cancer Explored in Chinese Study

Division of Cancer Control and Population Sciences

Endometrial cancer is the most common reproductive cancer in the United States, but occurs far less frequently in China. Chinese women also have lower levels of the hormone estrogen—and they consume much more soybean-based food—than do their American counterparts.

Scientists are trying to fit the pieces of this puzzle together. Beginning in 1997, Principal Investigator Xiao Ou Shu, M.D., Ph.D., and her colleagues at Vanderbilt University's Ingram Cancer Center began a pilot epidemiological study of endometrial cancer in China, working in collaboration with researchers at the Shanghai Cancer Institute. They initially recruited about 500 women with endometrial cancer and also a set of case-matched healthy individuals, to explore lifestyle and diet factors, including soy foods, that researchers believed might be involved in development of endometrial cancer.

NCI support allowed Shu and her colleagues to recruit more women and to explore genetic susceptibility to this malignancy. By the time they closed enrollment in 2005, 1,204 cases and 1,212 controls had joined what was now called the Shanghai Endometrial Cancer Study (SECS). Some of the study's findings have already been published and Shu expects the DNA data from study participants will provide

some important insights into how the progression of the disease might be affected by the interaction between an individual's genetic susceptibility to the disease and lifestyle factors such as soy and fiber in the diet, physical activity, obesity, and the history of weight change before the disease developed.

Some of the published findings include evidence that soy food intake—in a number of different forms—cuts risk of endometrial cancer by 33 percent. They also found that higher intake of vegetables, especially green and yellow, was associated with more than a 30 percent risk reduction.

This study showed that both overall obesity and central-body obesity are related to an elevated risk of endometrial cancer, with the latter condition being associated with a higher risk. More importantly, the study showed that weight gain during adulthood, even among current non-obese women, increases the risk of the disease. The investigators also found that life-time physical activity confers some protection against endometrial cancer. Women who exercised in adolescence and adulthood were 37 per cent less likely to develop endometrial cancer.

Accelerating Progress in Cancer Prevention

Prevention of Esophageal Cancer with Berries

Division of Cancer Prevention

For many years, in the popular press as well as in medical journals, a controversy has arisen over the healing powers of “antioxidants,” which are plentiful in certain fruits and vegetables. One abundant natural source of antioxidants is berries, including black raspberries.

The laboratory of Gary Stoner, Ph.D. at Ohio State University is seeking to discover whether black raspberries may help to prevent esophageal cancer. Effective chemoprevention for this disease would be significant, since by the time esophageal cancer is diagnosed in most patients, it has already metastasized, and their survival rate is less than 10 percent.

In previous work, Stoner showed that some cruciferous vegetables contain an ingredient known as phenethyl isothiocyanate, which blocks tumors from getting started in the esophagus. Stoner believes berries may have a natural substance that not only blocks these cancers from starting, but also inhibits the growth of cells that have already begun the carcinogenic process, thus preventing the disease from progressing to more advanced stages.

His NCI-funded study uses a rat model in which esophageal cancer is induced by the carcinogenic substance N-Nitrosomethylbenzylamine (NMBA). This is a relevant carcinogen, because it is found in the diets of Chinese citizens who are at high risk for esophageal squamous cell carcinoma. In this animal study, dietary freeze-dried black raspberries were shown to block and suppress cancer development in rats. The block-

ing agents in berries interfere with NMBA's ability to initiate tumors, Stoner explained. The suppressing agents also work on precancerous cells by inhibiting their growth and stimulating their death. Finally, the berries prevent the formation of new blood vessels that feed developing tumors, he added.

Work in the lab of one of Stoner's colleagues has developed a reliable method for producing extracts from black raspberries. Studies with these extracts suggest that the anthocyanins in the berries—the compounds that give them their color—are at least partially responsible for their anticancer activity, Stoner noted.

The results in the rat esophagus study have led to a human clinical trial in China to evaluate the ability of dietary black raspberries to prevent esophageal squamous cell carcinoma.

“Berries appear to contain an effective ‘cocktail’ of chemopreventive agents,” said Stoner. “They could have a significant role in the prevention of esophageal cancer. We hope not only to demonstrate that they work but to show persuasively why. We may also be able to demonstrate a synergistic effect, by testing the black raspberries along with dietary isothiocyanates.”



BLACK RASPBERRIES
contain compounds that offer potential in cancer prevention.

Accelerating Progress in Cancer Prevention

Chinese Herbal Agents Tested in Lung Cancer Prevention

Division of Cancer Prevention

In 1996, Stephen Lam, M.D., a senior scientist at the British Columbia Cancer Research Centre (BCCRC), attended a medical conference in Beijing, China, where he heard the presentation of results from a clinical trial of Anti-Cancer and Preventative Herbal Agent (ACAPHA) as a chemoprevention agent for esophageal cancer. ACAPHA is a combination of six herbs¹ used in traditional Chinese medicine. The Chinese research team found that the use of ACAPHA in patients with esophageal dysplasia reduced the incidence of invasive cancer by 40 to 50 percent.

Lam, who is the principal investigator of the Lung Health Study chemoprevention group at BCCRC, was impressed by these results. His research team joined the Chinese team on a follow-up study, which found that the patients who had taken ACAPHA also had a reduced incidence of lung cancer. Lam decided to test ACAPHA as a chemoprevention agent for lung cancer in a randomized controlled trial in North America.

The NCI-funded trial began in January 2003 and will finish by the end of 2007. During the 5-year trial, more than 2,000 former smokers will be screened for bronchial intraepithelial neoplasia (IEN)—a precancerous condition of the lung—using a multistep process. First, the investigators will examine sputum

samples for abnormal cells. If abnormal cells are found, the patient will undergo fluorescence bronchoscopy. If the investigators observe any abnormal cells in the airways during bronchoscopy, the region will be biopsied for pathologic analysis.

“In order to find people with precancerous lesions, we have to screen a lot of former heavy smokers who are at high risk for lung cancer, because not every smoker will develop lung cancer,” explained Lam.

Ninety patients with identified IEN will be randomly assigned to receive either ACAPHA or a placebo for six months. All patients will be evaluated with both repeated bronchoscopy and CT scans, and the regression and progression rates of precancerous lesions will be compared between the study groups. Because the investigators are blinded to the results until the end of the trial, preliminary data are not yet available. However, results from a preliminary Phase I/II open trial performed by the group at BCCRC indicated that ACAPHA is potentially effective in reversing pre-existing dysplastic lesions in the bronchus.

1. *Sophora tonkinensis*, *Polygonum bistorta*, *Prunella vulgaris*, *Sonchus brachyotus*, *Dictamnus dasycarpus*, and *Dioscorea bulbifera*



PRUNELLA VULGARIS,
one of the six herbs in ACAPHA.

Accelerating Progress in Cancer Prevention

Physicians Health Study II: Prevention Trial of Vitamins

Division of Cancer Prevention

Sequels to blockbuster movies usually don't do as well as the original—who remembers “Jaws III”? But the Physicians Health Study II (PHS II) on the possible prevention role for vitamins in cancer and cardiovascular disease (CVD) may affect the practice of medicine just as powerfully as did the Physicians Health Study I (PHS I).

In 1988, PHS I researchers announced the finding that daily, low-dose aspirin decreased the risk of a first myocardial infarction by 44 percent which helped focus the role of aspirin in primary prevention. In 2007 or 2008—about 20 years later—PHS II is expected to provide definitive evidence about whether or not long-term use of supplements for Vitamin E, C, or multivitamins are effective in the primary prevention of cardiovascular disease, cancer, and age-related eye disease.

“We believe our studies will be useful regardless of the outcome of the study since these vitamins are widely used by the general public and we need to better understand if they can prevent chronic diseases,” noted Co-Principal Investigator J. Michael Gaziano, M.D., Brigham and Women's Hospital in Boston. Unlike drugs, dietary supplements don't go through rigorous clinical testing and approval by the U.S. Food and Drug Administration, he added. “It's a multibillion dollar industry and the public

deserves to know one way or the other what is the utility of taking these supplemental agents.”

PHS II began in 1997 with industry support. It eventually enrolled almost 15,000 patients 50 years or older who were randomly assigned to receive either placebos or one of 16 possible combinations of vitamin C (500 mg) daily, vitamin E (400 IU) on alternate days, and a multivitamin (Centrum Silver) daily. NCI provided funding for the second 5 years of the study which will conclude in early 2007.

Primary endpoints for PHS II are assessing the impacts of vitamin C, vitamin E, and a multivitamin on the primary prevention of: cardiovascular disease; prostate and colon cancer; aging-related eye disease; and early cognitive decline.

“These agents have the potential to be part of our prevention armamentarium” for chronic disease along with smoking cessation, diet, and exercise, Gaziano commented. “Based on what we know from observational data, if there are any effects of these dietary interventions, the effects will be modest. It would be important not to give anyone the impression that they could take a supplement of some kind instead of exercising or stopping smoking.”

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THE PHYSICIANS HEALTH STUDY II is assessing the impacts of vitamin C, vitamin E, and a multivitamin on the primary prevention of cardiovascular disease, prostate and colon cancer, aging-related eye disease, and early cognitive decline.



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

Folate Depletion and Cancer Cell Resistance to Cisplatin

Division of Cancer Treatment and Diagnosis

During treatment with chemotherapy, cancer cells can develop resistance to the drugs in use, and most of the factors behind the development of drug resistance remain to be explained.

One aspect of resistance that is not well understood is what role the nutritional environment of the cell plays. Gary Johannung, Ph.D., and his research team from M.D. Anderson Cancer Center have undertaken laboratory studies to examine the role of folate depletion in the development of lung and ovarian cancer cells resistance to cisplatin, a commonly-used chemotherapy agent.

“If our current and follow-up studies are successful, a rationale for clinical trials aimed at evaluating the influence of high-dose folic acid supplementation on resistance to chemotherapy in cancer patients would be established,” said Johannung.

The researchers first propagated lung and ovarian cancer cells in normal culture media and in media acutely depleted of folate, and they then exposed the cells both to cisplatin. The number of cells surviving the exposure to cisplatin was significantly greater in the depleted media, though the magnitude of resistance varied between cell lines.

The researchers then performed cDNA microarray analysis to screen for genes that were dif-

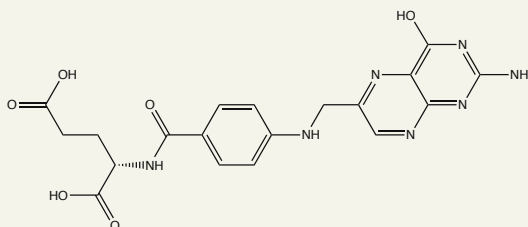
ferentially expressed in cells grown in normal and depleted media. Several genes were identified whose expression is altered by folate levels in the presence of cisplatin. A paper reporting these results has been published in 2006 in the journal *Nutrition and Cancer*.

Follow-up studies will examine the relationship between folate depletion and cisplatin resistance in greater detail, including possible alterations in molecular transport, DNA damage during the development of resistance, and changes in gene expression after supplementation with folate. All experiments will use very high doses of folate, which correspond to megadose supplementation in humans.

The investigators hope to eventually test whether depletion and supplementation of folate have the same effects in animal models. “If folic acid depletion is ultimately found to increase resistance to cisplatin, and megadose supplementation is found to block resistance to these agents. Then, a simple and inexpensive approach to prevent, at least in part, the resistance that limits the effectiveness of chemotherapy will be realized,” Johannung added.

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FOLIC ACID is being studied as a potential aide in decreasing cancer cell resistance to chemotherapy.



Developing Effective and Efficient Treatments

Scientists Study Response to Multivitamins/ Minerals During Cancer Therapy

Division of Cancer Treatment and Diagnosis

Researchers from the University at Buffalo (New York) Schools of Nursing, Medicine and Biomedical Sciences, and Public Health and Health-Related Professions are conducting a pilot clinical study that addresses the controversy over whether or not dietary multivitamin/mineral supplements that include antioxidants should be taken during radiation therapy for cancer. The study is funded by NCI's Division of Cancer Treatment and Diagnosis.

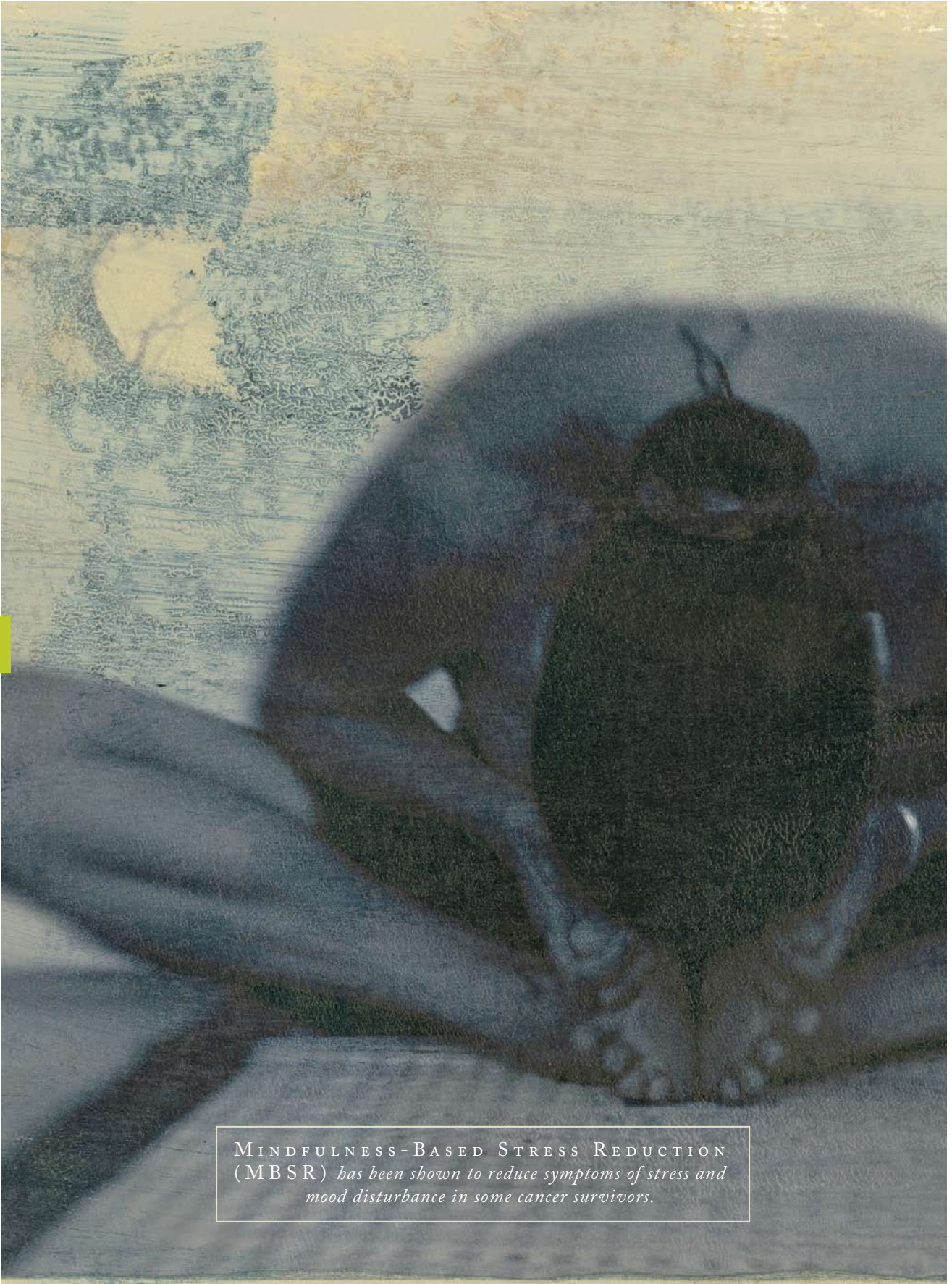
"One side of the debate argues that antioxidant vitamins and minerals repair cells, while the purpose of cancer therapy is to destroy cancer cells. Consequently, antioxidants may interfere with treatment by trying to repair cancer cells," explained Principal Investigator Jean K. Brown, Ph.D., RN, FAAN, Associate Dean for Academic Affairs and Nursing Professor at Buffalo. Others believe that antioxidants help repair healthy cells damaged by radiation and that the effects of collateral damage from cancer therapy may be minimized. "The bottom-line is nobody knows the answer to the controversy," she added.

Brown and her colleagues designed the double-blind, randomized study to try to replicate "what we believe patients might already be doing in their self-care management relative to taking multivitamin/mineral supplements that include antioxidants." Starting in January 2006, they began enrolling prostate cancer patients who are receiving radiation into one of three groups of the study: one group receives placebos; the second receives a regular "one-a-day"

dose multivitamin/mineral supplement; and the third group receives a "one-a-day" dose vitamin/mineral supplement with antioxidant components increased to about one-half of upper tolerable limits set by the National Academy of Sciences.

"We're looking primarily at the effects of antioxidants but secondarily at the impact of vitamins and minerals on the treatment," Brown noted. The researchers will track tumor response by monitoring the patients prostate-specific antigen (PSA) levels for 18 months and beyond. "We decided to also look at effects at a cellular level, so we're doing a series of assays on oxidative damage among the three groups," she added. "We're also looking at immune function, how side effects vary, nutritional status, and quality of life."

The researchers plan to enroll up to 60 patients in the Phase II study, and Brown hopes to have results in two years. They will then pursue a larger, multi-site study to confirm and expand upon the findings. Brown commented: "I believe the study will answer a question that physicians are dealing with from their cancer patients every day: 'Should I or should I not continue to take multivitamins during my treatment?' We really need the scientific data to advise patients about what they should be doing."



MINDFULNESS-BASED STRESS REDUCTION (MBSR) *has been shown to reduce symptoms of stress and mood disturbance in some cancer survivors.*

Developing Effective and Efficient Treatments

Meditation May Enhance Immune System for Breast Cancer Patients

Division of Cancer Biology

The focus of a pilot study at Loyola University of Chicago is the evaluation of the potential for the practice of “mindfulness” to improve both the psychological and immune outcomes for breast cancer patients.

Funded by NCI’s Division of Cancer Biology (DCB), the study has investigated the effects of a Mindfulness-Based Stress Reduction (MBSR) program, developed by Jon Kabat-Zinn, Ph.D., in women recently diagnosed with breast cancer. “MBSR had been shown, by a number of other investigative groups, to reduce symptoms of stress and mood disturbance in heterogeneous samples of cancer survivors,” reported Principal Investigator Linda W. Janusek, Ph.D., RN, and professor at Loyola’s School of Nursing. “In HIV-infected individuals, we have shown MBSR to improve immune function. Thus, there was a strong rationale to evaluate MBSR as a means by which to improve cancer-related immune dysregulation and psychological distress.”

The study began in Fall 2003 and enrolled 40 women who completed the MBSR program at the same time that they underwent their usual cancer care, while a comparison group of 35 women received only their usual cancer care. Karen Chroniak, Ph.D., a clinical psychologist, led the 8-week MBSR program and instructed the women in the practice of mindfulness. Janusek explained: “Mindfulness meditation is a non-judgmental awareness of the present moment and is learned through practices such as sitting and walking meditation, body

and breath awareness, and mindful yoga. With practice, mindfulness is brought to one’s daily life and allows an individual to respond mindfully to life events, instead of reacting in an automatic fashion. In essence, mindfulness becomes a way of living.”

There are sound biological links between the brain and the immune system that provide a scientific rationale for evaluating whether behavioral interventions, such as mindfulness, can boost immune function. “Our emotions produce chemical changes in our brains, which in turn, activate neurochemical processes that have the potential to alter immune function,” according to Janusek. “Clear biological connections link the brain and immune cell populations.” By reducing the emotional response to negative life events, including cancer diagnosis and treatment, mindfulness practice may prevent stress-related suppression of immune function.

The study completed enrollment in June 2006, and Janusek and her colleagues are starting to analyze the data. In the previous study on HIV patients, they demonstrated an increase in natural killer cell numbers circulating in those practicing MBSR. If the new study finds similar benefits for breast cancer patients, Janusek plans to conduct a larger, randomized clinical trial to further study breast cancer patients. “We will expand both our immune and psychological outcomes and will also evaluate neuroendocrine measures, biorhythms, and sleep,” she said.

Developing Effective and Efficient Treatments

Whole-Body Hyperthermia (Fever) May Help Tumor Control

Division of Cancer Biology

Immunotherapy as a treatment is meant to stimulate or restore the ability of the immune system to fight cancer, infections, and other diseases. Experimental immunotherapies under development for the treatment of cancer include monoclonal antibodies, vaccines, and substances such as interleukins, which can improve the body's natural response to disease.

Inflammation—the redness, heat, and swelling in injured tissue caused by white blood cells fighting an infection—occurs as part of the normal immune response. Some researchers working in the field of cancer immunotherapy have postulated that inflammation can augment anti-tumor immune responses.

Julie Ostberg, Ph.D., and Elizabeth Repasky, Ph.D., from Roswell Park Cancer Institute (RPCI), are investigating the thermal aspect of the inflammation. They have proposed that fever-range (39–40°C) thermal stimulation of the inflammatory activity of granulocytes such as polymorphonuclear neutrophils (PMNs) helps to eliminate cancer cells in the body and is at least part of the basis by which mild, fever-range hyperthermia helps to control tumor growth. Their current research, funded by NCI's Division of Cancer Biology, is using in vivo tumor models in mice to obtain cellular and molecular data that will test this hypothesis and help to identify potential mechanisms by which the thermal microenvironment enhances PMN activity.

“Our group had done a Phase I trial to show that whole-body hyperthermia was safe to use in terminally ill cancer patients,” said Ostberg. “Now we're going back to the bench and trying to really figure out what the cellular and molecular mechanisms are behind the anti-tumor potential of this treatment. Before we combine hyperthermia with other standard medical therapies or immunotherapies such as vaccines, we need to know what's going on mechanistically.”

Early results from their study looking at colon tumor models in mice showed that the antitumor effect of whole-body hyperthermia correlated with and enhanced granulocyte or neutrophil infiltrate in the tumors. “If you depleted the neutrophils or the granulocytes, you would lose the antitumor effect of whole-body hyperthermia,” explained Ostberg. Their results, published in 2005 in *Immunological Investigations*, showed not only an increased number of neutrophils at the tumor site but also increased activation of those cells.

Additional studies awaiting publication will further examine the effects of fever-range hyperthermia on neutrophil migration, including the adhesion molecules involved in this process, as well as the effects of mild thermal stress on the activation phenotype of these cells.

An advantage of hyperthermia as a complementary or adjunctive treatment is its familiarity, Ostberg noted. “Patients understand it, because everyone understands or is familiar with the concept of fever.”

Developing Effective and Efficient Treatments

Testing the Effects of Vitamin D on Prostate Cancer in Mice

Division of Cancer Biology

Many researchers are investigating vitamin D as a potential treatment for cancer. When converted into its active form, vitamin D promotes the differentiation of cells or inhibits the growth of cells, and preclinical studies suggest that it might help prevent metastasis. Analogues of the vitamin D hormone are being developed and tested in animal models of cancer.

To learn about the mechanisms by which vitamin D analogues might achieve their effects, researchers at the University of Texas Medical Branch (UTMB) in Galveston are investigating parathyroid hormone-related protein (PTHrP), a growth factor produced by prostate cancer cells. Excess amounts of this protein increase the survival, growth, and migration of prostate cancer cells.

The researchers have recently shown that giving vitamin D analogues to mice with prostate tumors decreases levels of PTHrP, and this, in turn, reduces the size of tumors and the cancer's spread to bone.

"The rate of the tumor growth goes down, and you see a dramatic difference in both the size of the tumor and the incidence of metastasis," said lead researcher Miriam A. Falzon, Ph.D. Her team is now trying to dissect the process by which vitamin D analogues alter PTHrP levels.

With funding from NCI's Division of Cancer Biology, the UTMB researchers are using mice to study the relationship among PTHrP, vitamin D, and the integrin $\alpha6\beta4$, a messenger protein that may mediate the tumor effects of PTHrP and the antitumor effects of vitamin D.

A recent finding in mice that may be relevant to humans, published in the February 2006 issue of *Steroids*, was the discovery that prostate cancer cells are less responsive to vitamin D if the cells no longer responded to androgen. In the human disease, prostate cancer cells progress from being androgen-responsive to androgen-unresponsive.

"The results suggest that it may be critical to start treatment with these vitamin D compounds at an early stage, because if you wait too long then the cells might not respond to vitamin D," Falzon noted.

The researchers are also testing these compounds against breast cancer, and many effects observed in prostate cancer have been detected in breast cancer. Falzon predicted that promising vitamin D compounds will be used in combination with other drugs to treat cancer.

"These compounds tend to have much milder side effects than other chemotherapeutic agents, and we think they are underutilized," she said. "They have a range of anticancer effects."

Developing Effective and Efficient Treatments

Chinese Herbal Extract Shows Promise for Treating Immune Disorders

Center for Cancer Research

For centuries, the Chinese have used an herb called *Tripterygium Wilfordii* Hook F to treat rheumatoid arthritis and other autoimmune diseases. *Tripterygium Wilfordii* Hook F, a vine-like member of the Celastraceae plant family, is known in China as Lei-Gong-Teng. The name, when translated, means the “thunder god” vine. The herb is being investigated in the United States as an agent to improve the outcomes of organ transplantation. It may also have anticancer properties, and researchers have been investigating the plant to identify derivative compounds that may be clinically useful.

One such compound is called triptolide that studies have shown may prevent graft-versus-host-disease and other conditions. Although triptolide clearly possesses immunosuppressive activity and has potential as a therapy, the mechanism of its action has not been clear.

To address this question, Xin Chen, Ph.D., of the National Cancer Institute-Frederick and his colleagues tested the hypothesis that triptolide acts on dendritic cells, which play a critical role in the body’s immune response. They found that triptolide does inhibit some of the key functions of dendritic cells, including their maturation and migration, according to findings published in the October 1, 2005 issue of the journal *Blood*.

The researchers say that because dendritic cells are involved in inflammation and autoimmune diseases, triptolide or herbal products containing this compound may be useful in the treatment of a range of disorders. “More research may yield a ‘conventional’ therapeutic agent—not just an alternative and complementary remedy—for a broad spectrum of diseases requiring immunosuppressive therapy,” said Chen.

Some evidence suggests that triptolide may also promote the death of tumor cells and therefore may have potential as a cancer treatment. The researchers point out, however, that dendritic cells are also critical in initiating the antitumor response, and triptolide may block the process.

“This potential adverse effect of triptolide should be taken into account and may negate the compound’s antitumor effects,” said Chen, who was trained in traditional Chinese medicine. He holds a C.M.D., which means Chinese medical doctor, and has been investigating the medicinal properties of traditional herbs at NCI-Frederick since 1999.

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

Stress Management and the Immune Response in Breast Cancer Patients

Division of Cancer Control and Population Sciences

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Women with early breast cancer now have more and better treatment options than ever before, but understandably still struggle with fear, stress, and other negative psychological reactions to this frightening diagnosis. Besides negatively affecting quality of life, the mental stress that accompanies a diagnosis of cancer can actually contribute to suppression of the immune system, aggravating the side effects of chemotherapy and slowing the healing process.

Stress triggers an endocrine cascade beginning in the limbic system, the brain's emotional center. This in turn triggers the pituitary gland to stimulate the adrenal gland to secrete cortisol, a hormone involved in regulating blood sugar levels and a known immunosuppressant. Nancy McCain, D.S.N., R.N., professor of Nursing at Virginia Commonwealth University, is leading a randomized trial to test if this pathway can be modulated by mind-body interventions that help patients manage their stress. "We think that anything that changes perceptions related to stress or changes the ability to deal with stress can have positive effects on the immune system," explained McCain.

The investigators plan to enroll into the study approximately 240 women who are receiving che-

motherapy for early breast cancer. After collection of blood and urine samples for measurement of immune and neuroendocrine biomarkers, women will be randomly assigned to one of two intervention groups designed to reduce stress—a tai chi group or a spiritual growth group—or to a control group receiving standard care. The intervention groups will begin 1 to 3 weeks after enrollment, and will meet once a week for 10 weeks. The investigators will collect physiological and psychological data at the end of the intervention and during two years of follow-up visits.

Pilot studies of both interventions in women with breast cancer and patients living with the AIDS virus showed positive improvements in quality of life and overall mood. If a positive correlation is found between the interventions and immune function, mind-body stress management strategies may provide important complementary therapy that can enhance not only psychosocial well-being and quality of life, but also the physical health of cancer patients, McCain said.



TAI-CHI is being studied as one activity that can manage stress and increase immune function.

Improving the Quality of Cancer Care

Complementary and Alternative “Comfort Care” at the End of Life

Division of Cancer Prevention

An NCI-funded study of massage therapy or guided meditation to ease suffering for patients in hospice care—in conjunction with standard treatments—is testing the feasibility of using complementary and alternative medicine (CAM) interventions for end-of-life care.

Investigators from the University of Washington School of Public Health and Community Medicine (UWSPHCM) identified the need for a randomized clinical trial to rigorously evaluate promising CAM therapies for this group of hospice patients. “A fundamental issue is that end-of-life care for patients in the United States is substandard, if you’re looking at ‘comfort care,’” said UWSPHCM Associate Professor William Lafferty, M.D., principal investigator of the study. “Anytime end-of-life care has been studied or rated, almost 60 percent of people described their experience of having a loved one die in traditional medical settings as, at best, either fair or poor. That is a pretty low patient satisfaction level for something that we’re all going to face.”

The study began in 2003 and has accrued more than 100 patients. Any patient in hospice care was eligible and approximately 70 percent of enrollees had cancer, Lafferty reported. Patients were randomized to one of three groups: massage, guided meditation, or a control group that received visits by hospice volunteers without either of the interventions. All CAM care was delivered by Bas-

tyr University, a naturopathic medical school, using licensed alternative providers.

The investigators are now analyzing data from about 3,000 patient visits. Outcomes measured include physical and depressive symptoms, mood, quality of life, and functional status. The patients’ families were administered a questionnaire on the quality of dying and death (QODD), which measures factors associated with more comfortable and peaceful deaths. Results from the study are expected to be available in 2007.

“The philosophy behind this study is that quality of life is just as important at the end of life as it is at earlier stages,” explained Lafferty. “Therefore, getting high-quality and effective medical care at the end of life is extremely important, and we think less technological methods of doing that through human touch and meditation will eventually play a greater role in improving comfort for people as they’re dying.”

“If you made the final transition for people more holistic at home, it might lead to fewer hospitalizations at the end of life,” he added. “Fewer hospitalizations, a better mental state at the end of life, an easier passing, a less arduous death—those are all the types of things we’re trying to measure and improve.”

Improving the Quality of Cancer Care

Massage May Enhance Quality of Life in Stem Cell Transplant Patients

Division of Cancer Prevention

Cancer patients undergoing autologous stem cell transplantation (ASCT) experience considerable stress and side effects from this aggressive treatment resulting in greatly impaired quality of life (QoL). In a bid to relieve those stresses and improve patients' lives, researchers at the University of Virginia (UVA) Center for the Study of Complementary and Alternative Therapies and Cancer Center Stem Cell Transplant Unit are testing a novel massage therapy intervention with the potential to improve QoL and reduce treatment-related morbidity of persons with cancer undergoing ASCT.

"Preliminary research suggests that adjunctive massage therapy may improve adverse symptoms and QoL of patients during treatment for cancer," noted Principal Investigator Ann Gill Taylor, R.N., M.S., Ed.D. "Unfortunately, few controlled studies of massage interventions have been conducted among persons with cancer, and most studies have only evaluated immediate within-subject changes across a few brief massage sessions."

Taylor, who is director of UVA's Center for the Study of Complementary and Alternative Therapies, and her colleagues are testing a 7-week massage therapy intervention (three 50-minute massages per week) encompassing both the inpatient and outpatient phases of ASCT treatment. The intervention includes in-home massages when patients

are resting at home and focused on their personal affairs. "This novel aspect of the intervention has the potential to provide continuity of care during the outpatient phases of ASCT, while minimizing treatment barriers and unnecessary patient burdens (e.g., travel)," added Taylor.

The researchers will evaluate the impact of the massage treatments by measuring of QoL, treatment-related symptoms (e.g., anxiety, stress, depression, pain, fatigue, nausea), short-term heart rate variability (HF-HRV), medication consumption (e.g., antiemetics), and perceived social support. Patients receiving the massages will be compared to a control group receiving standard medical care for ASCT.

Although the study is not complete, responses from the initial group of patients and family members have been very positive, Taylor reported. In one case, a patient who had experienced respiratory problems—unrelated to the study protocol—had to be intubated and transferred into one of the intensive care units for 24 hours. "The first request from this study participant immediately upon having his tube removed was 'May I have one of my massages now?'" recalled Taylor. "I think this speaks for itself."

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

Acupressure Used to Treat Nausea From Chemotherapy

Division of Cancer Prevention

Nausea and vomiting remain significant problems for patients undergoing cancer chemotherapy treatments, despite new anti-nausea (antiemetic) medications available to treat these unpleasant side effects. Researchers are looking into the Traditional Chinese Medicine (TCM) practice of acupressure as an “added value” approach to help relieve these problems.

To test this approach, Suzanne L. Dibble, D.N.Sc., R.N., professor at the University of California, San Francisco, conducted a pilot study with “absolutely marvelous results that we published.” She then gained NCI funding for a larger, multi-center clinical trial with 160 breast cancer patients who were undergoing chemotherapy.

The patients were randomly assigned to one of the following treatment groups: authentic acupressure applied by the patient’s fingers to the *neiguan* point located above the wrist on the inside of the forearm plus usual nausea care; or “sham” placebo acupressure plus usual nausea care; or standard nausea care. All patients received “antiemetics as ordered by their physicians,” Dibble noted. “A strength of

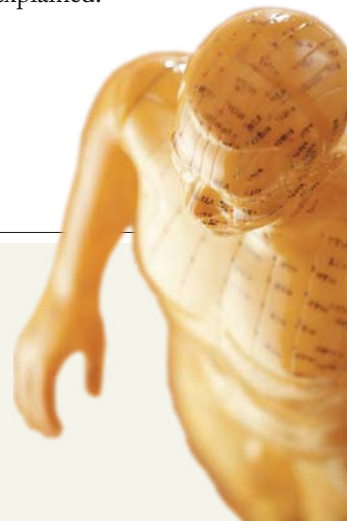
this study is that it does not pit modern Western medicine and TCM against each other.”

During the one-month treatment period of the study, patients were monitored on a daily basis through the use of diaries. “Every morning after the chemotherapy, they would treat themselves, continue to treat themselves on an as needed basis, and then they’d keep track of how many times a day they did the acupressure, took medications, or used other techniques to manage their nausea” Dibble explained.

Dibble plans to conduct a follow-up study in a similar patient population using a Transcutaneous Electrical Nerve Stimulation (TENS) device instead of finger pressure to trigger the *neiguan* point response. “The feedback we had from the women is that their fingernails got in the way when applying pressure,” and the TENS device might be an easier way to apply the treatment, she explained.

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ACUPRESSURE. Researchers are looking into the Traditional Chinese Medicine (TCM) practice of acupressure as an “added value” approach to help relieve these problems.



Improving the Quality of Life for Cancer Patients, Survivors, and Their Families

Foot Reflexology May Enhance Quality of Life in Breast Cancer Patients

Division of Cancer Prevention

Breast cancer is the most common cancer among women in the United States and the toxic effects of chemotherapy and other treatments have been a primary spur to the increasing importance of—and attention by patients, clinicians, and researchers to—patients' quality of life (QoL).

In a pilot study among patients at the West Michigan Cancer Center in Kalamazoo, researchers found that women with breast cancer expressed the most interest in complementary and alternative medicine (CAM). The researchers also learned that reflexology—a specialized foot massage therapy—was the intervention most likely to be chosen and maintained by such patients.

“We know patients are seeking such treatments, so the CAM field needs to establish the science behind the practice,” said Principal Investigator Gwen K. Wyatt, RN, Ph.D., at Michigan State University. Given the strong interest in reflexology, the question then becomes “what is the measurable impact of a consistently delivered therapeutic intervention, as measured by established and relevant QoL scales?” she added. Ryan and her colleagues will try to answer that question in a Phase III study of some 340 women with advanced (stages III or IV) breast cancer.

Reflexology is an intricate procedure oriented around specific pressure points in the human foot. The third of patients in the study with the reflexol-

ogy intervention will experience “the good hurt,” as Wyatt puts it. “The therapist exerts deep pressure with the thumb and then does a very specific movement known as the caterpillar crawl,” which is supposed to trigger an autonomic nervous system reflex relaxation response, as well as enhancing lymphatic drainage and flow.

Another third of patients will serve as controls and receive only conventional medical care. However, it is the final one-third group of patients that Wyatt is most excited about. “You could call them a placebo group,” she explained. “Current CAM research is beginning to emphasize the ‘active ingredient.’ With herbal medicines, for example, meaningful research tries to distinguish which chemical component of the treatment is responsible for the outcome.” Her placebo group will get a foot massage, but one designed to avoid the crucial pressure points.

In addition to the primary QoL scale (The FACT-G), her team will also try to isolate which “intervening variables” might be correlated with patient QoL outcomes. They will also recruit heavily in the African American communities of Detroit, Flint, and Saginaw Bay City, to reflect the fact that many advanced breast cancer patients come from that minority group.

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 5 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 percent reduction in the frequency of hot flashes and a 69 percent 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 or/and 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."

OVERCOMING CANCER HEALTH DISPARITIES

Overcoming cancer health disparities is a critical component of each of the research areas described in this Annual Report.

Minorities and other underserved populations variously distinguished by race, ethnicity, gender, age, socioeconomic status, geographic location, occupation, and education bear a far greater cancer burden than the general population.

Overcoming Cancer Health Disparities

CAM Survey of California Consumers Includes Underserved Minority Groups

Division of Cancer Control and Population Sciences

NCI staff are using data from the California Health Interview Survey (CHIS) of over 9,000 consumers to examine the use of complementary and alternative medicine (CAM) in preventing and treating cancer and other chronic illnesses, including among medically underserved minority groups.

CHIS-CAM is a collaborative effort of NCI and the University of California, Los Angeles and is the one of the largest population-based surveys conducted to date to document the use of CAM by people who have had cancer diagnoses. California's population includes many Asians, Latin Americans, and African Americans, so the study benefits from large samples of these groups. It is based on telephone interviews in 2003 among a sample of California adults regarding their use during the past 12 months of CAM providers (e.g., chiropractors, acupuncturists), special diets, dietary supplements, mind-body methods (e.g., yoga, meditation), self-prayer, and support groups.

The findings, published in the medical journal *Evidence-Based Complementary and Alternative Medicine*, counter the widely held assumption that whites are more likely to use CAM approaches than other ethnic groups.

“For example, Asian/Pacific Islanders have the highest use of acupuncture and Traditional Chinese Medicine (TCM), and African Americans are

most likely to report praying for their health,” the researchers noted. “In other instances, the differences between whites and other groups are minimal. Latinos consistently report a lower level of use than whites and other racial/ethnic groups on every measure of CAM utilization except self-directed prayer, where they report more use than any other group except for African Americans.”

Overall, the use of CAM by California consumers was found to be substantial. A quarter of the 9,187 respondents reported seeing a CAM provider in the past 12 months and even higher numbers reported using other CAM methods, including dietary therapy (41 percent) and two or more dietary supplements (62 percent).

Among the 1,844 survey respondents who reported a diagnosis of cancer, use of CAM providers and other methods were not distinctly different than for people diagnosed with other chronic illnesses.

“However, those in the cancer group are considerably less apt (36.1 percent versus 48.3 percent) to report employing dietary therapies and more apt to report self-directed prayer (58.4 percent versus 49.9 percent) and attending support groups (11.3 percent versus 7.9 percent),” the researchers reported. “These patterns may be due to the use of CAM to ameliorate the psychological distress that is typically associated with a diagnosis of cancer.”

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 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

Testing Traditional Chinese Medicines for Anti-Cancer Agents

Center for Cancer Research

When Joost J. Oppenheim, M.D., was introduced to clinical oncology research at NCI more than 40 years ago, he came away convinced that more research was needed to understand how the body's own natural defense mechanisms could be harnessed to cope with cancer. This objective led to a career focused on endogenous immune system regulatory proteins, cytokines, and chemokines.

Today, as head of the Laboratory of Molecular Immunoregulation at NCI-Frederick, Oppenheim's projects include an effort to identify components of natural products and Traditional Chinese Medicines (TCM) that act on proteins known as chemokines or chemoattractant cytokines. Chemokines play a central role in coordinating the body's natural defenses by recruiting immune cells from the blood to the sites of inflammation. Some chemokines also play a role in fetal development, tumor growth, and the growth of new blood vessels that feed tumors, also called angiogenesis.

A goal of the project is to identify both plant and animal components of TCM compounds that might inhibit chemokines or chemokine receptors. The hypothesis supporting this goal is that inhibitors of chemokine-induced cell migration are likely to have anti-inflammatory, anti-angiogenic and anti-tumor activities. "It could potentially be very useful to have inhibitors of the chemokines and the chemokine receptors that mobilize cells and promote angiogenesis and metastases," Oppenheim explained, noting

that inhibitors of chemokines can reduce the spread of tumors in some animal models.

Since 1999, these efforts have been carried out in conjunction with Oppenheim's NCI colleagues O. M. Zack Howard, Ph.D., and Xin Chen, M.D., Ph.D. Their efforts have identified several discrete chemicals that inhibit chemoattractant receptors. These include shikonin which blocks ligand binding to CCR1 and most other chemokine receptor intracellular signaling and ursodeoxycholic acid that blocks ligand binding to the fMLP receptors. These compounds are currently being evaluated in preclinical models as single anti-tumor agents.

Further, two TCM compounds—called Qiu Kai Ling and Shuang Huang Lian—have been shown to inhibit the function of the canonical regulator of inflammation, NFκB, and subsequently to suppress chemokine and chemokine receptor expression. Future studies will evaluate the ability of these compounds to inhibit inflammation associated with tumor growth and angiogenesis.

Currently, these NCI researchers are trying to identify agents in TCM that could promote the body's immune response by stimulating antigen-presenting cells and suppressing T-regulatory cells. This would expand the targets beyond chemokines and chemokine receptors to more general regulators of the tumor immune system.

NCI Scientists Spearhead Pioneering Research on CAM

Plant Compounds Protect Cells from Carcinogen-Induced Damage

Center for Cancer Research

Many phytochemicals—compounds found naturally in plants—have been shown to have preventative effects in animal models of cancer development. In addition, epidemiologic studies have suggested that diets rich in phytochemicals from fruits and vegetables may prevent or slow the development of certain tumor types. Phytochemicals of great interest to cancer-prevention researchers include: diosmin, from citrus fruit; kaempferol, found in leafy green vegetables; and resveratrol, present in grapes and red wine.

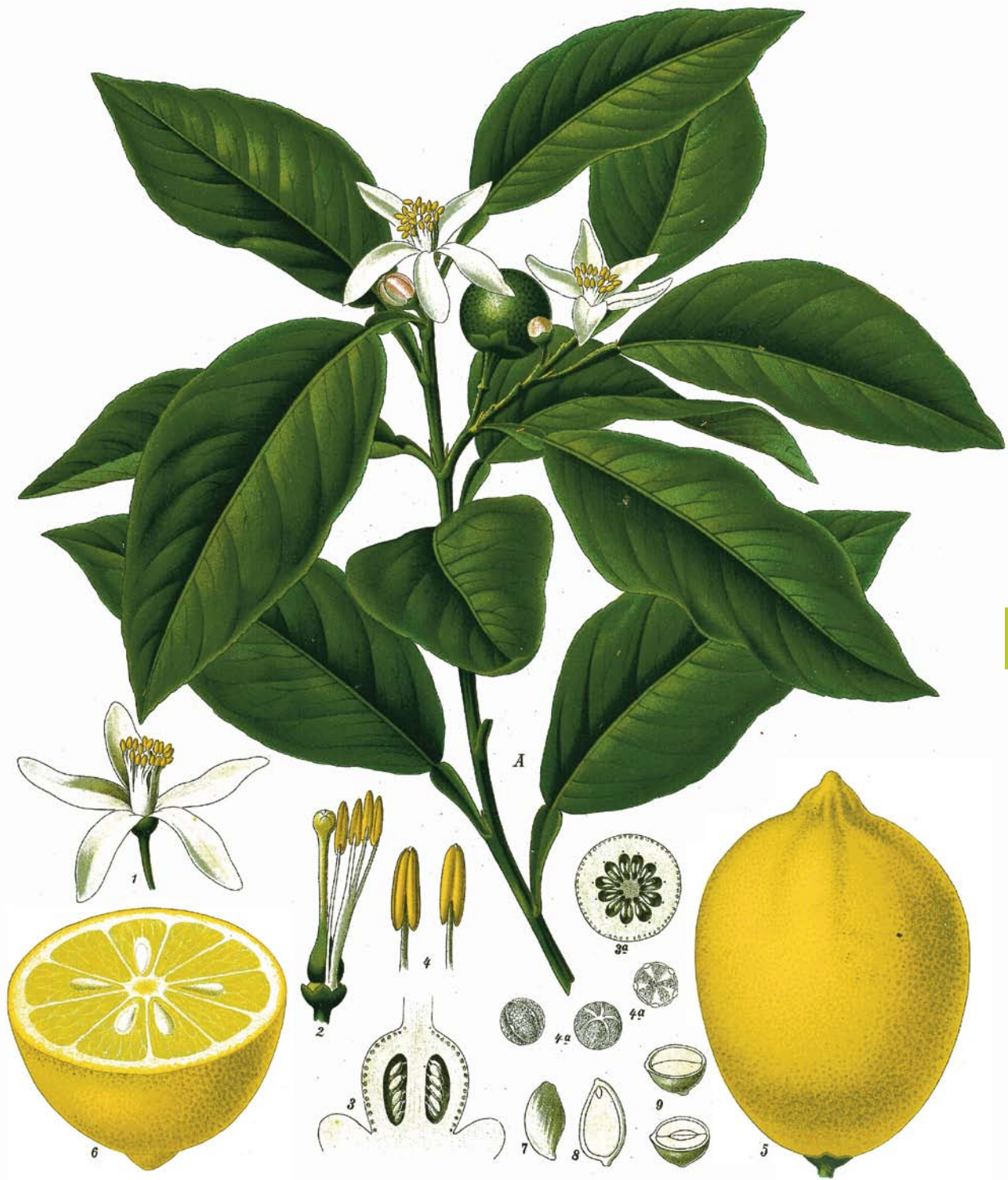
Since 1999, the laboratory of Grace Yeh, Ph.D., in NCI's Center for Cancer Research, has examined how these and other phytochemicals can protect cells against DNA damage caused by external carcinogens, possibly preventing the development of cancer. Their main focus has been on understanding the biochemical and molecular mechanisms responsible for the protective effect of phytochemicals and other chemopreventive agents against aryl hydrocarbon-induced carcinogenesis.

The aryl hydrocarbon receptor (AhR) is a cytosolic protein found inside the cells that mediates several important signaling pathways. When a carcinogen binds to AhR, it triggers a signaling cascade that leads to production of the enzyme cytochrome P450 1A1 (CYP1A1), which then activates the carcinogen into a form that can cause genetic damage. AhR also controls other genes that affect both the activation and detoxification of carcinogens.

Carcinogens under study in the Yeh laboratory include benzo[a]pyrene, a carcinogen found in cooked meat, cigarettes, and industrial waste, and members of the dioxin family of toxins. In a comprehensive study of all commercially available purified phytochemicals, Yeh and her colleagues found that the flavonoid and curcuminoid classes of phytochemicals bind to the AhR and modulate the cell's capacity to activate aryl hydrocarbons, thereby modifying the cellular response to environmental carcinogens. Yeh's lab also identified resveratrol as the first and only known pure antagonist of the AhR. Resveratrol blocks the activation of the AhR by carcinogens and inhibits CYP1A1 expression.

Other related work from the Yeh laboratory has examined the chemoprotective effects of Traditional Chinese Medicine (TCM) compounds and of salicylic acid, which was initially obtained from the bark of the willow tree. The investigators are now moving promising results from their laboratory experiments into animal studies. One study is looking at the ability of phytochemicals and other chemopreventive agents to prevent carcinogen-induced lung and breast cancers in rodents.

Other animal studies are examining the gender differences in lung cancer to investigate whether any chemopreventative benefit derived from phytochemicals differs between males and females. Because some phytochemicals have a weak hormonal effect, "one phytochemical may be more effective in one gender than another," Yeh explained.



DIOSMIN, found in the skin of lemons, is being studied by cancer prevention researchers.



DRY BEANS. *In one study, participants who tripled their intake of dry beans (legumes) had a 65 percent reduction in risk of advanced adenoma recurrence.*

NCI Scientists Spearhead Pioneering Research on CAM

Impact of Legume (Dry Beans) Diet on Colorectal Cancer Risk Studied

Center for Cancer Research

A large, 4-year clinical trial conducted during the 1990s found no benefit from a high fiber, low-fat, fruits, and vegetable diet for lowering the risk of recurring colorectal polyps (adenomas), the main precursor lesion of colorectal cancer (CRC). However, NCI scientists recently found in a post analysis of the data from the Polyp Prevention Trial (PPT) that participants who tripled their intake of dry beans (legumes) had a 65 percent reduction in risk of advanced adenoma recurrence—adenomas most likely to progress to colorectal cancer, reported Elaine Lanza, Ph.D., head of NCI's Colon Cancer Prevention Group within the Center for Cancer Research (CCR). These findings were published in the July 2006 issue of *Journal of Nutrition*.

Based on her analysis of the PPT data, Lanza has begun a feeding study using a legume-enriched, low glycemic (blood sugar) diet among men who are at increased risk for colorectal cancer because they have already had at least one polyp removed or are insulin-resistant—a condition that often leads to type 2 diabetes.

“Both colorectal cancer and insulin resistance are increasingly recognized as chronic, low-level inflammatory conditions,” explained Lanza whose colon cancer group is part of the CCR Laboratory of Cancer Prevention. “Therefore, we are looking for biomarkers of inflammation in the men which are related to colorectal cancer and we are also measuring the effect of diet on changes in gene expression by looking at changes in messenger RNA from colon cells sloughed off into the feces.” NCI has already begun enrolling the 68 men for the study. Lanza expects to have results by mid-2007.

If the high legume diet shows a beneficial impact on biomarkers of CRC risk, a larger clinical trial could be conducted to test whether dry beans lowers the risk of recurrence of advanced adenomas. Lanza believes that the combination of a dietary intervention, plus a pharmaceutical agent—such as aspirin, a well known anti-inflammatory drug—might be the most successful strategy for preventing colorectal cancer. “Drugs have numerous side effects,” she noted. “If you could have the right diet, you could hopefully, reduce the dose of the drug you might need for cancer prevention.”

NCI Scientists Spearhead Pioneering Research on CAM

NCI's Nutritional Epidemiology Branch Focuses on Impact of Diet and Activity on Cancer Risk

Division of Cancer Epidemiology and Genetics

NCI's Nutritional Epidemiology Branch (NEB) has for many years pursued investigations into the impact of diet, nutrition, and physical activity on the risk of cancer.

"Our primary objective is to clarify the relationship between what we eat—and other nutrition-related activities and exposures—and the development of and also the prognosis for a variety of cancers," explained NEB Chief Arthur Schatzkin, M.D., Dr.P.H. "In the last few years there has been a particular emphasis on 'energy balance'—the dynamic interplay of energy intake and physical activity that is reflected in body fatness—as an important risk factor for a number of cancers."

The Branch, which is part of NCI's Division of Cancer Epidemiology and Genetics (DCEG), has been involved in a number of major, pioneering studies into nutritional interventions, such as the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Trial conducted in Finland. "One of the unexpected but important findings in that study was a reduced incidence of prostate cancer among men who took vitamin E," Schatzkin recalled.

Other major studies with NEB involvement include the Polyp Prevention Trial (PPT) (see related article on page 65), an investigation of the effect of a low fat, high fiber, fruit- and vegetable-enhanced dietary pattern on the recurrence of colorectal adenomas (invasive cancer precursor lesions), and the ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT). NEB also led an analysis using data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) that showed a protective association between dietary fiber intake and colorectal adenomas.

NEB scientists are also leading the massive NIH-AARP Diet & Health Study. "This is the largest in-depth prospective cohort study of diet and cancer ever done, involving over 566,000 men and women," noted Schatzkin. "We went into the field in 1995–96 with the goal of looking at the nutritional and other lifestyle factors that are associated with cancer. This study was designed to include people at both high and low levels of intake of various foods and nutrients to make good biological comparisons."

Important findings from the NIH-AARP study have been submitted to be published. Schatzkin says these will include new discoveries on the role of being overweight or obese on risk of death and cancer.

NEB has also been on the forefront of developing methods for accurately measuring what people eat, including consumption of meat in its various forms. "There are a lot of concerns that many of the instruments nutritional epidemiologists used in past are somewhat inaccurate," Schatzkin commented. "That could cause us to miss relationships between diet and cancer that are important and that just won't show up if we use imprecise instruments."

For example, NEB has been collaborating with other NCI scientists involved in developing a web-based dietary "recall" survey tool for use by participants in nutrition studies. "It's very user-friendly and may enable us to see some things that have been obscured, because our instruments haven't been good enough," he said.

NCI Scientists Spearhead Pioneering Research on CAM

Selenium Studied for Prevention of Esophageal and Gastric Cancers

Division of Cancer Epidemiology and Genetics

Cancer rates can vary dramatically around the world and researchers often develop insights about risk factors for certain cancers by looking closely at populations with higher than average rates of those diseases. The rural county of Linxian in north central China, for example, has some of the world's highest cancer rates and more than 85 percent of those cancers occur in the esophagus and the upper stomach (gastric cardia).

For more than two decades, NCI scientists have been collaborating with their Chinese counterparts to examine and interrupt these disease patterns. After preliminary work, two major clinical trials were designed—collectively known as the Nutrition Intervention Trials—based on the “historical fact that the Linxian population has a diet deficient in several nutrients we have linked to cancer of the esophagus and gastric cardia,” explained Philip R. Taylor, M.D., Sc.D, a senior investigator with NCI's Division of Cancer Epidemiology and Genetics (DCEG).

In 1986, the General Population Trial enrolled nearly 30,000 people between the ages of 40 and 69 living in Linxian, and began to test four different vitamin/mineral combinations. After 5 years, participants who took a daily supplement of selenium, vitamin E, and beta-carotene had a 9 percent drop in the overall risk of death. Their risk of cancer mortality was down 13 percent, although the intervention reduced esophageal cancer deaths by only 4 percent.

The major impact was shown for sites located further along the digestive tract, with stomach cancer reduced by 21 percent overall, and by 28 percent

in the lower non-cardia region (the body of the stomach). Cerebrovascular events (stroke) were the second-leading cause of death in Linxian, and these too were reduced by 10 percent in the group receiving the daily supplements.

“Those findings were meaningful,” said Taylor, “but what has happened since that time is perhaps even more interesting.” Investigators have continued to follow trial participants since they stopped supplementation in 1991. “Surprisingly, the reduced risks observed for persons who were supplemented with selenium, vitamin E, and beta-carotene during the trial have continued for up to 10 years. In short, the advantage in survival we found initially has persisted and actually increased.”

NCI's partners in China are continuing this follow-up surveillance. You-Lin Qiao, M.D., Ph.D., who heads the Department of Epidemiology at the Cancer Institute, Chinese Academy of Medical Sciences, has done additional analyses of selenium levels in the blood from this same group of Chinese individuals. He and his colleagues were able to confirm that the mineral has a significant impact on the subsequent development of upper gastrointestinal cancers. They concluded that if selenium supplementation could be provided to high-risk populations—like the one at Linxian—it could have a strong protective effect against esophageal and gastric cardia cancers. Plans are now underway to fortify the salt in that region with selenium, Taylor reported.

NCI Scientists Spearhead Pioneering Research on CAM

Preventive Study of Gastric Cancer Emerges from Collaboration with China

Division of Cancer Epidemiology and Genetics

Gastric cancer—also referred to as stomach cancer—is second only to lung cancer as a cause of cancer deaths worldwide, though it is much less of a threat to public health in the United States than it is in developing countries. Gastric cancer incidence is disproportionately high in parts of China. For example, in the rural county of Linqu, gastric cancer accounts for 42 percent of cancer deaths.

To address this public health challenge, there have been a number of fruitful collaborations for more than two decades between NCI and scientists like Wei Cheng You, M.D., from the Beijing Institute for Cancer Research (BICR). You and researchers from NCI's Division of Cancer Epidemiology and Genetics (DCEG), obtained valuable clues to gastric cancer causes and the factors affecting precancerous gastric conditions by examining Linqu villagers' stomachs with endoscopes as part of a population-based screening study.

This and other work in China provided a solid framework for a follow-up study for preventing gastric cancer using a combination of drugs, antibiotics, and dietary supplements—such as garlic compounds, multivitamins, and minerals, said Mitchell Gail, M.D., Ph. D., current chief of NCI's Biostatistics Branch.

When the researchers examined tiny biopsies taken from the Chinese villagers who had been screened, they found a startling and very clear map of the progression to gastric cancer, Gail noted. Nearly every individual examined had some form of gastric histopathology, ranging from mild lesions—such as superficial gastritis—to dysplasia, which is a precursor to gastric cancer. Nearly 70 percent of the

study population was infected with *H. pylori* bacteria which cause inflammation and stomach ulcers and represent a major risk factor for gastric cancer.

“We wanted to learn more about the causes of gastric cancer, and how we might make an impact in preventing the disease,” Gail explained. “In our follow-up clinical trial, we will tease out the impact of treating the *H. pylori* infection, as well as the separate and combined effects of a giving a garlic supplement and the combination of vitamins C and E and selenium, which earlier epidemiological studies suggested might be protective against gastric cancer.”

You, Gail, and their colleagues enrolled 3,411 men and women into this prospective, randomized blinded trial in 1995. Those who were infected with *H. pylori* were randomly assigned to receive a placebo or treatment with amoxicillin and omeprazole. Those individuals who weren't infected still got a placebo. After 3 months, all participants began taking pills that contained the garlic preparation, the vitamin/mineral combination, or placebo. Treatment continued for more than 7 years. Gastroscopy and gastric biopsies will permit the researchers to evaluate the various and combined impacts of the interventions on the actual progression of gastric disease in each patient.

The study's findings were published in the September 2006 issue of the *Journal of the National Cancer Institute*.

NCI Scientists Spearhead Pioneering Research on CAM

Lessons from China Could Enhance Prostate Cancer Prevention in the West

Division of Cancer Epidemiology and Genetics

Although prostate cancer is the most commonly diagnosed cancer among men in the United States, the causes of most cases of the disease remain largely unexplained.

“We don’t really know much about the etiology of prostate cancer other than the factors of aging, race, and a family history of prostate cancer,” said Ann Hsing, Ph.D., a senior investigator with NCI’s Division of Cancer Epidemiology and Genetics (DCEG). While prevalence of latent, early-stage prostate cancer appears to be comparable around the world, clinical disease in western countries is 30 to 50 times higher than in Asian men, she noted. This large difference in risk cannot be explained entirely by population differences in prostate cancer screening, which is much less common in Asian countries.

Hsing and her colleagues are investigating this remarkable epidemiological pattern in the NCI-Shanghai Collaborative Prostate Cancer Study. The study, which began in the 1990s, was the first population-based interdisciplinary study in men who are at low risk for prostate cancer.

Working closely with the Shanghai Cancer Institute, the researchers identified 286 cases of prostate cancer and matched them with 471 randomly selected healthy controls. The data have provided several intriguing clues and the researchers have published more than two dozen papers exploring prostate cancer risk factors. In general, the study’s results indicate that both lifestyle and nutritional factors contribute to the disease.

Asian men are generally very lean compared to American men. Their diet also differs, and as a consequence, so too does their propensity for developing insulin-resistance. They found that prostate can-

cer risk is greater among those with higher levels of education, a higher waist-to-hip ratio (an indicator for abdominal obesity), and a higher intake of total calories, red meat, and animal fat and protein. Risk was found to decrease among those consuming more peppers, mushrooms, and allium vegetables—such as garlic and scallions.

Hsing thinks the data also support the likelihood that many of these measurable risks have an underlying hormonal and metabolic basis. Insulin-resistant men have an elevated risk, while those who are sensitive to insulin have a reduced risk. High levels of IGF-1, an insulin-like growth factor, more than doubled the risk, while high levels of the insulin-like growth factor binding proteins IGFBP-3 cut risk nearly in half.

“Most of the lifestyle factors that seemed to confer risk in the study are closely linked to westernization,” said Hsing. The scientists are in the process of developing what they call a “westernization index” to represent these lifestyle factors, which they found highly correlated with an adverse metabolic profile. It would include higher serum levels of insulin, IGF-1, and androgens—biomarkers that have been previously implicated in prostate cancer. The population-based data from the landmark Shanghai study provide a potential biological mechanism linking westernization and increased prostate cancer rates.



THE NCI-SHANGHAI COLLABORATIVE PROSTATE CANCER STUDY, which began in the 1990s, was the first population-based interdisciplinary study in men who are at low risk for prostate cancer.

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 2005. The articles are classified and grouped according to research type: cancer prevention, cancer treatment, and cancer side effect/symptom management. Abstracts of the articles are available online through the National Library of Medicine's "PubMed" database at www.pubmed.com.

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Cancer Prevention

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Cancer Treatment

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Katiyar SK, Roy AM, Baliga MS. Silymarin induces apoptosis primarily through a p53-dependent pathway involving Bcl-2/Bax, cytochrome c release, and caspase activation. *Molecular Cancer Therapeutics*, February 2005; 4(2):207–16.

Liu B, Edgerton S, Yang X, Kim A, Ordonez-Ercan D, Mason T, Alvarez K, McKimmey C, Liu N, Thor A. Low-dose dietary phytoestrogen abrogates tamoxifen-associated mammary tumor prevention. *Cancer Research*, February 1, 2005; 65(3):879–86.

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Cancer Side Effect/ Symptom Management

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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 CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005	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 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
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
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 CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005	PRIMARY ID	TYPE OF TRIAL	AGE RANGE	SPONSOR OF TRIAL	PHASE(S)
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
Adult Trials					
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 Inositol for the Prevention of Lung Cancer in Patients With Bronchial Epithelial Dysplasia Who Are Current or Former Smokers	BCCA-U98-0411	Prevention	40 to 74	NCI	Phase I
Phase I Randomized Chemoprevention Study of Genistein in Healthy Postmenopausal Women	UNC-GCRC-2107	Prevention	45 to 70	NCI	Phase I
Phase I Study of Lycopene as Chemoprevention for Prostate Cancer in Healthy Participants	UIC-2004-0040	Prevention	18 to 45	NCI	Phase I

PDQ CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005	PRIMARY ID	TYPE OF TRIAL	AGE RANGE	SPONSOR OF TRIAL	PHASE(S)
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 Study of Green Tea Extract (Polyphenon E) as Cancer Prevention in Healthy Participants	UARIZ-HSC-0499	Prevention	18 and over	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
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 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 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 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
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

PDQ CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005

PRIMARY ID	TYPE OF TRIAL	AGE RANGE	SPONSOR OF TRIAL	PHASE(S)
UARIZ-HSC-00142	Prevention	40 to 80	NCI	Phase III
MDA-CCC-0106	Supportive care	18 and over	NCI	No phase specified
CASE-2Z05	Supportive care	20 to 80	NCI	No phase specified
OHSU-ONC-99037-L	Supportive care	18 and over	NCI	No phase specified
OHSU-7235	Supportive care	Over 18	NCI	No phase specified
BIDMC-2003P-000299	Supportive care	18 and over	NCI	No phase specified
CCCWFU-02403	Supportive care	18 and over	NCI	No phase specified
CCCWFU-97202	Supportive care	Any age	NCI	No phase specified

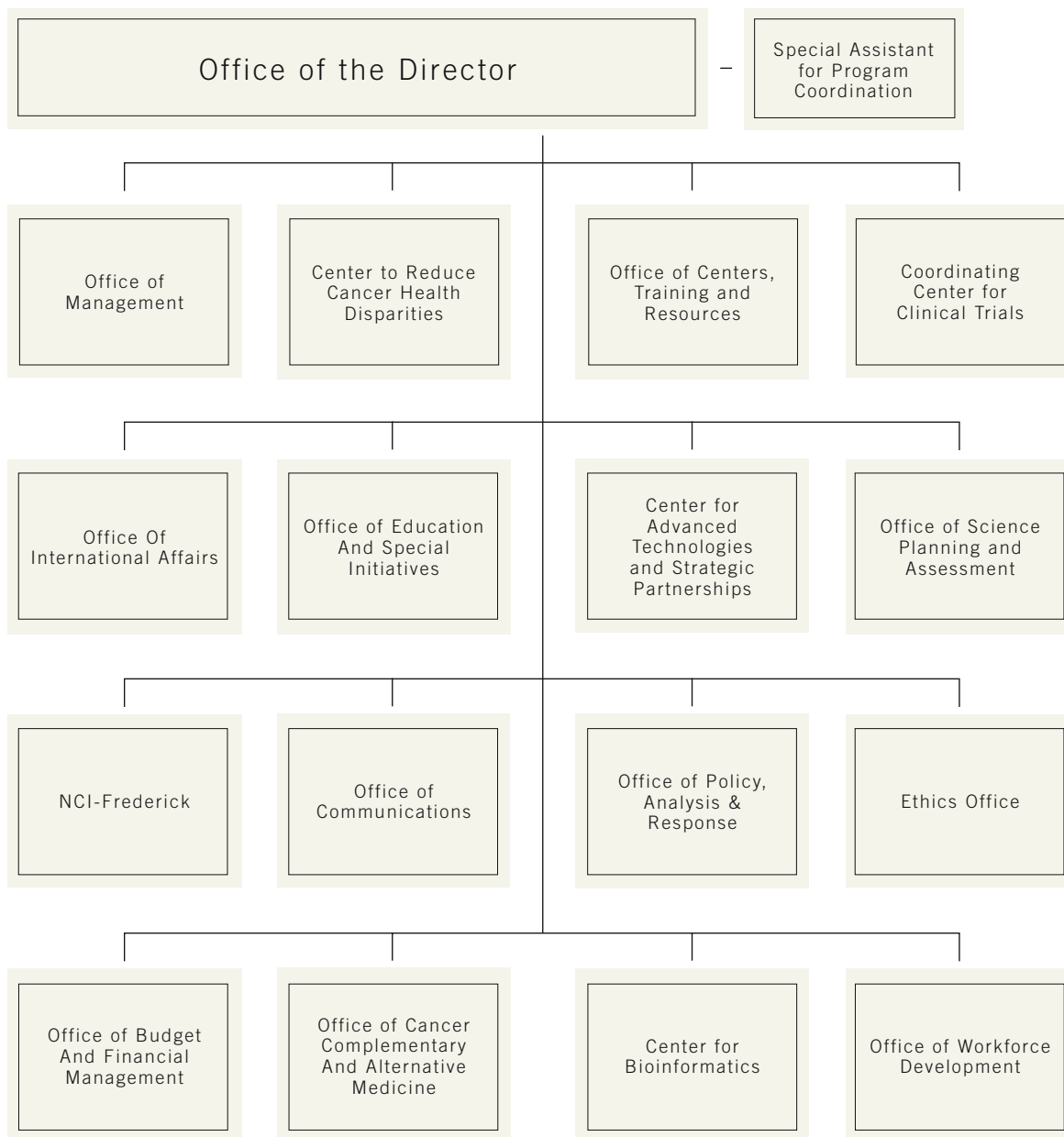
PDQ CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005	PRIMARY ID	TYPE OF TRIAL	AGE RANGE	SPONSOR OF TRIAL	PHASE(S)
Randomized Study of Hypnosis, Massage Therapy, and Healing Touch in Patients Undergoing Chemotherapy for Ovarian Epithelial or Primary Peritoneal Cavity Cancer	UMN-2000NT790	Supportive care	Any age	NCI	No phase specified
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
Phase II Randomized Study of Soy Protein in Postmenopausal Women With Breast Disease Taking Tamoxifen and Experiencing Hot Flashes	CALGB-79805	Supportive care	Postmeno-pausal (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	NCCAM; 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
Phase III Randomized Study of Zinc Sulfate for the Prevention of Altered Taste in Patients With Head and Neck Cancer Undergoing Radiotherapy	NCCTG-N01C4	Supportive care	18 and over	NCI	Phase III
Phase III Randomized Study of Acupressure for Chemotherapy-Induced Nausea in Women With Breast Cancer Receiving One of Three Combination Therapy Regimens	MDA-NUR01-396	Supportive care	Adult	NCI	Phase III

PDQ CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005	PRIMARY ID	TYPE OF TRIAL	AGE RANGE	SPONSOR OF TRIAL	PHASE(S)
Phase III Randomized Study of Juven® Versus a Non-Juven® Supplement in the Treatment of Cachexia in Patients With Unspecified Solid Tumors or Lymphoma With No Leukemic Aspect	RTOG-0122	Supportive care	17 and over	NCI	Phase III
Phase III Randomized Study of Sertraline (Zoloff®) Versus Hypericum Perforatum (St. John's Wort) in Cancer Patients With Mild to Moderate Depression	CCCWFU-98101	Supportive care	18 and over	NCI	Phase III
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
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 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; Pharma- ceutical Industry	Phase I

PDQ CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005	PRIMARY ID	TYPE OF TRIAL	AGE RANGE	SPONSOR OF TRIAL	PHASE(S)
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 Pilot Study of Scutellaria Barbata (Chinese Herbal Extract) in Women With Metastatic Breast Cancer	UCSF-CRO-00758	Treatment	18 and over	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 Supplemental Treatment With Mistletoe in Patients With Stage IIIB or IV Non-Small Cell Lung Cancer Receiving Palliative Chemotherapy	TJUH-01F45	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 Study of Pomegranate Juice in Patients With Indication of Recurrent Adenocarcinoma of the Prostate	UCLA-0210049	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

PDQ CANCER CAM CLINICAL TRIALS ACTIVE IN FY 2005	PRIMARY ID	TYPE OF TRIAL	AGE RANGE	SPONSOR OF TRIAL	PHASE(S)
Phase II Study of Lycopene in Patients With Asymptomatic Androgen-Independent Metastatic Prostate Cancer Who Have an Elevated Prostate-Specific Antigen Level	NCCTG-N0351	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 Neoadjuvant Genistein in Patients Undergoing Surgical Resection for Bladder Cancer	WCCC-CO-04307	Treatment	18 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 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	NCCAM; NCI	Phase III

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